

August 17, 2018

Akcea Therapeutics' Response to ICER's Draft Evidence Review on Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis (hATTR)

Akcea appreciates this opportunity to provide ICER with feedback on their review of therapies for treatment of hereditary transthyretin amyloidosis (hATTR). Hereditary ATTR is a rare, progressive and fatal disease [1]. Although hATTR affects a small number of patients, the disease represents a significant, serious healthcare and societal burden to both patients and caregivers [2] [3]. Our understanding of the disease process and etiology in hATTR continues to evolve – a task made more challenging by the wide range of symptoms affecting patients with hATTR, the large number of causal genetic mutations and phenotypic permutations, and the small patient population size [3]. And until recently, there was no FDA approved treatment for this fatal condition.

Both inotersen and patisiran represent a significant step forward in treatment for patients with hATTR. They are both truly novel, innovative therapies, with unique mechanisms of action. Patients with hATTR display a wide heterogeneity of symptoms and it is unclear if one product might have a better clinical effect in a specific mutation or phenotype. Akcea believes patients should have clinically appropriate but unfettered access to both therapies. Inotersen and patisiran also have different modes of administration and patients may prefer a self-administered formulation over a therapy that requires infusions at a hospital or physician's office (or vice-versa) depending on their unique situation or circumstance.

We have several specific and significant concerns including:

- Premature nature of ICER's assessment, particularly because inotersen does not yet have a label
- Inaccurate and inappropriate classification of inotersen's clinical effectiveness as "inconclusive" based on inconsistent methodology
- Unbalanced, highly unscientific, and inappropriate assessment of the relative efficacy and cost-effectiveness associated with inotersen and patisiran
- Unbalanced assessment of the risk associated with inotersen and patisiran (lack of inclusion of IV dexamethasone risk/harm, and no inclusion of the potential cardiovascular risk associated with patisiran)
- Significant assumptions and poor methodology in ICER's cost-effectiveness model, including unbalanced and incorrect assignment of two different best supportive care arms in the model

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 durable” for patients taking inotersen even though an open label extension study supplied to ICER under separate cover suggests otherwise [4]. 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.

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.

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 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.

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.

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 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.

Specific comments on ICER's clinical effectiveness assessment

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 [5] [6]. 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.

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.

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 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) [7]. 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.

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.

Specific comments on ICER’s cost-effectiveness assessment (CEA)

Assigning inotersen two-thirds of patisiran efficacy (i.e., health state transition probabilities) in the cost-effectiveness model in the absence of actual data is an assumption unsupported by any robust evidence and is inappropriate. This unfounded assumption^a 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.

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.

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

^a The basis for this assignment of efficacy is on Norfolk QoL-DN results, which is an instrument designed for the assessment of diabetic neuropathy

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 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.

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 [9]. 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.

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 context of developing therapies for ultra-rare diseases and the still-developing evidence base for hATTR.

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. Akcea appreciates the opportunity to comment on this draft evidence report and provide feedback that can help ensure a robust assessment of value for these two novel therapies to treat hATTR at an appropriate time in the future. Akcea looks forward to participating in the upcoming public meeting of the Midwest CEPAC and furthering the conversation on the value of inotersen in a way that ensures patient access and optimal treatment.

References

- [1] H. H. Schmidt, M. Waddington-Cruz, M. F. Botteman, J. A. Carter, A. S. Chopra, M. Hopps, M. Stewart, S. Fallet and L. Amass, "Estimating the global prevalence of transthyretin familial amyloid polyneuropathy," *Muscle Nerve*, vol. 57, no. 5, pp. 829-837, May 2018.
- [2] M. S. Maurer, S. Heitner, B. M. Drachman, C. J. Whelan, S. Guthrie, L. Tai, S. G. Hughes, B. P. Monia, E. J. Ackermann and M. D. Benson, "Inotersen Improves Quality of Life in Patients With Hereditary Transthyretin Amyloidosis With Polyneuropathy and Cardiomyopathy: Results of the Phase 3 Study NEURO-TTR," in *American College of Cardiology 67th Scientific Session & Expo*, Orland, FL, 2018.
- [3] M. A. Gertz, "Hereditary ATTR Amyloidosis: Burden of Illness and Diagnostic Challenges," *AJMC*, vol. 23, no. 7 Suppl, pp. S107-S112, 2017.
- [4] T. Brannagan, A. K. Wang, T. Coelho, M. W. Cruz, M. J. Polydefkis, P. J. Dyck, M. Scheinberg, V. Plante-Bordeneuve, J. L. Berk, F. Barroso, D. Adams, C. Whelan, G. Merlini, B. M. Drachman, S. B. Heitner, I. Conceicao, H. Schmidt, G. Vita, J. M. Campistol, J. Gamez, P. Gorevic, B. P. Bonia, S. G. Hughes, J. Kwok, S. W. Jung, B. F. Baker, E. J. Ackermann, M. D. Benson and M. Gertz, "Open-Label Extension of the Phase 3 NEURO-TTR Study to Assess the Long-Term Efficacy and Safety of Inotersen in Patients With Hereditary Transthyretin Amyloidosis," in *American Academy of Neurology*, Los Angeles, CA, 2018.
- [5] G. H. Guyatt, C. Bombardier and P. X. Tugwell, "Measuring disease-specific quality of life in clinical trials," *Canadian Medical Association Journal*, vol. 134, no. 8, pp. 889-895, 1986.
- [6] D. L. Patrick and R. A. Deyo, "Generic and Disease-Specific Measures in Assessing Health Status and Quality of Life," *Medical Care*, vol. 27, no. 3, pp. S217-S232, 1989.
- [7] D. Adams, A. Gonzalez-Duarte, W. O'Riordan, C.-C. Yang, Ueda, Mitsuharu, A. V. Kristen, I. Tournev, Schmidt, H. H, T. Coelho, J. L. Berk, K.-P. Lin and G. Vita, "Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis," *New England Journal of Medicine*, vol. 379, pp. 11-21, 5 July 2018.
- [8] U.S. National Library of Medicine, "Medline Plus: Dexamethasone Injection," July 30 2018. [Online]. Available: <https://medlineplus.gov/druginfo/meds/a616022.html>. [Accessed 13 August 2018].
- [9] S. Guthrie, S. R. Reddy, R. Tieu, J. Munday, M. Tarbox, M. S. Broder and M. R. Pollock, "Healthcare Utilization and Cost Among Patients with Hereditary Transthyretin Amyloidosis (hATTR)," in *ISPOR*, Baltimore, MD, 2018.
- [10] A. Hincapié, J. Penm and C. Burns, "Factors Associated with Patient Preferences for Disease-Modifying Therapies in Multiple Sclerosis.," *J Manag Care Spec Pharm*, vol. 23, no. 8, pp. 822-830, Aug 2017.

- [11] A. Louder, A. Singh, K. Saverno, J. Cappelleri, A. Aten, A. Koenig and M. Pasquale, "Patient Preferences Regarding Rheumatoid Arthritis Therapies: A Conjoint Analysis.," *Am Health Drug Benefits*, vol. 9, no. 2, pp. 84-93, 2016.
- [12] National Library of Medicine, "Guide to Understanding Genetic Conditions: Transthyretin amyloidosis," 14 August 2018. [Online]. Available: <https://ghr.nlm.nih.gov/condition/transthyretin-amyloidosis#statistics>.

August 17, 2018

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RE: Comments on Draft Evidence Report for ICER's Review of the Treatment of Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

Alnylam Pharmaceuticals, Inc. (Alnylam) has spent the past 16 years developing an entirely new class of medicines based on RNA interference, or RNAi. Last week, the FDA approved our first commercial product, an RNAi therapy called ONPATTRO™ (patisiran). The FDA noted that it is “the first FDA-approved treatment for patients with polyneuropathy caused by hATTR, a rare, debilitating and often fatal genetic disease characterized by the buildup of abnormal amyloid protein in peripheral nerves, the heart and other organs. It is also the first FDA approval of a new class of drugs called small interfering ribonucleic acid (siRNA) treatment.”

ONPATTRO was designated as a Breakthrough Therapy by the FDA, awarded to expedite the development and review of new therapies to “treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint.” In the FDA announcement of the ONPATTRO approval, Commissioner Scott Gottlieb said, “This approval is part of a broader wave of advances that allow us to treat disease by actually targeting the root cause, enabling us to arrest or reverse a condition, rather than only being able to slow its progression or treat its symptoms.”¹

We have spent years researching the complexities of hATTR amyloidosis—a devastating, rapidly progressive, multi-system disease that impacts all aspects of life—so we know how high the stakes are for patients and their family members, some of whom must live in apprehension of the onset of this hereditary condition. Underpinning all of our work has been a commitment to developing a medicine that delivers value to patients, caregivers and society.

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 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.

In addition, we have a number of concerns with the design of ICER's model, which excludes certain critical social benefits of treatment; extensively uses assumptions to close gaps in currently available evidence; and includes several statements that inaccurately represent clinical benefits observed in the trials. As a result, Alnylam believes that ICER's analysis, as detailed in the draft evidence report, fails to capture the clinical and social value of ONPATTRO in the treatment of hATTR amyloidosis. A detailed list of these concerns follows, and a list of recommended corrections to misstatements in the draft evidence report is included in the appendix.

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:

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.³

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 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.

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.¹⁰

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.

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 real world experience of hATTR amyloidosis patients, nor is it capable of capturing the full benefits of ONPATTRO.

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.¹¹ 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.

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:

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 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.

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.^{16,17} 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)⁵.

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.

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.¹⁶⁻¹⁸ 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.

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 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.¹⁵ 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.

Alnylam submits these recommendations with the goal of ensuring that ICER's forthcoming value assessment is as accurate as possible given available data. We also caution ICER to balance urgent patient need, demonstrated safety and efficacy, scientific advancement and disease complexity with the impacts to the health system and societal costs when making revisions to this draft evidence report. We thank ICER for its consideration and are available to answer any questions.

Sincerely,



Pritesh Gandhi
Vice President, Medical Affairs

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1. Food and Drug Administration (2018, August 10). *FDA approves first-of-its kind targeted RNA-based therapy to treat a rare disease* [Press release]. Retrieved from <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm616518.htm>
 2. Amyloidosis Research Consortium. *Burden of disease and perspectives on treatment*. July 27, 2018.
 3. Stewart M. et al., Characterizing the High Disease burden of Transthyretin Amyloidosis for Patients and Caregivers. *Neuro Ther.* (2018) doi: 10.1007/s40120-018-0106-z.
 4. Adams D. et al., Evaluation of Quality of Life and Disability in Patients with Hereditary Transthyretin-Mediated (hATTR) Amyloidosis with Polyneuropathy Following Treatment with Patisiran, and Investigational RNAi therapeutic: Results from the Phase 3 APOLLO Study. *Presented at the American Academy of Neurology (AAN)*. (2018).
 5. Adams D. et al., Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *New England Journal of Medicine* 379.1 (2018): 11-21.
 6. Gonzales- Duarte A. et al., Changes in Neuropathy Stage in Patients with Hereditary Transthyretin-Mediated Amyloidosis Following Treatment with Patisiran, an investigational RNAi Therapeutic: An Analysis from the Phase 3 APOLLO Study. *Presented at the International Symposium on Amyloidosis (ISA)*. (2018).
 7. Desser A. et al., Societal views on orphan drugs: cross sectional survey of Norwegians aged 40 to 67. *BMJ*. (2010) 341:c4715.
 8. Shiroya T. et al., WTP for a QALY and health states: More money for severer health states?. *Cost Eff Resour Alloc.* (2013) 11:22.
 9. van de Wetering E. et al., Are some QALYs more equal than others?. *Eur J Health Econ.* (2016) 17.2:117-127.

10. Sanders G. et al., Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *Jama*. (2016) 316.10: 1093-1103.
11. Coutinho P. et al., Forty years of experience with type I amyloid neuropathy. Review of 483 cases. *Amyloid and Amyloidosis*. (1980) 88–98.
12. Suhr O. et al., Long-Term Use of Patisiran, an Investigational RNAi Therapeutic, in Patients with Hereditary Transthyretin-Mediated Amyloidosis: Baseline Demographics and Interim Data from Global Open Label Extension Study. *Presented at the International Symposium on Amyloidosis (ISA)*. (2018).
13. Adams D. et al., Rapid Progression of Familial Amyloidotic Polyneuropathy: A multinational natural history study. *Neuro*. (2015) 85(8):675-82.
14. Coelho T. et al., Clinical measures in transthyretin familial amyloid neuropathy. *Muscle Nerve*. (2017) 55:323-32.
15. Vinik E. et al., Norfolk QOL-DN: Validation of a patient reported outcome measure in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Syst*. (2014) 19:104-14.
16. Gertz M. et al., Familial amyloidosis: a study of 52 North American-born patients examined during a 30-year period. *Mayo Clin Proc*. (1992) 67(5):428-40.
17. Swiecicki P. et al., Hereditary ATTR amyloidosis: a single-institution experience with 266 patients. *Amyloid*. (2015) 22(2):123-31.
18. Solomon et al., APOLLO a Phase 3 study of Patisiran for the treatment of hereditary transthyretin-mediated amyloidosis; 18-month safety and efficacy in subgroup of patients with cardiac involvement. *Presented at the International Symposium on Amyloidosis (ISA)*. (2018).
19. Coelho et al., Tafamidis for transthyretin familial amyloid polyneuropathy. *Neuro*. (2012) 79(8):785-92.
20. Berk et al., Repurposing Diflunisal for Familial Amyloid Polyneuropathy: A Randomized Clinical Trial. *JAMA*. (2013) 310(24): 2658-2667.
21. Adams D. et al., Patisiran, an investigational RNAi Therapeutic for Patients with Hereditary Transthyretin-Mediated (hATTR) Amyloidosis: Results from the Phase 3 APOLLO Study. *Presented at the American Academy of Neurology (AAN)*. (2018).

Appendix

Inaccuracies in the Draft Evidence Report for ICER's Review of the Treatment of Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

The draft evidence report makes a number of inaccurate statements regarding clinical benefits. We recommend that ICER make the following corrections:

p22: "About half of patisiran patients showed neurological improvement by mNIS+7 score."

Recommendation: Clarify that this improvement is compared to patient's own baseline

p24, paragraph below table: ICER flags several imbalances at baseline that may affect comparability of the two treatment groups.

Recommendation: Note that "The patisiran group had a higher proportion of patients with non-V30M genotypes and a higher proportion with echocardiographic evidence of cardiac amyloid involvement at baseline. These baseline characteristics are associated with more rapid disease progression and worse outcome; therefore, the imbalance in these features might be expected to favor the placebo group. Nonetheless, the patisiran group demonstrated a substantially better outcome with regard to neuropathy progression and quality of life compared to placebo, showing that the baseline imbalance that might have favored placebo was overcome by the strong treatment effect of patisiran on neuropathy."

p27, 2nd paragraph: ICER notes that it is unclear what magnitude of mNIS+7 change is clinically relevant

Recommendation: Note that "Prior trials of tafamidis and diflunisal in hATTR amyloidosis have used a <2-point increase in either NIS-LL or NIS+7 to define a clinically meaningful response to treatment.^{19,20} In APOLLO, the patisiran group demonstrated a mean 6-point decrease in mNIS+7 at 18 months, whereas the placebo group progressed by 28 points, representing a 34-point treatment difference between the two groups.⁵ Therefore, the change in mNIS+7 at 18 months in the patisiran group, as well as the magnitude of the difference in change in mNIS+7 between patisiran and placebo, greatly exceeded that 2-point threshold. Furthermore, a majority of patisiran-treated patients showed an improvement in their neuropathy at 18 months compared to baseline (change in mNIS+7 < 0). The clinical meaningfulness of that effect of patisiran on neuropathy was further supported by a beneficial effect on multiple secondary endpoints that assess how patients feel and function, including Norfolk QOL-DN (quality of life), 10-MWT (gait speed), R-ODS (limitations in activities of daily living), mBMI (nutritional status), and COMPASS-31 (autonomic symptoms). "

p34 1st paragraph: ICER questions the generalizability of the APOLLO study to the U.S. population

Recommendation: Note that "The APOLLO study enrolled patients with 39 different TTR mutations and included patients with a broad range of baseline neuropathy severity as well as patients with cardiac amyloid involvement.⁵ V122I patients often present with cardiac-predominant disease, but 30-50% of patients also develop neuropathy during the course of their

disease and therefore have a mixed phenotype similar to what is seen with other mutations, such as T60A and late-onset V30M.

p34, 3rd paragraph: In the context of long term safety, ICER notes that pretreatment with steroids was included in the APOLLO study

Recommendation: Note that “The use of intermittent (e.g. once every 3 weeks) steroids, as was administered as premedication to patients on APOLLO, is not associated with the toxicities observed with chronic daily doses of steroids. In APOLLO, both the patisiran and placebo groups received corticosteroid premedication once every 3 weeks for 18 months, and there was no evidence of chronic steroid toxicity.”²¹

August 17, 2018

Dear ICER,

I am a cardiologist at Indiana University in Indianapolis, IN and a member of the Indiana University School of Medicine Amyloid Center. Our amyloidosis research group has a significant experience with treating both neuropathy and cardiomyopathy patients with inotersen. Amyloidosis is a devastating disease with multisystem involvement. Historically there have been no effective treatments for this fatal disease. 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 had a large number of patients in the NEURO-TTR study and many of those patients improved. Moreover, we also have an investigator initiated study of inotersen at Indiana University for patients with transthyretin cardiac amyloidosis (either hereditary or wild type ATTR) causing congestive heart failure. In this study we have treated 33 patients. We have a number of patients who have improved cardiac function as measured via 6-minute walk test (6MWT) and improved cardiac structure as measured by MRI. More importantly we believe inotersen may have positively affected survival and quality of life (having treated some patients for >4 years). As a clinician it has been a pleasure to witness patients survive and thrive after being given a terminal diagnosis. Importantly, we have not seen any serious platelet issues in this study. We believe the platelet monitoring has reduced the concern about severe thrombocytopenia.

In conclusion, we believe inotersen is an effective treatment for both ATTR neuropathy and cardiomyopathy. We have felt fortunate to witness the positive effect of inotersen on patients quality of life and also believe that therapy can alter the course of a fatal disease.

Sincerely,

Noel Dasgupta, MD
Assistant Professor of Medicine, Krannert Institute of Cardiology
Indiana University, Indianapolis, IN

We read with interest your critique of the neuropathy endpoints used in the two therapeutic trials of hATTR-PN. The review, especially of the endpoint mNIS+7 seems somewhat uninformed and could be improved! We developed some of the measurement components of NIS and +7 and mNIS+7, therefore will comment about its special and successful use in the oligonucleotide trials published in *NEJM*, July 10, 2018. The articles would not have been published in *NEJM* had reviewers and editors not found the endpoint changes credible in showing an unequivocal therapeutic effect! We will provide specific information about the chosen endpoints encouraging you to modify your report. We used queries and responses to address our concerns.

Q1. A distinction appears to be made between mNIS+7_{Ionis} 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 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 (HR_{db}). 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 HR_{db} 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.

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 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.

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.

The assessment of graded severity of muscle weakness, decreased activity of muscle stretch reflexes, and clinical sensation loss impairments evaluated by NIS is based on a series of scientific and medical articles since the end of the 19th century.¹ Such grading is taught to medical students and neurology residents and is used in neurologic practice and in research. A special grading approach for grading muscle weakness was introduced to study nerve injuries. This MRC approach is widely used in medical and neurologic education and practice. Even prior to that date, Mayo Clinic physicians and neurologists had developed a measured grading approach for assessment of muscle weakness, decreased muscle stretch reflexes, and for loss of sensation, e.g., of touch, pin prick, vibration, cooling, or joint motion.¹ Other medical schools used similar grading approaches. All physicians are taught how to grade muscle weakness, muscle stretch reflex decrease, and sensation loss for the detection, characterization, and quantification of polyneuropathy. We introduced Neuropathy Disability Score (NDS), later called Neuropathy Impairment Score (NIS), using a standard number of neurological examination items and a standard percentile approach to grading of severity of abnormality. It was to be used for conduct of epidemiology surveys, and especially for therapeutic trials of polyneuropathy. Because NIS directly measures the main neurologic impairments of muscle weakness, reflex decrease, and sensation loss, it was chosen as an approximate measure for the oligonucleotide trials of hATTR-PN. Abnormality is to be judged by comparison to adequately obtained reference values. The score provides an overall score of polyneuropathy impairments. The NIS score has been extensively used and tested in NIH and pharmaceutical industry supported epidemiologic surveys, and especially in therapeutic trials of chronic inflammatory demyelinating polyneuropathy (CIDP), uremic

neuropathy, diabetic neuropathy, neuropathy associated with monoclonal gammopathy of undetermined significance (MGUS), and hATTR-PN.

To ensure that expert physicians (diabetologists and neurologists) could grade diabetic polyneuropathy accurately and reproducibly, we performed two international studies (CI vs NPhys 1 and 2 assessing physician proficiency).^{2,3} In the first trial without instruction of physicians and without consensus development, physician intra- and inter-rater agreement was excessively large. In a second trial, and after a consensus to use only unequivocal abnormality and taking age, gender, and anthropomorphic variables into account, intra- and inter-rater agreement was markedly impaired. These new insights were used in training and certification of all neurologists making clinical assessments in the oligonucleotide trials. The NIS has been a primary outcome measure in a series of therapeutic trials in chronic inflammatory demyelinating polyneuropathy (CIDP), diabetic polyneuropathy, neuropathy associated with monoclonal gammopathy of unknown significance, and in hATTR-PN (references can be provided if needed).

Has a meaningful degree of difference between treatment and placebo arms of a therapeutic trial been defined and demonstrated? At a special consensus session of the PNS in St. Paul, Minnesota, a meaningful and statistically significant difference of 2 points of NIS was agreed on. It should be noted that this modest level has not been obtained in trials of diabetic polyneuropathy but has greatly been exceeded by the recent oligonucleotide trials of hATTR-PN.

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 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.

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.

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.

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.

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.

References:

1. Dyck PJ, Boes CJ, Mulder D, Millikan C, Windebank AJ, Dyck PJB, Espinosa R: History of standard scoring, notation, and summation of neuromuscular signs. A current survey and recommendation. J Peripheral Nervous System, 10:158-172, 2005.
2. Dyck PJ, Overland CJ, Low PA, Litchy WJ, Davies JL, Dyck PJB, O'Brien PC, CL vs. NPhys Trial Investigators, Albers JW, Andersen H, Bolton CF, England JD, Klein CJ, Llewelyn JG, Mauermann ML, Russell JW, Singer W, Smith AG, Tesfaye S, Vella A. Signs and symptoms versus nerve conduction studies to diagnose diabetic sensorimotor polyneuropathy: Cl vs.NPhys trial: Muscle Nerve, 42:157-164, 2010.
3. Dyck PJ, Overland CJ, Low PA, Litchy WJ, Davies JL, Dyck PJB, Carter RE, Melton LJ, Andersen H, Albers JW, Bolton CF, England JD, Klein CJ, Llewelyn G, Mauermann ML, Russell JW, Selvarajah D, Singer W, Smith AG, Tesfaye S, Vella A: “Unequivocally abnormality” vs “usual” signs and symptoms for proficient diagnosis of diabetic polyneuropathy. Arch Neurol, 69 (12):1609-1614, 2012
4. Berk JL, Suhr OB, Obici L, Sekijima Y, Zeldenrust SR, Yamashita T, Heneghan MA, Gorevic PD, Litchy WJ, Wiesman JF, Nordh E, Corato M, Lozza A, Cortese A, Robinson-Papp J, Colton T, Rybin DV, Bisbee AB, Ando Y, Ikeda S, Seldin DC, Merlini G, Skinner M, Kelly JW, Dyck PJ, for the Diflunisal trial Consortium: Repurposing diflunisal for familial amyloid polyneuropathy a randomized clinical trial. JAMA, 310(24):2658-2667, 2013.

Sincerely,

Peter J. Dyck, M.D.

W. J. Litchy, M.D.

P. James B. Dyck, M.D.

August 17 2018

To whom it may concern:

Re: Draft Evidence Report on Inotersen and Patisiran for hATTR

I have just come across your draft document comparing the 2 transthyretin silencers, patiseran and inotersen for the treatment of familial amyloid polyneuropathy. I am the Director of the Brigham and Women's Hospital Amyloidosis Program, and have over 30 years' experience in the diagnosis and treatment of all types of amyloidosis. I have been following the development of the silencers for several years. Since the presentation of the preliminary data on both patiseran and inotersen in Paris in November 2017, in addition to the full publication in the New England Journal of Medicine in July, I have been carefully evaluating these 2 drugs with a view to determining how I would use them in my practice. By way of disclosure I have received consulting fees both from Alnylam Pharmaceuticals and Ionis Pharmaceuticals who manufacture each of these drugs respectively, but my comments are unrelated to any such fees.

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, particularly regarding inotersen, reflects the published and publicly available data and it is for that reason the I am writing this letter.

On page 37 of your report, addressing patiseran, 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 patiseran 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 patiseran, 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 patiseran 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 patiseran over inotersen, with regard to this particular outcome.

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 patiseran." 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 patiseran without any direct or in direct comparisons.*" (emphasis added).

With regard to your summary of the inotersen data, I would take strong issue with the third bulleted state that "(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 patiseran, 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 patiseran leading to an apparently greater response rate.

In my opinion, both publications in the July New England Journal of Medicine, on patiseran 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 patiseran 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.

Sincerely yours

Rodney H Falk M.D. FACC

Director, Brigham and Women's Hospital amyloidosis program,
Harvard Medical School
75, Francis St
Boston, MA 02115

August 15, 2018

Dear ICER,

I am Morie Gertz, a Hematologist at the Mayo Clinic. I previously served as the Chair of Medicine at Mayo. I have treated amyloidosis patients for over 35 years and have led the multi-disciplinary amyloidosis clinic at Mayo. In this time I have seen hundreds of hATTR patients. Our amyloidosis research group has a significant experience with treating both neuropathy and cardiomyopathy patients, and participated in both the inotersen and patisiran phase 3 trials. We are at a very exciting time for ATTR amyloidosis. We've had few options to treat these patients primarily liver transplantation, heart transplantation and diflunisal, none of which have been approved for this indication, and all with significant limitations. We are about to have multiple very effective therapies and the patients are excited to now have a choice.

I read your recent preliminary report on the clinical and cost effectiveness of these two new therapies with much interest. I would like to make a few comments about the disease and the therapies. First, we appreciate any new information on amyloidosis treatments as it provides much needed attention to the disease. And I applaud you for trying to understand this complex disease in such a short period. After 35yrs, I continue to learn something new daily as this is an extremely complicated and heterogenous disease.

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 think this is valid to compare these drugs based on the phase 3 studies for a number of reasons:

#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

#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.

#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.

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, 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.

#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.

#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 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 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.

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.

In conclusion, I believe that both inotersen and patisiran are remarkable advances for our patients, that both drugs are highly effective and have positive benefit risk profiles. We believe the efficacy results are comparable between the two drugs and we think the selection of the drug will be made by patients based on their personal circumstance. It is imperative that patients and physicians have equal access to the two drugs in order to make these choices.

Sincerely,

Morie Gertz



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New York, NY 10168

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ABC MISSION:

To promote the prevention and treatment of cardiovascular disease, including stroke, in Blacks and other minorities and to achieve health equity for all through the elimination of disparities.

August 17, 2018

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson:

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. Other variants, like V30M, may be more common worldwide. Carriers of this mutation are at increased risk of developing congestive heart failure. In fact, studies show that carriers of this mutation have increased prevalence of heart failure and an earlier onset age than noncarriers.¹ As noted in ICER's Draft Evidence Report on Inotersen and Patisiran for hATTR, this variant is most common among African Americans, with a prevalence of 3.4 percent of the general population.

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.¹

The ABC is encouraged by new treatment strategies under investigation and is particularly optimistic about the recent FDA approval of patisiran for treatment of hATTR and its potential to reverse or mitigate its debilitating manifestations, including a decline in cardiac functioning.

We applaud ICER's thorough scientific evidentiary review of new therapies for hATTR amyloidosis and encourage widespread availability to patients of FDA-approved treatments. For additional information or questions, please contact Cassandra McCullough, ABC CEO and Executive Director, at (212) 661-1438 or cmccullough@abcardio.org.

¹ Keyur S, Mankad A, Castano A, Akinboboye O, Duncan P, Fergus I, Maurer M. Transthyretin Cardiac Amyloidosis in Black Americans. *Circ Heart Fail*. 2016;9:e002558. DOI: 10.1161/CIRCHEARTFAILURE.115.002558.

¹ Ibid.

Sincerely,

A handwritten signature in black ink, appearing to read "Cheryl Pegus, M.D., M.P.H.", written in a cursive style.

Cheryl Pegus, M.D., M.P.H.
Board Chair
Association of Black Cardiologists

August 1, 2018

ICER

Public Comments:

Amyloidosis Support Groups (ASG) is a 501 (c) (3) nonprofit charity that initiates and maintains support groups for all types of amyloidosis. We now operate in more than 25 cities and grow each year. Our goal is to educate and empower our patients, as well as their families.

As an advocacy organization for amyloidosis patients and their families, we have met over 5000 patients with all types of amyloidosis. The most commonly seen type of hereditary amyloidosis is now referred to as hATTR, and it also appears to be the most insidious. This is because once becoming symptomatic, many patients suffer and deteriorate daily. While many think this form of amyloidosis strikes the elderly, we see it often in midlife (depending on the variant), and in rare instances, starting as early as in one's 20's.

When we see patients with the AL (primary acquired) form of the disease at our meetings, we usually see them improve meeting after meeting, because of the many treatment options available to them. These AL treatments are passed down from the world of multiple myeloma. For those with the hereditary form of the disease, we usually see the opposite.

We watched John, a young man in his early 40's, whom we met at a NYC support meeting in 2006, deteriorate over a six-year period. His variant was ATTR71. John had a liver transplant in 2005, which was hoped to stop the progression of the disease. It did not appear to help, as we watched him go from a man who drove his car and lived with his fiancé, to a lonely, diaper dependent, impotent, agoraphobic, who could not hold a pen, type, walk or drive. John died in May 2012.

John's half -brother, Kevin, shared a mother with John and that is how the gene passed to him. Like John, he had watched his mother and uncle die from this disease. When we first met Kevin at a NYC meeting in 2009, he was just starting to have a few peripheral neuropathy symptoms. In June 2012, Kevin was in his late 30's and in deep mourning for his brother John, when he went to Washington to testify before the Advisory Committee of the FDA for the passage of the drug Tafamidis. The drug had recently been approved in Europe and the advisory committee voted to approve, but the FDA chose not to adhere to its committee's recommendation at that time. By then Kevin was using a cane and his symptoms were coming on rapidly. Within a few months he was using a walker.

Late in 2013, Kevin moved to California in hopes of appealing to the ISIS (name changed to Ionis) pharma for participation in their clinical trial for their new anti-sense drug. He had

followed his doctor, Annabel, from Mt. Sinai in New York to Southern California as she was now one of the trial investigators at UC Irvine. Dr. Wang tried to help him, but by this time he was in a wheel chair and one of the criteria was that a patient must be able to walk.

In May 2014, at our Los Angeles support meeting, Kevin made a poignant appeal to the pharma liaisons from Ionis, Alnylam and Pfizer. Unfortunately, none could help him at that time, and Kevin died November 11, 2014. He was in his early 40's. Another family that we have been following since the early 2000's is this family. Jim was in his 40's and a recent recipient of a liver transplant when we met him. This was just prior to our 2004 support meeting in Phoenix. He too had watched his mother die of this disease, but he had been a teenager at the time. His variant was Asp18Glu. We met his cousin Ellen, a teacher, at a Maryland meeting, and his sister Anne, a dentist, at a Minnesota meeting. We were told that of his 18 first cousins, approximately half tested positive for the gene. Of his 6 siblings, only he and Anne were positive. At that time, none of the next generation had been tested to see if they too had the gene. Jim's diarrhea got worse after the liver transplant, and soon his heart was involved as well. Jim died in summer of 2006 leaving one offspring. Jim told us that when he was on leave from the army, he had a brief affair with a married woman in Iowa. She became pregnant and (we assume) passed the child off as her husband's. After Jim died, we shared this information with his sister Anne. Anne confirmed our story with one of her sisters, and then placed Jim's obituary in the newspaper in the town she suspected the mother had resided. We don't know what happened to the child.

Anne had a liver transplant in 2005. She had severe neuropathy, cardiac involvement and gradually went deaf as well. The clinical trials came too late for Anne, and she died in 2013.

When we met Anne's cousin Ellen in the mid 2000's, she was symptomatic and soon would be headed to Mayo in Rochester MN for a triple organ transplant (heart, liver and kidney). She wanted to see her daughter walk down the aisle and hold her first grandchild, which she did get to do. Ellen died in December 2014. Other cousins have passed as well. The good news is that several children of these cousins are on expanded access clinical trials and awaiting drug approval by the FDA.

We first met Stacey at the age of 28 when she attended our NYC support group meeting in 2004. Her fiancé accompanied her to the meeting. Stacey's variant was Pro36Ala. She had a liver transplant in 2003. She had lost her dad to this disease in the 1980's when he was in his 40's. Her mother told us that Bruce had difficulty walking, sexual dysfunction and diarrhea. Stacey told the group that she had to wear very heavy shoes, so she could walk as she could no longer feel her feet. Stacey died in November 2005.

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 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.

Sincerely,

A handwritten signature in cursive script that reads "Muriel Finkel".

Muriel Finkel

Amyloidosis Support Groups

www.AmyloidosisSupport.org

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**Amyloidosis Research Consortium response to ICER draft evidence report
Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and
Value**

September 17, 2018

The Amyloidosis Research Consortium (ARC) welcomes the opportunity to comment on the draft evidence report. We have focused our comments on two main areas: elements within the review of the effectiveness evidence, as well as the associated voting questions; and the position and weight given to patient and carer perspectives and the ‘other benefits and contextual considerations.’

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.

- (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.

- (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 deemed acceptable by regulators and in the context of these being ultra-orphan products we believe some uncertainty is reasonable and expected.

(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.

2. 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.

Patients and their families drive everything we do. This response draws on conversations with patients and carers with whom we are in everyday contact. In addition, we are including information from survey-based research we conducted with hATTR patients and carers in Spring 2018. 101 patients and 51 carers provided information about their experiences, the impact of the disease on their lives and their goals and concerns about treatment. In parallel, we held two online focus groups and telephone interviews with patients and carers to explore

aspects of this topic in more depth. The research was not limited to US patients, although two-thirds of the participants were from the US.

A copy of the report (unpublished) has been provided to ICER.

A summary of some of the key points that we consider should be given additional weight within the value assessment framework are set out below. In particular, we would like to see greater emphasis given to these points in Chapter 5 and, where relevant, these factors reflected in (rather than independently of) the conclusions on ‘net benefit’. Currently Chapter 5 has very limited information and we think it understates the importance of very key other benefits and contextual considerations. Please see specific comments below in relation to the generic potential benefits and considerations listed in Table 5.1 (page 59) and the subsequent discussion in the draft report (page 60):

(i) This intervention will significantly reduce caregiver or broader family burden.

The report states that ‘although 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.

(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.

(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.

- (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.

- (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 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.

- (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.

- (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-term risks of doing nothing have the potential to be greater.

- (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 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.

3. Comparative clinical effectiveness- draft voting question 3

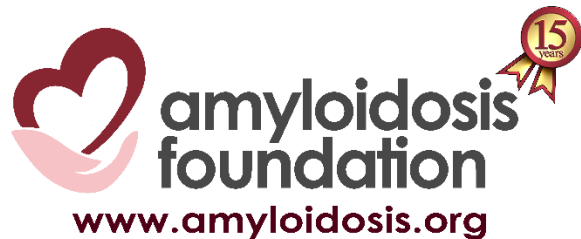
As detailed in our response section 1.iv above, we feel that it is inappropriate to compare the clinical effectiveness between inotersen and patisiran and as such the comparative clinical effectiveness draft voting question 3, “Is the evidence adequate to distinguish the net health benefit between inotersen and patisiran when added to best supportive care?” is an inappropriate question to ask at this point in time.

Conclusion

We recognise the challenges associated with evaluating drugs at such an early stage. As mentioned in our previous responses, we believe this review may be premature based on the degree of uncertainty ICER considers there to be and would reiterate our suggestion to postpone completion of the review to enable further data, including real-world data, to be provided.

Should ICER decide against this, ARC would encourage ICER to review aspects of the report, mentioned here, related to certain clinical effectiveness interpretations and to the key ‘other benefits and contextual considerations’.

This will help ensure that the report’s conclusions provide the strongest possible foundation for fair negotiation on price and timely, equitable patient access.



August 16, 2018

To Whom It May Concern,

We write to submit our comments regarding the draft Evidence Report “Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value.” Our perspective comes from patients and their families experiences with this disease. 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.

Autonomic neuropathy is a condition that results from damage to the nerves that assist in organ function. With the degradation of this system, patients can develop constipation alternating with diarrhea, nausea and vomiting, erectile dysfunction and incontinence. Imagine waking up to find that you have lost control of your bowels.

Polyneuropathy begins with the tingling of the toes and slowly progresses upwards. Carpal tunnel is common. Foot drop, wrist drop and disability of the hands and feet can develop leading to difficulty in walking and performing fine hand movements. A musician who can no longer play the guitar, a secretary that can no longer type, a person confined to a wheelchair.

Cardiomyopathy may be the predominant feature for some hATTR patients or may develop after the onset of neuropathy leading to progressive heart failure. The amyloid proteins build up on the heart walls making it difficult for the heart to function. With decreasing heart function continuing, kidney dysfunction can occur which can lead to the need for dialysis.

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 span is a greatly needed advancement.

Respectfully,
Mary E. O'Donnell
President/CEO

Thank you for the opportunity to comment on this report. We feel that it does a very good job of pulling together and evaluating information on both clinical and cost effectiveness of these new treatments. We have learned from it and have a better understanding of the issues than we did previously. Our combined backgrounds (patient as a clinical nurse specialist, supporter doing basic and applied research, and systems engineering including financial analysis) have been helpful in learning about clinical and financial aspects of dealing with this disease.

As a patient and a supporter we have dealt with hATTR for 17 years since symptoms first appeared and 15 years since a diagnosis was confirmed by Congo red staining of ocular vitreous. Among those afflicted by this disease we have been very fortunate, starting with referral to a retina specialist who had seen one case of amyloidosis and suspected it again. We experienced

- Progressive ocular involvement that required nine surgeries (three vitrectomies, two cataracts, four tube shunts) and expensive glaucoma medication to retain marginal vision.
- Slow progression of peripheral neuropathy (mainly carpal tunnel syndrome, CTS) that has been managed so far by wrist braces at night to prevent numbness leading to pain.
- Gastrointestinal symptoms and spinal stenosis that may be caused by amyloid deposits that have been moderated by diet, fiber supplements, exercise and positioning learned through physical therapy (PT).
- Participated in diflunisal (24 months) and inotersen (54 months so far) clinical trials after meeting the minimal qualifications for peripheral neuropathy.
- Sadly witnessed the arrival and departure of many patients and caregivers at meetings of the Amyloidosis Support Group (ASG). Recently we have been excited to see instances where these medications have stabilized or even improved the condition of those fortunate enough to join the trials. Many others unable to get into the trials continue to deteriorate and die.

As a patient I belong to a small subgroup of hATTR patients whose disease burdens and concerns are greatly underreported. Even 15 years after diagnosis my disease still primarily affects my eyes, and though this is not itself life-threatening it has major impacts on day-to-day functioning, quality of life and finances (covered later). Many other patients develop eye problems later on top of serious neuropathy, cardiac and other systemic organ issues. They then are likely to follow a course similar to mine, perhaps even faster, including

- Vitreous amyloid floaters, from mutant TTR locally produced in the retinal pigment epithelium. These seemed innocuous at first, but over about 18 months became cobwebs that degraded my vision enough to justify a vitrectomy. Thanks to my retina specialist a biopsy was done on the vitreous that confirmed amyloidosis. Tests at Boston University quickly confirmed that it was the inherited form, variant Val30Met, either from my late mother or from a spontaneous mutation.
- Within another three years I needed cataract surgery on the affected eye as well as a second vitrectomy to address further clouding and degraded vision from recurring amyloid deposits.

- My intraocular pressure gradually rose as amyloid clogged the eye's outflow channels. Glaucoma drops controlled the pressure for a while but 16 months after the second vitrectomy, even taking five different types of glaucoma drugs was insufficient. Surgery was done to add a tube shunt, then another cycle of rising pressure and adding the five glaucoma drugs took place, so a second tube shunt had to be added barely two years later.
- My other eye went through a similar cycle of surgeries and glaucoma drugs starting five years after the first eye and progressing leading to a second tube shunt even faster.

Normal healthy eyes are already very delicate and each surgery brings increased risk of many complications. Mine have included a torn retina, a painful pressure spike to over 50, recurrent retinal macular edema, permanent retinal damage/scarring, optic nerve damage leading to permanent vision damage, dry eye, blepharitis, decreased peripheral vision, and impaired depth perception. These problems have led to increasing limitations on daily activities such as driving and to curtailing small detail work for my silversmithing jewelry business. I have also suffered several falls due to my vision problems, but fortunately have had no serious injuries yet.

Although my eye pressures remained stable for more than four years, recently one eye pressure has gradually become very low, leading to other problems including blurred vision. In this eye I have amyloid floaters clouding vision as well. However, my doctors strongly recommend against additional surgery because of the high risk of more complications. Furthermore, in the future if I need another glaucoma surgery in either eye, I will face the choice of risking blindness from glaucoma or from other complications after surgery.

All these eye problems led to frequent visits with my four eye specialists (retina, cataract, glaucoma and cornea). It is stressful, often scary, time consuming and costly as finding or educating doctors about ocular amyloidosis is difficult and these experts are rarely local.

Thus far I have been very fortunate to have overall mild neuropathy (CTS) and no cardiac issues yet. I am thankful to be able to do all my self-care activities with help from my husband/supporter to deal with the vagaries of insurance, billing errors, the science of the treatments and free me from many household duties. The CTS has waxed and waned, at times being very painful at night, interrupting sleep significantly. Fortunately it improved with better fitting wrist braces over the past two years. Even with this I must sleep on my back or experience numbness in hands and arms.

I was fortunate to qualify for the diflunisal trial starting in 2009 and then the inotersen trial in 2014 after the thresholds for participation were lowered further. I received diflunisal during the double blind part and strongly believe that I received inotersen during the double blind part of the trials. Thus I have received the drugs for 6.5 of the last nine years, which may account for much of the slow progression of my systemic symptoms including CTS. Although my trial participation was largely uneventful I experienced adverse events (AEs) during the inotersen trial

- For the first two years I had mild injection site AEs that came more often in the third year. These included rashes/itching on my arms and once on my legs, and transient tired achy feelings overall. These intensified in the fourth year (third year of the extension) so that I

had several observed doses and additional lab work. The intensification, observations and lab results led to a protocol change so I now take two half-doses per week following pre-medications. This has stabilized these AEs to a very mild level.

- One test in the trial protocol, an electro-retinogram (ERG), once caused a painful corneal irritation reaction leading to multiple follow-up cornea visits and days of blurry vision.
- My experience points to the need for dose titration to body weight, as apparently was done in the patisiran trial. At about 117 pounds and BMI of 21 I probably would have had significantly fewer or milder AEs with a smaller single dose.
- Taking two half-doses also is wasteful of the drug and other supplies, as well as my time.

Your discussion of results in terms of clinical significance clearly shows the strong evidence for the effectiveness of patisiran in the data on mNIS+7 and Norfolk QoL, especially the real improvement in these metrics for patients on this drug. This corroborates what we have heard from friends who were in that trial and felt significant progress in their condition over the last four years. This is very good news to patients and Alnylam's plans to trial a subcutaneous injection approach later this year is encouraging as that treatment should be less disruptive to lives than intravenous infusion.

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 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.

One final thought on clinical effectiveness: Whole genome sequencing should be valuable to improve understanding of why patients respond to drugs or progress in their disease at very different rates. As the current cost of \$1,000 crashes toward \$100 with progress by Illumina and others, this should be part of everyone's thinking about this and other inherited diseases.

We understand that ocular amyloidosis receives little attention in this document because neither patisiran nor inotersen is likely to reach the areas in the eye where the mutant proteins in ocular

hATTR are produced. However, ocular amyloidosis is a big part of the base case costs, both medical and societal, and may not be adequately represented in your cost analyses. Some key observations from our experiences include

- The surgery costs, including facility charges, are substantial although often largely covered by excellent insurance, and should be part of your medical cost base case.
- Surgeries to delay serious vision problems and blindness make the eye vulnerable to other costly problems. The cheap generic drug treatments of glaucoma such as timolol cause irritation and eventual damage to the cornea, necessitating preservative-free drugs such as Timoptic ocudose that are much more expensive and rarely part of drug formularies. Add Restasis to improve tear production and the cost of drugs for the eyes can exceed \$10,000 per year. Much of this should be part of your medical cost base case
- The impacts of declining vision on ability to work, function independently, and enjoy many aspects of life are substantial and should be part of your societal cost base case.
- We noted that some research has shown that tafamadis penetrates the ocular vitreous to a small degree and might slow the progression of ocular amyloidosis. This enhances the case for patients with ocular involvement and would increase your medical cost base case.

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 note some financial impacts of the likely pricing of these drugs on patients and their families

- Alnylam apparently has cited a list price of \$450,000 per year that “after mandatory government discounts” will result in an average net price of about \$345,000. (Reuters staff report August 10, 2018) This is affordable to perhaps 0.1% of US families, i.e., to about 3 of the projected 3,000-3,500 patients with hATTR polyneuropathy in the US.
- Given the average ages of all patients in the trials of about 61 years and that US patients tend to be late onset, the largest block of US patients will be covered by Medicare or Medicaid. The best case for patient cost of these drugs is that at least one is covered by at

least one Medicare D plan, at either tier 4 or 5. The first month will exhaust the \$5,000 out-of-pocket expense that puts a patient into the catastrophic phase, and 5% of the remaining cost adds almost \$15,000 more (assuming ICER's \$300,000 cost) for a total of \$20,000 per year just for this drug. This alone is about 1/3 of the median US household income (Census Bureau 2016) and is in addition to the patient's share of the high base case amyloidosis medical costs plus other medical costs. Even households marginally in the top 10% of incomes in the US would be spending over 15% of their income on just this drug. The ICER Value Framework cites the threshold for individual willingness to pay of 2X annual income for the course of treatment. This implies that even in this best case little more than 10% of US households might be willing to pay the out-of-pocket cost of these drugs.

- A possible silver lining to these prices in that IF and WHEN (both big issues) inotersen or patisiran is covered by a Medicare D plan, other drugs in that plan will get catastrophic pricing. We might save \$4,000 on other drugs when spending \$20,000 more for inotersen or patisiran. Of course our reduced cost would come from the drug maker subsidy so the makers of all our drugs are likely to raise their prices even higher to maintain profits.
- For those who can't afford inotersen, patisiran or tafamadis, i.e., near 90% of US patients, diflunisal may be preferred, despite its risks as an NSAID, because it's affordable and has shown significant effects in slowing progression of neuropathy. (But many older patients also suffer from osteoarthritis or other inflammatory diseases and take more effective NSAIDs for these conditions, which should be stopped while taking diflunisal.) Contrary to your report, of our 22 New Jersey Medicare D plans diflunisal was not covered by eight plans, none covered it as tier 1, three as tier 2, five as tier 3 and six as tier 4. Diflunisal would cost us \$25/month in the initial and gap phases. It should meet your cost effectiveness tests in terms of cost/QALYs gained, but has not been approved by the FDA for amyloidosis and thus is not accepted by Medicare for this purpose!

To close these comments we note our main fears as we view our future dealing with hATTR

- As we age and natural healing slows down, the disease will progress more rapidly and we will suffer more systemic problems and decline into total blindness.
- Our children may have inherited this disease and will face similar burdens or worse. Their hope may be that when exclusivity expires in 2038 the drug costs might fall.
- It will take years to negotiate insurance coverage and bring the patient's share of costs to marginally affordable levels, leading many patients to further decline and early death.

Thank you again for sharing this information and providing an opportunity to comment on it.

Sincerely yours,

LGP and JSP

ATTRwt Patient Comment on Inotersen
Submitted August 15, 2018
V. Clayton Sherman

The ICER Draft Evidence Report of July 20, 2018 comparing Patisiran and Inotersen arrived at some points of view differing markedly from my experience as a patient taking Inotersen. Differences may have to do with length of time on drug, data measures, and my case type. The Report focused primarily on these drugs effects on hATTR in polyneuropathy patients, but its scope gave little insight to cardiac manifestations, a limitation in part caused by the studies designs that focused primarily on neurologic impacts. My comment is intended to enlarge the scope of consideration of Inotersen as having efficacy for cardiac TTR, whether familial or wild type.

Case Report

A. History: Initially diagnosed with hypertrophic cardiomyopathy, I was placed on amiodarone but had progressive arrhythmia and was finally diagnosed as ATTRwt by cardiac biopsy at Mayo Clinic in April 2014. I was placed on Diflunisal and Doxycycline with no noticeable improvement.

In December 2014 I was the 4th patient admitted to Dr. Merrill Benson's (Indiana University) investigator initiated study of Inotersen, giving me 3 years and 8 months, a substantially longer period than the studies compared in the Draft Evidence Report. In the study, in which all participants received product, I self-administered weekly subcutaneous injections of 300 mg of Inotersen. No other supplemental therapies or drugs were used.

B. Measures: In addition to the schedule of measures called for in the study design my Mayo cardiologist and I decided to institute more frequent measures to get a better serial picture of how the disease and its impacts were tracking. Example: Biomarkers were tracked monthly instead of every six months, and both Mayo and Indiana University data streams were checked for consistency (data charts below).

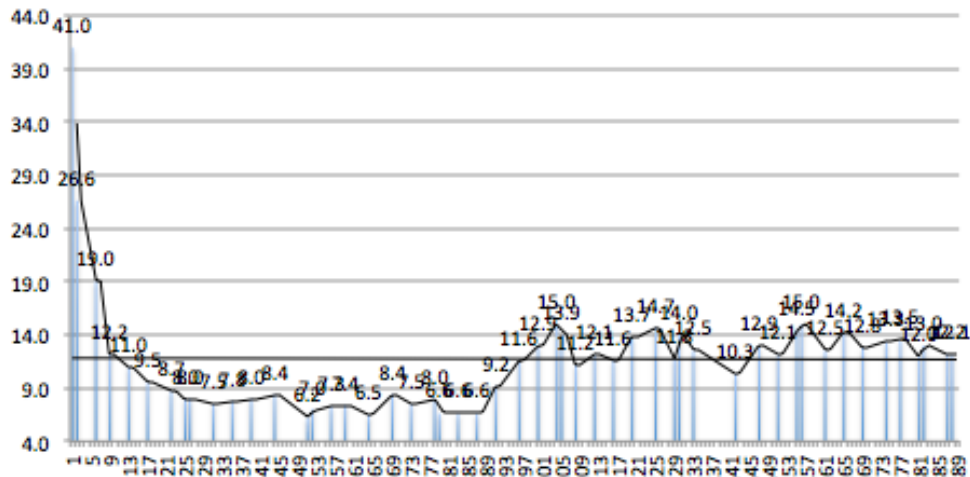
C. Continuing disease impacts in first two years: Even though I had begun taking Inotersen my overall condition worsened requiring a pacemaker, an AV node ablation, and cardiac resynchronization in 2015-16. Low energy was a common event. The drug was not able to immediately stop the momentum of the disease, a picture that began to turn in 2017. Over the last 18 months there has been noticeable improvement in energy and function.

D. Biomarkers

- TTR baseline 41.0, currently ranging 12-14, approximately 71% knockdown
- Troponin T baseline 26.6 mg/dL, currently <10 (normal). Note several higher peaks during disease momentum issues prior to last 18 months.
- NT-proBNP baseline 1717 pg/mL, currently 1647. Again, note several higher peaks during disease momentum issues.
- Using Mayo's Dr. Martha Grogan's staging system my classification is Stage 1, demonstrating that biomarkers have not significantly progressed.

TTR - prealbumin - IU/Mayo

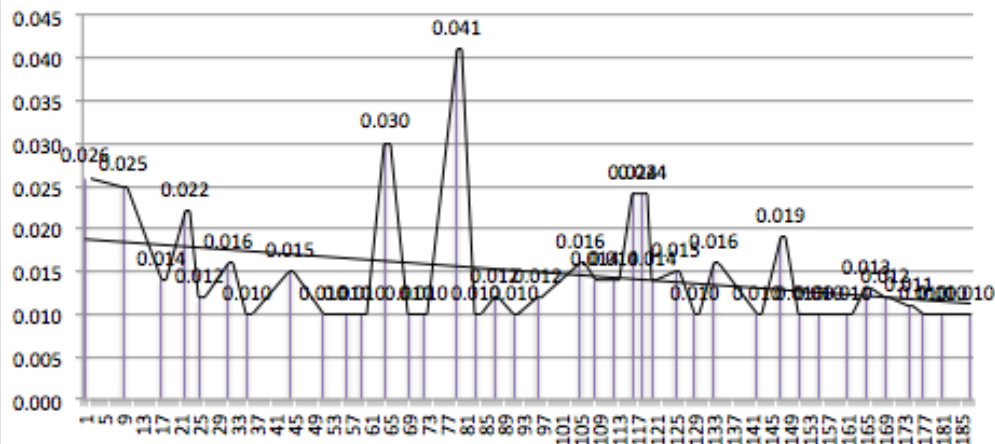
Normal = 18-36 mg/dL



Troponin T - IU/Mayo

Normal < or = 0.01 ng/mL

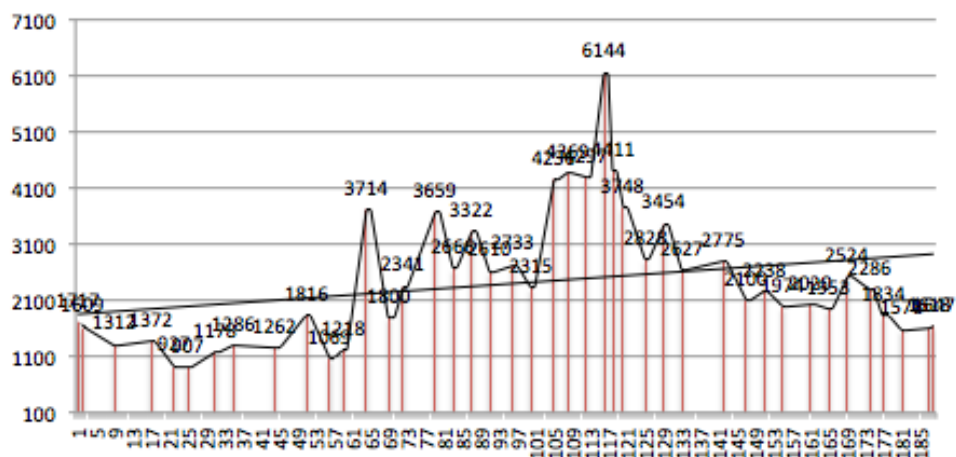
Grogan > 0.5 increases stage risk



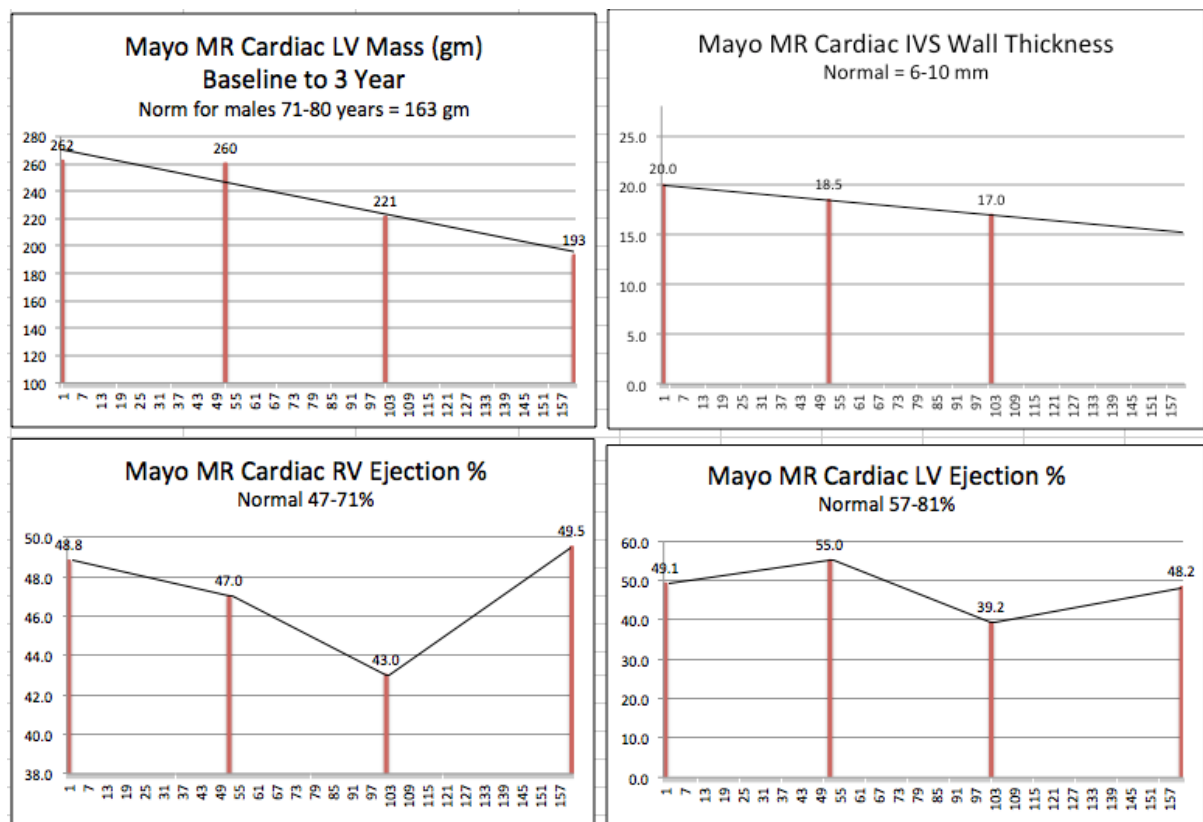
NT-ProBNP - Mayo

Normal < or = 107 pg/mL, 300 pg/mL in elderly

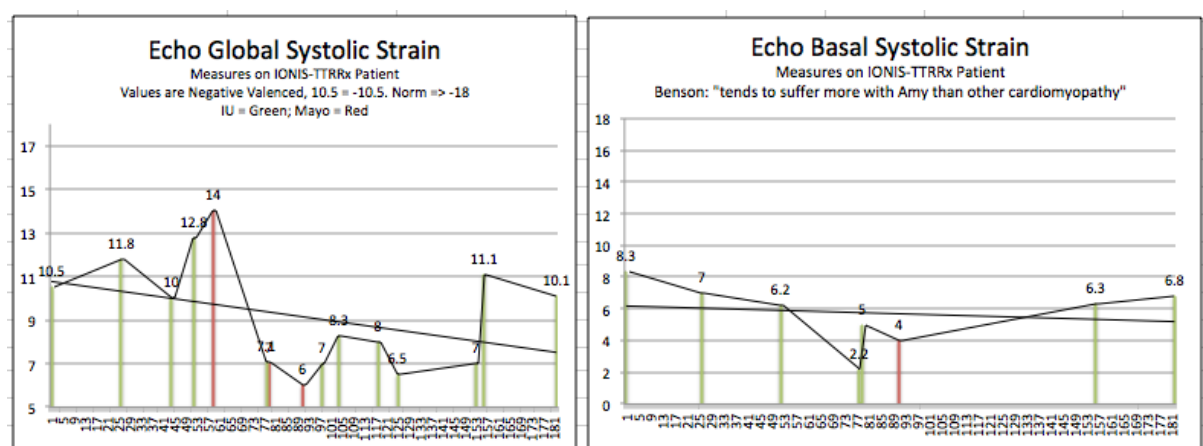
Grogan > 3000 increases stage risk



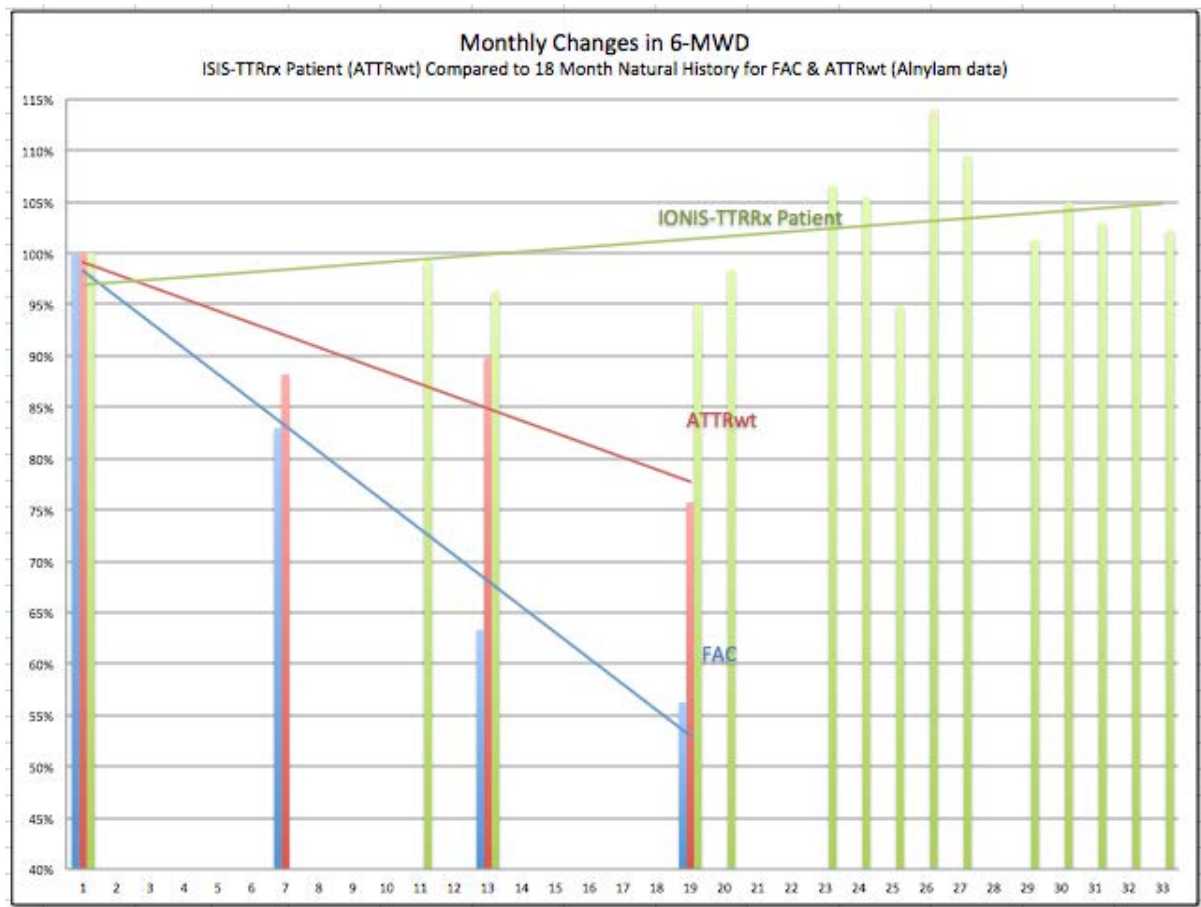
E. Cardiac MR Findings. MR shows stabilization in year one with no increase in LV mass, and sizable reductions in years two and three suggesting regression. Mayo researchers who have looked at this data postulate natural clearance of amyloid. By Inotersen substantially reducing the creation of new amyloid, the body's own phagocytic action may be occurring. Projecting further reduction of mass at 30-40 grams/year suggests that LVM may be back to normal by end of 2018.



F. Echo findings show similar ejection fraction, mass and thickness improvements as to MR, but also reveal improvements in strain over the last year and a half.



F. Function. Using the 6 MWD test my case shows no substantial deterioration. Baseline of 414.5 meters/6 minutes vs. 424 meters at 3 years. The chart expresses this as a percent of baseline and compares it to an Alnylam research natural history study showing deterioration rates for FAC and ATTRwt without treatment over 18 months.



G. Adverse Events. No AE or other issues arose taking the drug. I was monitored weekly for platelets and every six weeks for Creatinine/Urine Protein. All values were normal.

Discussion

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 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.



August 17, 2018

Steven D. Pearson, MD, MSc, FRCP
President
Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109 USA

RE: Draft Evidence Report “Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value”

Dear Dr. Pearson:

Patients Rising Now advocates on behalf of patients with life-threatening conditions and chronic diseases for them to have access to vital therapies and services. Access is a matter of survival for those patients, and it spans affordability, insurance coverage, and physical access. To support improved access, we are committed to engaging patients, caregivers, physicians, media, health policy experts, payers, providers, and others to foster realistic, patient-centered, solution-oriented discussions for particular conditions and the entire U.S. health care system. That is, our goal is to advance a balanced dialogue that illuminates the truth about health care in a just and equitable manner.

We appreciate the opportunity to provide our comments on ICER’s July 20th Draft Evidence Report, “Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value.” As the Draft Report articulates, amyloidosis is a complicated disease, and focusing on a hereditary sub-type of a rare condition both further specifies the condition and pathology, and reduces the patient population. Such rare diseases present patients and clinicians with clinical challenges. As the Draft Evidence Report describes, there are now at least two new compounds expected to be approved by the FDA for this patient population. Our specific patient-focused comments about this Draft Report encompass both the complexity of treatment as well as ICER’s approach and analytical methodologies. Our concerns are expressed in the following major sections: Patient Perspectives; Data Uncertainties and Assumptions; and Humanistic Perspectives on ICER’s Approach.

Patient Perspectives about Amyloidosis

As ICER’s draft report notes, “hATTR spans a spectrum of clinical presentations,”ⁱ and the “natural history of the illness also varies according to patient sex, geographic region, and genotype.”ⁱⁱ The Draft Report also describes the natural, downward progressive course of the disease, which for patients and their families is reality of great concern. Thus, this is certainly a medical condition where individualization of clinical decisions and patient-clinician coordination, communications, and shared decision making are needed.

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]oncerning, 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.”ⁱⁱⁱ 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.

For a rare disease like amyloidosis we believe that incorporating all information into assessments of utility is particularly important because, while the data clearly shows clinical benefits, the small numbers of individuals in the clinical trials means that there is less certainty about the findings and a less robust information repository for guiding individual patient decisions. That is, as with all rare conditions, there is less clinical experiences to help clinicians and patients in their shared decision making for individual patient circumstances. In addition, without head-to-head trials it is very hard to determine the comparative effectiveness of the two medicines. As one analyst noted, “the studies had different patient characteristics, different endpoints, and so on. Consequently, there are limits on the conclusions that can be drawn from the data.”^{iv}

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.^v 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. 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.

And lastly, in a previous letter^{vi} 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.

Data Uncertainties and Assumptions

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.^{vii} Specifically, tafamidis has been given breakthrough status from the FDA,^{viii} and the FDA gave the company another complete response letter in June 2018.^{ix} 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 net cost of those two medicines. This scenario has been described by analysts^x 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.^{xi} 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 tafamidis, and be given a more robust treatment, particularly concerning the effects of market competition from multiple treatment options on any cost projections.

Humanistic Perspectives on ICER's Approach for Rare Diseases

In constructing its value framework, ICER makes the overt assertion that health care spending in the United States is a serious problem, and that reducing the increase in spending – particularly for new treatments – should be brought down to close to the growth in the annual GDP. As we hope ICER's leadership recognizes, this is not a new assertion. Not only were national spending and affordability driving forces behind the creation of the Affordable Care Act, and more recently Federal rules regarding non-ACA compliant insurance products (Short Term and Association Health Plans), but it was also a factor for the health reform legislation in Massachusetts, the Health Security Act proposed by President Clinton, as well as many other governmental initiatives going back decades, including the creation of Medicare and Medicaid in the mid-1960, which specifically were driven by the problems of the elderly and poor affording health care. The data and historical record are very informative. For example, in the early 1970s when the U.S. spent about 7% of GDP on health care (which is now close to 18%), this statement was made to Congress: "All of these efforts were directed toward our goal of reducing the previous 7.7 percent annual price increase in total health care costs to half of that level, 3.85 percent this year. These actions should buy us some time. But they are, at best, a temporary tourniquet on health care price inflation. We must now direct our energies, attentions and action to the long-range factors affecting the cost, the quality and the availability of medical care."^{xii}

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.^{xiii}

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.

This leads to another problematic aspect of ICER’s approach, which is the inherent tension between its economically based analyses and its assertion of the “ethical vision inherent in ICER’s work,”^{xiv} which was “founded over 10 years ago with an ethical goal in mind.”^{xv} This tension was explored in a recent article about humanitarianism and economics, which observes that economics “has three systematic biases: it ignores the role of culture, it ignores the fact that ‘to understand people one must tell stories about them,’ and it constantly touches on ethical questions beyond its ken. Culture, stories, and ethics are things that can’t be reduced to equations, and economics accordingly has difficulty with them.”

Another aspect of this inherent tension is the dynamic nature of values and ethics. For example, the Pope’s recent declaration that “the death penalty is inadmissible because it is an attack on the inviolability and dignity of the person”^{xvi} is clearly a change of ethical position, and one that is not shared globally, nor even across the 50 United States. And of course, historically, the death penalty was seen as a norm for various crimes as well as assertions, such as witchcraft. Similarly, the current debate about requirements for work, education, or training for people receiving Medicaid or SNAP benefits reflects a potential shift in ethical perspectives in the U.S. Those are two recent examples from years of ethical changes across geographic and cultural realms. Thus, we are very concerned that the fundamental premise for ICER’s work having an ethical basis while heavily emphasizing economic and quantitative analysis, which we assert is inherently a contradiction. That is why we would encourage ICER to embrace more expansive and humanistic approaches to understanding value, and communicating it to stakeholders.

Additional Notes:

- Health care is two words. In this report it is one word. In previous reports it was two words.
- 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) 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.
- 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^{xvii} then this figure should be corrected. And second, the new rules about reimbursement for many 340B hospitals reduces reimbursements to ASP minus 22.5%^{xviii}. Thus, there should be changes to the calculations of patisiran costs.

Conclusions & Recommendations

Patients Rising Now believes that ICER's draft report on some treatment options for a subpopulation of people with amyloidosis inadequately reflects patients' perspectives, and it underplays the level of uncertainty of the information about the condition and potential treatments, leading to conclusions that appear overly precise. The Draft Report also continues ICER's oversimplified aggregation of economics and ethics in a manner that is both obfuscating and confusing rather than clarifying. The U.S. health care system is criticized for many things, but we should not add to the list that it sacrifices individual care goals and patient-clinician relationships to satisfy visions of societal uniformity or economic cost-effectiveness.

Sincerely,



Terry Wilcox
Co-Founder & Executive Director, Patients Rising Now

ⁱ Draft Evidence Report – Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis, p1

ⁱⁱ Draft Evidence Report – Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis, p2

ⁱⁱⁱ Patient's Rising Now Comment Letter on ICER Draft Evidence Report "Modulator Treatments for Cystic Fibrosis: Effectiveness and Value," April 12, 2018

^{iv} <https://www.biospace.com/article/alnylam-emerges-as-winner-in-rare-disease-study-showdown-with-ionis/>

^v Draft Evidence Report – Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis, p. 27

^{vi} Patient's Rising Now Comment Letter on ICER Draft Evidence Report, "Modulator Treatments for Cystic Fibrosis: Effectiveness and Value," April 12, 2018

^{vii} <https://www.fool.com/investing/2018/04/02/why-pfizers-big-win-is-bad-news-for-alnylam-and-io.aspx>

^{viii} <https://www.pfizer.com/news/press-release/press-release-detail/fda-grants-breakthrough-therapy-designation-for-tafamidis-for-the-treatment-of-patients-with-transthyretin-cardiomyopathy-1> and <https://www.nejm.org/doi/full/10.1056/NEJMe1805499>

^{ix} <https://www.pfizer.com/news/press-release/press-release-detail/fda-issues-complete-response-letter-for-pfizer-s-tafamidis-meglumine-new-drug-application>

^x <https://www.fool.com/investing/2018/04/02/why-pfizers-big-win-is-bad-news-for-alnylam-and-io.aspx>

^{xi} <https://www.forbes.com/sites/johnlamattina/2018/05/23/new-drug-costs-are-still-high-but-putting-prices-in-tv-ads-offers-little-value/>

^{xii} Special Message to the Congress on Health Care, March 2, 1972 <http://www.presidency.ucsb.edu/ws/?pid=3757>

^{xiii} <https://www.bls.gov/cex/csxreport.htm>

^{xiv} <https://icer-review.org/final-vaf-2017-2019/>

^{xv} <https://icer-review.org/patient-participation-guide/>

^{xvi} <https://www.cnn.com/2018/08/02/europe/pope-death-penalty-intl/index.html>

^{xvii} Draft Evidence Report – Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis, Tables 3.2 and 3.5

^{xviii} <https://www.idsupra.com/legalnews/cms-proposes-more-payment-changes-for-75612/>

August 17, 2018

To the ICER committee,

As representatives of Optum's Patient Insights division, we are writing this letter in response to ICER's Draft Evidence Report "Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value" dated July 20th, 2018. 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 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.

Burden of disease – generic health-related quality of life

Generic health-related QOL was measured in the NEURO-TTR trial using the SF-36v2, a self-reported measure that was administered at baseline, week 35, and week 66 of the trial. Baseline SF-36v2 scores were analyzed for the purpose of interpreting burden of disease.

The SF-36v2 is a 36-item patient-reported outcomes measure that captures eight domains of generic health-related QOL: physical functioning, role limitations due to physical health problems (role-physical), bodily pain, general health, vitality, social functioning, role limitations due to emotional health problems (role-emotional), and mental health.¹ Responses to constituent items for each domain are used to compute *T* scores for domains, which have a mean of 50 and a

standard deviation of 10, and are standardized using a normative general population sample. Scores on all eight domains are weighted and summed to produce global scores of physical QOL (the physical component summary [PCS]) and mental QOL (the mental component summary [MCS]), which are also represented as norm-based *T* scores.

Because the SF-36v2 is a generic measure, it can be used to capture health-related QOL for a general population or any disease population, and because SF-36v2 scores are expressed as norm-based *T* scores, it is possible to make comparisons of scores between a sample of patients with a certain medical condition (e.g., hATTR amyloidosis) and a general population sample, or between a sample of patients with one medical condition and a sample of patients with a second medical condition. When comparing untreated patients with a medical condition to these benchmark samples, one is able to put into context the burden of that medical condition on QOL relative to the general population or to patients with those other medical conditions. This is especially true when matching these benchmark samples to the age and gender distributions of the medical condition sample.

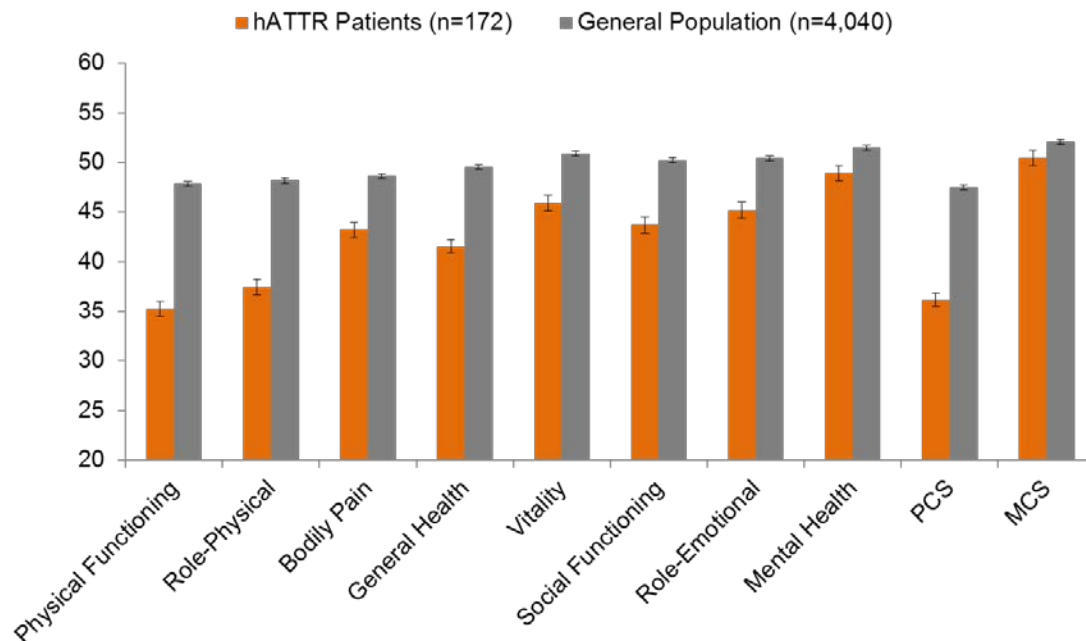
As described in a poster presented at the 2018 annual meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR),² we compared baseline SF-36v2 scores from patients with hATTR amyloidosis in the NEURO-TTR trial (n=172) with scores from an age- and gender-matched United States (US) general population normative sample (n=4,040). We also compared patients' scores to samples of patients who self-reported each of the following medical conditions that share some clinical manifestations with hATTR amyloidosis: congestive heart failure (CHF; n=137), Crohn's disease (CD; n=2,059), diabetic neuropathy (DN; n=5,682), irritable bowel syndrome (IBS; n=321), and multiple sclerosis (MS; n=1,901). The general population sample included participants in the 2009 QualityMetric Norming Study (QMNS). The QMNS was an online survey that used probabilistic sampling from the US non-institutionalized general population. Benchmark CHF and IBS samples were subsets of the QMNS sample who self-reported having those conditions. Benchmark CD, DN, and MS samples were subsets of participants from the 2015 and 2016 (pooled) National Health and Wellness Survey (NHWS) who self-reported having these conditions. The NHWS is an international health outcomes survey conducted annually by Kantar Health. Only US respondents to the NHWS were included in this burden analysis.

To conduct the burden analysis, scores from each benchmark sample were weighted based on a regression analysis that matched the age and gender distribution of the hATTR amyloidosis sample in the NEURO-TTR study. Then, univariate analysis of variance (ANOVA) models tested for statistically significant differences (burden) in SF-36v2 scores between the patient sample and each benchmark sample.

Results from comparisons of SF-36v2 scores between the NEURO-TTR sample at baseline and the general population sample are presented in Figure 1. The magnitude of burden (i.e., deficits relative to the general population) were observed for all domains and both summary scores,

although the burden is particularly large for physical functioning, role-physical, and general health domains, as well as the global physical summary. These data show that the health-related QOL of patients with hATTR is far below that of the general population, especially for physical aspects of QOL.

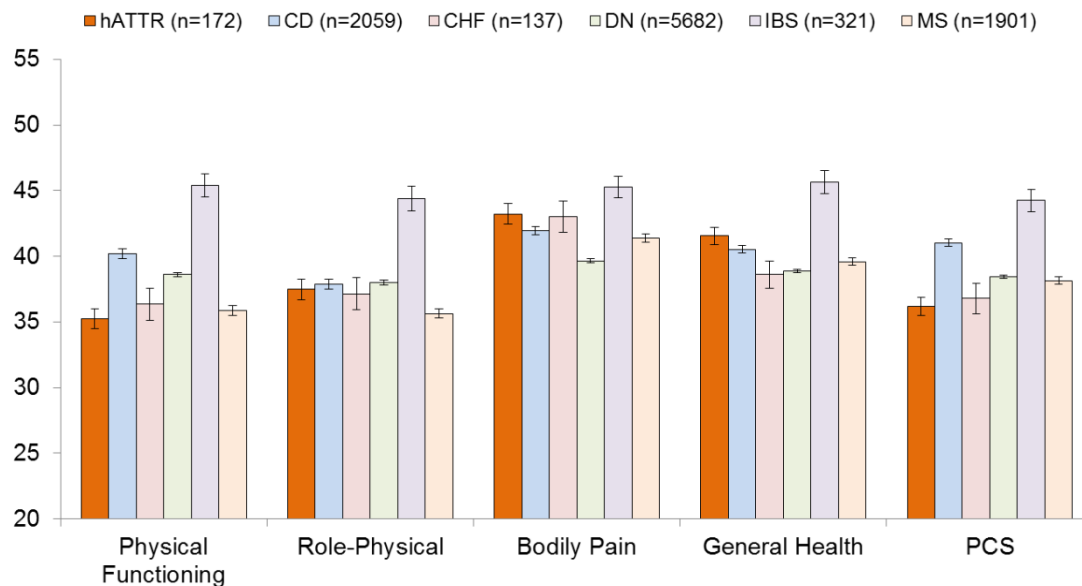
Figure 1. Mean SF-36v2 scores for hATTR patients and the age- and gender-matched general population



hATTR, hereditary ATTR amyloidosis; MCS, mental component summary; PCS, physical component summary
Error bars represent standard errors of means. Figure adapted from Lovley, Guthrie, Sikora Kessler et al²

Results from comparisons of physical-based SF-36v2 scores between the NEURO-TTR sample at baseline and from benchmark samples with other chronic diseases are presented in Figure 2. Scores for physical functioning and global physical QOL (i.e., PCS) were worse for hATTR patients than for CD, DN, and IBS benchmark samples, and similar to CHF and MS benchmark samples. Scores for role-physical and general health domains were worse for hATTR patients than for the IBS benchmark sample and similar to or better than that observed for CD, CHF, DN, and MS benchmark samples. Scores for the bodily pain domain was better for hATTR patients than for the DN benchmark sample, and similar to that observed for CD, CHF, IBS, and MS benchmark samples. Thus, these results show that the burden of hATTR amyloidosis on physical QOL is similar to that of other patient groups with established burden profiles, including CHF, DN, and MS.

Figure 2. Relative physical health burden: mean SF-36v2 physical-based scores for hATTR patients and the age- and gender-matched chronic condition benchmarks



CD, Crohn's disease; CHF, congestive heart failure; DN, diabetic neuropathy; hATTR, hereditary ATTR amyloidosis; IBS, irritable bowel syndrome; MS, multiple sclerosis; PCS, physical component summary. Error bars represent standard errors of means. Figure adapted from Lovley, Guthrie, Sikora Kessler et al²

Burden of disease – neuropathic-related quality of life

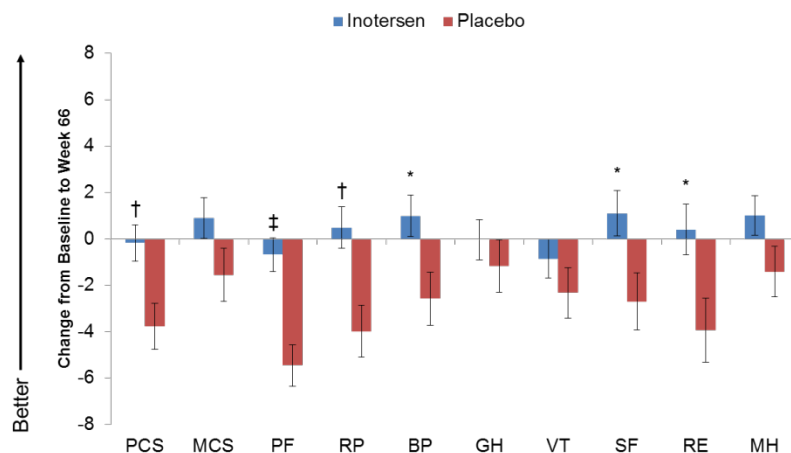
Neuropathic-related QOL was measured in the NEURO-TTR trial using the Norfolk QOL-DN, a self-reported survey that was administered at baseline, week 35, and week 66 of the trial. Baseline Norfolk QOL-DN scores were analyzed for the purpose of interpreting burden of disease.

As described in a poster presented at the 2018 annual meeting of the Academy of Managed Care Pharmacy (AMCP),³ we conducted an analysis in which we descriptively compared Norfolk QOL-DN total and domain baseline scores from the NEURO-TTR patient sample with scores reported by Veresiu et al⁴ for a large sample of patients with type II diabetes. Specifically, they reported scores from three subsamples: 1) patients with diabetes without DN (n=6,615); 2) patients with diabetes with DN but without a history of ulceration, gangrene, or amputations (n=10,704); and 3) patients with diabetes with DN and a history of ulceration, gangrene, or amputations (n=3,150). Results showed that Norfolk QOL-DN baseline scores from the hATTR amyloidosis patient sample in the NEURO-TTR trial were remarkably similar to scores from the third group, indicating that the neuropathic-related QOL burden for patients with hATTR amyloidosis matches that of patients with diabetes with DN and a history of ulceration, gangrene, or amputations.

Inotersen preserves generic health-related quality of life

As described in a poster accepted for presentation at the 2018 annual European meeting of ISPOR⁵, we analyzed treatment differences of change in SF-36v2 scores from baseline to week 66 in the NEURO-TTR trial. Changes in least-squares (LS) mean scores over this period for each condition, based on mixed-effect repeated-measures models, are presented in Figure 3. Inotersen preserved physical health-related QOL better than placebo: statistically significant differences were observed for physical functioning, role-physical, and bodily pain domains, as well as PCS. Inotersen preserved some aspects of mental health-related QOL better than placebo: statistically significant differences were observed for social functioning and role-emotional domains. Analysis of item level responses (not presented) found that at week 66, patients receiving inotersen were > 15% less likely than those receiving placebo to have substantial impairment in walking more than several hundred yards or climbing several flights of stairs.

Figure 3. Change in LS mean SF-36v2 scores from baseline to week 66 by treatment arm.



BP, bodily pain; GH, general health; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical functioning; RE, role-emotional; RP, role-physical; SF, social functioning; VT, vitality. * $p < 0.05$ † $p < 0.01$ ‡ $p < 0.001$. Figure adapted from Yaras, Sikora Kessler, Lovley et al⁵

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.

Sincerely, Aaron Yaras, PhD and Michelle K. White, PhD.
Optum, Patient Insights, Johnston, RI 02919 USA

References

1. Maruish ME. *User's manual for the SF-36v2 health survey*. 3rd ed. Lincoln, RI: QualityMetric Incorporated; 2011.
2. Lovley A, Guthrie SD, Sikora Kessler A, et al. The burden of hereditary transthyretin amyloidosis on health-related quality of life. *Presented at ISPOR Annual International Meeting*. 2018.
3. Yaras A, Lovley A, Guthrie SD, Pollock MR, Sikora Kessler A, White MK. Disease burden as assessed by the Norfolk Quality of Life Scale in hereditary transthyretin amyloidosis relative to diabetic neuropathy. *Presented at AMCP Annual International Meeting*. 2018.
4. Veresiu AI, Bondor CI, Florea B, Vinik EJ, Vinik AI, Gâvan NA. Detection of undisclosed neuropathy and assessment of its impact on quality of life: a survey in 25,000 Romanian patients with diabetes. *Journal of diabetes and its complications*. 2015;29(5):644-649. doi:10.1016/j.jdiacomp.2015.04.001.
5. Yaras A, Sikora Kessler A, Lovley A, Guthrie SD, Pollock MR, White MK. Impact of inotersen on generic health-related quality of life for patients with hATTR amyloidosis: results from a double-blind placebo-controlled trial. *To be presented at ISPOR Europe 2018 Meeting*. 2018.

August 16, 2018

Steven D. Pearson, MD, MSc

President, Institute for Clinical and Economic Review

Boston, MA, 02109 USA

RE: ICER Draft Evidence Report “Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value”

Dear Dr. Pearson,

We appreciate the opportunity to comment on the draft evidence report “Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value.”

Clearly there are challenges in modeling a condition for which data are so limited, and we commend the effort to do so. In the spirit of improving the model, we would like to raise several points.

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”¹, 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.^{2,3} In addition, we

¹ Institute for Clinical and Economic Review. Draft Evidence Report - Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value. Boston: Institute for Clinical and Economic Review; 2018 p. 41.

² Guthrie S, et al. Disease Burden of Hereditary Transthyretin Amyloidosis (hATTR): Analysis of Real-World Data. Poster presented at: AMCP Managed Care & Specialty Pharmacy Annual Meeting; 2018 Apr 23-26; Boston, MA.

³ Gurthrie S, et al. Healthcare Utilization and Cost Among Patients with Hereditary Transthyretin Amyloidosis. Poster Presented at: International Society for Pharmacoeconomics and Outcomes Research 2018; 2018 May 19-23; Baltimore, MD.

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.

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.⁴ Recall-based estimates consistently underestimate actual utilization, and the magnitude of the underestimate increases substantially with periods longer than 3 months.⁵ Consistent with this type of error, we estimated annual direct healthcare costs of \$51,140- \$77,548 across all disease stages.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 appreciate your consideration of these issues.

⁴ Schmidt H, et al. Impact of Hereditary Transthyretin-Mediated Amyloidosis on Use of Health Care Services: An Analysis of the APOLLO Study. Paper presented at: 16th International Symposium on Amyloidosis; March 26-29, 2018; Kumamoto, Japan.

⁵ Bhandari A, et al. Self-reported utilization of health care services: improving measurement and accuracy. *Med Care Res Rev.* 2006;63(2)217-35.

Sincerely,

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Concerned individuals at ICER:

The possibility of having Amyloidosis with no real treatments available has hung over my family for as long as I can remember. As a child I was determined to stay as strong and healthy as possible “just in case”. I watched my father go from a strong and vital young man to bed bound skeletal person barely able to lift his head and frustrated that he had to endure the pain and indignities of a horrible disease before he was even 50. My sister and I were terrified we might share his fate.

After bouncing from doctor to doctor during my 50s, trying to figure out why I had so many seemingly unconnected ailments including significant heart and breathing issues I was finally diagnosed in 2011 following a heart block that found me passed out on my kitchen floor. Fortunately, I woke up and was sped to the emergency room where they placed a through the neck pacemaker without anesthesia because of the necessity of speed to save my life. During the insertion of a more typical pacer two days later a cardiologist who had heard of amyloidosis had a hunch and performed a heart biopsy. The tissue was sent to Mayo and I was diagnosed with amyloidosis mutant type Glu454Gln.

Through amazing instances of luck and coincidence I found myself at Boston University’s Amyloidosis Center six weeks later where I was told I needed a heart and liver transplant and was referred to Johns Hopkins. Six grueling and exceedingly stressful months later, after every test I could imagine, Hopkins decided they would not do my transplants and referred me to Duke where I was transplanted on May 1, 2012. I live in Northern Virginia. It was exam week for my college freshman son! Fortunately, my hematologist oncologist brother-in-law and advanced practice oncology nurse sister both work at Duke and let me live with them for three months during my initial recovery. With the incredible care I have received from the Duke medical folks and the support of my family and friends along with my own determination I have done very well except that I have developed polyneuropathy and GI issues post-transplant.

My father died of this awful disease at 49 after being bed bound for several years and forced to take medical disability retirement in his early 40s. His version of this disease presented with significant polyneuropathy and GI issues initially. Mine did not. By the time of his death he could no longer turn himself in bed or lift even a cup for a drink of water. He was on opioids for GI issues and suffered severe pain. His doctors did the best they could with little knowledge or understanding of his disease. His illness, care, and death colored everything about my late childhood and teenage years. My aunt, his only sibling, lived to be almost 95 and had no children. Their mother, my maternal grandmother had been “healthy” until she died suddenly of a heart ailment at 60, about the age I was diagnosed. We now realize she must have had my presentation of amyloidosis. Dad had two first cousins on his mother’s side who died in their 40s with symptoms similar to his, one man and one woman. Evidently our type has no typical presentation or age or gender relationship but we do know it is very rare. When we passed our 40s my sister and I assumed we had avoided the disease. Obviously, we were wrong.

Until a few years before my diagnosis I, an architect, was an executive with one of the largest architecture firms in the US and enjoyed a wonderful career doing something I loved. I travelled often to our far flung offices and enjoyed travel to Europe with my family. In addition, my salary was far more than my husband’s and was an important part of our modest lifestyle that included our being able to send our two children to state colleges. In the year between my diagnosis and

transplants I became so disabled that I could not walk from my front door to my mailbox, about 50' away. The transplants saved my life but did not cure me of the disease which continues to progress. The stress of the emergency nature of the whole ordeal of my illness and transplantation had a tremendous effect on my family. My son experienced a first psychotic episode about a year after my transplants and through sheer strength of will was able to finish college, just barely, but has struggled with significant mental health issues since. My elderly mother who had nursed her husband, my Dad, through this disease was devastated and hopeless for me. My heart was destroyed and had to be transplanted and the only treatment for the disease at that time was liver transplantation. At least that allowed me to continue to live.

Like others have said, I feel that I am one of the lucky ones. I am followed twice each year at Duke but unfortunately, they are not experts about amyloidosis. I have the usual posttransplant issues with the side effects of the meds and immune-suppression but at least I am here. I did not expect to develop polyneuropathy post-transplant but I am now in the inotersen EAP at Johns Hopkins. Thank goodness for that program! In all of this I discovered that I have a much younger distant cousin also diagnosed with this awful hereditary disease and who is in the inotersen program at UNC.

I am beyond grateful for the work of the amyloidosis support groups and through them have been able to connect with experts besides those at Boston University but my local doctors in the Washington, DC area know very little about the disease. Diagnosis really did bring a devastating hopelessness and the prospect of transplant helped me imagine a future again but not a cure or even a possibility of stopping disease progression. Without the prospect of pharmaceutical treatments, I foresee a continued increase in my neuropathy and fear a fate similar to my father's. My GI issues already have a significant impact on my daily life. They have landed me in the emergency room with dehydration caused fainting spells and caused me to have a loop recorder implanted to monitor for a fib. I just had repeat carpal tunnel release surgery on both hands after first having it about 30 years ago, possibly an early symptom of amyloidosis. Several local hand specialists told me they could not help me with my carpal tunnel because they knew nothing about possible amyloidosis deposits. My balance issues caused me to fall in the shower two years ago and fracture my big toe significantly enough to require surgery. So far, I do not need a cane and I hope the inotersen will help delay that day. I have also had progressive hearing loss probably disease related and have hearing devices in both ears now. They are not covered by insurance of course.

My mother had a career in middle management in a small bank and was an exceptional money manager and my father's sister lived with us. They both took care of my father and hired in-house care for the hours when they both worked full time. My father's death was a relief he expressly hoped for and the lifting of a huge family care and financial burden from my mother and aunt. I do not know how we survived financially. I fear this for my own family too. We are fortunate that we had enough money saved to carry us through these past few years but given my inability to work since my transplants this is rapidly running out. Despite having good medical insurance through my husband's employer our portion of the cost of that insurance and our son's plus the increased co-pays for his and my medications have taken a real toll on us. I try not to think about the very real possibility of our running out of money soon much less imagine the time when my husband might retire. He cannot let himself think that he ever will.

Neither our daughter nor our son has been tested. Our daughter is anxious to do so as she is

married and considering children soon. Our son is in no emotional position to be tested quite yet given his mental health issues. Were there affordable pharmaceutical options available they would not need to fear knowing and could possibly start effective treatment early enough to be helpful. But the burden of knowing you have the mutation and yet have no options for treatment is too overwhelming for him. Our daughter's desire for healthy children pushes her past that fear of the possibility of finding out the worst. I sincerely wish their fears were unnecessary.

This horrible disease and the emotional burden of knowing you have it but have no real treatment is staggering on all levels. I remember that dark day for myself too well. The burden of dealing with the disease, the search for medical information and assistance, the travel to wherever you can find an expert or anybody who can help, the out of pocket costs for treatments and care, the practical burden of dealing with the disabilities it causes, the prospects of financial ruin and destitution in old age, and the paralyzing fear for our children makes it critical that those of us who suffer have access to and be able to afford any pharmaceutical treatments available. I implore you to use your influence to convince those who make the decisions to consider that it is one thing to develop a drug that helps those with this disease and another to make it available through both access and financial reasonableness to those who need it. We all struggle enough with the fact that there are so few physicians who know about the disease and can help us and the knowledge that this disease is so widely underdiagnosed. None of us can afford to let a potential treatment go un-used as well.

Sincerely,

RLA

Dear ICER,

I'm a 49-year-old female, who was identified as a carrier of the Ala-60 gene after my father was identified in the very latent phase of the disease process. It took him 10 years of attending NUMEROUS physician appointments, NUMEROUS test and multiple hospitals stays, to reach the verdict.... AMYLOIDOSIS. That was a very new word for our family at that time. He passed 18 months later., in 1991. He was 62 years old. His brother died at 56 years old. My uncle had passed out (hypotension) at the wheel of his truck, this resulted in a fatal car accident. He had never found out what was wrong with him before he passed away. My aunt, my father's sister, passed away at 53 years old. They all died with similar medical symptoms. My father lived long enough to be diagnosed. My grandmother lived long enough to bury all three of her children; my father, his older brother and younger sister. My grandmother died of a broken heart.

My father, was a strong man until he turned 50 years old. He worked. He traveled. He spent time with his family. About two months after he turned 50, he suddenly lost weight, had major bowel issues and became extremely tired. This quickly and aggressively progressed, as the untreated disease will do, ravishing his organs. This disease took a productive, big, strong, and active man to places he never deserved or wanted to go. He loved his job, he was forced to retire early because of the tiredness, the weakness, the bowel issues, the numerous physician appointments, the testing, and as it turned out, some unnecessary surgeries. In the last years of his life, he "existed". He had no quality of life. My mother had to stop working. She worked tirelessly to keep him at home providing for all his personal care needs. At one point, she had a broken ankle that resulted from trying to catch him during a fall (orthostatic hypotension) at home. He was unable to go anywhere, he slept most of the time, becoming so frail. It was very sad and "out of control" with no answers. She was devastated to watch the love of her life deteriorate. There was nothing she or we could do to stop it. His children had a front row seat to this, helping as much as we could during those years.

Having the gene? What is that like? I am now the oldest person on my father's side of the family at age 49 years old. My sister has also tested positive. She is currently asymptomatic at 43 years old. For me, it's like living with "my enemy". I watched what it did to my father, his brother and sister. They died so young. I am constantly aware that my enemy lurks in my blood waiting to wreak havoc on my organs at any time. Robbing me of the quality of life that my husband and myself have worked for. I wait in apprehension. I wait with dread. I wait scared, knowing that there is nowhere to hide. As I approach 50, I am constantly on the lookout for my enemy. A year ago, I randomly began to trip on my right leg. This has progressed. I currently trip approximately 4-5 times weekly on my right leg. Sometimes on my left, but mostly on my right. I have also developed numbness and tingling in my feet and hands. My feet no longer know the temperature of water. My feet actually don't know that they are in water at this point. It is a constant reminder that my enemy is there. My enemy waits, teasing me with the mild symptoms, reminding me that this is only the beginning. I am very aware of what the enemy is capable of.

When I first found out that I had the gene, I read a lot about liver transplants. I soon found that ALA 60's could not have a liver transplant. It turns out that liver transplants can make the amyloid worsen for certain genetic forms of Hereditary Amyloidosis. ALA 60 is one of them. "A

waste of a liver,” the doctor said. My enemy laughed at me when the physician told me that it would not be an option for me. I currently take Diflunisal, Green Tea Extract and Doxycycline, twice daily to hold the enemy at bay, slowing the enemy down. My enemy laughs at me each time I take these meds, reminding me that I am only giving the enemy a “speed bump”, not “a stopper” to its destruction on my quality of life. When I get my hopes up, thinking that there is a new treatment available (a stopper, a bigger speed bump), I find that it is not available for me or it is out of financial reach for me and others in my family. My enemy laughs again at me.

Last week, when a new drug was approved by the FDA, I was so excited. I the date marked in my calendar for months. I was so excited. Hope and excitement was in the air that day. I laughed at my enemy for once. However, the enemy laughed at me LOUDLY the following day when the price of the new drug was announced. I became sick to my stomach when I read the cost of it. My insurance will pay 80%. However, the 20% belongs to me. With or without a discount, that is not affordable. This company studied our amyloid community, out of our desperate situation. Then they made it unaffordable for us to obtain! I appreciate what they have done and discovered. I understand the cost of developing drugs and bringing them to market. I feel so shorted by them. My husband and I talked about selling everything we own. My family would suffer greatly. Selling everything would still not cover the year after year cost of the medication. My husband and myself would work and work to pay for it. We would have to give up everything. That would be too selfish of me to do. My enemy laughs at me as I contemplate one quality of life for another.

Without the medication, I estimate that I will work for the next 5, maybe 6 years. Until about the age of 55 years old. At that point, I will probably be unable to work. I am guessing only by history of our family disease progression. My college educated husband will be forced to care for me as well. My family has always worked, we never really appreciated people who could work but choose not to. My affected family only stopped working because they had to stop working. The enemy would not permit it. No one in my affected family ever simply retired. They got terribly sick before retirement age and had to stop working. Their spouses stopped working as well to attend to their increased care needs. I will assume that I will not be traveling in retirement, as most retired couples plan. I will probably not see my grandchildren graduate high school. My father only met two of his grandchildren and was only able to attend one football game for his oldest grandson. He was in a wheelchair, bundled to keep the cold away. He was unable to stay for the whole game, as exhaustion set in. He was 56 years old at that time. Dad loved football and waited each week for his grandson to tell him about the details of the game. He was never able to attend after that partial game. The disease robbed him of being the grandfather he longed and wanted to be. The other grandchildren came later. He never met them. My aunts and uncles never met any of their grandchildren. The enemy robbed them of these simple life treasures.

I have four children. My older children that knew and remember their grandfather when they were very young, seen what the enemy did. Now, they are aware of my “tripping”. They are aware of what the enemy has planned for us without a cure or a treatment. They are scared of the enemy. They are scared for me, for their four children and for themselves. So am I.

With new medications coming available, what good are they if no one can afford them? Even if my insurance asked me to pay out of pocket for 10% verses 20%, how many people can afford, \$49,500 a year? That's \$4,125 a month! My husband and I are both college educated, working in our fields of study and make a good living. This is not affordable. I don't know many working, middle class people who could afford this. I will also remind you that at age 50, I should be concerning myself with retirement planning. I should not be worried about how to keep a roof over my head, food in my mouth and the \$4,125 a month for ONE medication, plus increased insurance premiums, multiple physician appointment co-pays, and days off of work to see the physicians. By the way, my Amyloid physician is 4.5 hours, ONE WAY. There are no physicians around or in my area with any experience with this enemy. So, throw the extra gas and hotels in the mix of expenses. This is unreasonable, unaffordable and unattainable! And once again the enemy laughs even more loudly at me.

The enemy will force this full-time, college educated, registered nurse, who loves her job, years of being sick and unemployed. Just "existing", as others before me were forced to do. This will cost more to our working society than just making the medication affordable. We need to continue working and being productive in our families, churches, communities and society.

I am doing my part in this. I am in studies. I participate where I can. I am thankful that more studies are just becoming available for those of us in the early stages. I am helping the cause for myself, those in my family much younger than myself and others that I do not know. However, the enemy laughs at us when we do these studies but cannot reap the benefits because the treatments developed from the studies are financially unreasonable for us or most families to obtain them. Regardless, I will continue the studies. I will also continue to pray for a cure. I will continue to pray for affordable treatments. I will be defiant in the face of my enemy, I will remain positive and know that maybe someday, I did all of this for my family or someone else's. Right now, the treatment too costly and is far from being attainable for my family or others at this price.

Thank you,
RN

I am 42 years old, suffering from Hereditary Amyloidosis TTR (hATTR), Val30Met mutation, I live in São Paulo, Brazil.

I have memories from my earliest years, when I visited family members and saw people in wheelchairs, very thin people, with atrophied hands. He did not know and did not understand what was happening. Years passed, we received phone calls telling about the passing of a relative and my father went to the funerals.

My father worked in a multinational bank for over 20 years, had a good position and a good salary. He began to feel bad, thought he was living a very stressful life and resigned in 1987, he was 36 years old. He used to love cars so he went to work buying and selling cars along with a friend of his who had also asked to resign from the bank. He began to feel horrible pains in his legs, especially at night. I was a child was 11 years old, and my younger brothers 8, 6 and 2 years. No one said anything, it was a mystery.

Things began to worsen, and I remember that my father started attending various religions in order to find out an answer or get some kind of cure. I think I know he did not accept what was happening to him or he did not want to believe that he was suffering from hATTR. That's because the disease was a death sentence, we lost more than 2 dozen people in our family, usually between the ages of 23 and 40. In this period the person is building a family and stabilizing himself financially, when he begins to have serious health problems and he sees his income diminishing. That's what happened to us. My father spent nights in the bathroom due to diarrhea and vomiting and only emaciated. And nothing of the fateful diagnosis.

One day my father and mother were in the center of the city to go to the bank and my father who was already a little difficult to walk passed and bad and had to be hospitalized. The doctor who took care of my father for some time was emphatic: you have Amyloidosis! There are several cases in your family, you have to accept this. It was when the doctor called my mother and told her and in seconds her world fell: "and my 4 children can have this disease!" My father left the hospital with a catheter in the belly, had to have a cystostomy and used a bag that collected the urine, it was something shocking.

No longer able to escape the diagnosis and no treatment existed, we were seeing our father languishing, transforming into another person, into another being. We had to start saving money at home because my father could no longer practice his profession, and his income had fallen a lot. We left the private school and went public. I studied electronics and graduated and started to work, it was 1994.

My mother could not take care of my father alone, my brother who was a teenager had to help, sometimes all day. My father, who loved cars so much because he did not feel his feet any more, one day switched the brake on the accelerator and just did not hit the car because my brother pulled the parking brake. From that day on my father never drove a car, my brother drove for him, even without a license. My father had diarrhea and he did not have time to go to the bathroom so he wore diapers. When I got home many times my brother had to bathe in it.

At that time my grandfather seriously burned his feet in the hot water and felt nothing. The world falls again: another case of Amyloidosis. It was my grandmother taken care of my grandfather and my mother and my brother taking care of my father. I spent the whole day on the street working, I was afraid to go home. It was very difficult to face that situation, his father crying in pain at night or spending the night in the bathroom sitting on the toilet. Our family has been disintegrating.

At that time the first liver transplants began to be made in hATTR carriers but my father and grandfather were very weak. We knew the end was near. My father and

grandfather never left the bed. They could not feed themselves, they could not write anymore. They had to be carried on their lap for a shower. They lost tens of pounds. My father had bedsores, huge wounds, and my mother did the bandages. There was much suffering for everyone in that house.

My grandfather died in 1998 at age 74 and my father in 1999 at age 47, it was 6 months difference between burials. It was a relief to me because I could not stand to see my father suffer like that, I suffered with him. On the nights that I could not sleep because my father cried, I screamed in pain I prayed. God, take this pain out of it and give it to me!

We knew we had 50% inherit the gene and in 2006 I decided to do the DNA test. It was positive. I was not devastated, I was not depressed, I continued to live my life and work hard, travel and enjoy. Sometimes I would feel a prick in my toes and be very worried, but after a few days it would pass.

At the end of 2011 my brother started having some health problems, leg pains, he thought it was because he worked all day standing. The doctor diagnosed that he had circulatory problems and had to have an operation. He started with stomach problems and the doctor indicated that he had to have an operation to remove the gallbladder. It all started to intrigue me. In early 2012 when I got home I felt my legs tired, sitting on the couch and letting my legs up. This tiredness persisted for 1, 2, 3 months when I diagnosed myself: the symptoms started and I already knew that the same thing happened to my brother. I told him not to do any surgery and we went to see another doctor, who all said he was a specialist in hATTR. My brother did the DNA test tested positive, and the neurological tests indicated that he had symptoms of the disease. My exams did not indicate, but I already had terrible pains (neuropathic pains). The doctor even suggested that I was somatising symptoms but I was sure not. I did not trust this doctor anymore and as I did not know another I decided to go to Portugal in search of the diagnosis, so I contacted the patients' association and this one tells me a specialist doctor in a city near I live who closes the diagnosis: the symptoms started too. The struggle for life begins. I did not want to do a transplant because I had already lost 2 relatives who had this surgery.

A new drug had just been approved in Europe, the Tafamidis. We filed suit in court against the federal government the judge granted injunction, forcing the Ministry of Health to provide the drug. We did the treatment for 2 years with Tafamidis but the supply of the medicine was always interrupted, which was compromising the treatment, was when it began the phase 3 clinical trial of Inotersen, laboratory Ionis. Even as a risk of falling into the placebo arm my brother and I decided to go into the clinical trial in April 2015 and it lasted 15 months. After 6 months we already knew that we were on the placebo because our health began to deteriorate rapidly, I began to lose weight and the sensation of temperature in the feet and my brother weight loss, diarrhea, lack of sensitivity, vomiting, difficulty to feed, difficulty to walk. It was a very hard time, I even thought I could lose my brother, the situation was on the limit, edge! I stopped working to be able to take care of my health and I get social security pension. I can not afford all the bills but I saved up for retirement when I worked and I'm using those resources. My focus was to win this battle, this disease, which condemned a few dozen people in my family.

Finally, after 15 months, we entered the open phase of the trial, starting to use active treatment, the drug. Already in the first application we felt something different, a burning during when the liquid entered our body. The next day after waking we felt terrible, like a bad flu. I stayed in bed for 3 days and it took me over 10 days to recover. At the next dose the symptoms were much weaker, and thus the symptoms were

disappearing. After 6 months from the start of the applications my brother who had lost about 50 pounds and was very thin began to gain weight. And I had a kidney problem (proteinuria) and I had to stop the treatment for 2 months. After the kidneys returned to normal I started the treatment again. We completed 22 months of treatment with Inotersen.

We had a new chance at life, even with all the sequels we have. A hope to change history. What happened to my father will not happen again. We will not pass the terror on our children or nephews. We will give them a chance at a normal life even if they were carriers of the disease gene. The drug has just been approved in Europe and in October must be approved by the FDA in the USA. Our sacrifice can also help other people, hundreds, thousands that we do not even know.

We thank you for this chance and we want all patients to have a better life, more quality of life, less limitations.

In our group we have 15 people in the clinical trial and during the double blind period we saw people with stable or improving symptoms and others with symptoms being aggravated. When everyone finished this period and started using the active drug we saw people, like us, in a short time to see some symptoms recede, it's like a miracle. We started to have other plans of life now. Before we only thought of surviving, now we want to LIVE!

F.A.

August 14 2018.

(I used google translator for translate from my native language)

This is a letter is to the ICER recommending the approval and positive findings on Hereditary TTR Amyloidosis (hATTR) drug treatments that have been approved by the FDA or in-process for approval.

Background:

This is a devastating disease that has affected many generations in our family but was not realized until about 12 years ago by my mother.

She had symptoms for about 7 years, was subjected to many missed diagnosis and unnecessary surgeries before finally identifying the root cause to be hATTR. She passed away 3 years later as her body shut down from the amyloid deposits. This was almost 7 years ago.

I was tested 9 years ago as my mother requested and found out that I had the gene and was active to my extreme surprise since I had no symptoms.

A couple years later I developed very minor symptoms and progressed slowly. I started to take Diflunisal prior to it being announced to slow down the effect of hATTR.

I also was on the liver transplant list which took me three years to move up... The fact that it took so long is now a true blessing as I removed myself from the transplant list due to all the promising drugs that were in trials.

I have participated in numerous Amyloidosis group meetings to always educate myself on current and future activities associated with this deadly disease. I have lobbied on Capitol Hill and attended meetings at the National Institute of Health (NIH) during Rare Disease Week to further the cause and funding for rare diseases.

Current Situation:

We live in a very exciting time for hATTR with a few drugs going for FDA approval (one already approved for Alnylam) and there is so much hope with the new gene therapy. Now there are drugs you can take to help hold off the progression of this disease. Before if you were diagnosed there was no good solutions that could help extend your life.

I currently am on an Extended Access Program (EAP) and have not seen my symptoms progress which is fantastically awesome. At this point holding off the progression of disease is such a magnificent win for me and my family.

I have a daughter that has been tested positive for the gene but is not active. She is pregnant with their 1st child and these new drugs mean the world to all of us.

We definitely need as many good drug solutions for hATTR as possible to provide people with choices since some drugs react better than others on different people.

Amyloidosis research has come a long way in 7 years since the passing of my mother. Then the only option was a liver transplant (which was like placing a nuclear device on an ant hill in a healthy person, way overkill) to now having multiple drug option solutions. Implementation of these drugs is different and patients can chose the method that suits them the best.

A lot of us have lost many loved ones over the years not to mention the monumental burden the disease placed on the caregivers. Many of us patients will do almost whatever it takes to extend our lives with a quality of life. Also, our adult children that have the disease, to provide them a solution that they never have to experience the effect of hATTR would do to their bodies.

Forward Looking:

We are elated that these new drugs are in the approval process and provide us with the ability to lead a life that manages the disease. I still want to work with these companies on the next generation of drug that performs even better with the drug treatment being more infrequent (More time between drugs applied to the patient).

The cost needs to be reasonable by the developers with insurance companies agreeing to cover the vast majority of the cost. If the cost is unaffordable then the solution is not real. It is my dream that these solutions are real for everyone.

I would also like to see in the future that young adults can start treatment prior to any symptom. This would manage the hATTR disease in a person that test positive for the gene but not active with testing or symptoms.

We look forward to the future when further drug advances can reverse the effects of the disease and eventually prevent / eliminate the disease.

Take Away:

We (the patients) are willing to do almost whatever it takes to manage/eliminate this disease for ourselves and even more important for our children,

The positive approval for these drugs is imperative to the hATTR patients, caregivers, families, friends and coworkers to enable us to live a life that we can manage this deadly disease that has already taken to many loved ones from us way too early in life.

Thank-you for the opportunity to express my thoughts and I hope my input has provided you with facts and emotion on hATTR from a patients prospective.

We need these solutions now as we are trying to buy time in managing the disease until the ultimate dream of preventing hATTR.

I would sign my name as I am very active in advocating for hATTR, but my daughter who is pregnant has the gene. Since this is for public record I did not want that direct link. She is also very active in advocating for solutions for hATTR.

Always the Best,

DA

Hi ICER and all that it concerns

My name is Susanne Berglund and works full time at the association FAMY-Norrbotten in Sweden. I have been employed for 20 years and have always worked towards the following goals:

- * To stand up for all affected by the disease and their relatives, MEMBERSHIP
- * INFORMATION about the disease for healthcare professionals and the general public
- * To raise funds to SUPPORT THE RESEARCH (in total we have given research € 1,3166,734)

As an employee of such a association, you get very close members, you become like a big family. I myself is not affected by the disease, but my father-in-law had it so I have seen the disease and the problems very close up. The risk is big for my husband to have the disease and I am also thinking of our children and grandchildren. If you are a carrier of the disease, it is not obvious that you develop the disease and therefore there are many who do not get the test. If we know there is medicine available more people will get tested.

Here in Sweden, we have had access to Tafamidis and Diflunisal in recent years, but unfortunately not everyone has been able to take part of the medicine. We have a few members who participated in the Patisiran study and feel much better. I believe Patisiran and Tegsedi are the treatments for which we have been waiting for many years.

Therefore, I hope, and many with me, that the health insurers will see the value these new drugs provide and make them available to patients as soon as possible. Let people live a good life even with the disease!

Sincerely

Susanne Berglund
FAMY-Norrbotten, Sweden

My Mother and an Uncle were both diagnosed with amyloidosis. At age 46 I tested positive, but had only slight symptoms, at best I considered them annoying. From age 58 to 61 my symptoms progressed slowly. My feet felt swollen even though they weren't, the neuropathy was worse when I stopped and thought about it so I tried to keep busy. The pain seemed intense and there were moments of self pity. In hind sight, by today's standards, the pain was mild. I tried Dolabid for about 8 months but quit in anticipation of a Clinical Study Drug. I didn't think the Dolabid was doing anything anyway. I knew a drug (later named Inotersen) was being developed for hTTR Amyloidosis and there was a chance I could qualify for the clinical study. Although I wanted to wait for the study at age 62 the neuropathy suddenly got worse, I started to lose weight, and almost overnight I could not stand still and keep my balance. Balance became a big issue both at home and at work. I decided I could not wait for the study and reluctantly went on a liver transplant list in Oct 2012. In Jan 2013 I was offered a Liver which I turned down because the start date for the study was suppose to be just months away. I turned down another liver in Feb 2013. Thankfully, Apr 2013 I was able to start the clinical study. I had dropped 40lbs in the six months prior to starting the drug. The first 18 months was a double-blind placebo study but there was no doubt in my mind that I got the drug, not the placebo. My weight immediately stabilized. I took my name off the liver transplant list after being offered a third liver just months after starting the study. I was told the drug should slow the progression, possible stop the progression, but not to expect any improvement. It has been over five years since I started the study and I've not had a single day of regret. Has my neuropathy progressed – yes. Is it harder for me to stand and keep my balance-yes. But the progression of both has been at a snail's pace compared to the six months before I started the study. My weight has stabilized, the diarrhea and constipation are pretty much the same. It's worth repeating, no regrets. I know some people in the study have had reactions and side effects from the weekly injections. I had none for the first four and a half years, but must confess recently I have been experiencing some shaking. It starts about an hour after injecting, and usually last 15-20 minutes, then I'm back to normal. I want to believe it is NOT a physiological reaction, I like to think it's a psychological but I haven't been able to control it. Regardless of the recent slight inconvenience I believe in Inotersen and am so thankful that I was accepted into the study.

In spite of the slowed progression we have made adjustments. We closed our photography studio we had run for 40 years. We downsized from a large house on a large wooded lot to a condo, and I quit driving after several close calls and one accident from not being able to find the brake. Within months of closing the business, moving to a condo, and giving up driving I realized I was quickly going downhill, physically and mentally. I found a part time, on my feet, job. I found hand controls for the gas and brake, practiced a little, passed the driving test, and now legally drive with hand controls and feel much safer. The part time job has been heaven sent. Days that I don't feel good, I know I would skip taking a walk or working out, but I won't skip my commitment to show up at work. Usually, even though I may be tired after a shift, I feel more alive on days that I have worked than on days off. I believe Inotersen is the main player in the state of my physical health and working is critical for my mental state of mind.

The clinical study site is a four hour drive. Early in the study it was a lot of driving but throughout the study we were reimbursed for travel expenses. Currently the study consist of a weekly self injection, a weekly Home Health Care Nurse blood draw to check my platelet level, and just two visits per year to the clinical study site. I am so thankful for Inotersen. I feel worse than I did April 1, 2013 when I started phase 1, but I knw I would feel much worse without the drug. I cannot do most of the physical things I use to but that's but I am alive. The tingling is irritating but manageable. The sharp pains are intense but I know they are temporary. I am very weak compared to 10 years ago, but my life has far less physical demands. The diarrhea is literally a pain in the ass, but thank goodness for diapers and pads. 10 yards seems like a long ways away so I plan my steps, and look ahead for a sturdy destination I can lean on. Having a cane is often inconvenient, but it's a life saver when I trip over my own feet or stop where there's nothing to lean on. I am so thankful, other than the symptoms of amyloidosis, I think I am in pretty good health. I rarely get down and when I do it's usually only for a short time. TWB

ICER

August 15, 2018

RE: Living with hATTR Amyloidosis (Amended August 16, 2018)

To Whom it May Concern at ICER:

I was diagnosed last year (age 60) with hATTR (my gene type is PRO44SER) after watching my mother's brother suffer and become an invalid with the disease. It took several years for him to be diagnosed at Stanford Medical Center – one of the top U.S. hospitals and an Amyloid Center of Excellence. From his diagnosis and my similar symptoms, we decided to undergo genetic testing to determine whether my peripheral neuropathy that had no known cause other than “familial” could also be hATTR – and it was confirmed. We looked at the rest of the family to determine who else and where the defective gene may have come from and determined that my mother is suffering from the disease, her mother (my grandmother) died from the disease, and my grandmother's brother likely died from the disease. All three suffered from gastric and cardiac issues with physicians unable to diagnose their ailments or able to help alleviate their symptoms. My grandmother also had the peripheral neuropathy in her feet and hands. I have two adult children who are very concerned that they too may have the disease, but are not willing to test for fear that a positive result could make insurance unaffordable for them and their families.

This is a devastating disease that takes a toll on the patient and their entire family. Knowing the cause gives me a slightly different perspective than the others in my family, but it is also frightening knowing what to expect in my not-to-distant future.

I live in Birmingham, AL and have access to the University of Alabama Medical System – with no one experienced with or treating hATTR. I searched for other centers familiar with the disease and found a center in Jacksonville, FL; one in Atlanta, GA; and one in Nashville, TN – all of which are focused on the AL type of amyloidosis; not on hATTR. My wife and I agreed that to get knowledgeable care we would have to travel at least 1000 miles and decided to go to Mayo in Rochester, MN for treatment. Needless to say, this is a financial strain even before the cost of specialized drugs are factored in!

I worked my entire life and saved to provide for my retirement. Now that I have reached that point in life, I am faced with potentially catastrophic financial impacts due to this disease. Typically, the Government steps in to help patients who do not have the means to pay for care, but leave those that have worked and saved to fend for themselves. This puts me in a situation to choose between financially ruining my wife's retirement in order to treat my disease. This is something I am not willing to do. If the drug costs are not affordable and/or covered by insurance companies, as far as I am concerned, the drugs will be left on the pharmacist's shelf!

The new drugs offer hope, but I fear they are nothing more than teasers as only the poor and wealthy will be able to access them. I pray that ICER will help to ensure this fear does not come to fruition and that the drugs will be covered by insurers and affordable.

Thank you for your support!

SB

(You have my permission to publish this letter.)

Amendment: My uncle, mentioned above, died last night from complications of hATTR. He had just received his second infusion treatment from the Patisiran Extended Trial.

Hello there,

My name is Kristen Bennett. I currently reside in Green Bay, WI. On July 16th 2018 I received a positive gene test for hATTR. On August 13th I will be having my first of many appointments. I'm 26 years old.

There were so many things going through my mind when I found out. One phrase rings true though, I'm a warrior. You see, I've been over 5 years clean and sober and that doesn't come easy. I'm a woman who has a lot of wisdom to share and help to give. After the hell I went through to get clean, I've met a man who loves me. I graduated college last year and just started my own editing and photography business. I was finally able to move out on my own. Point being...

I've just started my life.

I found out about hATTR the day before my 26th birthday. I won't be able to responsibly have children because I cannot afford IVF. I have watched family members die. I don't want to cause anymore pain because of hATTR.

It would be really wonderful if this treatment would be affordable and available to everyone. Because as of right now I have 2 siblings, 4 cousins, 3 nephews, 1 niece, my mother, my uncles, my cousins children, who are all at risk of hATTR.

I've just started living.

The thing about a miracle is it's always better when it's shared. You've done something amazing but it will only continue to be amazing so long as our people get access to this.

I've just started the hATTR journey and I'm so excited to see this miracle grow.

Oh and by the way, you guys are doing a really good job and keep up the miracles.

Thank you,
Kristen Bennett

I write this letter with a heavy weary heart because patients and families are literally put through hell living with Amyloidosis. We felt so alone trying to find anything for a treatment or a far off cure. Medical professionals do not know what it is, based on the majority of our interactions, and neither do your family and friends. Talk about isolating emotionally and physically. It took a long time to find a support group. Some of our friends with Amyloidosis went years without diagnosis. They traveled to numerous doctors to find someone who deals with amyloidosis. My husband is blessed that we discovered he had it. It was a mere fluke. An orthopedic hand surgeon was willing to go out on a limb and test tissue from his right hand in a carpal tunnel release surgery. His hand troubles were our first clue. He had surgery three times when he decided to check for it. The majority of people that have that surgery only have it once in each arm. My husband has had it done six times as of July 2018. We have yet to find another patient that has been diagnosed this way. Some of my husband's family were told by medical physicians that "it was all in their head." His cousin and his mother were both told that from different medical physicians. Our health care system is failing these patients. The burden of this disease does not have room for pride, egos, or indifference. This disease is a chameleon. It masks itself as one single disease that is common. As a result when many different things start happening no one knows it is linked together. It requires a constant vigilance that most diseases do not. The treatment plan is per patient per symptom. There is no universal protocol. Amyloidosis has made us feel like hypochondriacs for my husband. Is it or isn't it causing this? We have had to rule in as much as rule out symptoms/tests to make the most informed decisions he can. If they can not stop the progression the patient has to decide what they can live with and where the line in the sand is. Who wants to constantly wonder what is wrong with themselves for years on end with no answers? A patient can not make an informed decision about their health with scarce information. The doctors do not have the time to investigate and consult with other doctors with the time/paperwork constraints in offices these days. As patients and caregivers we wait. We wait for a cure, a treatment, a better healthcare system, and more medical professional awareness.

My husband has Hereditary Amyloidosis due to mutation of Romanian descent. It is one of the rarer mutations out of over 120 types. I have only found two medical case studies from Romania about his particular type. There is nothing else available on peer reviewed searches. I have spent hours looking. Both Romanian patients were experiencing some of the same things he is or has. I have the last three years of his mother's medical records to try and have a rough outline of what she endured for his doctors before her death. A list of things to look for so to speak. We have nothing else. As caregivers are just waiting on the next "new normal". His mother did not want to burden her children with what was happening to her. My husband is 44 years old. He was 36 years old when he was diagnosed. He was 27 years old when his Mother passed away from this disease at age 48. She was diagnosed in 1997 at age 44. His maternal Grandfather passed away (age 50) of Amyloidosis when his daughter was 10 years old. He never met his daughter's children. My husband's youngest sister was 17 years old when their Mother passed away. His Mother has four children total. Two of the four children have been tested and found positive for the mutation. The other two sisters are trying to decide if they should get tested. One refuses to discuss it.

My husband and his father worked different shifts at the same manufacturing plant to make sure there was always someone home with his Mother and sisters. They never once placed her in a

nursing facility for respite. It was important that she spend what ever time she had with her family. Early on in her Amyloidosis journey she was scrambling to a restroom and not able to control her bowels. She went from walking with ankle braces to a walker to a wheelchair and then not at all. She was bed ridden the last two years of her life. She laid there in constant pain. Emotional and physical pain. She had the burden of knowing she may have passed it on to her children. They were changing her IV Saline bags to her IV port daily. She was given IV Saline to help keep her blood pressure up along with oral medications. They would adjust the rate of the infusion based on her dizziness and blood pressure. Neither of them had medical training and were taught by the home nurse to do so. Nurses were not apart of the routine daily. They only interacted with them if something new was happening medically. She maybe weighed ninety pounds at the end of her life. Her son's girlfriend (myself) helped feed her, medicate her, and take her to the restroom at the end. I loved my now husband enough to do that for him long before we were engaged. Her daughters were not strong enough to help her. She could not stand or position herself moving from bed to bedside commode. Can you imagine anything like that for yourself? Besides her local primary doctor they sought treatment at UNC Chapel Hill, University of Virginia, and University of Pittsburgh. Two to four hour drives in a large passenger van with a camping toilet in the back so that they could make it back home. Her need to go was right now and not the next exit. The gastrointestinal aspects are the worst part of this disease. A patient feels full all the time(stomach slowing digestion down), you loose weight you do not need to loose, and you run to the bathroom at any given moment. You have no control over your bowels. You can not eat no matter how much you need to. You would be surprised at quickly this can affect your quality of life. All of the facilities decided she was not a good candidate for liver transplant. By the time all the tests/exams were done to go before the Internal Review Boards at each place, she was going down hill fast. It took her years for a diagnosis. You wither away from no food, no life you had or wanted, and no treatment to help make it bearable. Not long after that the doctors offered Hospice care. My husband's family constantly were worried over bills and growing medical regimen for her care from 1997 to 2001. They were raising two teenage daughters in high school, working forty hours plus, and getting up all hours of the night for around the clock care for her. The total price paid for her care can not be measured. What she and her immediate family went through has scarred the ones left behind.

The only reason my husband received testing is because I insisted after three carpal tunnel surgeries on his hands in 2010. Since we married in 2003 he has had twenty surgeries total so far. We decided to not have children because we did not want to pass this disease down. If he was able to get treatment, then we would seek adoption. We are still waiting to have children fifteen years into our marriage. I am 41 years old and he is 44. We have never made plans for retirement because we are not sure he would even live long enough to and I might have to work many more years before I could retire. He has been laid off twice before he was declared disabled. When he was rehired by the company in 2011, he was only able to work two full years. After that he was not able to work a full year due to medical leaves for surgeries. In our state the employer company is only allowed to pay 68% of what his pay would have been if he was able to work. So we have medical surgeries, more medical bills, more recovery time efforts, and less take home pay to help recuperate at home with. One year his insurance paid out \$175,000 for his care alone. We were fortunate to only pay 4% of that. Four percent is a lot on a limited income though. He decided to file for disability in 2016. He could not keep up with production. His legs were causing pain and tingling that would keep him up at night. He could sleep for fourteen hours and

still dose off because of the fatigue Amyloidosis causes. He never feels rested even with his CPAP. His household chores are whatever he feels he can do that day. I can not and will not place lofty expectations on him. Everything else falls on me. I work four ten hour days a week. I spend my one day off taking him, my ailing parents, and myself to the doctors each week. I do whatever errands that day or cram in house work too. Occasionally I have a day without errands and demands but they are fewer and far between.

His mutation attacks the heart, eyes, the nervous system, organs, intestines, ligaments & tendons. We have always believed that if we sought care early enough that it could make a difference even without a reliable treatment available. My husband went through the process to be a liver transplant candidate in early 2017. It was three months that I never want to repeat. Amyloidosis patients have a compromised immune system. Everything done to them takes longer to fully recover and heal. He was recovering from a tendon and ligament repair on his right ankle from November 2016. If he was not able to walk, he would not be considered. It was as cut and dry as that. At that time the only thing FDA approved based the criteria on ambulatory condition of the patient, then a larger number will not ever get help/treatment. He was able to walk but he had an ankle brace on the entire time. He has to have an EMG test by his neurologist every six months since 2010. I was worried that his ankle may worsen and the transplant team would not help him at age 43. The thought was that when his nervous system started showing decreased nerve response, that if it reached a certain low point, that would be the time to transplant his liver. His numbers took a sharp dive down in early 2018. We are constantly checking organ function and neuropathy changes. We know his Red Congo stain biopsies have been positive in his stomach, small intestines, and wrist tendons. His heart is checked each year and we wait. Our thoughts on the liver transplant are that it was road bump to slow it down but not stop progression. Why transplant a perfectly functioning liver? His liver just has the wrong set of directions programmed. You also add complications from transplant surgery to an already complex disease. Some of the clinical trials would not allow transplant patients. I understand it is for patient safety but there is nothing safe about this disease. If it is all you have then you will take what you can get.

We placed him on inactive status on the transplant registry to obtain early access treatment from either Inotersen or Patisiran. The fact that there are two transthyretin knock down medications is nothing short of a miracle. We tried to join one of the two Early Access Programs three different times within six months. We were anywhere from ten to two days out from leaving to get the evaluation and the FDA/company stopped patient admissions. We were contacted through a patient advocacy group to talk with the other drug company's executives. They wanted to discuss what patients' lives were like, medical treatments, and burdens. We astonished them to the fact that it can happen so early in life. We attempted that drug company's Early Access Program. He has been receiving it since April 2018. We are waiting to see results and drug approval. These drugs are all we have to look forward to. We are worried about the cost of the medications. He is disabled and not able to work. Medicare is his primary and he has his workplace insurance as secondary for one more year. We have been living off of my paycheck and whatever Social Security pays him. It is even less than what his medical leave pay was. He does not have long term care insurance because he was tested and diagnosed before we even knew what long term care was. I will be his around the clock care.

The psychological toll Amyloidosis demands are inconceivable. His family thought we were all done with this disease after his mother's passing. My husband and I came to terms through grief and discussion among ourselves. The rest of his family buried their heads in the sand when my husband received his diagnosis. It is easier out of sight, out of mind to deal with something traumatic. You block it out. Using that example my husband's family treated him like he was the disease for years. They blocked him out. He had no emotional support from the ones that are supposed to support and love you the most. We sought counseling because I realized that amount of rage I had towards his family. I realized he had the scars of being ridiculed for seeking treatment and trying to discuss it with his family. I could not understand that this was the "support" they could offer. He went two years without speaking to his father. A year or two not speaking with one of his sisters and one sister moved across the United States to seek shelter from his amyloidosis. The counseling helped. The support group we joined helped. We learned a lot of families deal with Amyloidosis like that from other patients. The patient and caregiver feel very isolated and frustrated. Fear, isolation and anger are very volatile if left simmering in someone's mind. If someone has cancer, most people understand the burden and treatment. You mention Amyloidosis and nearly all will say what is that? When we sought a transplant for my husband I spent nearly three hours explaining to a Gastroenterologist why my husband was asking for a new liver. We had to be cleared by him before ever speaking with a transplant surgeon and accepted as a candidate. He never bothered to read the chart. Ninety-nine percent have liver failure and my husband had perfect function walking into his office. He had never heard of Amyloidosis. I have a six inch notebook that has my husband's lab results, copies of MRIs, Pet scans, and X-rays, vaccination records, death certificates, medical journal articles, a master list of medications, and list of surgeries. I have gathered any and everything I can think of to help my husband. I can not invent a cure though.

Look at how HIV/AIDS outlook was ten years ago or more for patients. The advancements are resulting in many more years survival of patients. Any treatment that can help should be accessible to all Amyloidosis patients. We are marginalized due to the nature of this disease. "Neuropathy is from your diabetes, spinal stenosis is the result of not taking care of your back at work, and you are just lazy. You can not stay awake?" are just some of things that have been said to or about my husband. He looks like a normal adult male so why would people think otherwise. Treatment protocols should not be cookie cutter for some diseases and Amyloidosis is one of those.

Quality of life should be the bottom line value. Waiting on test results to decline wastes precious time away from patients and their families. How a patient feels about their existence is more important than any number or mutation you can quantify. Quality of life needs dire attention. These patients need access to treatments and more research. Amyloidosis is not a legacy that my husband and I want to hand down. I maybe generalizing this but no family with a hereditary disease wants that for a legacy. We want to know that the hell we have experienced and have yet to come will help someone else with this disease. We are willing guinea pigs. Please help make these two treatments available to all Amyloidosis patients regardless of socioeconomic status. They are each priceless treatments to this patient population and their families. The ripple effect of treatment would be astonishing for future generations. Please help us make this as easy as possible to obtain. We have enough to deal with especially the cost of care.

Sincerely,
B.M.D.

August 16, 2018

Dear Sir/Madam,

My name is Jennifer Kaehr Brink. I am 54 years old, married for 33 years and have two daughters ages 28 and 26. I am a Professor of Respiratory Care and the Program Chair of the Respiratory Therapy Program at Ivy Tech Community College, Fort Wayne, Indiana. I have 34 years 'experience as a Registered Respiratory Therapist, Neonatal- Pediatric Specialist, Registered Pulmonary Function Technologist. This is my Familial Amyloidosis story.

1956 Dr. Gene Jackson publishes "Primary System Amyloidosis: A Review and Experimental, Genetic and Clinical Study of 29 cases With Particular Emphasis on the Familial Form". Dr Jackson diagnosed the first cases of Familial Amyloidosis in the United States. This is my kindred. I was born in 1963 and I have literally known about amyloidosis my entire life. I am kindred from the IN-Swiss-FAPII also known as Serine84Ile mutation. My paternal grandmother brought the gene to our family. She died in 1969, I was 6 years old and I knew she died of amyloid. Fast forward to 1983. I was a respiratory student when my uncle became gravely ill. I was at his bedside trying to assist my aunt in making end-of-life decisions because like many lay persons, she did not understand what was happening. I was 19 years old. He was 61. One year later my other uncle dies. He was 54.

In 1990 my father was evaluated for a heart transplant and denied due to the amyloid being systemic at that time and therefore, he was not a candidate. He died in 1995 at age 61. I was assisting my mother as his care-giver. Therefore, I not only have experience as a patient, but I also have experience as a care-giver and understand the burden of disease from many angles. 2009 my brother Scott dies. He was 53. 2013 my brother Mark dies. He was 58. Not only did I have to endure the death of my immediate family but during this time there are also many of my kindred dying. I have lost count of the number of funerals I have attended for my family all dying early due to Familial Amyloidosis. The oldest survivor of amyloid in my family just died in July 2018. She was 80 years old. However, she was in hospice care for 3 years. She also had a total of 19 eye surgeries due to amyloid complications. Although she lived the longest, I know her quality of life was poor.

Kaehr Family tree as of this date: Grandmother, Elma Dubach Kaehr was the original carrier. She had seven children. Of those seven children, four died from Amyloidosis. Those seven children had 24 total children. Of that generation, 8 children have amyloidosis. 3 have already died from the disease. The next generation already has 3 positives and 1 negative amyloidosis diagnosis. My nephew, 42 years old and my daughter, 28 years old are 2 of the 3. We are starting the 4 generation of the Elma Kaehr family. Currently, based on statistics, there are 34 family members with hATTR, IN-Swiss, FAP II.

2005 I had my first carpal tunnel release. At that time a tissue biopsy was completed and analyzed for amyloid. It was positive and it was then I confirmed positive penetrance of the amyloid plaques. I did not seek any additional medical treatment for the amyloid because at that

time we still had no treatment available. Because of my medical background and knowledge of hATTR in my family I knew I would need to proactive in my healthcare. 2013 I had a routine EKG which showed “low voltage” which is the beginning of cardiac involvement of the amyloid. I knew this was the time I need to do something. 2013 and 2014 I spent being evaluated for the clinical trials for both Alnylam’s patisiran and Ionis TTRRx clinical trials. I was denied for both because even though I had an EKG change, I did not meet the trial admission criteria as I did not have significant neuropathy in my lower extremities. I do have significant neuropathy in my upper extremities but that was not part of the inclusion criteria for the clinical trials. In 2013 I was asked to testify before the Indiana Senate Health Committee on support for the IN Right to Try Law. The law went into effect July 2014. I contacted both Alnylam and Ionis requesting “my right to try”. Both rejected my request because I did not meet inclusion criteria. Just because the state of Indiana said I had a “right to try” the corporations had a right to say no!

2014 I had a routine echocardiogram. In comparison to my previous echo’s, my left ventricle measurement changed from 0.8mm to 1.1mm. This thickening of my ventricle was due amyloid.

I had to do something. In 2014 I began to pursue liver transplant. It was my ONLY option for a treatment. I had a complete transplant workup at IU Medical Center. A cardiac biopsy verified that I had amyloid in my myocardium. I felt completely desperate. I was 51 years old and having intimate knowledge of amyloid, I knew that my life span had just been significantly shortened. I just been handed my death sentence. IU declined the liver transplant stating that they felt it was necessary to do a liver and cardiac transplant. Since IU did not perform the double transplant, I now needed to find a facility that would take my case. I then went to Vanderbilt (7 hours from my home) and Henry Ford (3.5 hours from my home). A complete cardiac work-up showed that I still had normal cardiac function. Therefore, Vanderbilt and Henry Ford agreed to list me for just the liver transplant as long as that came immediately. I spoke to both teams about the on-going drug trials and the possibility of FDA approval and asked if I could wait for the drugs to become available. I was told by both teams that “it is too late for you to wait. You must have a liver transplant as soon as possible to stop further cardiac involvement”. I had a successful liver transplant at Henry Ford Hospital on September 23, 2017. Henry Ford actually completed a domino transplant and my liver was successfully transplanted.

I am the only of my kindred and my mutation to undergo liver transplant. Although it was the correct decision at the time, I would not wish a liver transplant on anyone. I have had some significant complications post-transplant the worst being Graft vs. Host Disease (GvHD) which has a 70% fatality. I survived the disease but it required multiple hospitalization and large doses of steroids for multiple months. Obviously, if an Amyloidosis medication would have been available to me I would have not chosen to have a liver transplant.

As you can see, I have intimate knowledge of this horrible disease. Both as a care-giver and a patient. I was diagnosed when I was 20 years old. I then watched for the next 3 decades as this disease progressed and my family became very ill and then died. I have waited 3 decades for a pharmaceutical therapy. There has not been a male in my family that has survived over the age of 61. Every time I attended a funeral I saw myself lying in that coffin with my husband and

daughters mourning my untimely death. Knowing I had a fatal disease with no medications available and the ONLY option was a liver transplant was a huge burden to my mental health as well. My husband of 33 years has been a part of this entire journey with me. He was a caregiver for his father-in-law and then my caregiver and with me every step of this journey. My daughters had to watch their uncles become ill and die. They do not remember their grandfather. My daughters have also been part of this journey. Amyloidosis has taken a mental toll on all of us.

Not only has the mental burden been excessive, the financial burden has been significant for our family. Fortunately, I do have amazing insurance coverage. Without this insurance my liver transplant would not have been feasible. My husband and I worry about future finances as well. I have contacted my investment company to discuss my options for early withdrawal of my life savings if I need to pay medical expenses.

2018 there are now two medications available to treat polyneuropathy and hopefully cardiomyopathy caused by hATTR. One, Onpattro (patisiran) has been approved by the FDA. The other, Inotersen is currently an Open-Label-Enrollment. This is something that the entire Familial Amyloidosis Community has been waiting on since 1956 when it was first identified in my kindred.

Although these medications are now physically available to the hATTR patient that does not mean they are financially available. According to Forbes magazine, “The price of the new medicine, though, may give people who haven’t paid attention to the cost of treatments for rare disease pause. Onpattro will have a list price of \$450,000 per patient per year for the average patient” (1). Inotersen is currently free to the patients until it receives FDA approval. At that time, I anticipate the cost will be similar to Onpattro. I do not know a single person in my kindred that could afford this cost. It is also unknown what if any of the cost of this prescription will be covered by the insurance companies. Although these drugs could have prevented my liver transplant, the liver transplant over time will be much less costly than the pharmaceutical options. How sad! My only option would be pharmaceutical bankruptcy or risking my life with a major organ transplant. I really don’t think I had much of an option.

I do commend the FDA for keeping a promise to fast-track rare disease medication approval process. The approval of Onpattro and anticipated approval of Inotersen was much faster than expected. However, there is still much to be done. Pharmaceutical companies need to receive financial support in order to cover the cost of orphan drug development. It took 16 years and \$2.5 BILLION to develop Onpattro (1). There are currently no additional pharmaceutical agents in development for the treatment of hATTR. Not only is there concern about cost, I, like ICER also have concerns about adverse effects of the medication. With only 3,000 to 3,500 patients in the United States with hATTR, it is still not known if these drugs will have any significant adverse effects other than what was identified during the trial (2). The other concern is these drugs are injection only. This adds to the possibility of infections from injections.

In conclusion, I commend ICER for evaluating the effectiveness and value of Onpattro and Inotersen. As you complete your review, please remember that the Familial Amyloidosis

Community has never had any significant hope that they may live a healthier and longer life until the development of these drugs. Liver transplantation being the only option available has not been a popular choice of treatment and very few hATTR patients have been recipient of a liver transplant. Therefore, as you complete your final analysis I hope the outcomes are favorable and a realistic value-based price can be obtained.

Respectfully,

A handwritten signature in cursive script that reads "Jennifer Brink".

Jennifer Kaehr Brink

References

1. *Alnylam Prices First Gene Silencing Drug At \$450,000 Per Patient, But Offers Money-Back Guarantee*. Retrieved August 13, 2018 from <https://www.forbes.com/sites/matthewherper/2018/08/10/alnylam-prices-breakthrough-drug-at-450000-per-patient-but-offers-money-back-guarantee/#>
2. Gertz MA. Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. *The American Journal of Managed Care*. 2017; 23 (7 Suppl):S107-s112.

Anger, sadness, fear, confusion, hopelessness, and helplessness. These are the emotions that I associate with Amyloidosis. It's a scary feeling when you KNOW that something is wrong with you, but no one, not even the doctors can offer a diagnosis, let alone a solution.

My father, Jerry, was a strong, loving, hard-working, and a seemingly healthy man. You would never know if he were hurting or in any discomfort. He would hardly even take a Tylenol. He retired in 2011 after working for 43 years. He suffered a mild stroke in September 2012. This seemed to be the beginning of his declining health.

Due to family history, he was already a heart patient and he kept his appointments faithfully. After his stroke, his weight ballooned progressively due to fluid retention. He also developed shortness of breath and his mobility became limited (he could only walk a few feet before having to stop and catch his breath). The yearly exams showed that his heart function was declining but the heart doctor couldn't offer any reasons why or why he was retaining fluid. He attributed the decline in heart function and the shortness of breath to the additional fluid/weight. He suggested installing a pacemaker/defibrillator in December 2015. Months after receiving the pacemaker/defibrillator, there still was no improvement so my mother pushed for a referral to another doctor.

The heart doctor in Jackson, MS suggested he be tested for Amyloidosis. It was 4 years after his stroke before he was finally diagnosed with Amyloidosis. Once he was diagnosed with the V122I gene, then came the task of learning about this condition and also trying to educate the local doctors and others about it. When we mentioned his diagnosis to doctors, we would get the statement, "We only spent a few hours on this in medical school." When we asked "Why such little time?" the response was, "We were told that the chance of ever getting/treating an amyloid

patient was slim and highly unlikely.” How could any medical professional ever think that just because a condition is uncommon that there won’t ever be a person who is diagnosed with it? I wonder if this was the thinking whenever cancer wasn’t as prevalent as it is now. While trying to overcome the anger and shock of the disregard for amyloid patients, my answer was, “Well, you have one now.”

It was evident that no doctors in our home state of MS could offer any help, so my mother researched and found that there was an Amyloidosis center in Boston, MA. When my mother mentioned our plans to go to Boston, the doctors advised that we shouldn’t; mainly because they said that there was nothing that could be done and that they didn’t think that he could make the trip. Against their advisement, we took the 64 hour round-trip train ride, which he made without any problems, from Laurel to Boston in December 2016. We met with specialists but in the end, they echoed the MS doctor’s response, “There is nothing that we can do for you. Due to your age, the health risks resulting from any possible treatment are too great.” My dad was 70 years old, but he was active and full of life. Looking at him and knowing the man that he was, I realized that 70 was NOT old. It was the amyloid that had caused his problems. Although this wasn’t the news we wanted to hear, we at least felt like we had tried our best and explored all of our options.

My father passed away in April 2017. To this day, I still struggle with thinking that the doctors rushed his death. I feel like they didn’t try their hardest BECAUSE he was 70. Granted, we knew that there was no cure for Amyloidosis, but I still feel like because he was not THEIR father or THEIR family member, they weren’t that invested in trying to help. I continually pray that God would remove these feelings from me and help me realize the blessing in my father’s suffering.

Because of our father's diagnosis, my two brothers and I were tested and we too have the V122I gene. I was the first to be tested because I have Proteinuria and Tricuspid Regurgitation. No doctor has formally said that these issues are related to Amyloidosis partly because I'm in my early 30's. It has also been said that the amyloid doesn't affect people until much later in life. I have mixed emotions about this. On one hand, I'm happy because the doctors do not think it's anything to be concerned about. However, on the other hand, I'm thinking, "SHOULD it be a concern?" Sometimes I feel like because of this wait-and-see game, I'm a walking time bomb. I'm afraid for my brothers because they are approaching the age-range of when it's believed that the amyloid deposits begin to accumulate and affect organs. I also worry about our mother who has to deal with the loss of her husband and wrestle with the possibility that her children could meet the same fate.

Even in death, my father is still taking care of his family. It was because of his diagnosis that we even heard of Amyloidosis and in our journey to learn about it, we found that there are many others in the world who are battling this. We've gone to conferences and learned that pharmaceutical companies are working to find cures and treatments. I'm so thankful that God has allowed there to now be a solution to the amyloid problem instead of the common response of "I'm sorry, there is nothing that we can do for you." While great strides have been made, I do know that there is still more work to be done in the learning, coping, and hopefully elimination of this terrible condition. I pray that medical schools and doctors devote more time in learning about Amyloidosis and how it not only affects the patients but their families, too. I pray that Amyloidosis testing becomes a medical practice standard. I pray that the medication and treatment is affordable and available to those who so desperately need it. I pray that the insurance companies don't penalize and punish the people who have the amyloid gene. I pray

that my father and the countless others who have died without ever being correctly diagnosed with Amyloidosis would not have died in vain.

-Kimberly

To whom it may concern:

My name is Linda. I am 71 years old. I have hereditary ATTR Ala60 amyloidosis.

My aunt, dad, and three cousins have died from this disease. Symptoms that my relatives have had are heart trouble, wasting away of muscles, autonomic nerve issues, and gastrointestinal issues. My cousin was told that her intestines were like a glass jar. No food was being absorbed, and she had constant diarrhea. The food just went straight through her body.

When I started having symptoms in 2013, I was distraught thinking about the horrible future that I was about to face, and my husband would have to be my caregiver. My first symptoms were extreme fatigue, numbness in hands and feet, and gagging when seeing and smelling certain foods.

December, 2015 I was blessed to be one of the last people to get in Alnylam's Partisiran clinical trial. After eighteen months on the trial, I have been on open label for thirteen months. Partisiran has stopped the progression of my disease. Not only did it stop the progression of my disease, it gave me hope for a brighter future.

Other people in my family have the gene for this disease. When they develop symptoms, they need medicine and hope. What a miracle it will be if the Alnylam and Ionis' drugs are approved by the FDA.

Then comes the question will we be able to afford the medicine. I understand that a great deal of money has been spent to develop these drugs, and the drug company needs to make a profit. If the drug is priced at a reasonable price, more people can get the drug. Therefore, more profit can be made. If it is priced at the upper limits and only a few people can afford it, less profit will be made.

I am very grateful for all the companies, researchers, doctors, nurses, and patients who have been a part of this journey. Without them none of this would have been possible. And thank you for your time in considering the pricing of these drugs.

I am 67 years old, female and a val30met carrier. I am not symptomatic at this point. My father was about 80 when he was diagnosed with hATTR and he died about 8 years later from complications of the disease. He was too old for a liver transplant and also for any of the few clinical trials that were available during that time. He only received symptomatic treatment, which was not much.

There are 4 other known members of my family who also carry this gene mutation, with numerous members of the next generations who have not yet been tested, so this disease may impact many of my family members. We are anxious to have better treatment options.

My brother, who is 69, is having symptoms of peripheral neuropathy, and he is very likely headed toward needing to take some drug therapy to deal with his disease. I have read some of the projections of costs of the potentially approved drugs and the numbers are staggering. Even if we had the funds, would we want to spend hundreds of thousands of dollars per year for the medication? For how many years? What if Medicare or private insurance don't cover them? Is it worth it for the insurers to pay that much? I certainly want the drug companies to recover their costs and make a profit, as I am very grateful to the companies who have taken a chance on developing drugs for rare disorders. But what amount is reasonable?

I hope the pricing will be manageable for all concerned and that insurance companies will cover them. And I hope they will be available for all needy folks.

Thank you for your consideration.

Sally

I have had six generations in my family that have died from Amyloidosis. We have traced it back to my Third Great Grandfather due to the nature of death certificates we have researched. I have felt so alone trying to find anything for a treatment or cure. Medical professionals do not know what it is, based on my interactions, and neither do your family and friends. It took a long time for me to find a support group. I have traveled to numerous doctors to find someone who deals with amyloidosis. I am lucky that we discovered it when we did. An orthopedic hand surgeon was willing to go out on a limb and test tissue from my right hand in a carpal tunnel release surgery. I had surgery three times when I decided to check for amyloid deposits. My wife kept researching the research on Amyloidosis even after my mother passed from it. She had information when my family may need it. The majority of people have that surgery only have it once in each arm. I have had it done six times as of July 2018. My family were told by medical physicians that "it was all in their head." My cousin and my mother were both told that from different medical physicians. It requires a constant vigilance that most diseases do not. There is no universal protocol. Amyloidosis has made me feel like a hypochondriac. We have had to rule in as much as we rule out symptoms/tests to make the most informed decisions I can. A patient can not make an informed decision about their health with scarce information.

I have Hereditary Amyloidosis of mutation of Romanian descent. It is one of the rarer mutations out of over 120 kinds. My wife has only found two medical case studies from Romania about his particular type. There is nothing else available on peer reviewed searches. Both Romanian patients were experiencing some of the same things I have. We are just waiting on the next "new normal". I am 44 years old. I was 36 years old when I was diagnosed. I was 27 years old when my Mother passed away from this disease at age 48. She was diagnosed in 1997 at age 44. My maternal Grandfather passed away (age 50) of Amyloidosis when my mother was 10 years old. My youngest sister was 17 years old when our Mother passed away. Mom had four children total. Two of the four children have been tested and found positive for the mutation. The other two sisters are trying to decide if they should get tested.

My father and I worked different shifts at the same manufacturing plant to make sure there was always someone home with Mom and my sisters. We never once placed her in a nursing facility for respite even though she asked to be. It was important that she spend what ever time she had with her family. Besides her local primary doctor we sought treatment at UNC Chapel Hill, University of Virginia, and University of Pittsburgh. Two to four hour drives in a large passenger van with a camping toilet in the back so that we could make it back home. Her need to go to the restroom was right now and not the next exit. All of the facilities we sought decided she was not a good candidate for liver transplant.

My mutation attacks the heart, eyes, the nervous system, stomach, intestines, ligaments & tendons. I went through the process to be a liver transplant candidate in early 2017. Amyloidosis patients have a compromised immune system. Everything done to them takes longer to fully recover and heal. I was recovering from a tendon and ligament repair on my right ankle from November 2016. If I was not able to walk, I would not be considered. I was able to walk but had

an ankle brace on the entire time. I have an EMG test by my neurologist every six months since 2010. The thought was that when my nervous system started showing decreased nerve response, that if it reached a certain low point, that would be the time to transplant my liver. My numbers took a sharp dive down in early 2018. We are constantly checking organ function and neuropathy changes. My Red Congo stain biopsies have been positive in my stomach, small intestines, and wrist tendons. My heart is checked each year and we wait. One day it will be my new normal too. Our thoughts on the liver transplant are that it was road bump to slow it down but not stop progression. Why transplant a perfectly functioning liver? You also could add complications from transplant surgery to an already complex disease. Some of the clinical trials would not allow transplant patients. The possibilities limited my already existing treatment as it was.

I decided to be placed on nonactive status on the transplant registry to obtain early access treatment from either Inotersen or Patisiran. I tried to join one of the two Early Access Programs three different times within six months. We were anywhere from ten to two days out from leaving to get the evaluation and the FDA and or Company stopped admissions. We were contacted through a patient advocacy group to talk with the other drug company's executives. They wanted to discuss what patients' lives were like, medical treatments, and burdens. We attempted that drug company's Early Access Program. I have been receiving it since April 2018. We are waiting to see results and drug approval. These drugs are all I have to look forward to. I am worried about the cost of the medications. Medicare is my primary and I have my workplace insurance as secondary for one more year as September 2018.

If someone has cancer, most people understand the burden of disease and current treatments. You mention Amyloidosis and nearly all will say what is that? When we sought a transplant for myself and we spent nearly three hours explaining to a Gastroenterologist why I was asking for a liver. We had to be cleared by him before ever speaking with a transplant surgeon and accepted as a candidate. He never bothered to read the chart. Ninety-nine percent have liver failure and my husband had perfect function walking into his office. He had never heard of Amyloidosis. My wife has a six inch notebook that has my lab results, copies of MRIs, Pet scans, and X-rays, vaccination records, death certificates of family members, medical journal articles, a master list of medications, and list of surgeries. She laid it all out for him to see and copy.

Any treatment that can help should be accessible to all Amyloidosis patients. Quality of life should be the bottom line value. Waiting on test results to decline wastes precious time away from patients and their families. How a patient feels about their existence is more important than any number or mutation you can quantify. Quality of life needs accessibility. These patients need access to treatments and more research. Please help make these two treatments available to all Amyloidosis patients regardless of socioeconomic status. They are each priceless treatments for the patient population and families. These drugs are our ONLY hope.

T.D.

Alnylam's FDA approval of ONPATTRO

This letter is to give a patient's perspective after being on this drug for 18 mo. I was diagnosed at age 59, and the first person in my family to be diagnosed. I have no underlying health or disease processes and was not on any medications prior to diagnosis. Since diagnosis I am on Patisiran, Vitamin A and a proton pump inhibitor. In the last 2 months my neurologist has added Diflunisal as well.

I have been enrolled in the EAP w/ patisiran since February of 2017. I have had treatments every 21 days since then. I continue to progress.... The peripheral neuropathy, before i started on Patisiran had progressed just above my knees. It has NOT progressed significantly further up my legs since I started on the medicine. But the weakness and numbness has worsened below my knees. I now have neuropathy carpal tunnel in my hands and up forearms. I had carpal tunnel surgery some 20 years ago on both hands. Since on the patisiran - I have had another carpal and elbow release on my right arm for continued worsening symptoms. I have more trouble walking.... I now wear bilateral ankle foot orthotics, I always use at least 1 hurry cane and an electric cart at the supermarket and big box stores. But now I have a brand new symptom since starting on the Patisiran, I have documented neuropathy in my tongue.....I am having trouble swallowing , pushing food to the back of my mouth. I am having trouble talking, frequently cough and choke.

The effect on my job is drastic. I am still working along with a lot of grace from my company. I am a sales rep for a large manufacturer...where I obviously need to talk and present my products. (But I now slur my words!). The things most people take for granted are obstacles for me. I need to park, walk a distance, climb up a curb, and carry in heavy samples (which is becoming more and more difficult), and I need to stand ...problem is - I really can't stand up for more than about 60 seconds at a time before i have to sit. My job requires me to set up fixtures that come off of a truck and get them in the store to organize them. This last part is impossible to do as I really can't carry anything and walk. I get a lot of assistance.

I am socially isolated after my work day. I lack any further energy. At meals I cough, choke and work hard to move food around in my mouth making a ticking noise.

After saying all of this ... I am certain Patisiran has not halted the progression of my disease... True- I am not progressing at such a rapid rate as I did in the Fall of 2016 . I lost 45 lbs prior to diagnosis and the neuropathy progressed from my ankles to the knees. I have gained back about 25 lbs since on the Patisiran. Being misdiagnosed as pre diabetic causing my neuropathy, I religiously cut out all starches and sugars from my diet. After seeing a dietician, I have been eating high protein, high fat, sugar, and starches. And have doubled my caloric intake.

Presently, I am still very weak in the legs, the neuropathy is above the knee, into my hands and arms now . Even after another carpal tunnel surgery in the Fall of 2017, I have little to no improvement. I am now slurring my words. A video documented my gait under the exact conditions before i started the patisiran, in Feb 2017and then 1 yr later in February of 2018. There is a deterioration in my gait after being on the medicine for 1 year.... My neurologist has subsequently - put me on diflunisal in addition to the patisiran.

I understand that Alnylam wants to recoup their \$2B and 16 year investment... I understand market share/ proprietary products...

But- I am looking at the \$450,000 price tag and wonder: Costs vs. Benefits? It is unnerving to think of this cost for a medication that is not a cure and has no end point in sight. I am also the first family member to be diagnosed so I am walking totally in unknown territory about this disease.

- 1.) I AM still progressing! ...Maybe I need a higher dosage?
- 2.) Will my company's insurance even cover this at all? (it's a private company w/ private insurance for their employees)
- 3.) If they cover it - will my company pay such a large expense for just 1 employee?
- 4.) I am a 30 year employee But- Will they find a way to terminate me....To eliminate this cost,
- 5.) And If I lose my insurance My wife and daughter do too!. As they are on my insurance.
- 6.) We are too young for Medicare,,,,, We are 4 years away from Medicare coverage.
- 7.) When I retire/ go on disability-Will Medicare cover the cost of this drug?

To whom it may concern:

My name is Kendra Eaken. I will be 46 in October, married with two sons and live in Antwerp, OH. I received a positive diagnosis back in 2003 from Dr Merrell Benson. Dr Benson has been a life-long presence in our lives, even coming to my grandmother's funeral.

Like my cousin, Dustin Kaehr (who is way more eloquent than I will be!), I also remember getting blood drawn as a child by doctors who needed it for research. When I was 24, my grandmother passed away at the age of 72. Three of her brothers also passed away (ages 55-61); two of their sons also passed away in their early 60's. My mother also lived with symptoms but cancer took her first.

So far, I am experiencing numb hands. I wake up every morning with numb hands and no strength. My kids have to help me open a water bottle etc. It is difficult to do everyday things: wash dishes, dry my hair, eat a sandwich, type, drive, talk on the phone, walk my puppy. I have to drop my hands every so often to refresh them. I know that these things aren't the worst thing that can happen and I'm thankful. But I know that it will get worse. I've seen it with my own eyes. Fortunately, the disease has not progressed to other organs yet. I keep a close eye on my eyes, no pun intended, and my heart. But it will progress and it scares the heck out of me and my family. I want to be around to see my son's graduate and get married. I would love to hold a grandbaby. Enjoy a retirement. I desperately need access to the drugs that are coming out. And the drugs should be reasonable. I can't afford \$450,000. No one can. I won't live long enough to pay off that bill.

My whole family has provided tissue and blood for research in hopes of one day finding a cure. Most recently, my cousin had to fight to receive a liver transplant and my other cousin signs up for every treatment/program test in the surrounding area. I am beyond thankful and grateful for all of the doctors and researchers who have given thousands of hours to creating a drug to help families like mine.

Thank you so much for your time and consideration,

Kendra M Eaken

Mark D Erwin

August 14, 2018
Regarding inotersen

My experience with inotersen (TTR Rx to me) in Dr. Merrill Benson's cardiomyopathy study has been miraculous. My Cardiologist at Scripps has been blown away by my progress.

This drug is saving my life and has enabled me to reverse the damage done and symptoms of cardiac amyloidosis. My heart function is nearly normal again. My heart thickness has decreased over the last 3 1/2 years I have been on this drug. My energy levels have been returning to normal despite my getting older. My GI tract function is dramatically improved and nearly back to normal before the onset of this insidious disease that I saw kill my father slowly.

I have been a Masters swimmer for many years. Three and a half years ago I had difficulty completing a workout. I needed an afternoon nap. It was apparent my heart function was impaired as I have been an athlete most of my adult life. In the last few years I complete all the workouts, am swimming faster with more endurance. I swim 14,000 to 20,000 yards a week.

I have no side effects from this drug. This drug is literally saving my life. It has given me my health back. I fully believe I can live a normal lifespan now based on my overall health and activity level thanks to Dr. Benson and inotersen (TTR Rx to me).

I am glad to talk to or meet with anyone to further progress on getting this miracle drug approved. I am glad to submit actual reports if requested. I was told only five pages and only word in Times New Roman 12 font.

Baseline Echo 2/9/2015 Clinical Indication Congestive Heart Failure
IVS Diastolic Thickness 1.7 cm
LVPW Diastolic Thickness 1.7 cm

Echo 8/3/2018
IVS Diastolic Thickness 1.2 cm
LVPW Diastolic Thickness 1.3 cm

Baseline Cardiac MRI 2/20/2015
Classic MRI findings of cardiac amyloidosis with outer wall and inner wall four-chamber enhancement
Myocardial Mass ED 231.12
End diastolic volume 62.85

Cardiac MRI 12/29/2017
Addendum: Additional LV parameters: Myocardial mass 161 g. End diastolic volume 192 mL.
IMPRESSION:

1. Significantly and progressively improving LV hypertrophy since 2015 with residual hypertrophy in the basal and mid septum measuring up to 1.9 cm. No other LV hypertrophy or RV hypertrophy identified.
2. Progressively improving myocardial enhancement as described.
3. Stable mild bilateral atrial enlargement. Stable preserved biventricular wall motion and function.
4. Mild aortic regurgitation. The other findings are unremarkable.

Other findings: Mild aortic regurgitation. The other cardiac valvular structures are without significant abnormality. Unremarkable pericardium. Normal aortic and pulmonary arterial calibers measuring 3.8 and 3 cm, respectively.

Sincerely,

Mark D Erwin ChFC MA Spiritual Psychology

To ICER:

Amyloidosis FAP-TTR-Hereditary

My day-to-day life has changed tremendously. I actually feel like I'm being eaten alive with this disease. My legs and hands have become numb, therefore, my walking has gotten worse and worse. Holding objects, or just eating with utensils, has become a struggle for me. I'm constantly dropping things. I live with my girlfriend and that's a big help for me. She drives me to my doctors' appointments. She tries to take me out everyday so I don't get depressed. So I'm thankful for her. As far as my children go, I'm so devastated that they have to one day be tested to see if they carry this horrible disease also. I have joined a few trials just so I can contribute to helping with this disease for the next generation and so on. I'm 76 years old, and I have this disease for 9 years already. I'm hoping this drug is a miracle drug for all concerned.

I had to retire approximately 5 years ago because I drove a school bus with children. I wouldn't want to put anyone in danger due to my legs being numb. So as I stated before, I more or less don't drive anymore so I'm thankful I live with my girlfriend as she does all the driving.

This new treatment means the world to me because it gave my kids possible hope for a normal life. They won't have the struggles I have. They have hope and I'm truly thankful for that.

My emotions are all over the place. There are days I'm so depressed and then there's days I'm hopeful. Patisiran will help me at 76 years old. I'm an entertainer and singing on stage is becoming rough because just standing is a struggle for me. So now I'm still able to sing because I sit on a high stool. If I have to give up singing, it will be another major disappointment in my life that I have to bare. If it wasn't for my amyloidosis diagnosis, I would be a very healthy, strong individual. I was a school bus driver, along with being a construction handy man.

I'm so worried about my insurance challenges that lie ahead of me. I'm on medicare and I have a supplement (the supplement usually doesn't pick up any of the bills). I'm praying medicare can help us elderly patients with paying for this drug.

I'm one of three brothers that have this disease. My oldest brother called me one day and told me had the disease and that I should be tested for the gene. Needless to say, I had the gene and a few short months later, symptoms started. I then called my younger brother and told him to be tested too. He was convinced he didn't have it. Sad to say, he had the gene and the symptoms surfaced on him too. My oldest brother has since passed from this horrible disease.

This is a nightmare for my family. It's scary. I have three children and six grandchildren that I worry about constantly.

I pray this drug is our answer and I hope we don't face future challenges with the insurance companies giving us a hard time for payment. Life is precious ... Please help us all.

Sincerely,

Thomas Ferrara

To: Whom It May Concern – ICER

From: Edward Ferry - Hereditary Amyloidosis patient

Dear Sirs and Madams,

I would like to introduce myself. My name is Edward Ferry. I am a 57-year-old plumber from NYC. I was diagnosed with HATTR in April of 2017. Before that, I spent three years of being tested by multiple doctors for different illnesses and getting only negative tests results for all of them. In the interim I lost 30 unintentional pounds and could not walk up a flight of stairs. It was a medical odyssey and an emotional roller coaster. When I was diagnosed, I was told that I would lose the ability to walk and take care of myself before my death within three years. The doctor told me that the only treatment for the disease was a heart and liver transplant, but that I would not be a candidate. You are never the same after hearing that. And unfortunately, I know now, that there are many people like me. I am so not alone. There are so many people walking into a doctor's offices with the unknown and living through nightmares like this.

The disease has affected all aspects of my life, including and most dramatically my family. I am a husband and a father of two adult children in their early twenties, one female and one male. The disease has changed all of us. I am a much more emotional person and have acquired a vulnerability that I never had before. The experience was dreadful for my wife. It has turned her into one some hell of a fighter. My kids are devastated but have toughened up as well. The fact that the disease is genetic makes it unbearably painful. Of course, it's still torture, but I say to myself and my family, "No more crying." One of the only things that I remember from that dreadful day that I was diagnosed was "no treatment". It still hangs over my head. But fortunately, I was lucky enough to get on a clinical trial with Alnylam pharmaceuticals in December 0f 2017. This treatment has given me hope, encouragement, and optimism with a different outlook for my future and the future of my children.

Before this disease, I had a charmed life. If I wanted it, and I set my eyes on it, and worked hard enough at it, I obtained it. I felt like I was the luckiest man in the world. And wouldn't you know, since being on that drug, every once in a while, I think that maybe I still am lucky. At least I have a chance. "No treatment" is not the future that I am facing right now. I hope that my letter has some impact on YOU the representatives of the ICER and that the people on the other side of the desk understand what WE the patients are going through. Believe me, the treatment (Patisiran) is helping me, and I could not be more grateful to Alnylam pharmaceuticals. I have been experiencing enjoyments this year that I never thought that I would last year. How do we put a price on that? What if this was happening to you or a loved one? Could YOU put a price on it?

My story is no different and no more dramatic, than everyone that I have met with this disease. The reason that I wrote this letter is hopefully that the organization can have effectiveness over the insurance companies. We need to find a way that all patients can get treatments when needed and that Drug companies will have funding for new research and development. My story would be completely different if not for Drug companies investing in research. Never mind the fact that myself and most have been paying insurance premiums for

their entire life. Good health care at an affordable rate should be part of the American dream. Please do whatever you can so that drug companies can have money for research and development, and that insurance companies can fund the cost of these drugs without devastating a family financially. I realize that this is a monumental task and I personally want to thank each one of you. I am sure that everyone that reads this letter would love to solve this dire problem which can potentially affect any one of us. And God forbid should something happen to you or a loved one, maybe they can have a little good luck as I and my family did. I wish all who read this letter the best health. Hug the ones that you love tonight and remember your life can change in a second. You never know how good you have it until you don't have it. Thank you for your time.

To Whom It May Concern:

My name is J.F. I am 60 years old, married with 3 adult children (28, 26, 24). I have ATTR Amyloidosis (T60A) that I inherited from the paternal side of my family. My Dad went to numerous physicians for cardiac related symptoms before he was referred to the Mayo Clinic in the late 1980's and was diagnosed with ATTR Amyloidosis. He was fortunate to have experts diagnose him so at least we knew the cause for his symptoms. But there was no treatment. In 1989, my siblings and I were given the opportunity for genetic testing to see if we also carried the ATTR mutation. One of my sisters and I have the gene; two additional siblings do not have the gene; two others chose not to be tested.

My Dad's diagnosis came late in the disease process and he died at age 67 in 1993. His type of Amyloidosis (T60A) included peripheral and autonomic neuropathy with cardiac involvement. It was awful watching my Dad decline over the years—numbness in hands and legs, walking difficulties (eventual use of walker, a wheel chair, and being bedridden), out of breath constantly, swelling in legs, extreme loss of weight and dehydration due to constant diarrhea. It was hard to watch him die, by slow measure over the years, as his body's systems and organs shut down, becoming more and more "infested" with amyloid. His heart became "leathery" and was simply unable to pump anymore. (It is probable that my paternal grandmother also died from ATTR T60A, given that she had similar symptoms as my father, but diagnosis was not available to her at that time. We just knew she got skinnier and skinnier as she had significant diarrhea and literally wasted away.)

Watching my Dad die, I was very aware that this is likely I would follow the same path.

It was 25 years after my genetic testing when I began experiencing any symptoms (2014). I was always aware that it could happen to me. It was easy to somewhat "ignore" but it was always in the back of my mind. However, following my Dad's pattern of symptoms appearing in his 50's, I began experiencing numbness in toes, feet, lower and upper legs, fingers and hands. Mayo physicians confirmed the Amyloidosis diagnosis. I did not have to spend huge sums of money trying to figure out what was the problem as so many do with this disease. I know what awaits and I know the general timeline. Without any treatment, I can expect increasing peripheral neuropathy symptoms, autonomic symptoms, and my heart becoming leathery...my body wasting away just like my grandmother and my Dad.

I have been recently included in the Expanded Access portion of Alnylam's Patisiran study at the Mayo Clinic, beginning in late February 2018. My husband and I drive 6 hour one-way to get the treatments, 4 hours of infusions, and 6 hours drive back. I am willing to do this because there are no other treatments available to me. It's something I can DO rather than fatalistically wait while symptoms increase. I have been encouraged, not because I have noticed any reduction in symptoms yet (at this early involvement in the program) but because there is a real chance to limit progression of the disease. It gives me hope. It seems to be a lifeline while more research is done to identify future treatments and possible preventions of this horrible disease.

PLEASE help make new ATTR related medications affordable, giving reasonable access to all of us with this disease. While the idea of facing the same death as my father is frightening, despair comes when there is a known/available medication but is unaffordable. Yes, there is certainly a cost to bringing these drugs to market. But I hope that it will be prorated over the lifetime that individuals will be using it.

I have only told my story. I consider the many others I have met along my Amyloidosis journey who have the disease, have the gene, or have a fear of having the gene.

Please give us hope. PLEASE give us hope with affordable medications.

As an aside, I would like to share additional thoughts on the ATTR Amyloidosis Support Groups and their impact on me. They are part of the Amyloidosis journey for so many of us. I am so thankful to be connected to this group and I am grateful for the “team work” concept that they have developed in fighting ATTR Amyloidosis. They build HOPE. That cannot be underestimated. Nor can the impact of education, the coordination of resources, and the momentum they help to build.

I have attended two of the Chicago area conferences on ATTR Amyloidosis (2015 and 2017) and walked away extremely encouraged. Admittedly, I was hesitant to go to the first time. I was fearful I would be only one not in a wheelchair or on a ventilator. Boy, was I wrong! These conferences educate and inform on latest research into the disease and the medical and pharmaceutical developments. I, in turn, have been able to educate many others. Ultimately that results in a savings of money and emotional energy. So many people with this disease spend excessive amounts of money going to many, many doctors trying to figure out what all these weird symptoms are, only to be given inaccurate diagnoses and inappropriate treatments due to it being a rare disease.

I live in a rural area and that simply complicates finding physicians who have any knowledge about Amyloidosis of any type. Almost every physician I have met says that they know what it is. Surely,...they do know it is a disease related to misfolded proteins. A few family physicians have admitted, however, that they have only had a brief lecture on it and were told that they will not likely ever see this in their practices. I do my part to give them the written information available from Amyloidosis Support Groups. And then I drive 6 hours to the Mayo Clinic to be treated.

And I continue to work with the Amyloidosis Support Group and the various other organizations and companies that are working together towards greater understanding and treatment of this disease.

Thank you for letting me share part of my Amyloidosis journey.
J.F.

Ohio

August 11, 2018

Dear Members of the ICER group,

Thank you for allowing input from members of the Amyloidosis community for your project on drug pricing.

I am a late-60's aged female from Ohio, one of a large family. About a year and a half ago I was diagnosed with the Val 122 Ile familial amyloidosis mutation, as were three of my siblings. One has no symptoms yet, but the other three of us have a number of troublesome neurologic symptoms, some undiagnosed for as long as 20 years. Perhaps more important than the neurologic issues, this mutation is also responsible for heart failure. Our Dad and his mother had heart failure in their seventies, but amyloidosis was under-appreciated and not usually diagnosed then. All four of us have been checked for heart failure and none have any early signs, but it develops over time and none of us is out of the woods yet on heart failure development.

My daily life is somewhat restricted by the changes from amyloid neuropathy. The nerves to my sweat glands are involved by my disease, so that I don't sweat during exercise or in hot rooms or hot weather. This puts me at risk for heat-related illness. I do strength-training at a specialized facility that is intentionally kept at 62-65 degrees, but I don't regularly do endurance or cardio-type workouts because of the warmth of most other gyms. The potential of overheating keeps my husband and I from many outdoor activities. Also, one of my feet has lost its arch and the ankle turns in; coupled with some balance issues in my feet, this keeps me from consistently walking well on uneven ground, or up and down hill inclines.

My work involved fine motor skills with my hands for about 90% of the job and I realize now that those skills were weakening over the last several years that I worked. They have diminished even more in the years since retirement. My fingers and hands are now very numb, weak and uncoordinated. I have lost my ability to type with more than two fingers, my handwriting has become unreadable, and my printing resembles first grade. (Of course the other 10 percent of my job required writing up slips and then typing info into the computer. At the time I blamed the writing and typing difficulties on my morning coffee.)

There are other hidden symptoms due to the nerve problems from amyloid, like the sweating problem. There are a number of digestive problems caused by amyloid nerve effects also. I only have a few of those effects, but they are somewhat troubling. My husband is quite a good cook, and new recipes, our garden and the farmers markets are a source of pleasure. However, the amyloid has diminished my sense of taste and my appetite, so the hobby is less enjoyable. I do,

however still lead a reasonable life, shopping, driving around town. My amyloid doctor is in Columbus, about two hours away, and I go there alone.

A new treatment would presumably slow the progression of the neuropathy. To know that my strength, my breathing and my swallowing would remain mostly intact would be exciting, since I fear loss of mobility, a feeding tube and a ventilator in my future. However, I would ideally embrace a drug that could stall the neurologic progression as well as any cardiac disease progression.

Financial considerations have been troubling for us. I am pretty well-read about the financing of expensive drugs in the US over the past few years. We both have Medicare and their Part D drug coverage, which I understand does not negotiate drug prices like, for example, the VA negotiates. I also have read that drug cost-assistance cards, etc. are not acceptable to Medicare. It seems that over the past years there have been an escalating series of strategies used by Medicare patients (and others) to deal with rising out of pocket drug costs: tighten your belt, skip doses of pills, go back to work, ask your kids for money, mortgage/sell your house, move in with your kids, have a bake sale/fundraiser/go-fund-me page. In the amyloid-medication situation, we have been quoted impossibly high list prices for the new drug and others still in the pipeline. All of these numbers have come with justification that the investors demand that the list price be as high as possible. Well, those “old” methods of raising money for drug purchases probably aren’t enough since the sums needed now are up to the heights found in winning lottery tickets or extremely high net worth families.

Fortunately I have an amyloid specialist who has me on the “old” drugs, four of them that are relatively cheap and have been proven to slow the progress of the neuropathy. I have the luxury of continuing with that plan, waiting not only for a drug to slow cardiac amyloid but also waiting for a change in drug pricing in the USA.

Thank you for your attention to my situation. C.A., Ohio

To whom it may concern:

My name is Dustin Kaehr. I am 42 years old, married with 4 sons (ages 15,13, 11, 9), and live in Bristol Indiana. I have hereditary ATTR Ser84Ile and have been around the world of Amyloidosis my entire life.

From an early age, I remember getting blood drawn by doctors who wanted it for research. When I was 18, my grandfather, Phil Kaehr died at the age of 63. In 2009, at the age of 53 my father Scott passed away. My uncle passed away at 57. I had a two great uncles pass away at 62 and 54. All deaths were the result of ATTR and no male with the disease in my family has lived passed the age of 63. My aunt, age 53, just underwent a liver transplant because of deposits showing up in her heart.

I confirmed my positive diagnosis in 2003 via blood work after the birth of my first son. That blood work diagnosis was confirmed in 2013 via a tissue sample after having carpal tunnel surgery on my right hand because of numbness and loss of strength. While that surgery was just a few years ago, the symptoms have already returned to both hands, due to the continued build of the amyloid. Until recently there have been no other treatment options for the symptoms because there are none. All treatment of current (and future symptoms I know I will have) have been strictly management in nature, designed to maintain quality of life, but do nothing for the inevitable outcome.

The impact of the disease on my life is noticed and felt daily. I have lost considerable about of hand strength and flexibility. I am woken up daily with numb hands and unable to fully close them for the first 15-30 minutes I am awake. The numbness in my hands comes and goes during the day. My hands go numb as I type this (and anytime I type), causing me to stop to lower them and regain feeling. They go numb as I shave. Fingers on both hands are always tingling like they are "asleep". The more work I do with my hands (wrestling with the boys, mowing, running my garden tiller, woodworking, etc) the more severe the pain and numbness become in my hands the days and weeks after the activity. In the last 6 months, I also have been begun experiencing the numbness in my toes, feet, and lower legs.

Fortunately, the disease has not measurably progressed to other parts of my body to the point of causing problems (kidneys, eyes, heart), but it will and my overall health will continue to deteriorate.

In seeing my father and grandfather live with the disease, I know those other areas will be effected in the next 10 years and have negative impacts on my life. I am a runner, participate in triathlons, and other outdoor activities, but as my heart begins to become infected with the amyloid, I know those types of activities will become impossible.

I desperately need reasonable access to the drugs coming for a few reasons:

1. Without it, hATTR will take my life possibly as early as 10 years (I'll be 52) or 20 years (I'll be 62).

2. Even if I were to live to 63, my sons would be 36, 34, 32, 30. I would like to be around to see them marry, enjoy grandkids with Amber, my wife.
3. While we don't know if any of my sons have the disease, the odds are at least 2 do. I would like there to be treatment options for them early. I don't want them to experience the numbness and other things I live with.

My grandpa and father both provide endless samples of blood, tissue, and even their organs after death to Dr. Merrell Benson as he worked on a drug. Today (July 30), I head to Northwestern University to begin taking Inotersen as part of the Expanded Access Program. I wept last night thinking of those two great men and because of their willingness to share and publically battle hATTR, I am receiving a drug. I want the drug for myself, but more so for my younger cousins and kids who may have this disease. I want to show them the given projection of our lives is changing and we can begin to dream different dreams and plan accordingly.

But, this only happens if, when the drugs come to market, they are affordable. This disease does not discriminate based on economic status. Without reasonable access, the consequences, decisions, and/or sacrifices that will have to be made to get the drug will be painful at best and unimaginable at worst. I do not want to have to choose to help send my boys to college or have access. I do not want to have to have to work into my 70s only to pay for access the drug that even allowed me to live that long. Why work to take a drug that prolongs my life, when that prolonged life will have to be spent working to pay for the drug. Irony. At what point will I, or other ATTR families, have to decide the best option for them as a family, is to stop taking (or not take) the drug and let the disease take it's natural progression. Maybe pay for it through your 50's or mid-60's, but stop then because you can't live the lifestyle you'd like to, and simply enjoy the remaining years as best you can.

I am beyond grateful for those doctors, researchers, and companies that have made the investments into helping families like mine overcome this disease. I realize there will be a cost for these drugs. I realize the law of Supply and Demand. I realize there is a fair market price for the cost of goods. My hope and prayer is all of those things can be balanced in a way the average family living with hereditary ATTR can afford these life-saving medications.

Thank you for your time and consideration.

August 17, 2018

Dear ICER,

My husband K. M. is treated by doctors Merrill Benson, Noel Dasgupta and a wonderful amyloidosis at Indiana University in Indianapolis,

My husband, for four years has been in an investigator initiated study of inotersen at Indiana University for patients with transthyretin cardiac amyloidosis causing congestive heart failure. He has improved cardiac function as measured via 6-minute walk test (6MWT) and improved cardiac structure as measured by MRI and echo. My husband has survived and living a full life after being given a terminal diagnosis.

My husband has not had a problem with his platelets. He is monitoring these every week and has not seen platelet issues or concern of thrombocytopenia.

I believe inotersen is an effective treatment for both ATTR neuropathy and cardiomyopathy. I am blessed my husband has been able to be in this study and alive due to the drug. I have seen first hand how awful this disease was for my father in law and the helplessness when my husband was diagnosed with cardiac amyloid at the age of 60. I had no hope until he began this drug and immediately became better, symptoms reduced and no side effects from the inotersen shot I give him weekly.

P. M.

August 16, 2018

Dear ICER Staff and Consultants,

My family has a long history with TTR amyloidosis. Out of eighteen cousins in my mother's generation, nine of them were affected - a perfect example of autosomal dominant inheritance. I never knew my grandfather because he passed away at the age of 49 in 1975, the same year I was born. Ultimately, my family believes we've traced the source back five generations to our Irish ancestor who immigrated to the United States in the late 1800s.

In our family, with the Asp18Glu mutation, the affected men and women have a poor prognosis. Beginning around age 40 for the men and age 50-55 for the women, those who carry the mutant gene can look forward to progressively worsening cardiomyopathy, neuropathy, and "autonomic" symptoms, leading to extended disability, and eventually an early death. Of all the ways to go, this disease likely ranks among the least dignified, with symptoms including incontinence, inability to exert, lightheadedness and syncope, pathological arrhythmias, reduced mobility, recurring secondary infections, and in my mom's case, even total hearing loss.

When my uncle received his diagnosis in the early 2000s with the help of doctors at the Mayo Clinic in Scottsdale, we finally had an answer for why my grandfather died so young and why other family members were getting sick with mysterious illnesses. At the time, the state of the art in hATTR (hereditary transthyretin amyloidosis) treatment was to remove the source of the mutant TTR protein by transplanting the liver. Several family members, including my mother and uncle, received liver transplants, and one of my second cousins received a combined liver/heart/kidney transplant. Whether the transplants prolonged these family members lives is uncertain, although it is clear that the transplants themselves come with their own set of problems, including a lifetime of immune suppression and related issues.

Now, with the near simultaneous approval of two gene-silencing medications for TTR amyloidosis, we are entering a new era of potential treatment options that directly target the source of the disease. The cost of these drugs may be high, at least at first. However, the cost of treating the disease with multiple organ transplants is also high, with arguably worse outcomes. From a patient standpoint, these new drugs move us closer to the ideal goal of treating TTR amyloidosis as just another chronic health condition requiring regular medication, similar to how diabetes is now easily treated with insulin and other drugs.

I represent the new generation of patients who already knew they were gene-positive thanks to prior DNA testing. I was fortunate to catch the disease very early when I was 40 years old and immediately began taking diflunisal. Two years later, I enrolled in the Expanded Access Program (EAP) for Patisiran on the basis of my neuropathy symptoms. I realize this is only

anecdotal evidence, but within about three months my appetite came back and my uncontrolled weight loss reversed. Now, at eight months, most of my gastrointestinal issues have resolved, and the neuropathy and cardiomyopathy symptoms have been stable. I sincerely believe that the Patisiran has stabilized my disease progression, where diflunisal only slowed it down.

Thanks to the early diagnosis and the new drugs, I am still relatively healthy. I'm still able to work as an IT consultant, be a father to two children (ages 10 and 4), and retain a fairly active lifestyle. I've had to slow down a little due to disease-related limitations, but if I can even maintain this level of health indefinitely and continue to work and provide for my family, I will be very happy. Ideally, I would prefer to continue with Patisiran or other new drugs currently in development, completely avoiding organ transplant with its associated expense and risk. For my kids' sake, I hope to break the pattern set by my uncle and grandfather who were already too sick to work at my current age of 43 and neither of whom made it to age 50.

I believe Patisiran and Inotersen are the treatments for which we have been waiting for many years. Combined with early diagnosis, what used to be a death sentence may soon become simply another manageable chronic health condition. I hope that health insurers will see the value these new drugs provide and make them available to patients as soon as possible.

Sincerely,

S. M.

August 17, 2018

To Whom It May Concern:

I was diagnosed with hereditary amyloidosis in December 2016. I am fortunate in that I have a neurologist in my hometown that was able to quickly diagnose that I have hATTR. She referred me to the University of Chicago where I am currently seeing a neurologist and a cardiologist who are both familiar with Amyloidosis. Shortly after my diagnosis I was referred to the University of Iowa and was able to enroll in Alnylam's Patisiran Expanded Access Program. I have been receiving infusions every three weeks since March 2017. While I have not noticed improvement with respect to my symptoms, I think they have not gotten worse. I believe that Patisiran has and will allow me to have a relatively normal life for a person my age. I see others around my age that don't have Amyloidosis and appear to be in much worse health. Everybody's got something.

Amyloidosis has affected me both physically and emotionally. On the physical side I have constant discomfort in my hands in the form of numbness along with sensitivity to temperature. The numbness makes it difficult to pick up small objects, to maneuver clothing such as buttons and zippers, to handle paper such as turning pages. I seem to have lost my coordination with respect to small motor skills. The quality of my handwriting has deteriorated which makes me worry that my signature may not be acceptable as a form of identification. I can no longer touch-type. I have to use the hunt-and-peck technique which is much slower. I have also experienced a reduction in strength. For about a year my gastrointestinal issues were mostly constipation, but it has now taken the form of alternating diarrhea and constipation. I'm still trying to learn my body's signals so I can determine when I'm about to transition from one cycle to the next so I can manage my diet and use over the counter medications to mitigate the symptoms.

On the emotional side I get frustrated when I cannot perform, simple everyday tasks. I feel like I'm a burden on my family, asking them to do the simple things I used to be able to do. I feel that I complain a lot and talk too much about my disease, but talking about it helps me understand it better and accept my disease and its consequences. I try to just suck-it-up and keep my mouth shut, but I seem to fail at doing that.

Financially, Since Patisiran (Onpattro) has been approved by the Food and Drug Administration, the price has been announced to be \$450,000 per year, \$345,000 with discounts. I am afraid that even with financial assistance, I will not be able to afford the drug at all, or will burn through all my retirement savings, then will not be able to afford the drug and leave my widow penniless. I expect that other drugs in the pipeline, Inotersen and Tafamidis will have similar pricing structures that will keep them out of reach of the average patient.

I am in awe of what the pharmaceutical companies have accomplished and I realize that they have invested billions of dollars in research and development and need to recover at least some of their investment. The cost to the patient is clearly out of reach. I wish I had a solution to this dilemma.

Despite all of these negatives, I think that I have been blessed with many positives. I was diagnosed very quickly after the onset of my symptoms. I was referred to knowledgeable doctors who were able to connect me with Alnylam's Expanded Access Program for Patisiran and Patisiran has helped me to have a nearly normal life. I only hope and pray that my blessings continue and I will be able to continue with my Patisiran treatments.

Thank you,

M.M.

To whom,

I have been in treatment for Amyloidosis for two years today. I have had many positives and negatives during that time. I have neuropathy that has weakened me to unable to use my hands or legs for basic functions. I am lucky to have a great wife who has been unbelievably helpful in building a great support team that makes me able to deal with the disease.

15 months ago I started on Patisiran treatment at Penn. Since then between the treatment, physical therapy, and good home care I have improved my ability to function on most basic in home activities.

I am hoping that the FDA approval of Patisiran is made it an option for Amyloidosis patients. As I can see the people who suffer can be diagnosed and treated much faster and better.

I can handle the changes in my personal, business activity, and financial burdens that have me very drained physically and financially. However I think there are people who are suffering more and less than I so please support anything that moves treatment of Amyloidosis.

Thank you,
MR

Report to ICER

I started on the Inotersen open label trial for wtATTR in January, 2018.

As of my 6-month follow-up visit, most of my “metrics” were as good or better, and those close to me think I’m definitely improved.

I can supply further details and numbers, however what I’d like you to understand are the importance of the emotional and psychological aspects of being on this treatment.

Given the proclivity of BioPharma to focus on trials for patients with the mutant for of TTR amyloidosis, despite the mounting evidence that the wild type may be more prevalent, but not being diagnosed by most physicians, I am grateful for “any ship in the storm.”

When one has an unerringly progressive disease, leading to death, it is terribly frustrating not to have treatment options, regardless of their flaws. Being accepted into the Inotersen trial gave me new hope for extended quality longevity, allowing me to remain professionally productive (see below).

I am hoping that decision-making bodies in this country, and elsewhere, take into account the expected course of a disease process, the usual ultimate outcome and the lack of treatment options for those afflicted.

Now, why would treating an elderly patient like me, in this type of setting, be worthwhile? Here’s a little about me personally that help answer the question:

- always athletic and still am, but not with great talent....1960 semipro soccer, U.S. Eastern District League; 1964 guard on the University of London basketball team (lost in the national championship game), competitive tennis until about 10 years ago, playing in local USLTA championship matches, workout for 1.5-2 hours weekly

- following retirement from active practice, continue to teach at and periodically present Medical Grand Rounds, Inova Fairfax Hospital

- multiple ongoing informal medical consultations for friends, friends of friends, and acquaintances.....i.e., sort of a “medical ombudsman”

- set up local and national email groups for wtATTR patients, interpreting recent related medical articles, providing a Primer in layperson’s terms on Gene Editing, etc.

Thanks for your interest,

Paul G. Rochmis, M.D., FACP, FACR

Clinical Professor of Medicine, Georgetown University Medical School
Emeritus Chief, Rheumatology Section (1972-2005), Inova Fairfax Hospital

August 16, 2018

To committee members:

August 2018

Let me first thank each ICER member for your participation in this review of Patisiran and hATTR amyloidosis. I hope that the outcome of your collaborative effort will lead others to improve patient outcomes and control patient costs associated with this terrible disease.

Overview:

I have a personal perspective regarding this disease as my family and I live with it every day. My name is Buddy and I have hereditary hATTR Phe84Leu amyloidosis. I fit the traditional profile as I am a 66 year old male and I exhibit all of the hATTR neuropathy symptoms of an FAP stage 3 patient. I have also been evaluated with a polyneuropathy disability score (pdn) of stage IV. I am not able to work, drive a car, nor care for myself. As you will read, knowledgeable local medical attention is hard to come by. I have been permanently disabled for five years and confined to a power wheelchair.

Family background:

I have been married to my wife for 38 wonderful years. We are blessed with a daughter who is happily married. We experience the joy of three grand kids ages 2, 7 and 8. Neither my daughter nor grand kids have been tested for hATTR. I am fortunate to have both of my parents still living and active. My father is 93 and my mother is 89 and both were tested via Alnylam. My father tested negative. My mother tested positive with Phe84Leu. My mother throughout her life has not been hATTR symptomatic. I have one 60 year old brother, married and they have three grown children. No one in their family has been tested for amyloidosis, nor is systematic.

My journey:

I have been chasing the symptoms of this disease for the last six years. The first four of the six years, my doctors, my family and I did not even know what disease we were chasing. To make a long story short I have been seen by seven different neurologists, treated at five different hospital institutions (three of them world renown), I underwent four surgical procedures for diagnosis and treatment, received weekly outpatient infusion treatments for six months of an alternative drug, and my list continues on and on. Clarity was finally brought to us when a young neurologist in desperation for an answer had me tested for amyloidosis. The results of that simple test eventually lead me to Dr. Berk.

Alnylam:

Eventually I was accepted into the Patisiran EAP clinical program. I began my infusion program with flights to Boston every 3 weeks for myself and my aide. Then I transferred my EAP slot to Mayo Jacksonville, FL where I now continue receiving infusions every three weeks. I am now 15 months into my participation of Patisiran.

Along with infusions of Patisiran, I work in a healthy dose of exercise supervised by clinical therapists four times a week. I believe that this exercise routine combined with the Patisiran infusion program is slowing down the progression of my disease.

I am very happy to hear that Alnylam received FDA approval of Patisiran for stage I & II patients. I am very sad to hear that Patisiran is not being proposed to the FDA for stage III & IV patients.

Summary:

My request is for each committee member to look at the clinical intervention and value of this drug through my set of lenses. With my clinical presentation it is too late for infusions of Patisiran to cure me of this awful disease; but it is not too late for my daughter, my three grandkids and thousands of others laced with this gene mutation to benefit.

Having received FDA approval, I would like to imagine that by the end of Q3 2018, a directive might be proclaimed by the Alnylam board of directors. This directive would authorize the Alnylam leadership team to make this drug patient-affordable, commercially and readily available at all cost to the U.S. patient population; and to accelerate and prevent any further disease progression for those patients living with stage I and II of hATTR. This responsibility will be shared by many, however it begins with your assessment. Please make this drug affordable for many.

Thank you,

B D

We are writing this letter on behalf of ourselves and family members that have passed from Amyloidosis htrr and that are currently living with this disease. We have had my husband's grandfather, two uncles, mother and one brother pass from the disease. Currently one uncle and my husband are on a drug trial. Several cousins and nephews and a sister carry the gene. It was when his brother went to Mayo years after the first Uncle did they discover it was hereditary in the family. My husband's symptoms were worsening in 2014. Since we were aware of the symptoms and knew he carried the gene, we went to Mayo for conformation of the onset. He went on the liver transplant list and also the drug trial. We believed since he continued to worsen that he was on the placebo the first 15 months. Once he started the actual drug we saw a big difference in the use of his hands improving some and his walk staying the same. After being on the drug trial for a full year he decided to stay with the drug and go off the transplant list.

The struggles are great for both of us. As the patient, he struggles with being able to hold onto items, pick up things, writing with a pen and has no strength to use them other than to eat a certain way. His walk is a shuffle with one foot dragging more than the other. Loss of balance, dizziness, light headed, memory loss, depression and has had huge bouts of stomach issues, constipation/diarrhea. He is no longer able to help with indoors or outdoors upkeep of our home. He turned 65 in May and had been on rail road disability which has rolled over to rail road social security. He has a health supplement now and the minimum Medicare drug coverage at this time. He is thankful for the drug trial for the future of his family, including two daughters.

As his caregiver, it is a fulltime job. It's hard for any caregiver. It is stressful, overwhelming and depressing. I have struggles on top of this as I have been disabled since 1996 from a factory explosion I was in. We have an adult daughter diagnosed with mental illness who needs overseen also. So our struggles are real.

Needless to say we are not in a good financial position. Yet we also know without his injections he will deteriorate quickly and pass away. We are in high hopes Medicare will cover the drug and we will be able to afford to keep him on it.

Thank you for reading our story. August 13, 2018 KS & SS

My journey with HATTR FAP is quite long. In fact, it began at birth as did my brother's, my sister's, two maternal cousins, and my son's, the only ones I know are positive for this mutation, Thr60Ala. Our family's story does not begin with us, nor does it begin with my mother, her mother, or her grandmother. It begins perhaps 5 or 6 or 7 hundred years ago when the mutation occurred and became autosomal dominant in my ancestor in County Donegal, Ireland. My family has been living with this disease, and its' horrors, as long as it's been around. That fact coupled with the propensity of Irish Catholic families to have many children tells me this underdiagnosed malady is not as rare as it is portrayed. My mutation is only 1 of 100+ mutations that can cause this condition.

I first became aware of this disease in the spring of 2002 when my brother Dick came to my daughter's college graduation in Pullman Washington. My 6'1" athletic brother (9.5 years my senior) was barely 100 pounds. We lived in Seattle, he lived in my hometown Boulder, Colorado and we rarely saw each other. I knew he had been sick but the shock of seeing him in this state was devastating. Nobody knew what was wrong with him. He had cardiac problems, GI problems and was slowly starving to death. By October 2003 at the age of 60 he was diagnosed with HATTR Amyloidosis and started seeing Dr. Martha Skinner at Boston Medical. He passed from kidney failure in May of 2007. They were unable to do anything for him.

My brother's diagnosis put us all on the road to knowledge and awareness. My brother was reading my maternal grandmothers journal and we discovered that she too had many of my brother's symptoms. She had passed in the winter of 1947 at the age of 58. My mother's diary confirmed the GI suffering and "frail heart" that eventually took my grandmother's life. She was never diagnosed with Amyloidosis though it was a known ailment. I credit my brother, his real for life and fighting spirit with saving my life. Because of what we all learned from his research and experience I took precautionary steps even before my diagnosis.

I have two children. They saw first-hand the suffering and horrible death of their uncle. My worries shifted from my brother to them. I knew that I had some of the symptoms, but I also knew that I only had a 50/50 chance of inheriting the mutation. If I had it then my children only had a 50/50 chance of getting it from me. That being said, my family's track record is pretty dismal. Of the four children my parents had one died of Leukemia right before I was born and the rest of us are positive for the HATTR mutation. So, I set out to have the genetic test to prove to myself that I did not have the "death sentence" disease of my brother.

My primary care Doc of 19 years, Karen, helped me through my brother's death and we began searching for a reason for me to have the genetic test. At that time it was quite expensive and the insurance company needed a better reason than family history. I also suffer from Psoriatic Arthritis, first diagnosed in 2006 and was put on a regimen of Methotrexate, Folic Acid, and Remicade by my Rheumatologist. For the pain I was given high doses of the NSAID Ibuprofen with constant liver monitoring. Through the research I did with my brother I learned of a different NSAID, Difflunisal, and after my brother's death I cajoled my Rheumatologist into a dose of 500mg of Difflunisal per day in lieu of the Ibuprofen. Why not? If I did have HATTR then it might help. If not, it still dulled the arthritic pain. But no reason for the genetic test. By 2009 the numbness in my hands was such that muscles were atrophying and through nerve conductance testing I was diagnosed with Carpel Tunnel problems and the Neurosurgeon

performed the release. At the same time, my knees were shot (I played soccer until I was 45). They were replaced in 2009 and 2010. Still no reason for the genetic test. Shortly thereafter the numbness of my feet needed to be addressed so finally a diagnosis, Charcot Marie Tooth disease. But still no need for the genetic test. "Couldn't possibly be Amyloidosis, that's too rare". But along with the CMT diagnosis came the realization that I was suffering from severe Stenosis of the spine and would need surgery.

My cardiologist found little wrong with me and when they put a catheter in to look around at my heart I asked them to pull some tissue for a Congo Red stain. They did this, punctured my heart, I almost died, and the stain came out negative for Amyloids. Karen sent me next to a Hematologist, after all blood is at the core of this thing. After 2 years with the Hematologist he finally gave into my request for the genetic test. The positive result for HATTR Thr60Ala came back in March of 2014. I was devastated. I pictured myself as a walking skeleton being fed intravenously becoming a tremendous burden on my family. Perhaps I would last 4 more years. My wife and I met with the Genetic Counselors from Upstate Medical in Syracuse, NY. They looked at me, recognized my denial, and said straight out "of course you have Amyloidosis, your symptoms started back with your carpal tunnel problems". The CMT was a misdiagnosis because my numbness is bi-lateral, the stenosis is a known problem however there is a lack of cardio involvement. I have FAP not the FAC my brother had.

So, my journey led me to Boston Medical and Dr. Berk. He did one of the definitive studies on the benefits of Difflunisal in aiding the body in removing Amyloid proteins. That was a positive thing I did long before my diagnosis. I can still remember my brother telling me about it and it has probably helped in slowing the progression of this disease in me. In retrospect, there are three major problems that I had to overcome on my path. The first was getting to the diagnosis. It took me almost 7 years from my brother's death to get a Doctor to order my genetic test. The huge barrier of denial by all of my medical professionals (except my primary care physician) to the idea that, even though my brother died of this disease, I could have HATTR was almost insurmountable. The second was my own denial and fear of the disease. Even though I had done a tremendous amount of research I was still ignorant as to what it would mean if I had it. The third thing I had to overcome was the misdiagnosis. If the Neurologist had recognized the bi-lateral nature of my numbness, and considered my family history it could have shortcut the diagnosis by years. Boston medical took another look at the Congo red stains on the heart biopsies I paid so dearly for and found some Amyloids and after 2 back surgeries for stenosis if they would have known this to be a symptom of Amyloidosis my diagnosis would have come sooner.

I need to note that my mother only showed carpal tunnel and stenosis symptoms though she suffered from Rheumatoid arthritis. Of her 5 siblings I can find only 1 with any problem that could be related to Amyloidosis and as far as I know her children do not have the disease. 2 other siblings have produced children with Thr60Ala Amyloidosis. My hobby is the family genealogy. Thr60Ala is a very specific mutation on the TTR Gene on the 18th Chromosome. Everyone with this mutation is my relative and I have positively tracked the lineage back to County Donegal, Ireland. I am actively working on linking those that have known deaths from HATTR Amyloidosis back to myself. My journey is not over. I have one child that is positive for the mutation and he has two children of his own. My other child has yet to be tested and with the

current climate in the country towards pre-existing conditions I recommended she wait, she has two children. Both of my children know the symptoms, know what to look for, and are aware of current research. I'm confident that they will be part of the solution. I am also involved as a patient advocate, entering an Extended Access Program for Inotersen, and have made myself available to help in any way I can.

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Hello. I have Hereditary TTR (hATTR) amyloidosis. My version of this disease mainly wreaks havoc on the heart, gastro, and polyneuropathy. As you know it is a progressive disease that there is no cure for, and it is fatal. The average life expectancy for someone with hATTR is 5 years after onset of symptoms.

I first noticed symptoms (heart failure) in 2013 and was officially diagnosed in 2016. By that time I was too far along and did not qualify for a heart/liver transplant.

Due to the rapid progression of the disease I can no longer work. I was forced to retire a year ago on meager savings, and go on social security. I am homebound, cannot drive due to the neuropathy. Due to neuropathy in the hands I can't hold things.

A year ago I could still walk short distances. Now I can no longer walk. I currently get around using a rollator for short distances, and a portable mobility scooter for any distance. It won't be long before I won't be able to use a rollator.

Every day I notice some change. More instability when stand. More muscle weakness. Harder to go to the bathroom. Changes I have to adapt to as the disease progresses daily.

My cardiologist says I will likely be bed-bound within a year or two, sooner if I have to come off Patisiran.

Thanks to Medicare we have been able to keep up with prescription costs since all drugs I'm on are approved.

My wife is my caretaker and tends to all my needs. She has to take off a LOT of work (sometimes 15 hours a week) to get me to all my doctor appointments (primary, cardiologist, electrophysiologist, gastroenterologist, neurologist, etc.). She prepares all meals thinking ahead to such details as opening bottles, containers I can open with my teeth.

But we are VERY concerned about what's going to happen when the Alnylam Patisiran compassionate trial ends. I have been on the Alnylam Patisiran compassionate trial for a year. It has almost stopped the progression of the heart damage at 50%, and slowed the progression of the polyneuropathy significantly. I feel continued use of Patisiran will add 5 years to my life.

I'm afraid it will be my death sentence if Patisiran is not covered by my Medicare Part D (or A or B), and I have to come off the drug.

T.S.

Personal Experiences with HATTR

The only way I can describe hATTR is that it is a nightmare. I watched my mother suffer from this disease. She lost her fight with it seventeen years ago. Since that time, my brother and my older sister have both been diagnosed with this horrific disease. Perhaps one of the worst things about this disease is that most doctors have never even heard of it. If a doctor has heard of it, they do not know anything about it. If they do know something, they only know about the first type, not the familial type, and therefore do not test for it. This nightmare called hATTR leaves everyone feeling helpless and hopeless. Below, I will attempt to give you some insight into my personal experiences with this disease. Please know, however, that my words will never be enough. No one truly knows how utterly cruel hATTR is until they have lived it for themselves.

When I was young, my mother began having symptoms and not feeling well. I didn't know the extent of it, as my parents tried to shield my siblings and me from what was going on. I do remember that she went from doctor to doctor. One doctor told her it was in her head. Another doctor would give one diagnosis and treat it, but she wouldn't get any better. Finally, one doctor told her she had Crohn's disease and began to treat her as such. She still didn't get any better. On the first day of my sophomore year of high school, my mother was in the hospital with three iv's hooked up to her at once. The doctors had no idea what was wrong. Imagine being just fifteen years old and seeing your mother in this state. I was too afraid to ask questions, because I was afraid of what the answers might be. Looking at my mother in that hospital room will forever be etched in my memory. I was truly afraid that she was dying. At that point, I had never heard of amyloidosis.

While I had never heard of amyloidosis, my mother had. She had watched her own father suffer and die from this same disease when she was a little girl. She lost her father when she was only nine years old. My mother relayed some of her experiences to my own father. When my mother kept getting sicker and sicker and not any better, they told every doctor that amyloidosis ran in the family. Despite telling them this, not a single one of the doctors checked for this disease. My father thought that he was getting my mother the best possible care he could. He was driving her forty-five minutes to an hour to see doctors in Charlotte. The Charlotte doctors and hospitals were supposed to be better. Yet here she was, lying there with three different iv's, and no one able to tell her what was wrong.

Thankfully, my mother was released from the hospital. Unfortunately, she still did not get any better. She kept getting worse and worse. Finally, one evening, it became apparent to my father that my mother needed to go back to the hospital. This time, however, he decided he was not taking her back to Charlotte. He decided, instead, to go to Statesville. At Statesville, my parents, once again, told this new doctor that amyloidosis ran in the family. Upon hearing this, amyloidosis is the first thing the new doctor checked. I have no idea how the doctor knew what amyloidosis was, but I am very thankful that not only had he heard of it, he knew that should be the first thing to look at. The test results came back and it was confirmed that my mother did indeed have hATTR.

The next several years following my mother's official diagnosis were difficult, at best. My parents and the doctor kept searching for answers, for something to help, for a cure, for a

miracle. At the time, it was believed a liver transplant would be the answer. While a liver transplant would not help the damage that had already taken place, it was believed that it would prevent any future damage from occurring. My father took my mother to Chapel Hill for tests and to see if they would take her as a candidate to be placed on the liver transplant list. After several visits, Chapel Hill told my parents that they would not add my mother to the liver transplant list. The doctors there believed it was too risky and they didn't know enough about the disease to feel comfortable taking a chance and performing this procedure on my mother.

Chapel Hill proved to be a disappointment, but my parents and the doctor didn't give up. My father took my mother to the University of Virginia, almost five hours away from our home, to see if they would help. After a few visits, the University of Virginia acknowledged that they didn't know much about amyloidosis, but that they would add her to the transplant list and give it a try. It was the hope everyone was looking for. It was the miracle everyone was praying for.

I learned that when someone is placed on the liver transplant list, there is a sense of urgency that is used when deciding which candidate is chosen for the liver. My mother had a functioning liver and kept getting passed over for people whose liver was not functioning. During this time of waiting, my mother kept getting progressively worse. When my mother could no longer walk and was losing feeling in her legs and feet, she decided to remove her name from the transplant list. She had long since lost the ability to control her bladder and bowel functions. Her chance at surviving a major procedure, such as a transplant, was very slim. The liver transplant that had provided so much hope before, was not the miracle everyone had been praying for.

After the removal of her name from the transplant list, the focus on my mother's care was to make her comfortable. Her doctor was not aware of anything else that would help improve her condition. My father and my brother worked different shifts at the factory so that someone was able to be with my mother for as many hours during the day as possible. We had a home health care nurse that came to our house once, sometimes twice a week. We had iv fluids shipped directly to our house, along with other supplies. My mother wanted to remain at home and not in a medical institution, so my father went to great lengths to ensure that this was possible.

As a teenager in high school, I watched helplessly as my mother continued to get worse and worse. I prayed to God that He would end her suffering. I did everything in my power to make my mother smile and I cherished the time I had with her. I helped her with simple tasks such as changing clothes and brushing her teeth. I helped her when she had to use the bathroom. I cleaned up after her when she didn't make it to the potty chair next to her bed. I even did more difficult tasks. I was taught how to check blood pressure. I was taught how to set up an iv and change the fluid bag. Every morning, before school, I brought her some medicine and the phone to keep in arms reach in case she needed something. Sometimes, when she wasn't doing well, I would take my younger sister to school and then make up an excuse for why I had to leave school. I would go home and check on my mother, make sure she was really ok, and then I would return to school. Sometimes, I would come home from school in the afternoons, and find my mother lying face down on the floor. She had been trying to move from the potty chair to the bed or the bed to the potty chair and had missed and fallen, unable to pick herself back up. One afternoon, I came home to find my mother face down on the floor, unconscious. At just seventeen years of age, I picked my unconscious mother up off of the floor, put her back in bed, set up the iv, and started running iv fluids. I was terrified, but I didn't have time to be. I had to focus on my mother. Amazingly, my mother survived for another two years. I went through all

of this, with the knowledge that my father went through so much more. He and my mother had decided to shield my younger sister and me from as much of it as they could because we were so young.

My mother lost her battle on August 14, 2001. Her doctor said that the only reason my mother had survived as long as she did was because of the care she received. My father had amazing insurance at the time. The insurance covered almost everything that was medically necessary for the care of my mother. In the years since, insurance costs have sky rocketed and insurance coverage has drastically decreased.

My brother was diagnosed with amyloidosis while I was in college. He had a routine surgery done on his wrist and asked that they check for amyloidosis. He began searching for answers, for cures, for a miracle. He tried different drugs when they became available to see if they would help. He is the oldest and he is trying to pave the way for the rest of us. He is now unable to work and relies on disability and Medicare. My brother is only forty-four years old and he qualifies for disability and Medicare.

My older sister was recently diagnosed with hATTR. She is a teacher and does not have very good insurance. She has opted to not take her medicine regularly because she cannot afford it. My sister went to several doctors that kept telling her the same thing, it was all in her head. Many of the doctors had never heard of amyloidosis. It was the year 2017 and the doctors had never heard of it! She finally was able to find a doctor to test for the disease and confirm her diagnosis.

I worry about the care that my siblings are able to receive. Insurance has changed and become so much worse than it was when my mother was receiving care. I worry that if drugs are found that can help, that these drugs will not be affordable. I worry that doctors will not know of the availability of these drugs. I worry that should my younger sister and I start to show symptoms, that we will not be able to find a doctor that will know what hATTR is and that they should test for it.

HATTR is truly a horrific nightmare of a disease. It has ravaged my family and continues to do so. Doctors have little to no knowledge of the disease and the possible treatments that are available. In the seventeen years since my mother has passed, I feel as though we are still stuck in the same place as we were before, except this time insurance costs are high and the coverage is poor. Each and every day I pray for a miracle that will end this nightmare. Sadly, I worry that if a miracle is found, it will be unaffordable. I pray for hope. Yet, in the end, I, like the rest of my family, feel helpless and hopeless.

My first memories of amyloidosis is looking back to my Grandfather. He was a strong, trim, active farmer when I was very young and I remember him lifting me up on his tractor to ride out to the fields with him. By the time I was 7 or 8 he could no longer farm and was using crutches. When I was 12, and he was 70, it was too difficult for him to walk and his hands were frozen in that folded position and wheelchair bound. He had moved from an upstairs bedroom into the small den converted to a bedroom, then finally the hospital bed was moved into the now repurposed dining room so my Grandmother could better help him from either side of the bed. By that time he didn't want to see many people – including his grandchildren. He was a proud man who was reduced to a man who depended upon his wife for all of his care to a disease that stripped him of the dignity and pride of being a strong bread-winning, patriarch of the family; a man who could not even dress or feed himself. He died at age 71 in 1965. It was thought he had ALS until 3 of his 4 daughters developed the same disease almost 30 years later.

After my aunt died in 2001 at age 83, an autopsy revealed she had hereditary amyloidosis. After my aunt's autopsy results, my mother, her remaining two sisters along with some of their children were also tested. My mother and a sister and myself were positive for the genetic mutation – the fourth sister and 3 of the other children were negative. I was not too concerned for myself since I was only 49 and my mother and her sisters were not symptomatic until their 70's.

I watched my mother and 2 of her sisters follow my grandfather's path from very active and independent individuals who loved to travel and participate and organize family events. They had very similar patterns with amyloidosis. In their early 70's the neuropathy started in their feet and progressed up their legs. It was difficult to watch them lose their mobility and start staying closer to home. Their hands and arms were affected next. They were all avid readers and letter writers as well and I recall the times they would get frustrated with difficulty in turning the pages of a book with their now slick, curled fingers, and their writing was finally barely legible printing. With all this came the change from wearing nice tailored, stylish clothes to pull on pants and button-free pull on tops. There was also the utensils with curved handles with straps, plates with rims to scoot the food against to load up a spoon and 2 handled mugs that could accommodate folded, frozen fingers until later, they set what little dignity remained aside and were fed. They depended upon others, just like their father had, for almost everything from eating, brushing their teeth, dressing and personal hygiene. My second aunt died in 2006 at age 86 and my mother died in 2008 at age 83.

Everything changed for my which I experienced onset at age 53. I had been researching the disease since 2002 in an effort to find some help and relief for my mother and found very little to offer. However, since her death in 2008 advances are being made which finally show some hope for me. I have tried to slow the progression of the disease as much as possible while researchers work on solutions which I hope will include reversal of some of the neuropathy.

I still work full-time as an accountant but I need to take more breaks and down time as my stamina decreases with the disease. I still drive but cannot walk more than a block or so and struggle to do that some days. I no longer travel alone because I need assistance with luggage and getting around using a wheelchair at the airports. I cannot carry many groceries into my house even though I have only 3 steps to climb using my cane. I miss my independence and

spontaneity. I need to plan trips to the store, work, family gatherings, etc. in order to build in a recovery period or even recovery day because of the extra energy and effort it takes to participate in these activities. I think weekly strength and weight training has helped to slow the decline in my mobility by strengthening and challenging the muscles, but the amyloid is still winning.

I desperately want and need these drugs that will fight the mutant amyloid and I need it to be accessible and affordable – this is part of the reason I continue to work since I am not sure how expensive these medications will be and if they will be covered by health insurance or medicare. I want the quality of my life and my independence back and I want to make it far past my family's average lifespan with this disease of 11-14 years, especially as I am in year 11. And I want to be the last in my family to suffer from its symptoms as well.

Anna

I am a gene carrier for hereditary amyloidosis after having been tested by Dr. Benson at IU Medical school in 2008. It was and continues to be a huge and unsettling concern as my grandfather died of the disease and I watched my mother and her 2 sisters battle the disease and then die. I now am watching my older sister struggle with it and sadly she has had early onset starting at age 53. I am at age 56 and everyday I wake up I wonder if the first family symptom of a pain in my right foot will appear. We also have one brother who is a gene carrier as well.

I had carpal tunnel surgery a month ago which is often a precursor of the disease and had my tissue sent to the lab to be stained with congo red to see if amyloid fibrils are present and sadly they are. My mother and sisters had onset around 71/72 but with my sister having early onset and my grandfather having onset in his early 60's, I feel that pain and numbness will be on my horizon sooner rather than later.

It's a terrible wasting disease. My mother, aunts and grandfather were all active vibrant people with no other health issues just like me. The pain my mother endured for 10 years and watching her waste away slowly, painfully, turning her into a shell of the can do vibrant woman she was, continues to haunt me. There was nothing to do but try to manage pain and quite frankly the effectiveness of that was lacking. Because of the neuropathy, she would burn herself without knowing she had done so, bruises were common because she had no feeling, falls and broken bones happened until she succumbed to a wheel chair and then finally bed ridden. The same things that I saw with my grandfather and aunts. It wastes a person's body even as their minds were sharp, till the very bitter end. Some of her final words the night she died was that "nobody should have to endure this much pain". She often described it as "white hot stabbing knives slicing through her body". She never knew when the pain would spike. She would be happily reading in her chair and then she would swiftly breathe in as pain tore through her body. Her hands became curled and slick leaving her unable to do the simplest of tasks. My father became her primary care giver and then my sister and I took over the job which was 24/7 that last year of her life. This awful disease doesn't just effect the person battling it, it affects their entire family. I was powerless to lessen her suffering and only could try to keep her comfortable. She was an RN by trade and nutrition was her speciality and she loved to cook. The disease in the last years of her life robbed her of all ability to make even the simplest meal and by the last year eating had become such a chore, coaxing her to eat was necessary. The last few months swallowing and getting nourishment left her weaker and weaker even as her body withered and her bowel functions became affected.

When my sister had symptoms at age 53, it was a shock she has the earliest onset of any in our family that we know of. Watching her slowly loose mobility, activity and the ability to travel and do all the things she loves has been awful. We started to go to National Amyloid conferences so that we can stay up to date on treatments and breakthroughs. She tried to get on an amyloid trial a couple years ago but her symptoms weren't "bad enough" at the time to allow her in the study. With the extended access trial her symptoms have progressed enough that she is now on the trial. However, with weekly blood draws and shots it's time consuming plus we are all concerned about the cost once the drug goes on the market; especially as she will be in medicare soon.

I have 2 children, not tested, and I am hopeful that my sister, brother and I will be the last ones who have to endure this awful wasting disease which until now there were no treatments for. As I know that my future is set to include onset of this disease, I am hopeful this drug and others in development will be available to mitigate its effects. However, I am extremely concerned that the cost will be too prohibitive for me to be able to use the medications. Facing a future of slowly wasting away with pain so breathtaking one can't sleep, eat, participate in life is intolerable to think about. I am so grateful that finally we were granted orphan drug status so that scientists and doctors could put their brilliant minds to work to help us.

While I am hopeful about treatments for our disease, I am also very concerned about the potential cost and if I will even be able to afford it. I work for a small firm with a high deductible on my insurance policy with minimal drug coverage. My husband is unemployed since his extensive back surgery so our savings has dwindled even as we are helping our children through college. If onset happens before I'm eligible for medicare, I do not know if my insurance will cover any of the cost. Like my sister, who is soon to be on medicare, we don't know if government medicare will allow her to access the drug either and what the costs maybe. I plan to work as long as I can as my health is excellent but once the gene produces physical symptoms, I will be unable to work because of my lack of mobility and dexterity.

Sara

To who it may concern:

My name is John “Mark” Watson. I am 59 years old. I am originally from Paragould, Arkansas but currently live in Springfield, Illinois. I am married and have 2 sons, ages 31 and 28. My 28-year-old son was born with Down’s Syndrome and still lives at home with us. Due to having a handicapped child, I have been the primary income earner while my wife has served as caregiver.

I was diagnosed with hATTR in March of 2015 after three years of multiple doctor visits and treating symptoms all while trying to work and support my family. During this time, I had 2 carpal tunnel surgeries, pacemaker, and multiple treatments related to gastro intestinal issues. In March of 2015, at the advice of my local hospital, I sought out further answers to my health issues at the Mayo Clinic in Rochester, Minnesota. In a matter of weeks, I was diagnosed with amyloidosis through a fat pad biopsy. Later, through genetic testing, it was determined I had the mutation of SER97ty.

You could say I was one of the “lucky ones”. I was able to get on the Apollo trial from Alnylam and received my first treatment on June 1, 2015. As I write this letter I have completed 52 treatments. Let that sink in. I have traveled 52 times (plus additional diagnostic and testing time) to Mayo Clinic from Springfield, Illinois. During this same time, I have continued to work and was even promoted last November from Sr. VP of Global Operations to the Executive VP of the company. I believe this is both a testament of how well I have responded to this drug and my own will to keep going so I can support my family.

The impact of this disease has taken much of the joy out of day to day living. Before this disease, I was an avid runner, biker, and cross fitter. I completed over a dozen marathons and several 150-mile bike rides for Multiple Sclerosis. It was during a cross fit workout that I first realized that my body was starting to shut down.

I am now numb from my thighs to the tips of my toes as well as numbness from my shoulders to my fingertips. I also have had several electrical issues with my heart resulting in 3 ablations to correct atrial fibrillation and sinus tachycardia (irregular and fast heart rate).

While life today is much different, I am starting to enjoy a few things again. While I still have sensory loss in all my limbs, I can walk, hike, and do short 10-15-mile bike rides. The fact that I can type this letter is incredible compared to the early prognosis of this disease. I also still work 50+ hour work weeks and do limited travel. I believe I am only able to do this because of the quick diagnosis at Mayo, and the immediate entry into the Apollo drug trial. Not to mention the incredible support of my family and my employer.

Now that the drug is approved, I will soon be at a crossroad of what I need versus what I can afford long term. While I am no doubt more blessed financially than many, I cannot allow this disease and treatment to break my family. I have a wife and handicapped adult child to think of long-term. They have almost no income potential. Working for a private company that is self-insured does not give me unlimited access to funds. We will play this out to whatever our insurance carrier can provide and see what is left. If my portion becomes an amount that starts

eroding my ability to care for my family, I will have no choice but to discontinue and eventually enter palliative care. My life insurance along with other provisions I have made will hopefully carry them to the end of their natural life.

As far as other family in relation to this disease, we have not tested our two sons. Our oldest has chosen at this point to not be tested and we have not had the emotional fortitude to test our son with Down's Syndrome.

I am the youngest of three sons. My oldest brother does not carry the gene, while my middle brother does have the gene and was diagnosed with the disease last December. He began the open label extension Patisiran trial in January of this year. He has three sons that were tested and one of them carries the gene, but the disease is not active.

As you can see, this disease can wipe out whole families and their livelihood in a short amount of time. It is my hope that through your influence and direction that we can all have access and afford to participate in this drug and remain productive members of society. Otherwise the research and development were for naught.

Thanks for your time and consideration.

John "Mark" Watson