INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis

Response to Public Comments on the Draft Evidence Report

August 29, 2018

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Response to Comments from Individual Patients

We would like to thank the amyloidosis patient and caregiver community for submitting public comments on our draft report. We received an incredible number of comments from individuals on this review – 36, to be exact – and we deeply appreciated the amyloidosis community's willingness to share how the disease has affected patients and their families.

We heard from many of you how the hereditary nature of the condition adds significant burden to the lived experience of the symptoms and the impact of those symptoms on your quality of life. We heard from many caregivers of family members they have lost to the disease that remember the courage their loved ones demonstrated in the face of a devasting illness. And we heard about the hope the new treatments are offering patients and their families. In the Evidence Report, we have included a summary of these comments in Section 1.4 (Insights Gained from Discussions with Patients and Patient Groups), and updated Chapter 5 (Other Benefits and Contextual Considerations) to reflect what you told us. When a patient comment required a specific response or change to the report, we included it below.

Importantly, we heard a near-universal call for reasonable, affordable pricing of the new drugs to ensure that everyone can gain access. Thank you for giving voice to the access issues patients face when prices are set well out of line with the value the drugs deliver to patients.

We also would like to clarify a few misunderstandings about ICER, as some commenters appeared to suggest that we either set the price of drugs, or that we create insurance coverage policies. Actually, neither is the case. ICER encourages drugmakers to set prices that align with the benefits patients receive, and when that happens, we put pressure on insurers to open up broad patient access. As part of our process, ICER hosts public meetings where all stakeholders, including patients and doctors, can participate in discussions about what insurance policies should look like and what a fair price for a treatment is. More information about ICER's work, goals, and funding can be found at https://icer-review.org/about/.

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Manufacturers		
Akcea		
1.	Akcea also has specific concerns about ICER's processes, methodology and assessment in their development of the draft evidence report on inotersen and patisiran for hATTR. In addition, we are concerned about the potential impact on patients' well-being due to the premature publication of ICER's preliminary assessment. Given the small patient population, limited clinical evidence, and wide heterogeneity of symptoms, it is premature to consider the clinical or cost-effectiveness of these two novel treatments. As with any novel therapy, especially with small numbers of patients in the clinical trials, our understanding of its value evolves over time as broader utilization reveals the product's true safety and effectiveness. These two therapies are so new that there are no long-term studies that can be used to adequately inform ICER's evaluation. In particular, evidence on the long-term outcomes that ICER requires for their cost-effectiveness assessment are unavailable. For example, ICER hypothesizes that the "neuropathy-related quality of life gains may not be	Patients, clinicians, and payers need to make decisions about how to treat patients using approved medications shortly after the time of regulatory approval. We agree that it would be easier if more data were available and appreciate that broader utilization reveals the product's true safety and effectiveness. At the same time, when a new drug is being sold to treat patients, decisions must be informed by considering the currently available evidence related to the incremental cost and outcomes associated with the new drug. One of the benefits of constructing a model and populating it with the current evidence is that the results can illuminate which assumptions are consequential and which are not. The economic evidence section contains many sensitivity and scenario analyzes that can be used to guide future research for those interested in real world evidence of the value of the drug.

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	durable" for patients taking inotersen even though an open label extension study supplied to ICER under separate cover suggests otherwise. Attempting to assess a drug before it is approved risks promulgating under-informed determinations of effectiveness and value that can significantly and inappropriately impact patient access.	For example, the base case analysis allows the new drugs to reach the maximum utility gain amount (at the end of the trial length). After this time point, the new drug enjoys the benefit of the full utility gain for the rest of the model's time horizon. While neither drug reported such a difference in quality of life, and this utility gain is maintained beyond the time horizon of the trial, future studies could verify whether gains this large are actually being realized.
2.	Akcea strongly believes that ICER's assessments should reflect best practices for comparative clinical and cost effectiveness assessments and apply these methods and standards consistently throughout their assessment. ICER found a single RCT assessing the clinical evidence for patisiran and a single RCT for inotersen but judged the evidence base supporting clinical effectiveness for patisiran as "B+" while the evidence base supporting the clinical effectiveness of inotersen to be "promising but inconclusive." This finding is disconcerting given that the two products each have only one randomized, controlled, double-blinded Phase III study and that these two studies met their primary endpoints with high statistical and clinical significance. ICER judged the quality of the NEURO-TTR study to be merely "fair" because of a 4.4-point difference in baseline severity in neuropathy between the treatment groups [sic] (mean baseline mNIS+7 score for inotersen: 79.2; for placebo: 74.8). However, ICER later determined that the 19.7-point difference between treatment and control group – a statistically significant difference (95% confidence interval [CI], −26.4 to −13.0; P<0.001) – in mNIS+7 score to be uncertain in clinical meaningfulness. ICER should apply their standards of evidence consistently; if a 4.4-point difference is significant, a 19.7-point difference should be judged even more so. Also, the fact that the difference in baseline severity in neuropathy between the active and control groups in the APOLLO study was 6.3 points was conspicuous by its absence.	We rated the quality of the NEURO-TTR study to be fair due to the differences in sensorimotor and autonomic neuropathy discussed in the published literature. Our report does not discuss the numerical difference at baseline, though we do present those data in our baseline characteristics table. We also note the lack of a validated threshold establishing a clinically meaningful change for patients (MCID), without which we cannot state the clinical meaningfulness with certainty for either new drug.
3.	At the same time, ICER also seemed to ignore the fact that the APOLLO study did not include a true placebo arm and had higher cardiovascular mortality in the treatment arm. Conversely, ICER indicated that the benefits of inotersen were "inconclusive' because of a "non-zero" likelihood of net harm due to safety uncertainties around platelet reduction which were addressed with a safety monitoring plan and, if necessary, dose adjustment. Some patients are now beyond 4.5 years on treatment with no serious	We have received a number of comments requesting that we reconsider our evidence ratings for the two therapies. For the case of inotersen, we have changed the rating from P/I (promising but inconclusive) to C+ (comparable or better; moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit). Our rationale for this change is as

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	platelet reductions. In contrast, ICER did not address the clearly higher rate of cardiovascular mortality observed in patients in the treatment arm of patients treated with patisiran.	follows. Relative to placebo patients, inotersen patients had more favorable outcomes on the mNIS+7 and Norfolk QOL-DN measures. However, the C+ rating remains a lower rating than patisiran's B+. Inotersen patients did not experience improvement from baseline in neuropathy symptoms, as patisiran patients did, but rather a slowing in worsening of neuropathy relative to placebo. Regarding safety, there remains some uncertainty given that 1) all deaths in the Phase III trial occurred in the inotersen arm, one of which was considered possibly-drug related; 2) other antisense oligonucleotides (nusinersen, volanesorsen) have demonstrated similar risks of thrombocytopenia; and 3) anti-inotersen antibodies were reported in 30.4% of NEURO-TTR patients, the long-term significance of which is unknown at this point. The enhanced monitoring protocol added to the trial provides some reassurance that thrombocytopenia risks can be managed, and this was the primary reason we upgraded the rating. However, the long-term implications of the other safety and antibody concerns are currently unknown; therefore, we felt that we could not move any higher than C+ given these uncertainties.
4.	ICER's report also began with the notion that each drug would be independently assessed but then determined inotersen as 2/3 as effective. Akcea, as well as numerous clinical experts, do not believe comparisons can be made using these single phase 3 trials. There is significant heterogeneity amongst the patients in the studies; there was wide difference in the distribution of the more than 40 mutations represented, differences in geographic enrollment and phenotypic expressions, and differences in trial and trial duration and endpoints.	We agree that a direct comparison between the two drugs cannot be made with the data from the two Phase III clinical trials, and have stated this in the report. Our evidence ratings are based solely on the performance of each drug relative to its trial-based comparator. The two-thirds assumption in the modeling section was originally made because of a lack of available stage-change data for inotersen. This has been modified now that such data are available.
5.	While the overall quantity of evidence supporting the benefit of inotersen is limited, this is an artifact of the exiguousness of the disease itself. Due to the small population of patients affected by hATTR, studies naturally have small sample sizes. Akcea has significant concerns that ICER has mistakenly depreciated the high quality of RCT trial data because of the paucity of available data quantity; a single high-quality study demonstrating significant patient benefit should be more than sufficient, particularly in comparison to lower quality post-hoc subgroup analyses. Regardless, Akcea has also shared additional data with ICER supporting the benefit and value that inotersen provides to patients. Based on these additional data and the strong	Please see our revised evidence rating for inotersen, and its rationale, above.

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	results of the NEURO-TTR study, Akcea believes the evidence base clearly demonstrates the clinical effectiveness and value of inotersen, and that ICER should revise their conclusion to reflect this fact.	
6.	ICER noted that inotersen demonstrated statistically significant differences between treatment and placebo groups for important study outcomes, including mNIS+7. The mNIS+7 represents a direct and referenced measure of neuropathic impairment in hATTR and is a key efficacy measure that represents improvement or worsening of neuropathic impairments. As a composite measure, mNIS+7 is able to directly measure muscle weakness, muscle stretch reflex decrease, sensation loss, and neurophysical test abnormalities which directly measure the neuropathic impairments characteristic of hATTR-PN. Research has shown that specific, multidimensional measures are better able to characterize outcomes that are meaningful from a clinical perspective as well as to patients. In this vein, the mNIS+7 is an improvement upon the NIS+7, due to its specificity in assessing neuropathy in patients with hATTR. In order to represent the true nature of clinical response in patients taking inotersen, ICER must acknowledge the meaningfulness of mNIS+7 and systematically incorporate the measure in the economic models.	While there is some clinical opinion that the mNIS+7 measures clinically meaningful differences, we are unaware of studies that have validated that changes in the mNIS+7 reflect significant clinical improvement. Moreover, the only available data linking functional change to improved quality of life (as measured by health-state utilities) are for FAP stage. For these reasons, we did not systematically incorporate the mNIS+7 measure in the economic models; however, our model assumes quality-of-life improvements from both improvements in ambulatory stage and stabilization in the same stage (based on Norfolk QoI-DN data), an assumption that we feel is quite favorable to both drugs.
7.	Additionally, while ICER reports a 2-point difference in the NIS+7 scale represents a clinically-significant difference, they are unable to interpret the clinical significance of improved mNIS+7 in patients taking inotersen. In NEURO-TTR, patients taking inotersen experienced a 19.7-point improvement in mNIS+7 compared to placebo, a magnitude which should be a clear indication that inotersen achieved clinically-meaningful results. Furthermore, as noted earlier, ICER downgraded the NEURO-TTR study quality due to a 4.4-point difference in baseline mean mNIS+7 scores between inotersen and placebo arms. If the 4.4-point difference (well within the standard deviation) is considered meaningful in this context, a 19.7-point difference should be even more conclusively meaningful. Thus, Akcea encourages ICER to recognize the clinical importance of using mNIS+7 as an appropriate outcome measure for patients with hATTR, and the clinical significance of a 19.7-point difference between treatment and placebo groups.	As described above, our quality rating of fair is based on differences in neuropathy between the inotersen and placebo group at baseline, as discussed in the published literature of the NEURO-TTR trial. While there is some clinical opinion that the mNIS+7 measures clinically meaningful differences, we are unaware of studies that have validated that changes in the mNIS+7 reflect significant clinical improvement. Our reasons for giving inotersen an evidence rating are outlined in the comments above. The 4.4-point difference in baseline mean mNIS+7 scores between inotersen and placebo arms did not influence our evidence rating.
8.	In the draft evidence report, ICER highlighted the importance of cardiovascular outcomes in patients with hATTR and reported a variety of exploratory cardiac outcomes from the APOLLO study. However, while several intermediate outcomes (e.g., LV wall thickness by ECHO) as	We agree that there are important unanswered safety questions with both medications. We were especially interested in analyzing cardiac outcomes given that many hATTR patients in the US have cardiac involvement. We also agree that

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	well as a change in the biomarker, NT-proBNP were considered, ICER does not report on cardiovascular-specific mortality – a cardiovascular outcome of the utmost importance. In APOLLO, higher cardiovascular-specific mortality was realized in the patisiran arm compared to the control arm (i.e., 7 deaths in patisiran-treated patients – all cardiovascular-related; zero cardiovascular-related deaths in the control arm). Alternatively, in the NEURO-TTR trial while there were five deaths among inotersen-treated patients, despite having 63% of patients with cardiac disease, only one was due to a cardiovascular issues - heart failure. While we see the cardiac data on imaging and biomarkers to be encouraging in both patisiran and inotersen, we believe the outcomes data on cardiovascular deaths may be a more important consideration. The ICER report also includes a post-hoc subgroup analysis from APOLLO looking at a "composite" of cardiac hospitalizations and all-cause mortality. We have some concern about the methodology and validity of that analysis because the data were collected from adverse event (AE) forms and was not adjudicated by an external committee as is common in cardiovascular outcomes studies. Akcea also questions whether the outcome is truly a composite if almost all the benefit is derived from the hospitalization component of the composite and the fact that the overall death rate was similar between the patisiran and control arm, with a clear imbalance in cardiac deaths. This brings to question the validity of using these "composite" data.	the preponderance of cardiovascular deaths in the patisiran arm is a concern, and that post-hoc analyses based on adverse events represents lower-quality evidence. As such, this evidence did not influence our overall evidence rating for patisiran, and inclusion of cardiac outcomes in the model was reserved for a scenario analysis only. Neither the APOLLO nor NEURO-TTR trial was powered for cardiac outcomes including mortality, echocardiographic, or biomarker outcomes, and we reflect the uncertainty associated with these outcomes in our report.
9.	In order to ensure that stakeholders base decisions on all available evidence, ICER should present all data which are available and should consider the level of evidence within their review. Additionally, ICER characterizes inotersen's evidence base as "inconclusive" and representing a "non-zero likelihood of a net harm" due in part to a platelet risk that has been shown to be effectively managed by the monitoring program instituted by Akcea and evidenced by patients on the open label extension study who have had over 4.5 years' of exposure to inotersen without significant platelet issues. Using a similar logic, ICER should characterize patisiran's safety evidence as uncertain, and "non-zero likelihood of a net harm", given the increased cardiac deaths in the trial. Therefore, if evaluated under a similar lens as inotersen, ICER should have concluded that patisiran exhibited a promising but inconclusive net clinical effectiveness profile. In sum, to ensure a consistent characterization of the evidence, ICER should apply equivalent logic/principles across treatments.	Please see our revised evidence rating for inotersen, and its rationale, above.
10.	Assigning inotersen two-thirds of patisiran efficacy (i.e., health state transition probabilities) in the cost-	We agree that a drug's efficacy is best estimated from that drug's data; however, when no such

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	effectiveness model in the absence of actual data is an assumption unsupported by any robust evidence and is inappropriate. This unfounded assumption presents an inaccurate picture of comparative effectiveness. Health state transitions drive the clinical course of events, as well as the accumulation of costs to each treatment arm. A clinical parameter of this significance cannot be purely assumption-based. An inappropriate assumption of this magnitude results in a significant impact on both the QALYs and costs accrued under each treatment, leading to potential access restrictions without robust supporting evidence. In addition, ICER has made a number of significant assumptions in order to develop the cost-effectiveness model; of the 18 inputs required by the model, only 13 are based on actual trial data; the rest were inputted or extemporized by ICER. These major assumptions call into question the validity of ICER's cost-effectiveness results.	data are made available, alternative options must be considered. At the time of the draft report, we had no information available on inotersen's impact on ambulatory stage (either FAP or PND). Information on PND stage change is now available for inotersen, and so we have integrated this information into our revised model.
11.	As the symptoms of hATTR are significant and eventually fatal, at a minimum, ICER should conduct a thorough sensitivity analysis and heavily caveat the results throughout the report to support the fact that treatment and coverage decision-making may be flawed and misinformed if based solely on ICERs cost-effectiveness analysis. Consequently, Akcea encourages ICER to use the PND outcomes provided to ICER under a separate cover to assess rates of health state transitions. These outcomes are based on trial data, rather than unfounded assumptions based on relative efficacy.	We agree that a thorough sensitivity analysis is necessary and have included it in the revised version of the report as well. ICER recognizes that decision-making is a complex process, especially for drugs for rare diseases. As a result, ICER introduces into its process other facets besides cost-effectiveness analysis that can be considered in making a value determination. We appreciate Akcea making available the PND outcomes with their comments. As suggested, we have used the PND outcomes to assess rates of health state transitions.
12.	An important aspect of any comparative evidence/value assessment is to ensure that proper comparisons are made, ensuring an "apples to apples" evaluation, and providing stakeholders with reliably comparable data from which to base key decisions. In NEURO-TTR, inotersen was compared to a true placebo, while in APOLLO, patisiran was measured against a control ("placebo") arm that received 20mg of IV dexamethasone (changing to 10mg near the end of trial), which is not a true reflection of BSC, as IV dexamethasone is not considered part of BSC by clinicians treating this disease. It is unclear what effect that this high dose of dexamethasone may have had on the safety or efficacy of the control arm. ICER must be careful not to expose their models' efficacy parameters to confounding as a result of non-equivalent control groups across trials. In similar situation, we would strongly advise ICER to avoid making explicit or implicit assumptions of comparability among trial effect estimates through indirect treatment	We agree that an important aspect of any comparative evidence/value assessment is to ensure that proper comparisons are made, ensuring an "apples to apples" evaluation, and providing stakeholders with reliably comparable data from which to base key decisions. We agree that the trials are different enough so that each drug should be compared to its own placebo arm. Unfortunately, the trial design rules out an "apples to apples" evaluation of one drug compared to the other. We are careful not to expose the models' efficacy parameters to confounding as a result of non-equivalent control groups across trials. Using PND data from each trial we are able to create separate transition probabilities for each drug (based on their own trial data). We avoid making

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	comparison or economic modeling, or at a minimum utilize a mean value. Again, ICER technically used two different BSCs in its analysis, and neither is actually representative of true BSC. Consequently, in the absence of a single disease natural history arm for the model, the best approach would be a single, blended average of the two "best supportive care" values in NEURO-TTR and APOLLO.	explicit or implicit assumptions of comparability among trial effect estimates through indirect treatment comparison or economic modeling. We chose not to blend the placebo arms from the two separate trials to create one Best Supportive Care (BSC) arm to avoid inviting assumptions of comparability among trial effect estimates.
13.	Finally, ICER fails to note the potential clinical implications, disutility, and healthcare service use associated with long-term use of IV dexamethasone, including glaucoma, osteoporosis, and other serious side effects. [8] ICER also failed to note that approximately 25% of hATTR patients have diabetes and long-term dexamethasone use may be contraindicated. Patients with significant or long-term diabetes were excluded from the APOLLO trial, but will most likely receive treatment in real world setting. Because patisiran must be administered with adjunctive IV dexamethasone, the models should capture the utility decrement associated with the negative clinical/safety outcomes associated its long-term use, as well as the costs to treat these negative health outcomes. It is critically important to capture the full spectrum of benefits and limitations of patisiran and inotersen therapy to arm key decision-makers with the comprehensive, current, and accurate information then need in order to optimize their decision outcomes.	The "Limitations" section of Section 4 now acknowledges the potential implications associated with long-term use of IV dexamethasone. We do not know the effect of dexamethasone in hATTR, but we have received clinical input that the low dose used in the trial poses a relatively low risk of long-term sequelae. The overall risk would not be considered high given the dose. Certain patients, such as those with diabetes, may be at higher risk. However, this remains an uncertainty with patisiran as such patients were excluded from the Phase III trial. We have added this additional detail to the "Controversies and Uncertainties" section of the report. Regarding effectiveness, we note that the placebo arm progressed more in the patisiran trial than the inotersen trial. This is reflected in the transition probabilities that differ for the patisiran analysis compared to the inotersen analysis. The economic model estimates the costs and outcomes for populations reflected in the clinical trials, so the fact that approximately 25% of hATTR patients who have diabetes and long-term dexamethasone use may be contraindicated did not affect the calculations. We agree that it is critically important to capture the benefits and limitations of patisiran and inotersen therapy to arm key decision-makers with the comprehensive, current, and accurate information they need in order to optimize their decision-making.
14.	Akcea believes that novel therapies that treat such rare and debilitating conditions deserve careful consideration when being assessed for clinical and economic value. In the context of ultra-orphan diseases, ICER's assessment of the clinical evidence supporting the benefits of inotersen as "inconclusive" does not fully consider the inherent challenges in developing therapies for these diseases. Akcea encourages ICER to revisit this draft finding for inotersen in a way that appropriately acknowledges the	We agree that clinical trials in rare diseases are limited by a number of factors, and we've updated our conclusions sections to echo that these limitations are common and not unexpected in rare disease research. At the same time, we strive to highlight areas of certainty and uncertainty in a clinical evidence base. Please see our revised evidence rating for inotersen, and its rationale, above.

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	context of developing therapies for ultra-rare diseases and the still-developing evidence base for hATTR.	
15.	Akcea also encourages ICER to reexamine their cost-effectiveness assessment by using a single 'best supportive care' scenario and using data supplied by Akcea to ICER under a separate cover by using PND outcomes to reassign patient progression through disease states. Ultimately, Akcea urges ICER to proceed with caution when evaluating novel therapies, particularly those treating a condition with such a high unmet medical need. A rush to evaluate therapies before their evidence base has fully been developed may negatively impact appropriate patient access to these therapies and may lead to sub-optimal outcomes for patients in need of treatment.	We agree that an important aspect of any comparative evidence/value assessment is to ensure that proper comparisons are made, ensuring an "apples to apples" evaluation, and providing stakeholders with reliably comparable data from which to base key decisions. We agree that the trials are different enough so that each drug should be compared to its own placebo. Unfortunately, the trial design rules out an "apples to apples" evaluation of one drug compared to the other. We are careful not to expose the models' efficacy parameters to confounding as a result of non-equivalent control groups across trials. Using PND data from each trial we are able to create separate transition probabilities for each drug (based on their own trial data). We avoid making explicit or implicit assumptions of comparability among trial effect estimates through indirect treatment comparison or economic modeling. We chose not to blend the Placebo arms from the two separate trials to create one Best Supportive Care (BSC) arm to avoid inviting assumptions of comparability among trial effect estimates. We recognize that for newly approved treatments there is often limited data available. However, patients, clinicians and insurers are still faced with decisions about how best to use these new agents once approved for use. As such, we view comparative clinical effectiveness research, and cost-effectiveness modeling as a useful and important way to identify the key inputs that impact the effectiveness and cost of a new therapy. Even when there is uncertainty about the actual values used in the models, sensitivity analyses can highlight the range of plausible values and their impact on overall cost-effectiveness.
Alnylam		
1.	As ICER continues its modeling efforts for hATTR amyloidosis therapies, we appreciate its recognition of the strong level of clinical evidence and net health benefits related to ONPATTRO in treating this serious condition. At the same time, Alnylam appreciates this opportunity to raise ongoing concerns related to ICER's review. Central to	We recognize that for newly approved treatments there is often limited data available. However, patients, clinicians, and insurers are still faced with decisions about how best to use these new agents once approved for use. As such, we view comparative clinical effectiveness research, and

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	our comments to date is that any conclusion at this early stage about the long-term assessment of value for money of ONPATTRO is premature. Several peer-reviewed publications of the Phase 3 and Open Label Extension studies for both investigational therapies in the scope of this review are yet to be published, limiting ICER's ability to fully analyze and evaluate the long-term clinical- and cost-effectiveness of ONPATTRO. We believe these limitations will result in underestimating the long-term benefits of breakthrough treatments like ONPATTRO.	cost-effectiveness modeling as a useful and important way to identify the key inputs that impact the effectiveness and cost of a new therapy. Even when there is uncertainty about the actual values used in the models, sensitivity analyses can highlight the range of plausible values and their impact on overall cost-effectiveness. This report uses data that are currently available, and highlights the limitations of these data as well as the qualitative input of a range of stakeholders. All stakeholders are invited to submit unpublished data through our Data-in-Confidence policy.
2.	Model omits critical societal benefits: Rapidly progressing and deeply debilitating, the burden of hATTR amyloidosis is tremendous for both patients and those who care for them. This disease significantly impacts patients' independence and sense of normality. It also takes a profound toll on the emotional well-being and careers of caregivers, who must often leave the workforce to assist individuals with hATTR amyloidosis in performing tasks of daily living. The draft evidence report fails to quantify several considerations critical to both individual patients, carers, and society at large, the impact of which is highly relevant for a value assessment of a rare, debilitating disease such as hATTR amyloidosis: (See below)	We agree that there are special considerations with severe, rare diseases. It is for this reason that ICER developed an adaptation of its framework for ultra-rare diseases. This framework includes a societal perspective as an additional base case and provides information on prices to achieve cost-effectiveness thresholds in addition to ICER's standard range of $50,000 - $150,000 per QALY gained. While cost-effectiveness produces an estimate of the extra cost to achieve an extra QALY, the value determination that ICER asks its panels to vote on includes many additional attributes that are highly relevant for a value assessment of a rare, debilitating disease such as hATTR amyloidosis.
3.	Productivity: By assuming that productivity costs accrued in FAP Stage 2 and FAP Stage 3 are the same, ICER's model underestimates the burden of illness associated with FAP Stage 3. Based on patient and physician accounts, caregiving costs in FAP Stage 3 are far higher as patients become entirely dependent on others due to their level of disability.2 From conversations with patients, their caregivers, clinicians and in exploratory analyses, Alnylam has learned that essentially all patients and caregivers lose their ability to work. The level of burden reported by caregivers of hATTR amyloidosis patients is similar to that reported by U.S. caregivers of patients with Alzheimer's disease	We appreciate the sharing of this information and have incorporated it into scenario analysis to explore the impact of these experiences on our conclusions.
4.	Failure to measure improvements within FAP Stages: As previously mentioned, ICER's model fails to consider the wide spectrum of impairments faced by patients in each FAP Stage, given the insensitivity of this measure. Evidence from the APOLLO trial indicates that patients on best supporting care (BSC) experience rapid and substantial	We based the model on FAP stage given the availability of data from the APOLLO trial and an explicit linkage of stage to resource use, costs, and utility data. To address the concern that there may be some differences between treatment and BSC within the same FAP stage, we introduced a

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	deterioration in their ability to perform activities of daily living (ADL) or engage in social activities, as measured by the ADL domain of the Norfolk QOL-DN and R-ODS, even if they fail to worsen on a FAP Stage.4-6 In contrast, ONPATTRO demonstrated substantial ability to stabilize these aspects of hATTR amyloidosis. ICER should consider that ONPATTRO's ability to mitigate disease progression would likely lead to differential impacts between ONPATTRO and BSC with respect to both formal and informal costs associated with this disease.	differential quality-of-life gain for treatment that improves over the time period for which the trials showed improvement and then plateaus at a maximum value that is maintained for the rest of the patient's life. Thus, benefit from the drug is hard wired into the model beyond the time measured in the trial and on the appropriate outcome scale (i.e., the QALY utility). Formal and informal costs are varied in scenario analyses. The results show the impact on the conclusions when different values for costs are assumed.
5.	Societal value of treating rare, severe disease is not captured: A number of empirical studies have shown that society places strong value in treating rare, severe diseases, including placing equal or even greater priority on treating the most urgent or dire cases, etc.7-10 QALYs, however, do not reflect the true value of substantial health gains for a small number of people, instead equating them to marginal health gains for a large number of people.	Attempts to measure whether the public expresses preference for treatment of rare diseases over more prevalent ones have found weak or inconsistent preference for rarity. There is also an ethical implication of using different thresholds, in that this implies different valuations of health improvements for patients with rare diseases than for patients with common diseases. That said, ICER has created a separate procedure for evaluating drugs for rare diseases. As part of that procedure, we adapt our analyses to provide willingness-to-pay threshold results for a broader range, in addition to a scenario analysis inclusive of broader societal costs. In addition, our report sections on "Other Benefits and Disadvantages" and "Contextual Considerations" include a broader frame to seek evidence and perspective on the potential for these treatments to affect positively the family, school, and community.
6.	Forward-looking value: The interventions in this review are the first therapies to effectively treat hATTR amyloidosis, and as such, they may generate a so-called "option value," i.e., extending patients' lives to benefit from future effective therapies. ONPATTRO also represents the first in a new therapeutic class of medicines, RNAi therapeutics, which have the potential to help medical science address a wide array of serious diseases. The cost of research and development and investment that Alnylam has committed to developing this new class of medicines is expected to result in substantial scientific spillovers, as other manufacturers benefit from these investments when using this novel approach to develop future medicines.	We agree that real option value is a key consideration, and that is captured in our "Contextual Considerations" section, as an important element of our reports and public meetings. We believe most treatments in the health care system provide option value, so we cannot use it as a metric for distinguishing the comparative value of different treatments. Option value has not historically been a standard element of cost-effectiveness analyses, and more methodologic research and data are needed before their standard inclusion.
7.	Model design fails to capture treatment benefits: As designed, the structure of ICER's model significantly underestimates the rapidity of disease progression and significant disability experienced by patients living with this devastating disease. By systematically underestimating these factors, ICER's model is not designed to mirror the	The model uses trial data reporting progression by PND stage (and FAP stage). The model links the difference in progression (by new treatment or BSC) to differences in cost and QALY data reported by FAP stage. To the extent that these trial data capture the experience of hATTR patients, the

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	real-world experience of hATTR amyloidosis patients, nor is it capable of capturing the full benefits of ONPATTRO.	model can estimate the differences in expected costs and QALYs. Uncertainty surrounding the values for each disease stage are illustrated in the sensitivity analysis, scenario analysis, and probabilistic sensitivity analysis. The overall conclusion appears robust to assumptions about most parameters. The Tornado plot indicates (by size of the bar) which parameters have the most impact (e.g., the drug's price).
8.	Notably, ICER uses FAP Stage progression to model natural history of hATTR amyloidosis in the cost effectiveness model; however, FAP Stages are defined only by gross changes in ambulatory status and this understates the impact of the multi-system effects of the disease, the rapid deterioration in quality of life and mortality risk that these patients face within each FAP Stage. Notably, FAP Stages may be too rudimentary to capture changes in ambulatory status during the 18-month time period of the APOLLO study. Every other ambulatory measure evaluated in the APOLLO study showed substantially more separation between ONPATTRO treatment and placebo over this time period, suggesting that FAP Stage is simply not a sufficiently sensitive instrument for measuring changes in ambulation over this time period.7 As a result, ICER's model design significantly underestimates ONPATTRO's ability to improve critical patient outcomes, including ambulation, autonomic symptoms, quality of life, and mortality.	We agree that the full value of a product should include other facets besides simply ambulation; for this reason, we decided to include an assumption that quality of life improves on treatment as disease stage improves but also while patients remain in their current stage. However, the only data available from the trial that can be reliably linked to utility information are provided by FAP, PND, and Norfolk Qol-DN values, all of which we used in the model.
9.	ICER has updated its model to introduce limited utility gains for patients within FAP Stage to account for changes in patient outcomes not captured in FAP stage, and introduced FAP stages with and without severe cardiac involvement. While we credit ICER for attempting to mitigate some of the limitations of FAP Stages, significant improvements are needed in ICER's model to fairly assess the value of innovative products in this therapeutic area. Addressing the following would likely generate very different—and more accurate—results: (See below)	See below.
10.	Area #1: ICER should maintain adjustments in quality of life / utility beyond 18 months. ICER's approach assumes no benefits for patients treated with ONPATTRO after 18 months if they are within the same FAP Stage; however, results of open label extension studies show that ONPATTRO has persistent treatment benefit, as measured by mNIS+7, for at least 36 months.12 Similarly, there is ample evidence in the natural history to show that patients treated with BSC will inexorably deteriorate on quality of life and other disease measures as a function of time.13-15 Failing to adjust for these changes over time implies that patients who do not progress on a FAP Stage are assumed	We agree that there is a possibility that improvement in the mNIS+7 may be linked to improvement in utilities. The new base case for the economic model maintains QALY gain among treated patients for the entire model time horizon as described earlier.

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	to worsen on quality of life at the same rate after 18 months, which is inconsistent with currently available evidence. To address these issues, ICER should consider maintaining utility gain among ONPATTRO-treated patients for at least 36 months (and consider extrapolation curves beyond 36 months) and utility loss among patients receiving BSC.	
11.	Area #2: ICER should consider differential impacts of ONPATTRO and BSC on neuropathy-related mortality, even "within health state." In the U.S., the leading causes of mortality from the neuropathic manifestations of disease in hATTR amyloidosis are related to wasting attributed to progressive peripheral and/or autonomic neuropathy. FAP Stage is fundamentally linked to ambulation and fails to adequately measure how these manifestations impact mortality. In the APOLLO study, ONPATTRO demonstrated an ability to stabilize or improve wasting of disease, as evidenced through multiple measures of peripheral and autonomic neuropathy (e.g., modified Body Mass Index, COMPASS 31). By failing to incorporate the role these autonomic-related disease impacts have on hATTR amyloidosis progression, this model underestimates impact of disease on patients whose mortality risk increases under BSC, and the impacts of ONPATTRO on mortality. ICER should consider differential impacts of ONPATTRO and BSC on neuropathy-related mortality even within FAP Stage.	We would like to base a differential mortality benefit with FAP stage between a new drug and BSC on evidence (e.g., a hazard ratio). We estimated input parameter values for the disease-specific mortality rate for each stage of disease and stage-specific disease progression rates through calibration. The calibration targets were the distribution of outcomes from the APOLLO trial (for patisiran) and the survival curves presented in Swiecicki et al. (2015). The 100-best fitting input sets tended to result in slightly higher (but well within the 95% confidence interval) 18-month mortality, but fit long-term mortality curves for the "Stage 2" and "no severe cardiac involvement" populations well.
12.	Area #3: ICER should improve the approach to model cardiac progression and mortality benefits in the base case analysis. Cardiac involvement is a major contributor of death for patients with hATTR amyloidosis in the U.S. Unfortunately, ICER's base case model does not allow for changes in the proportion of patients with severe cardiac involvement over time; in other words, the current analysis fails to consider whether patients will improve from treatment or whether patients progress on disease with alternative treatments, including BSC. Assuming that patients do not progress to more severe cardiac involvement under BSC and do not improve with treatment is completely inconsistent with data from clinical trials and underestimates the leading cause of death among patients with hATTR amyloidosis living in the U.S. We urge ICER to consider that patients can both improve and worsen on severe cardiac involvement in the base case to reflect existing clinical data and the current understanding of the disease.	The model incorporates severe cardiac involvement using three separate health states (i.e., one for each FAP stage) for people with NT-proBNP > 3000. These states exist to recognize the extensive toll that severe cardiac involvement imposes with a) lower quality of life, b) higher costs, and c) greater mortality. In this way, the model acknowledges that severe cardiac involvement is a major contributor of morbidity and mortality for patients with hATTR amyloidosis in the US. However, the base case does NOT assume that treatment with either patisiran or inotersen affects this trajectory, as we did not find or receive any data to support claims of changes in the proportion of patients with severe cardiac involvement due to treatment.
13.	Comparator analyses should be better substantiated & more transparent: ICER's modelling effort for comparators is opaque and we encourage ICER to improve its transparency. For example, the model relies on	We agree that a drug's efficacy is best estimated from that drug's data; however, when no such data are made available, second best options must be considered. ICER is grateful for recently

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	assumptions unsupported by the available evidence to assign value; consider, FAP Stage shift data is not available from the NEURO-TTR trial, but ICER derived these relative transition probabilities for the inotersen model based on the relative efficacy compared to ONPATTRO for an entirely different endpoint, Norfolk QoL-DN. The Norfolk QoL-DN measures different aspects of hATTR amyloidosis than FAP Stage, since this instrument was developed to measure domains aside from ambulatory status, including symptoms, ADL and autonomic neuropathy. It is clinically inaccurate and highly implausible to use the relative efficacy difference between ONPATTRO and inotersen on Norfolk QOL-DN to extrapolate the relative efficacy as measured by FAP Stage. In addition, Table 4.15 shows the undiscounted total cost of inotersen to be approximately $1.5 million for 9.1 life years gained, or around $172,500 per life year gained. From the available information in the report, there is insufficient information on how ICER arrived at the costs for therapy, given ICER's assumed annual list price of $300,000 for inotersen. We urge ICER to increase transparency into the methods used to derive costs for inotersen in related economic analyses in this report.	received data that allow inotersen's efficacy to be based on inotersen's data. Regarding costs, please note that lifetime costs of therapy are dependent on (a) survival; and (b) continuation on therapy. We feel that the inputs for costing each of these therapies are clearly and explicitly described in the report.
Clinical Experts and Societies		
Noel Dasgupta, MD, FACC, Indiana University School of Medicine		
1.	Our group believes the conclusion that the inotersen data is promising, but inconclusive, is not appropriate. The phase 3 study was extremely positive and the results were positive across all types of patients, regardless of stratification factors, whether patients had cardiac disease, and across almost all endpoints. We think comparisons to patisiran, even indirectly, are not appropriate due to the heterogeneous patient populations. Because amyloidosis is considered a rare disease, trials need to incorporate patients with multiple different hereditary mutations to obtain a sufficient study population size. The phenotype of different mutations is quite varied and would be similar to comparing apples to oranges. Because there were more than 40 different mutations included in these small phase 3 trials it is impossible to make direct comparisons. We are concerned that patients will see these ratings and make misinformed decisions without talking to experts.	We agree with you that key differences in the NEURO-TTR and APOLLO trials preclude direct comparison, as we point out in our report (please see Section 3.3 and Table 3.1). To this end, we've summarized the clinical evidence for both drugs separately and relative only to the comparator of the respective trials Our evidence ratings are also non-comparative.
Peter J. Dyck, MD; W. J. Lichty, MD; P. James B. Dyck, MD, Mayo Clinic		
1.	Q1. A distinction appears to be made between mNIS+7Ionis and mNIS+7, the endpoint used by Alnylam. Response: mNIS+7 is a composite measure of neuropathic impairments used for the Ionis and Alnylam trials and are similar but there are differences, also. In the Ionis mNIS+7, sensation loss is tallied both in NIS (in NIS-S) and in S ST	Thank you for bringing further clarity to the input differences for these two scoring systems in your comments. We made a distinction between the two endpoints because they are in fact different (e.g. the possible scores for the inotersen trial can range from 0 to 346. In the patisiran trial, the

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	QSTing (test 6 of 7 neurophysiologic tests) in +7. In Alnylam mNIS+7, NIS-W scores of cranial nerve and NIS-S are omitted. The second difference is choice of the autonomic endpoint. Ionis, Inc. used heart rate decrease with deep breathing (HRdb). In the Ionis trial, both points and normal deviates were used whereas in the Alnylam study only points were used. For the seventh nerve tests (in +7 of mNIS+7), Alnylam used a clinical postural hypotension test. The third difference was use of normal deviates (from percentiles) in Ionis assessment of HRdb whereas Alnylam used points from percentiles for postural hypotension. The possible scores for the Ionis trial can range from 0 to 346. In the Alnylam trial, the score varies from 0 to 264. These differences in scoring are being described in subsequent publications. The important point is that both versions score muscle weakness, muscle stretch reflex loss, sensation loss, and neurophysiologic test impairments quantitatively, using appropriate healthy subject reference values. Each composite score measures the major functional categories of neuropathic impairment.	score varies from 0 to 304). While we agree that there are common domains of each version, the differences in some measures and total scoring confirm our inability to do formal indirect comparisons between inotersen and patisiran on this and other measures.
2.	Q2. The reviewers state that mNIS+7 is a surrogate and does not measure neurological outcomes. Response: Wrong! mNIS+7 is a direct and referenced measure of neuropathic impairment of hATTR-PN and is used to measure outcomes, i.e., improvement or worsening of neuropathic impairments. The disease, hereditary transthyretin amyloidosis polyneuropathy (hATTR-PN), is expressed as varying severities of muscle weakness, decrease of muscle stretch reflexes, sensation loss of both large and small fiber sensation and neurophysiologic test abnormalities. These neuropathic impairments and dysfunctions are broadly and quantitatively measured in both versions of mNIS+7. The endpoints assessed are direct and referenced measures of polyneuropathy severity! Also, to be emphasized, the measurements made are by experts—the latter an important concept in assessment of impairment. Each of the components of mNIS+7 has been chosen to be a direct measurement of muscle weakness, muscle stretch reflex decrease, sensation loss, and neurophysiological test abnormalities which directly measures neuropathic impairment characteristic of hATTR-PN. Even the chosen attributes of nerve conductions are valid direct measures of muscle weakness, sensation loss, or nerve fiber loss. None of the chosen components of mNIS+7 are surrogates of neuropathic impairment! While some attributes of nerve conduction, e.g., conduction velocities and latencies, are surrogate measures of neuropathy, the chosen compound muscle potential and sensory nerve action potential amplitudes	The word “surrogate” does not appear in the evidence report. The report states: “In both scales [mNIS+7Ionis and mNIS+7], a lower score represents better neurologic function (e.g. an increase in score reflects worsening of neurologic impairment)." We do note in the report that, because mNIS+7 is a composite measure, it is difficult to extrapolate improvement on this measure to specific clinical changes.

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	used in this disease, are not! The attributes of NCs (CMAPs and SNAPs) may be surrogate measures in some neuropathies, i.e., when there is segmental de- and remyelination of nerve fibers, but this is not the case in hATTR-PN. In hATTR-PN, we specifically use only compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAP) amplitudes, which, in this disease, are known to relate directly to muscle force (a direct measure of muscle weakness), muscle stretch reflex decrease, or to sensory loss or pathologic loss of nerve fibers. Another component of the +7 neurophysiological tests is Smart Somatotopic Quantitative Sensation Testing of touch pressure and heat as pain with a possible score varying from 0 (no sensation loss) to 80 (body surface area sensation loss). This also is not a surrogate measure! It is a direct clinical measure of neuropathic impairment. It is especially useful in scoring clinical measure of sensation loss in hATTR-PN because it not only scores loss of both large and small nerve fiber sensation and assesses both severity and body surface distribution of this sensation loss. The autonomic test used in the Ionis trial is heart rate decrease with deep breathing considered by many experts to be a direct measure of autonomic neuropathy. For the Alnylam trial, postural hypotension was used as a direct measure of autonomic dysfunction.	
3.	We emphasize that both versions of mNIS+7 are valid measures for the diagnosis and grading of severity of hATTR-PN not only because they are referenced quantitative measures of neuropathy impairment, but also because they are specific measures of polyneuropathy as evaluated by experts using appropriate reference values. Functional activity scores, e.g., 10m walk test, measurement of hand grip, or health scores are valid measures of dysfunction, but they are not specific measures of neuropathy impairment and may be due to non-neuropathy dysfunction. We also emphasize the criteria advocated by the USA Social Security Administration that disability should be based on an assessment of objective measure of impairment by expert physician, i.e., disability should be based on objective measures of impairment. mNIS+7 provides such a measure of objective, quantitated, and referenced impairments and based on expert physician judgment. Both versions of mNIS+7 use quantitative and referenced measurements of "impairment" as defined by the Social Security Administration.	Thank you for providing additional detail about the mNIS+7.
4.	Q3. The reviewers state that it is unclear if mNIS+7 measures clinically meaningful differences. Response: As judged by the St. Paul consensus criterion, a meaningful	While there is some clinical opinion that the mNIS+7 measures clinically meaningful differences, we are unaware of studies that have

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	response was obtained! Also, as noted above, reviewers and editors of the NEJM found the responses to be meaningful. Furthermore, whereas mean scores of mNIS+7 remained essentially unchanged in oligonucleotide treated patients, while the scores increased by a large degree in the placebo arm of the trial. This large difference speaks for itself. A further approach could be used to illustrate what a mNIS+7 score difference of ~20 points means. It is possible to represent this change of the score in only one domain of the mNIS+7, e.g., of weakness of lower limbs. In the placebo arm of the trials, 50% weakness of toe extensors, ankle dorsiflexion, ankle plantar flexion, and knee extensors (a very large neuropathy impairment) in the plantar group would represent worsening of placebo patients by 16 points.4 Oligonucleotide treated patients would not have worsened. In the Diflunisal trial, we used this approach to indicate the clinical implications of an observed difference of the NIS+7 score.	validated that changes in the mNIS+7 reflect significant clinical improvement. In addition, while a minimum clinically-important difference (MCID) has been established for the NIS+7, we are not aware of a published MCID for either of these modified forms.
5.	Q4. For other measures, there is a specific statement that they are validated but that is absent from mNIS+7 descriptions. Response: There should have been such a statement. Simply an oversight.	As discussed above, we are unaware of any studies that have validated the mNIS+7 in patients with hATTR.
6.	Q5. Statement that the authors of the report are unable to assess impact of the oligonucleotide therapies in hATTR-PN because it is unclear what the reported change in mNIS+7 means. Response: This has been extensively described in previous sections.	The report states, "We identified uncertainties pertaining to clinical data for patisiran and inotersen." The report does not state that we were unable to assess impact of the oligonucleotide therapies. In fact, in the summary of Section 3, we describe the benefits of both drugs with respect to polyneuropathy and quality of life, as illustrated by changes in the co-primary endpoints of both pivotal trials.
7.	Q6. Use of responder analyses. Response: We favor not emphasizing responder analyses in assessment of these trials for two reasons. The trials were designed to address a primary hypothesis that oligonucleotide treatment would favorably influence the overall course of hATTR-PN neuropathic impairments. Because of the rarity of hATTR-PN, mild and severe cases needed to be recruited. This heterogeneity makes it difficult to select appropriate responder criteria.	We present responder analyses for diflunisal in the report. We emphasize results of intent-to-treat analyses of inotersen and patisiran throughout the report, and describe attempts made in both studies to identify those responding to treatment (e.g., FAP and/or PND stage change, ≥30% and ≥300 mg/L decrease in NT-proBNP levels).
8.	Q7. The response to inotersen therapy is "promising but inconclusive." Response: We do not agree!; mNIS+7, its subscores and health scores show an unequivocal large beneficial effect of inotersen as compared to placebo.	Please see our revised evidence rating for inotersen, and its rationale, above.
Rodney H. Falk, MD, Brigham and Women's Hospital		
1.	I found the analysis in your document to be extensive and, generally quite accurate. However, I was quite taken aback by the conclusions on pages 36 and 37 regarding the individual drugs. I do not believe that these conclusions,	Please see our revised evidence rating for inotersen, and its rationale, above.

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	particularly regarding inotersen, reflects the published and publicly available data and it is for that reason the I am writing this letter.	
2.	On page 37 of your report, addressing patisiran, it is described as “the first drug to show improvement in disease stage, most patients experiencing at least stabilization of disease progression as measured by FAP stage." This statement is imprecise. Disease staging is stated, in the main publication, to have been a "exploratory endpoint". There are no data regarding stability or otherwise of the disease, utilizing this staging system, that are published in the New England Journal of Medicine. However, you do reproduce a figure from a non-peer-reviewed abstract (your figure D1) which does show that 14% of patients treated with patisiran had a worsening neurological stage, that only 3.4% improved and 75% were stable. Data were missing in some patients and I believe it is relevant that only 27% of the placebo patients had worsening documented disease. The improvement in disease stage was in only 5 patients, all treated with patisiran, but this is a very small number and it is inappropriate to draw the conclusion that this is the "first drug to show improvement in disease stage" based on an improvement in only 3.4% of patients and from data that have not been verified in a peer-reviewed publication. Furthermore, it is feasible that inotersen also showed improvement in disease stage, but that data has simply not published yet. So, you cannot say that patisiran is the first to have shown this, merely that it is the first to have suggested, in abstract form, that a very small proportion of patients had improvement in FAP stage. Furthermore, the way you have worded the sentence implies that inotersen did not show any improvement in the staging score, but, as noted, there are no data to confirm or to rebut this. I feel that the way in which this statement is not only inaccurate, but produces, for the reader, an unwarranted bias in favor of patisiran over inotersen, with regard to this particular outcome.	We have edited the language in the report about patisiran to “Exploratory endpoint of neuropathy stage stable or improved compared to best supportive care (placebo).” We have also obtained data from inotersen and have added the following language: “Relative to best supportive care, no evidence of improved stabilization of disease progression, as measured by PND score.” We also note that our interpretation of the evidence on mNIS+7, a co-primary endpoint in the inotersen trial and a primary endpoint in the patisiran trial, suggests statistically-significant improvements relative to placebo for both patisiran and inotersen, but improvement from baseline in this measure was only seen for patisiran.
3.	I am even more concerned about your characterization of the utility of inotersen. On page 111, following immediately after figure D1 in you make the statement that "we used this observation to support the assumption that inotersen’s effectiveness is two-thirds that of patisiran." This statement is completely at odds with the very clear statement on page 16 of your report that "as a result, we present data on inotersen and patisiran without any direct or in direct comparisons." (emphasis added).	We agree that a drug’s efficacy is best estimated from that drug’s data. ICER is grateful for the data that accompanied the public comments allowing inotersen’s efficacy to be based on inotersen’s data. As explained above, we now can analyze the drugs separately without any direct or indirect comparisons.
4.	With regard to your summary of the inotersen data, I would take strong issue with the third bulleted state that	In the NEURO-TTR trial, mNIS+7 and Norfolk-QOL-DN data showed delayed progression of

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	"(there is) no evidence of stabilization or reversal of disease progression." Reference to the New England Journal of Medicine paper of July 25, page 25, states, "further analysis of patients who completed the intervention showed that 36% of the patients in the inotersen group had an improvement (no increase from baseline) in the mNIS+7 and 50% had an improvement in the Norfolk Quality of Life Score." It would seem to me that these published data clearly contradict your conclusions. It should also be borne in mind that "stabilization" as defined by the inotersen group was defined as a 0-point change from baseline mNIS +7, whereas for patisiran, the "74%" who were considered to have responded to treatment were defined as those who had less than 10 point increase from baseline. Clearly, there is a looser definition for patisiran leading to an apparently greater response rate.	polyneuropathy. PND score data, however, did not show a clear difference in disease stage progression or stabilization compared to placebo. It is unclear where the 74% response rate you cite comes from, as this is not reported in our clinical evidence summary. The response rate we report is defined by a change *greater than* 0 points on the mNIS+7 (<0=improvement), as shown in Table 3.8.
5.	In my opinion, both publications in the July New England Journal of Medicine, on patisiran and inotersen showed a remarkable effect of these drugs on the progression of polyneuropathy in patients with familial amyloid polyneuropathy. Had either of them been the sole drug to have been tested and shown to have these results, it would have been an enormous breakthrough for this disease. I am therefore greatly perturbed and puzzled by your apparent negative review of inotersen, especially as you stress that you had no intention of making direct or indirect comparisons (which was subsequently done). I find that your conclusion that inotersen showed only a "moderate certainty of a small or substantial net health benefits" where patisiran has a "moderate certainty of a substantial net health benefit" seems imbalanced. While recognizing that there are concerns about the safety of inotersen, (which will doubtlessly be considered in depth by the FDA), the data on efficacy are strong and deserve a stronger statement in your document	Please see our revised evidence rating for inotersen, and its rationale, above.
Morie Gertz, MD, Mayo Clinic		
1.	mATTR Amyloidosis is a multisystemic disease that can affect nearly every organ, produces a high burden on patients and their families, results in very significant morbidity and leads to early death. Patients die of cachexia, literally wasting away after years of significant progressive decline, or from their cardiac disease. There are over 130 mutations, each with a different clinical phenotype. The phenotypes also vary within a single mutation, by region and within the same families. It is important to understand that no two hATTR amyloidosis patients are the same. I would like to point this out because you have compared the clinical effectiveness of inotersen and patisiran in your report. Our group does not	In the clinical effectiveness section of the report, and in the model, we do not compare the two therapies; we model their cost-effectiveness separately, and discuss their clinical effectiveness separately, relative to the supportive care treatments represented in each placebo arm of the trial.

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	think this is valid to compare these drugs based on the phase 3 studies for a number of reasons.	
2.	#1: Heterogeneity: there were patients with 26 mutations studied in the inotersen trial and 37 in the patisiran trial, more than 14 countries participated in each trial, and enrollment varied greatly by region between the two studies. The US was the largest enroller in inotersen, whereas the EU and Japan were the primary accrual sites for patisiran. The phenotypes, rates of progression and symptoms vary greatly between these regions. And although V30M was the most common mutation in both studies, the 2nd and 3rd most studied mutations were different in each study and both studies including a significant number of patients with only one mutation	Thank you for your comment. We agree, and echo these key differences in Table 3.1, and cite these in our decision not to directly compare NEURO-TTR and APOLLO outcomes.
3.	#2: Sample size: both studies were small, including <200 treated patients. This leads to higher variability: Patient selection and placebo performance become even more important in these small sized trials. As mentioned above the patients are very different and the placebo performance was also significantly different. In addition, while there was a Placebo only arm in the inotersen trial, all placebo patients in patisiran arm received antihistamines and 20mg of dexamethasone to lessen infusion reactions. We do not know the effect of dexamethasone in hATTR. Does it make the patients worse, better? There are no data on this, but the placebo arm progressed more on the patisiran trial than the inotersen trial. The performance differences in placebo underscore the inability to compare across trials.	We agree, and have not attempted to make formal indirect comparisons for the reasons you state. In the model we do not compare the two therapies; we model their cost-effectiveness separately. We have added additional detail to the report regarding the uncertainty regarding the long-term effects of dexamethasone in hATTR.
4.	#3: Treatment duration: the inotersen trial was 15 months and the patisiran trial was 18 months. We know from both studies that the rate of progression increases over time in the PBO arms and the difference between inotersen would most likely have been larger with 3 more months (although we can't accurately predict what it might have been). The evaluation at trial completion occurred in patisiran with 20 % more drug exposure thus longer time for benefits to accrue.	Again, our intention is *not* to compare the two drugs given the many differences in trial populations and design. As you note, it is impossible to speculate on what might or might not have occurred with disease progression with a shorter or longer duration of follow-up; we can only interpret the data that are available to us.
5.	# 4: Endpoints: the primary endpoints were different. The inotersen trial had two primary endpoints, mNIS+7 and the NORFOLK-DN, while patisiran has one primary endpoint, the mNIS+7. Importantly, the mNIS+7 tests were also different for the two trials leading to an inability to directly compare changes across trials. We know they both have significantly improved the mNIS+7 scores versus placebo and both were highly statistically significant. We developed these tests at the Mayo Clinic under the leadership of Peter Dyck in the peripheral nerve center. We worked very closely with both companies in developing these scales,	We do not draw or report a determination of whether either drug is more effective than the other. We agree that there are differences in reporting of outcomes between the NEURO-TTR and APOLLO trials, however our report reflects the currently available literature on both drugs. Please see our revised evidence rating for inotersen, and its rationale, above.

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	Peter provided in person training to every center, and we did a central review of the results. As the experts and the developers of this validated scale, we cannot determine if one drug is more effective than the other, so it's hard to understand how you were able to do so. Both drugs are highly effective. There were a number of other secondary and exploratory endpoints and both drugs also achieve success on most of these. In addition to the positive impact on peripheral neuropathy, both drugs appeared to show improvement in autonomic neuropathy, some GI related symptoms and both had encouraging exploratory data in cardiac patients. While your report captures the effect of patisiran on multiple domains, it does not do so for inotersen.	
6.	#5: Death rate: Zero patients died on the inotersen placebo arm, and five patients on inotersen. Only 1 was inotersen related. We would have expected at least 3 deaths on placebo based on the natural history, and do not think this imbalance is meaningful. In comparison, there were 6 deaths on the patisiran placebo /steroid arm (7.8%), more in line with the anticipated natural history. And while the overall death rates were similar for patisiran as compared to placebo /steroid arm, there was an imbalance in cardiac deaths with seven on patisiran and none on placebo. This may not be a meaningful imbalance, but this is to highlight that it's challenging to compare across the studies.	Again, our intention is *not* to compare the two drugs given the many differences in trial populations and design.
7.	#6: The 2 trials had different eligibility criteria. The lower limit of neuropathy score was 5 in 1 trial and 10 in the other. Therefore patients with milder degrees of neuropathy could have been enrolled in patisiran but would have been ineligible for the inotersen trial. In addition in the former trial patients did not require histologic proof of amyloidosis in the latter trial biopsy proof of amyloid deposits were required and this generally requires more extensive deposition before they become detectable.	In the report, we note that the lower limit of the NIS score was 10 for the NEURO-TTR study and 5 for the APOLLO study. We agree that it is possible that patients with milder degrees of neuropathy could have been enrolled in the patisiran trial but would have been ineligible for the inotersen trial. We also note in the report that the NEURO-TTR trial eligibility criteria include presence of a positive amyloid biopsy. We agree that this difference in trial eligibility is important. Again, our intention is *not* to compare the two drugs given the many differences (including the ones noted here) in trial populations and design.
8.	In addition, the conclusion that inotersen data was not conclusive was partially based on your assessment of safety. While there were concerns about severe thrombocytopenia after the 3 events including the intracranial hemorrhage, these concerns have been effectively eliminated by the safety monitoring plan put into place. Of note, the patient in Argentina who died of a intracranial hemorrhage had not had platelets checked for 9 weeks, out of compliance with the original protocol. The current protocol has weekly platelet checks and significant	Please see our revised evidence rating for inotersen, and its rationale, above

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	drops in platelets are managed with pauses and resumption of therapy when platelets rise above 100,000. Again this is a very devastating and fatal disease with significant morbidity. These side effects are acceptable to the majority of our patients, reflecting the low withdrawal rate and the benefit risk profile remains highly positive.	
9.	Our group believes the conclusion that the inotersen data is promising, but inconclusive is not appropriate and may be misleading for patients. The phase 3 study was extremely positive and the results were positive across all types of patients, regardless of stratification factors, regions, whether patients had cardiac disease, and across almost all endpoints.	Please see our revised evidence rating for inotersen, and its rationale, above
Cheryl Pegus, MD, MPH, Association of Black Cardiologists		
1.	In connection with the Institute for Clinical and Economic Review's (ICER) examination of new therapies for the treatment of hereditary transthyretin-related (hATTR) amyloidosis, the Association of Black Cardiologists (ABC) wishes to express the critical need to expand the types of treatments for this rare, progressive, and deadly disease that disproportionately afflicts black Americans. The most frequent variant of transthyretin in the United States is the V122I mutation that is predominantly isolated to the heart. Transthyretin-related cardiac amyloidosis mimics hypertensive and hypertrophic heart disease and may, consequently, go undiagnosed. Beyond improving awareness of amyloid heart disease and improving diagnosis, there is an unmet need for better therapies. There is no Food and Drug Administration (FDA)-approved drug for this indication and traditional medications for heart failure have had no proven role in the treatment of amyloid heart disease. In fact, most medications have potential to cause harm. We applaud ICER's thorough scientific evidentiary review of new therapies for hATTR amyloidosis and encourage widespread availability to patients of FDA-approved treatments.	Thank you for your comment and for highlighting the important unmet needs in this patient population.
Patients and Patient Advocacy Groups		
Muriel Finkel, Amyloidosis Support Groups		
1.	Every other year the ASG holds a special support group meeting in Chicago for our ATTR patients. The first of these meetings was in 2009, and we had 85 attendees from several states, and Canada. The second was in 2011, and we had 150 attendees. Our most recent meeting was in October 2017, with over 400. We must keep in mind that many of these people have limited resources and are quite ill. They come because we offer hope by inviting the Who's Who of ATTR amyloid physicians, along with all the current clinical trial liaisons. The doctors and clinical trial people present and share, and they answer questions. Our	Thank you for this comment. We agree that evidence and public dialogue about new treatments enhances the lived experience of patients. We do want to clarify a misconception. ICER does not set the price of new drugs, nor do we create insurance coverage policies. ICER encourages drugmakers to set prices that align with the benefit patients receive, and when that happens, we recommend that insurers allow broad patient access. At our public meeting in September, all stakeholders, including patients

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	patients and their families have told us that these meetings, and all our ASG meetings, are life altering. "Knowledge is power" is a statement that has been proven to be true in the world of Amyloidosis Support Groups. We urge you to make these drugs, when approved, available to every amyloidosis patient.	and doctors, will participate in discussions about what insurance policies should look like and what a fair price for a treatment is.
Kristen Hsu, Amyloidosis Research Consortium		
1.	Review of and conclusions on the effectiveness evidence. (i) The conclusion that ICER has moderate certainty of 'a small or substantial net health benefit' and 'a small likelihood of net harm' associated with inotersen compared to best supportive care. We believe the evidence on both drugs should enable ICER to have at least moderate certainty about a substantial net health benefit. The conclusion that there may be a small benefit is a surprising conclusion from the available evidence and also with how patients view the potential benefit from inotersen, based on its benefit and risk profile. We also do not think the evidence naturally leads to the conclusion that there is a small likelihood of net harm with inotersen compared to supportive care, due to 'identified safety concerns.' The safety concern primarily relates to the risk of thrombocytopenia and glomerulonephritis. However, there is stringent monitoring in place to identify and manage the risk early on. We understand this risk management approach would continue as part of routine practice. There is no evidence to suggest any other significant short or long-term risks are associated with inotersen. As such, we do not believe there to be a risk of 'net harm' compared to supportive care.	Please see our revised evidence rating for inotersen, and its rationale, above.
2.	(ii) The suggestion that there is uncertain benefit of inotersen due to a lack of cardiac outcomes data. We recognise that cardiac outcomes have strong correlation with survival; however, the Neuro TTR trial was not powered for cardiac outcomes. While inotersen may well have an impact on cardiac measures, it should be neither favourably nor unfavourably evaluated based on outcomes it was not powered for. As such we would encourage ICER to evaluate the strength or otherwise of inotersen in relation to its primary endpoints. Concluding that it has uncertain effect on outcomes the trial was not powered to measure could inadvertently misinform patients, payers and the public.	We acknowledge this concern and have edited the report accordingly.
3.	(iii) The overall conclusions about the uncertainty of clinical effectiveness of both drugs. ARC agrees that there is a degree of uncertainty about both drugs, partly due to composite endpoints, the numbers of participants and duration of study. However, this is a common problem in rare disease research. Both drugs' trial designs were	Thank you, we agree. Our methods for studying treatments for ultra-rare conditions direct us to acknowledge this exact fact. We have updated the report so the reader understands the specific context regarding the potential challenges of generating evidence for these treatments,

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	deemed acceptable by regulators and in the context of these being ultra-orphan products we believe some uncertainty is reasonable and expected.	including considerations of challenges to conducting RCTs, to validating surrogate outcome measures, and for obtaining long-term data on safety and on the durability of clinical benefit.
4.	(iv) The assumption that inotersen and patisiran can be compared for the economic model. We strongly believe it is flawed to base the model on the assumption that a comparison of the two products can be made. There were considerable differences in the patient populations – both prospective differences in eligibility criteria as well as genotypic, phenotypic and geographic differences in the enrolled populations– and trial designs which would prohibit being able to make direct comparisons. We are concerned that this indirect comparison has negatively affected ICER's conclusions on inotersen in particular, and may inadvertently misinform patients and physicians that (a) the trials were equivalent and directly comparable; and (b) that a face value direct comparison can be made on the results. Patients and physicians need full and accurate information about the options that are available. At ARC we see it as important to provide information on both drugs, based on their own merits, including how they were studied, what these studies measured and what this showed. It is up to patients and physicians to make an informed decision that is in the best interests of the individual patient; however, we are concerned that the modelling approach taken could inaccurately suggest that the trials were equivalent and a direct comparison between the drugs can be made.	We agree that the drugs should be evaluated separately. It is for this reason that we built separate models to estimate their cost-effectiveness. Recently, we have received data on PND progression for inotersen that allows us to model disease progression separately for inotersen and patisiran.
5.	Position and weight given to patient and carer perspectives, other benefits and contextual considerations. Patient and carer perspectives need to be front and center to the question of value. Similarly, the 'other benefits and contextual considerations' are of paramount importance and relevance to this issue. Determining the value of any solution to a disease problem requires understanding of both the impact of the disease on patients and their families and the solution's ability to provide outcomes that are meaningful to them. It is not clear to us from the draft report how these have been factored in to a contextual-based consideration of the evidence and the potential value these drugs have. While we appreciate that some of these outcomes and benefits are not fully captured in the clinical evidence and may require consideration in parallel, the conclusions around 'net health benefit' should still take account of these broader factors.	Thank you for your comment. We agree that patient and carer perspectives are important to consider when evaluating the value of new treatments for hATTR, and that much of the clinical evidence does not adequately capture these considerations. To this end, ICER discusses other benefits and contextual considerations as additional considerations alongside our clinical evidence review and comparative value analysis. These are additionally captured during our public meeting, during which the Midwest CEPAC will discuss the key benefits and considerations that are relevant to inotersen and patisiran. Finally, the economic analyses for ultra-rare conditions also incorporate a societal perspective when indirect costs and effects are large and represent a large proportion of total costs, and such an analysis has been done here.
6.	(i) This intervention will significantly reduce caregiver or broader family burden. The report states that 'although	We agree that the APOLLO and NEURO-TTR show positive effects on polyneuropathy and quality of

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	evidence showing impact on these outcomes [disease progression and reduction in symptom burden] is not yet available' … such outcomes 'can potentially have a significant impact on [patients and carers] remaining at work, returning to work and/or overall productivity in the hATTR population.' ARC disagrees that there is not yet any evidence on these outcomes as the trials do demonstrate clinical effect on disease progression and symptom burden. We therefore believe this statement to be inaccurate. ARC also wants to emphasize that while remaining at/returning to and/or productivity at work is a key potential benefit (our findings clearly show that the disease has a considerable impact on patients' and carers' working lives), it does not exclusively define the patient or caregiver and family burden. Missing from this section is the disease's considerable impact on patients' and carers' physical, emotional, social and financial wellbeing. The disease has a pervasive impact on all domains of patients' and families' lives. Treatments which can slow progression and minimize the effect of symptoms would therefore have multi-faceted benefits – not just work and productivity-related benefits.	life, including symptom burden; these effects are captured in both our clinical evidence review and comparative value analysis. We also agree that a patient's ability to work does not exclusively define the patient, family, or caregiver burden, and echo earlier input from patients who expressed the large impact of hATTR on worklife. This potential other benefit is one we consider for all new treatments we evaluate under our ultra-rare framework. W e also note that we aim to capture benefits extending to caregivers and/or family burden under the consideration "This intervention will significantly reduce caregiver or broader family burden."
7.	(ii) This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed. The report states that patisiran and inotersen have the 'potential' to be novel treatments approved in the US for patients with this condition. While this reflects the ongoing FDA review status of both treatments, they are unarguably novel, offering a novel mechanism of action and approach.	Thank you for your comment.
8.	(iii) This intervention will have a significant impact on improving the patient's ability to return to work and/or their overall productivity. ARC agrees that this is a key benefit that needs to be taken into account for both patients and carers. As well as looking at this from a societal productivity viewpoint, we also believe the evaluation needs to account for the personal financial losses and gains to a family unit and the intangible benefits – anxiety, family dynamics etc that are often associated with (un)employment.	Thank you for your comment.
9.	(iv) 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. We agree that this is a relevant contextual consideration. hATTR is an extremely severe, life-limiting and disabling disease. Patients' and carers' quality of life are considerably affected by the disease.	Thank you for your comment.
10.	(v) This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness. We agree that this is a relevant	Thank you for your comment.

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	contextual consideration. hATTR represents a very high lifetime burden of illness for patients and their families. It is also relevant to consider the additional burden on families in terms of the generational effect of the hereditary disease. Individuals who are currently caregivers may also be future patients themselves or continue to care for children who develop the disease.	
11.	(vi) This intervention is the first to offer any improvement for patients with this condition. ARC believes this consideration is missing from the narrative and ought to be more explicitly included. These are the first interventions to address the underlying cause of symptoms.	Thank you for your comment.
12.	(vii) Compared to best supportive treatment, there is significant uncertainty about the long-term risk of serious side effects of this intervention. ARC disagrees that 'there is significant uncertainty about the long-term risk of side effects with both treatments, given the identified safety concerns with inotersen (e.g., thrombocytopenia and glomerulonephritis) and potential risks associated with long-term steroid use that may be anticipated with patisiran.' Based on the evidence for both drugs, these are well-managed risks. On the other hand, best supportive care carries minimal/no long-term risk of side effects only because there is no treatment. As best supportive care, by definition, allows for disease progression and increased symptom burden, it is our view that the long-terms risks of doing nothing have the potential to be greater.	Thank you for your comment. We believe it is important to highlight the lack of long-term safety and efficacy data for both drugs. As noted above, we have updated the report to provide additional context to the unique circumstances that accompany the development of treatments for ultra-rare conditions.
13.	(viii) Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention. ARC would like to see patient and carer preferences for treatment and views on what would be meaningful outcomes to them reflected in this section. Our research found that: • The prospect of new treatments designed for slowing/stabilising hATTR offers significant hope to patients and their families. This is especially so given the context of the disease being hereditary, the negative impact it has on patients and carers' quality of life, and there being no other licensed alternatives available with which to treat the disease. • The most important factors for treatment relate to the impact a treatment can have on slowing the underlying disease and improving symptoms. While patients would desire significant outcomes, they still highly value what might be perceived as 'modest' improvements in their health condition. • Alongside this there was a strong preference for a local or home-based treatment option. Patients and carers expressed concern about fatigue and taking time off	Thank you for your comment. We have updated the report with these additional potential other benefits.

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	work should frequent travel be required. However, they also said that a current lack of alternatives means they would be willing to put up with some inconvenience and that efficacy is the most important consideration overall. As treatments that can stabilize the disease and be administered at home as an option, both patisiran and inotersen therefore offer highly valuable potential treatment options to patients and carers.	
14.	Comparative clinical effectiveness- draft voting question 3. As detailed in our response section 1.iv above, we feel that it is inappropriate to compare the clinical effectiveness between inotersen and patisiran and as such the comparative clinical effectiveness draft voting question 3, "Is the evidence adequate to distinguish the net health benefit between inotersen and patisiran when added to best supportive care?" is an inappropriate question to ask at this point in time.	We have made changes to the report to be sure to communicate that we are not attempting to compare the two treatments. However, asking the question is incredibly policy-relevant, as payers and purchasers will need to know the state of the evidence distinguishing the two drugs. During the public meeting, we will be sure to emphasize the lack of data comparing the two drugs, but we will nevertheless be asking the Midwest CEPAC to vote independently on the state of the evidence.
Mary E. O'Donnell, Amyloidosis Foundation		
1.	At this time there is only one FDA approved drugs for hATTR, therefore development and approval of other drugs is greatly anticipated by the hATTR community to aid them with dealing with their disease. The development of these new drugs is essential for the improvement of outcomes for hATTR patients. Being able to minimize the effects of the disease on patients and in turn extending the life spam is a greatly needed advancement.	Thank you for this comment. We heard from many patients and caregivers throughout our process of the important advancement these new therapies represent. Our work on this report was greatly enhanced by the engagement of your group, other patient advocates, and individual patients and caregivers.
LGP, Patient; JSP, Caregiver		
1.	Your discussion of results in terms of clinical effectiveness of inotersen seems to understate the significance of evidence for its effectiveness, especially in view of the continuing OLE phase. We believe that you should expand the discussion at the end of the section on Neurologic Impairment and Quality of Life to point out details including • The patisiran double blind trial ran 20% longer (18 months vs 15 months) and included 30% more patients (225 vs 172) than the inotersen double blind trial so one should expect 20% more progression in the placebo patients and 12% smaller error bars on data points for the patisiran trial. This is a significant part of the difference between the results of the two trials and may be why the FDA review of inotersen was delayed three months. • Both trials show linear deterioration of about 20 points per year in mNIS+7 and about 10 points per year in	Please see our revised evidence rating for inotersen, and its rationale, above.

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	Norfolk QoL for their placebo groups. The estimated deterioration of 3 points in mNIS+7 and 3.6 points in Norfolk QoL with inotersen over one year of OLE imply further widening of the gap between those on the drug and those not on it, by 17 points in mNIS+7 and 6.4 points in Norfolk QoL per year. (Alternatively, deterioration over one more year on placebo might equal nearly seven years of deterioration in mNIS+7 and nearly three years in Norfolk QoL.) This greatly strengthens the significance of clinical effectiveness of inotersen although it's still only roughly the same as was achieved by patisiran in just the 18 months of its double blind trial.	
2.	We also found many puzzling oversights and calculations that have large impacts on patients and their families. A small sample includes • It specifically ignores all medical costs paid by patients out of pocket in both the Health Care Sector and the societal impacts! (Appendix Table D1) This is what will destroy patients' families' finances, as we will address later. • In modeling costs and QALYs (Tables 4.14 and 4.15) the discounted model assumes that years of life and QALYs are discounted at the same rate of inflation as for costs. This seems to be an artificial fix to address the likely action of the drug makers to raise their prices over time. You would be more realistic to have one deflation factor for the value of money and an inflation factor for the cost of the drugs and leave the life years and QALYs unchanged. The QALY year numbers then will make more sense to patients. • In the costs and QALYs for inotersen (Table 4.15) you come up with a total cost that is inconsistent with the assumed pricing of the drug. For example a total cost of $1,570,633 over 9.1 years is hard to reconcile with a cost of $300,000 per year for the drug alone.	We appreciate the importance of considering costs when making treatment funding decisions for a population. Out of pocket costs are very important for patients and their caregivers. Our use of a health care sector perspective includes out of pocket costs for direct medical expenses, but does not call them out separately, as copayments, coinsurance, and deductibles vary widely by payer. We also incorporate productivity losses related to missed work days in the societal perspective. As per ICER's policy and standard practice, the costs and QALYs are discounted at the same rate. Discounting is performed to account for the present value of costs and QALYS, not to account for inflation. The discount rate is varied in a sensitivity analysis to show how sensitive the results are to assumptions about how we value things that occur in the distant future compared to the immediate present. Regarding costs, please note that lifetime costs of therapy are dependent on (a) survival; and (b) continuation on therapy. We feel that the inputs for costing each of these therapies are clearly and explicitly described in the report.
Clayton Sherman, Patient		
1.	My experience with Inotersen suggests that it is quite effective at reduction of TTR amyloid, allowing for stabilization in year one, and regression in years following. Cardiac measures all signaled improvement. I recommend considering a more positive stance regarding this drug if that is appropriate given the objectives and constraints that must be followed in the ICER overall evaluative effort. In	Please see our revised evidence rating for inotersen, and its rationale, above. Because neither trial was powered to detect differences in cardiac outcomes, the primary focus of our evidence ratings is effect on neuropathy outcomes. We do evaluate potential benefits on significant cardiac endpoints in a scenario analysis of our economic model. It is unclear what impact

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	future it might be useful to: 1. Compare the cardiac subgroup data from both studies. The focus on the polyneuropathy side does not adequately picture either drugs potential benefit. 2. Evaluate the delivery mechanisms used. Is the subcutaneous injection route inherently less effective than IV in terms of dropping TTR levels? 3. Reports that Alnylam is pursuing a sub-cu version, and that Ionis is attempting a more potent version, leaves the current effort to distinguish benefit differences unresolved. This apples-to-oranges problem complicates the task. 4. Given the extended time frame for both drugs to have full effect, recommendation for better and earlier diagnostic approaches are essential for patient survival.	the mode of administration has on levels of clinical effectiveness, although we recognize that there may be differences in patient convenience and preference (see Section 5 of the report).
Terry Wilcox, Patients Rising Now		
1.	The clinical value of the two potential new treatments discussed in ICER's Draft Report clearly provide significant advances for some patients. However, as ICER's Draft Report also makes clear, these new treatments are not expected to be cures for amyloidosis, so additional treatments that have better efficacy - or can be used for other forms of the disease - are certainly needed. Because of this clinical and personal reality, we urge ICER to also discuss additional values that such new treatments will create, including real option value, and the spillover effect on research and development (R&D). We previously discussed both of those important concepts in letters to ICER, but feel it is important to restate that those elements are critically important to patients with serious and life-threatening conditions. And "[c]concerning, real option value, ICER fails to recognize the importance to patients of extending life with reasonable function and quality of life so that they are able to take advantage of new treatments that will become available in the future and that may dramatically improve their health and wellbeing." This was the situation for people with AIDS in the early 1990s, just as it is the hope of people today with other conditions like amyloidosis that still lack adequate treatments.	We agree that real option value is a key consideration, and that is captured in our contextual considerations, as an important element of our reports and public meetings. We also believe most treatments in the health care system provide option value, so we cannot use it as a metric for distinguishing the comparative value of different treatments. Option value has not historically been a standard element of cost-effectiveness analyses, and more methodologic research and data are needed before their standard inclusion.
2.	Another aspect of the Draft Report that we feel is inadequate is the consideration of data from open label extensions (OLE) of the clinical trials, which indicate significant and ongoing clinical value. We recognize that this data is not as robust as formal clinical trials data, but because it represents additional time in treatment, this information may be more like real-world clinical experiences than the original clinical trials, and thus it is important to factor it into the analysis as a primary input.	ICER is concerned that patients who continue in open label extensions (OLE) of the clinical trials represent a selected group of patients who may not be representative of hATTR patients who ultimately take the drugs, and as the commenter is aware, we are unable to make comments on the incremental effects of these drugs. We present the OLE data in the report for both medications.

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	However, if ICER largely disregards the OLE data as too uncertain, while underplaying the vast array of uncertainties about other aspects of the clinical trials data, ICER is creating an uneven analytical tableau of warped perspective for payers, patients, and clinicians.	
3.	And lastly, in a previous letter we mentioned that ICER's framework modifications for ultra-rare diseases does not consider how pricing considerations affect research and development spending. While we are limited by ICER's space constraints here, we note that there is a direct and causal relationship between what and how payers reimburse for different therapeutic options and the investment decisions made in those disease areas. This was seen 20 years ago for mental health conditions, and is still a concern in the field of substance abuse treatment. It is heightened in the area of rare diseases because the costs of those therapies are inherently higher than average, and if payors or regulators are going to adopt broad upper limits on any and all new treatments, then that will dramatically diminish investment into new diagnostics and treatments for diseases with limited patient populations. The long-term consequences of this will be fewer treatment options, and higher morbidity and mortality for those individuals. That of course, could be characterized as a moral and value choice of society, but if that is the case, then it should be explicitly recognized and stated.	We respectfully disagree. There are a number of practical and conceptual reason to align prices with value for even rare disorders. We have examples of tremendous innovation for rare disorders, such as the CAR-T therapies for pediatric cancer, where the prices are in line with how much better the drugs improve patients' lives. Unarguably, CAR-T therapies are the type of ground-breaking innovation we want to see for all diseases, and the manufacturers' decisions to pick a value-based price has not slowed future innovation. Improved patient access will be the direct result of moving toward a health system anchored in sustainable access to high value care, especially for rare disorders.
4.	An inherent complication factor in ICER's analysis is limiting it to two yet to be approved compounds. The challenges of evaluating the clinical and market potential of medicines prior to approval – and by definition prior to the final FDA label of indications and warnings – is extremely difficult. We recognize that the Draft Report includes some discussion of diflunisal as an off-label option in the U.S. However, as with many rapidly evolving scientific and clinical areas, there are other compounds that could significantly change the clinical and market landscape. For example, tafamidis appears to be poised to possibly do that for amyloidosis, yet ICER's Draft Report discounts tafamidis as a significant clinical option, in contrast to recent analyst and editorial assessments. Specifically, tafamidis has been given breakthrough status from the FDA, and the FDA gave the company another complete response letter in June 2018. And because tafamidis is not restricted to a subtype of amyloidosis it will not require a genetic test prior to use, and as an oral medicine it may also be seen as more convenient and acceptable for patients. With a likely broader patient population of potential users, its price should also be lower than the two compounds ICER's Draft Report evaluates, producing market competition and lower	In the section "TTR Stabilizers" we discuss tafamidis. We have also referenced tafamidis in the "Treatments on the Horizon" section of the report. We did not include tafamidis as an explicit intervention in our project scope, however, as the manufacturer had not yet filed with FDA at the time of the scoping process.

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	net cost of those two medicines. This scenario has been described by analysts but is missing from ICER's modeling, analysis, and discussion. We believe ICER should consider such real-world situations because it is not uncommon. For example, the highly effective treatments for chronic hepatitis C have seen their net costs decrease by more than 60% over the past four years. While that might be a greater than normal cost reductions, it is a benchmark to consider. Therefore, we believe that the Draft Report's section on "Treatments on the Horizon" should be expanded to include tamadisis, and be given a more robust treatment, particularly concerning the effects of market competition from multiple treatment options on any cost projections.	
5.	Clearly the "crisis" of health care spending and affordability that has been going on for at least 50 years has not resulted in the collapse of the U.S. health care system or the U.S. economy. It is sometimes asserted that increased spending on health care push out or replace other options, such as savings, transportation, or education. What is missing from that push-out argument is the understanding that economies are not static, and that with economic growth, the creation of new industries, and productivity improvements, resulting in the replacement of one type of good or service with another. This evolution means that the percentages of spending in different areas will naturally and appropriately change over time. For example, with efficiencies in food production and transportation, along with economic growth and expansion, have led to the U.S. consumer spending much less on food (as a percentage of income) than they did in the past, i.e., 45% of consumer spending in 1901 went for food, but that declined to 38% in 1918, to 24.3% in 1961, to 13.8% in 1996, and to 12.6% in 2016. Establishing an appropriate growth rate for health care (or other areas of consumer or societal spending) implies some basic tenet of what is the "right" amount. But as is clear for the discussion above (and explored more below), those perspectives are fluid and evolve. Further, what gains can (or should) be made from spending in one area versus another (e.g., social services v. health care v. transportation v. education v. technology) are complicated analyses that are as much derived from social mores as from macro-economic projections.	Potential budget impact has been the dominant way that payers have looked at value, so we include it in our reports. Our potential budget impact analyses are intended to provide an alert to health care payers and others when an intervention has the potential to cause a rapid increase in spending, so that they can proactively plan for and manage such increases in spending to ensure that access and affordability to new interventions are sustainable over time. We believe that patients deserve a public conversation about potential budget impact, instead of a private conversation that takes place with no patients present, to ensure that we avoid access issues for patients. Our threshold is a discussion point - not a spending cap - and our analyses mirror provisions of the Affordable Care Act and the health care cost-control laws in Massachusetts.
6.	Health care is two words. In this report it is one word. In previous reports it was two words.	Thank you - we have updated the report.
7.	The Draft Report's statement "We were unable to identify coverage policies for inotersen or patisiran, as they have not yet been approved by the FDA." (p. 11) is nonsensical, since all insurance contracts (that we are aware of)	Thank you - we have updated the report.

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	explicitly do not provide coverage for experimental treatments, and as compounds not yet approved by the FDA, inotersen and patisiran, are by definition, experimental. The language should be clarified to reflect that fact.	
8.	The assumed costs for patisiran (p. 46) contain several errors. First the assumed mark-up of 6% is incorrect. Although that is the statutory amount under Medicare, under sequestration that amount is reduced to 4.3%, and since approximately 50% of people with hATTR are over age 65 then this figure should be corrected. And second, the new rules about reimbursement for many 340B hospitals reduces reimbursements to ASP minus 22.5% Thus, there should be changes to the calculations of patisiran costs.	The correct mark-up percentage is related to how long sequestration will continue; given the lifetime model horizon, that amount remains an uncertainty. Although 6% is the statutory amount under Medicare, under sequestration that amount is reduced to 4.3%. When the drug price was initially assumed to be $300,000 per year, the mark-up costs were $18,000 (with the 6% assumption); however, now with the newly increased price of $345,000 per year, the mark-up costs are $14,835 (with the 4.3% assumption). The revised estimated price of $345,000 takes into consideration the manufacturer's statements about providing discounts in line with what 340B hospitals receive (i.e., an approximate 23% discount from the stated list price of $450,000 annually).
Other		
Optum		
1.	We found the report to be generally informative and accurate. However, we believe that there is additional information that could be added to the report regarding the burden of hereditary transthyretin amyloidosis (hATTR) on patients' functioning and well-being, and evidence that inotersen reduces that burden. We have conducted analyses, which are described in this response, that indicate that patients with hATTR amyloidosis suffer a tremendous burden on quality of life (QOL), similar to that of patients with congestive heart failure (CHF), multiple sclerosis (MS), and with diabetic neuropathy (DN) accompanied by a history of ulceration, gangrene, or amputations. Further, we found evidence supporting inotersen as efficacious in preserving numerous aspects of health-related QOL, including physical functioning (e.g., walking more than several hundred yards, or climbing several sets of stairs), for patients with hATTR amyloidosis. Optum conducted analyses (with funding provided by Akcea) that examined in more detail the QOL experienced by patients with hATTR amyloidosis who participated in the NEURO-TTR trial. Specifically, we examined the burden of disease for these patients by comparing their baseline scores on measures of neuropathic-related QOL (Norfolk QOL-Diabetic Neuropathy [DN] questionnaire) and generic health-related QOL (SF-36v2® Health Survey [SF-36v2]) with	Thank you for informing us about this important research; we would be grateful for any publications or presentations you are able to share. An important next step in such research would be to map information on the burden of disease to estimates of utilities for discrete health states. Currently, the model is using directly-elicited utilities reported for FAP Stages 1 and 2. The base case uses a previously-published utility estimate for FAP Stage 3 of 0.17, indicating a very poor quality of life. Even lower QALY utilities for FAP Stages are tested in the scenario analyses.

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	scores from the general population and/or patients with other chronic diseases that share clinical manifestations with hATTR amyloidosis. These comparisons with general population and disease benchmarks aid in interpretation of the QOL experienced by patients with hATTR amyloidosis relative to population norms and to medical conditions that have established burden profiles. We also conducted analysis examining treatment comparison of changes in mean SF-36v2 scores from baseline to week 66. The objective of this response is to provide to ICER findings from these analyses, to help put into context the QOL experienced by patients with hATTR amyloidosis, and the impact of inotersen on their health-related QOL.	
2.	In conclusion, these results indicate that patients with hATTR amyloidosis suffer a substantial burden on QOL, matching that of patients with CHF, MS, and with DN accompanied by a history of ulceration, gangrene, or amputations. Further, results show inotersen has been shown to be effective for preserving generic and disease-specific health-related QOL, particularly related to physical health outcomes such as physical functioning, for patients with hATTR amyloidosis. Based on our extensive experience working in the area of PROs for QOL, we think these results provide a high level of evidence. Further, the impact on generic QoL means that inotersen likely had an impact on the systemic nature of the disease, not merely impacting neuropathic symptoms.	With your extensive experience in the area of PROs for QOL, we recognize that you appreciate the difference between health-state utilities and other types of PROs for QOL (that are not preference based). As such, you recognize that this difference allows one to see changes in generic and disease-specific health-related QOLs that do not lead to changes in QALYs. It is the changes in QALYs that are relevant in economic evaluation. In addition to using utilities reported for FAP stages, the model also introduces QALY utility "bonuses" for treatment within each FAP stage that grow over time and then reach a plateau. The plateau bonuses are carried forward over the lifetime of the model. In this way, patients in the same FAP disease stage are able to experience different QOL based on treatment option, even though their FAP stage does not improve.
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1.	First, the assumption that liver transplant is not frequently used to treat hATTR in the US may not be accurate. The statement is reported to be based on “clinical expert opinion”, but we recently analyzed 2 commercial insurance claims databases covering 2012-2016 and found between 5%-13% of patients identified with hATTR had a liver transplant. In addition, we have internally estimated the cost of transplant to be as high as $800,000 in hATTR (and, although we did not quantify them, heart and heart/liver transplants are also performed in this population). Our experience and published literature suggest that experts may underestimate the time it takes for new practices to be widely adopted, which may explain the discrepancy between clinician opinion and our findings. By excluding transplants, the model may underestimate the clinical and economic burden of hATTR.	We agree that there is uncertainty about liver transplant for treating hATTR in the US. Given the lack of relevant data and clinical consensus on whether transplant would remain a viable option in the setting of inotersen or patisiran treatment, we did not include liver transplant in the model.

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2.	Second, we believe the model substantially underestimated disease costs. The model used a cost input of $8,701-$37,528 per year, with estimates derived from a survey asking patients about their health service use over the entire preceding year. Recall-based estimates consistently underestimate actual utilization, and the magnitude of the underestimate increases substantially with periods longer than 3 months. Consistent with this type of error, we estimated annual direct healthcare costs of $51,140-$77,548 across all disease stages.	We agree that trial data may not be representative of non-controlled settings due to a variety of factors, including recall. It is for this reason that we tested the base case cost inputs of $8,701-$37,528 per year in a variety of scenario analyses featuring much higher costs for all disease stages. The results of these tests suggest assumptions about disease stage costs do not affect the overall results in a meaningful way.
3.	Finally, we found patients with hATTR experience a number of comorbidities that do not appear to have been considered, either as to their effect on quality of life or on cost.2 Insurance claims studies are not ideal for identifying comorbid conditions because of coding limitations, but our findings suggest that a more thorough analysis of clinical data would likely reveal additional comorbidities that were previously overlooked.	We agree that data on comorbid conditions are difficult to come by. In RCTs, patients may be healthier than "average" patients and claims studies can only be conducted after the drug is in use. The key issue is the differential impact of the drug on comorbidities. It is not clear that such an impact exists, and data are not available at this moment to support modeling efforts.