April 2, 2018

Institute for Clinical and Economic Review (ICER)
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RE: Comments on Draft Scoping Document for ICER's Review of the Treatment of Hereditary Transthyretin-Mediated (hATTR) Amyloidosis

Alnylam Pharmaceuticals, Inc. (Alnylam) appreciates the opportunity to provide comments on the draft scoping document for ICER's review of new therapies for the treatment of hATTR amyloidosis. Alnylam is a biopharmaceutical company developing an entirely new class of novel therapeutics based on ribonucleic acid (RNA) interference, or RNAi. If approved, our investigational RNAi therapeutic candidate, patisiran, will be a first-of-its-kind medicine.

As a Flagship Member of ICER, Alnylam shares its objectives of enhancing patients' therapeutic outcomes while reducing overall health system expenditures. First and foremost, however, Alnylam supports patients, families and physicians by bringing greater awareness, understanding, and effective treatment options for hATTR amyloidosis. Any value assessment must balance urgent patient need, demonstrated safety and efficacy, scientific advancement and the multisystemic nature of the disease with health system impacts and societal costs. To that end, we have carefully reviewed ICER's draft scoping document and provide the comments below.

Alnylam believes ICER's review is premature. In the U.S., there is no approved treatment for hATTR amyloidosis. Published data are still emerging on the investigational therapies for this disease and there is an incomplete understanding of the disease itself. Full peer-reviewed Phase 3 trial and Open Label Extension results for these investigational therapies are on the horizon. Conducting the review at a later time would yield more meaningful analysis with less uncertainty.

If ICER chooses to move forward, notwithstanding the current uncertainties, we ask it to consider the recommendations outlined below. Failure to address the concerns underlying the recommendations would result in an inaccurate assessment that will be unhelpful to payers and providers alike and may lead to adverse patient impact.

Key Recommendations:

1. ***hATTR amyloidosis is a rare, debilitating, rapidly progressive and often fatal, multisystemic disease with fewer than 10,000 patients diagnosed and no approved treatment in the U.S. ICER's analysis should use the current understanding of the disease and model survival estimates from time of diagnosis.***

ICER defines hereditary ATTR (hATTR) amyloidosis as familial amyloid polyneuropathy (FAP), separating the condition from familial amyloid cardiomyopathy (FAC) and leptomeningeal amyloidosis. Subsequently, ICER proposes to consider disease progression as a function of neuropathy stage, specifically FAP Stage.[1] However, this approach does not take into account the current medical understanding of hATTR amyloidosis as a single, multisystemic disease in which the majority of patients develop symptoms related to both polyneuropathy and cardiomyopathy.[2-5] The development of cardiomyopathy substantially shortens survival in patients with hATTR amyloidosis and is the most common cause of death among patients in the U.S.[6,7] Modeling disease progression as a function only of neuropathy stage is inconsistent with the multisystemic nature of the disease and with ICER's "key measures of clinical benefit," which include both neurologic and cardiac endpoints (Fig. 1.1 in the draft scoping document).

ICER also notes that, if untreated, mortality occurs "approximately 10 years after onset," with a median survival of 5–15 years. Measuring mortality from symptom onset is generally inaccurate, as it relies on patient perception and memory in a multisystemic disease that often makes pinpointing initial symptoms difficult. For the purposes of ICER's evaluation, disease progression should be measured from diagnosis—which is when true treatment decisions begin—rather than symptom onset. Using diagnosis as the basis for assessing mortality, studies show that median survival is 4.7 years, which decreases to 3.4 years for patients presenting with cardiomyopathy.[6,7]

We also suggest that ICER use NT-proBNP, a cardiac biomarker shown to be an independent predictor of survival in cardiac amyloidosis that was collected in both the APOLLO and NEURO-TTR trials, when developing its model.[8-11] ICER's draft scoping document focuses on modified body mass index (mBMI) as a measure associated with survival in hATTR amyloidosis. However, the association of mBMI and survival is limited to patients who have undergone orthotopic liver transplantation (OLT), where mBMI at the time of transplant has been shown to predict survival post-OLT. Given the current absence of published data on the impact of mBMI on survival in the broader hATTR population, NT-proBNP should be prioritized over mBMI as a measure correlated with survival outcome.

To appropriately review treatments, ICER should approach hATTR amyloidosis as a single, multisystemic disease and develop a comparative effectiveness model that includes both neuropathy and cardiomyopathy outcome measures.

2. ***Data in hATTR amyloidosis continue to emerge. Current information in the public domain is limited, so any review at this time will be highly assumptive and likely to generate inaccurate results or results that would be unreliable. ICER's therapeutic comparisons must be bound by the current standard of care for hATTR amyloidosis as a multisystemic disease.***

ICER presents orthotopic liver transplantation (OLT) as an event in the model and assumes that people with hATTR amyloidosis do not progress beyond FAP Stage 1 after OLT. Along with a 1-year mortality rate of 7-14%, many patients undergoing OLT eventually exhibit neuropathy progression, including loss of ambulatory status.[12-15] In addition, clinical recommendations do not support OLT among patients with amyloid cardiomyopathy, since these patients have a worse survival prognosis post-OLT.[16] A U.S. registry of all organ transplants shows that only 168 patients with hATTR amyloidosis received a transplant between March 2002 and March 2016, indicating low utilization of OLT for this disease consistent with the poor outcome in patients with more advanced neuropathy and/or cardiomyopathy at the time of transplant.[17]

In addition to OLT, ICER also suggests that it will include diflunisal, a generic NSAID that is not indicated in the U.S. for treatment of hATTR amyloidosis, as a therapeutic comparator for this review. There are no published data supporting the use of diflunisal to treat both the polyneuropathy and cardiomyopathy that occur together in most patients. Diflunisal is not recommended for use in patients with advanced renal disease or severe congestive heart failure, and carries a serious risk of gastrointestinal effects, all of which are common manifestations of hATTR amyloidosis. Moreover, an analysis of U.S. electronic medical records and claims in three separate databases shows use of diflunisal in less than 1-2% of all patients diagnosed with hATTR amyloidosis,[18] making its inclusion as a comparator inappropriate and inconsistent with real world standard of care.[19-21]

As neither OLT nor off-label use of diflunisal address the multisystemic nature of the disease or represent common treatment options for hATTR amyloidosis, ICER should disregard both for the purpose of this review. A fair and meaningful HTA process should use approved products for comparators, not promote off-label use in the absence of robust scientific evidence.

3. ***Given the dual burden of disease on patients and caregivers, the analysis must capture direct and indirect treatment impacts, in addition to safety and efficacy, relative to system and societal costs.***

ICER cites an estimate of $154,819 as the lifetime cost of an untreated person with hATTR amyloidosis, which is inappropriate for many reasons. The estimate is based on direct health care costs incurred by patients with early onset V30M, a phenotype common in Portugal, but unique and different from the typical phenotypic expression of hATTR amyloidosis in late onset V30M and non-V30M patients in the U.S.[22-24] Also, as ICER's framework purports to consider the value of treatment to a wide array of stakeholders, a more appropriate calculation of lifetime cost of treatment must consider high disability, lost productivity and lost wages of both patients and caregivers, as well as larger social impacts of the disease.

We strongly encourage ICER to consider patient and caregiver perspectives as provided through contextual considerations consistent with its ultra-rare framework. These perspectives will demonstrate the urgent need for broad access to disease-modifying treatments, such as patisiran, that halt and potentially reverse disease progression.

Patients and their families face significant disease burden and have no approved treatment options today. Any review intended to inform access and treatment decisions should be conducted when published evidence is sufficient to make those evaluations accurate; therefore, we reiterate our strong recommendation to postpone the review. Should the review move forward, we urge ICER to incorporate the foregoing recommendations consistent with approaching hATTR amyloidosis as a multisystemic hereditary disease. Thank you very much for your consideration.

Sincerely,

Pritesh Gandhi
Vice President, Medical Affairs

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ICER review of Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis
Amyloidosis Research Consortium comments on draft scoping document - April 2018

About the Amyloidosis Research Consortium (ARC)

ARC was established as a non-profit organization in 2015 to accelerate development of and access to new and innovative treatments for systemic amyloidosis. We are focused on developing the critical research tools, assets and infrastructure needed to drive progress in both commercial and academic research.

ARC builds collaborations across industry, academia, regulatory and other relevant stakeholders to align research strategies, ensuring that scarce research resources are optimized and directed to prioritised areas. We are also focused on understanding patients' unmet needs and ensuring the successful approval, adoption and diffusion of valuable new treatments and diagnostic tests.

Comments on draft scoping document

1. Proposed patient population for the review

The scoping document states that 'the population of focus for the review is adults with hereditary (hATTR) amyloidosis, formerly known as familial amyloid polyneuropathy (FAP).' This is not an accurate description of hATTR. hATTR is characterized by the deposition of amyloid derived from transthyretin in various organs and tissues, including peripheral nerves and the heart. hATTR-FAP and familial amyloid cardiomyopathy (hATTR-FAC) – also known as hATTR-PN and hATTR-CM - are two clinical presentations of hATTR, but they are not mutually exclusive; many hATTR patients will experience both polyneuropathy and cardiomyopathy.

For the avoidance of doubt, the background and population sections should clarify that this is a multi-systemic disease. While all patients in the studies for the drugs under review had familial amyloid polyneuropathy (hATTR-FAP or hATTR-PN), patients may have also had cardiac involvement; as such, exploratory cardiomyopathy endpoints were also included in the studies and may be relevant for this evaluation.

2. Current treatment of hATTR

ARC considers it important to clearly outline the current treatment paradigm for the hATTR patient population to set the right context for the evaluation of the new treatments. Currently there is no licensed or off-label disease-modifying treatment approach that constitutes standard of care in hATTR.

Tafamadis is not approved by the FDA for hATTR-FAP and clinical trials for use of tafamidis in hATTR-CM remain ongoing. Some patients continue to receive open-label treatment with patisiran or inotersen following their participation in controlled studies, or through each product's expanded access program.

While liver transplantation is a potential treatment, it is only indicated for a very small minority of this patient population with very early stage polyneuropathy. Furthermore, due to

personal preference, concern over transplant-related risks and shortage of organ availability, very few patients receive this treatment.

The scoping document refers to diflunisal as being 'currently considered first line treatment'. Diflunisal is used off-label with a considerable number of hATTR patients. However, it is contraindicated for certain patients (for example, those who are on anticoagulants). It is also unlicensed for this patient population and there is only limited evidence of its effectiveness. Clinical experts tell us that while it is used in the absence of alternatives, there is no clear evidence of its effectiveness. As such we do not think it is an appropriate comparator for this evaluation.

Symptom management approaches are the basis of current standard of care alongside diflunisal. These approaches do not delay the course of the disease but can alleviate disabling symptoms and improve quality of life, for example, by reducing neuropathic pain (e.g. gabapentin) and improving autonomic function, particularly gastrointestinal symptoms (e.g. immodium, codeine, erythromycin and rarely colostomy), cardiac function (e.g. diuretics) and blood pressure control. To this end, ICER should consider the main symptom management approaches as being the mainstay of standard treatment.

3. Analytic framework – direct comparison

hATTR patients and their families are eagerly anticipating the availability of the two treatments covered by this evaluation (patisiran and inotersen) as well as future new licensed treatments that have the potential to modify and delay progression of their disease.

We note in the analytic framework that ICER intends to directly compare patisiran and inotersen should data allow. Despite some obvious similarities between the two drugs they should not, however, be considered as equivalent. Both drugs offer considerable potential benefits and a significant step change in the management of hATTR. ARC believes it is important that both options should be available for patients and their physicians to choose from, based on personal preference, feasibility and other factors.

From a patient perspective the different administration of these drugs is a critical consideration alongside the differences in their potential efficacy benefits and side-effects. For many patients, regular infusions in hospital or in alternative setting (patisiran) will not be feasible or desirable, while for other patients such a regimen may be feasible and/or preferred over inotersen after consideration of all the factors associated with both treatments.

In addition, should patients need to discontinue one of the treatments for any reason (for lack of efficacy or undesired effects) they should have the option of trying an alternative. Assuming equivalence could limit choice for clinicians and patients and jeopardise their to effectively manage the disease.

4. Analytic framework – potential other benefits and contextual considerations

This patient population has very significant unmet need. The disease is extremely debilitating and life-limiting for which current standard of care is predominantly limited to symptom management.

The physical effects of the disease impact the ability of many patients to function day-to-day and to participate in family, work and social activities. As symptoms deteriorate, many patients are no longer able to be independent. They may lose the ability to walk, drive and work, leading to additional financial, emotional and caregiver burden.

The disease causes a tremendous emotional burden, and this often extends to caregivers and family members. The hereditary nature of the disease means many patients have been caregivers for loved ones before succumbing to the disease themselves and live with the knowledge that they may pass it onto their children. The disease has a substantial lifelong impact on entire families.

The disease places a significant burden on family members as they provide physical and emotional care to patients while experiencing a considerable emotional burden of their own in dealing with the realities of the disease. Family members often become full or part-time caregivers with consequences on their work, social and financial situations.

In offering an option that can stabilize and stop further deterioration these new treatments can make a considerable improvement to patients' and families' quality of life. Effective control of the disease could support patients and caregivers to remain at work, retain independence and participate in family and wider life. It could also significantly reduce patients' reliance on and use of supportive care treatments.

The technologies themselves are also innovative in the way they offer a novel treatment approach for this disease. To date there are no alternatives that inhibit the production of transthyretin, thereby slowing the progression of the disease.

In providing an effective disease-modifying option, these treatments represent a significant step change in the potential management of hATTR and in meeting the unmet need of this patient population.

There are numerous health benefits that are not fully captured by the clinical data. hATTR is a heterogenous disease and patients are affected by symptoms in different ways. Fatigue, peripheral neuropathy, gastrointestinal events, incontinence, erectile dysfunction, muscle weakness, pain, insomnia and vision problems are particularly cited by patients and family members in our research as having a significant impact on their quality of life. Not all of these are captured by the clinical data or quality of life tools, yet it is important to recognise that control of the disease could improve the specific symptoms that matter most to patients.

We have conducted several projects on patients' needs and preferences in relation to treatment. In 2015 ARC hosted an externally led Patient-Focused Drug Development meeting with the FDA to share with the Agency and other stakeholders the perspectives of people living with systemic amyloidosis, its impact on their daily lives, and their perspectives on approaches to treating amyloidosis. We have attached the resulting *Voice of the Patient* report to this submission to help inform this evaluation.

To Whom It May Concern:

My name is Susan. Our family has Familial Amyloidosis ATTR 60ALA (now referred to as hATTR Amyloidosis.) My mother and her three brothers all died of this disease. One of my brothers is in Stage Two of this disease; the other in Stage One. My sister was the first to die in our generation of the disease Oct. 2, 2014. I too have the mutation. As the youngest I am as yet asymptomatic. I have been a caregiver and watched my loved ones die one by one.

Our family was one of the fortunate ones in that our uncle found what the disease was in the early 1990's after five years of suffering severe and baffling symptoms. He went to several specialists in that time period including gastro-intestinal specialists, cardiologists, internists, and neurologists in Seattle. He was unable to get a diagnosis. He decided to go to Mayo Clinic Rochester where he met Dr. Morie Gertz and was diagnosed. Although there was no cure or even hope of one at least he did find out and no one else had to go through years of countless visits to specialists, knowing that something was terribly wrong and getting no answers.

My mother lived the longest with the disease, almost 12 years from onset; her brothers were 6, 8, and 9 years at the onset of serious symptoms of hATTR Amyloidosis. All had carpel tunnel syndrome much younger as well as eye problems such as dry eyes and retinal detachment. The first more life threatening symptoms were gastro-intestinal, with drastic and unexplained weight loss, fatigue, then cardio issues as well as more severe peripheral-neuropathy symptoms. The progression of the disease and life expectancy of each individual depended on which part of the body was most affected and the progression thereof.

The second generation, our generation is now experiencing the same things. I am speaking for all my extended family as well. Out of 22 people tested for this mutation within three generations 18 tested positive. Even early onset symptoms can severally disrupt the lives of the patient and caregivers. It makes it difficult to travel or even leave the house at times. It is not a pleasant way to die; it can be long and agonizing. The last years and months no one should have to endure. The last two to three years, sometimes my mother and sister would have good days, then it went to a few good hours in a day, then down to minutes in a day, at the end there is none. I have watched this disease cost loved ones their jobs, drain their finances and put huge emotional stress and even physical strain on their loved ones that desperately try to care for them and make them as comfortable as possible.

My sister lived only four years from the onset of this disease. She went from walking by grabbing furniture, not being able to leave home, then to a walker and finally in a wheelchair in a matter of months. She fell several times. She could not eat without feeling nausea after and having to immediately lie down. It did not matter what or how small a meal she ate. She was either extremely

constipated or had bouts of diarrhea. The last several months she needed total assistance with dressing, bathing, going to the bathroom, and she could not prepare her own food. My sister could no longer write or use her hands except to grasp a spoon with her fist to eat and that with much effort. She was constantly thirsty all the time and it could not be quenched. At times even just a small amount of water would foam back up her throat and into her mouth. She died at home totally bedridden at 88 pounds.

To know what is coming is overwhelming and beyond frightening. I fight the fear and depression. The fear and worry is doubled because I know my son may have it also. Now triple that mental and emotional anguish by those that have to worry for their darling grandchildren. You try to not let this disease define you, yet you cannot escape, you cannot forget those last days of your loved ones, you cannot help but feel terrible for those going through it now and stand by helpless.

I do not want my husband to change my diapers when my time comes. I do not want my husband, son and his wife whom I love so dearly watch me slowly waste away until there is nothing left of my body it is so emaciated. I do not want them to have that last picture in their mind of me as I do my beloved mother and sister.

The last generation had no hope, now at long last we do have hope with the innovative therapeutic RNAi Patisiran and antisense Inotersen that target RNA to stop the production of mutated protein. My brother was on one of these trials and he was fortunate that he did not get the placebo. His improvement scores were dramatic for FAP. His pain in his legs from neuropathy lessoned greatly within 3-4 months. By six months he could resume many of the activities he could not do for a very long time. He was able to enjoy taking his grandkids for walks, play with them, he even built them a tree fort. There is no way he could have done any of those things without the medication. He and our entire family know he would be bedridden by now or not here with us if not for this innovative medication.

My family has prayed for a miracle for thirty years. These treatments that are waiting for FDA approval are the miracle that we have been reassuring our children would come. Now we do not have to wonder if we were just telling our children this to ease our own fear and theirs. This is real, this is now. All families with hATTR Amyloidosis now have the chance to live a full and productive life. We are truly thankful.

Sincerely,

Susan E Bye

Akcea Therapeutics Response to ICER's Scoping Document on Inotersen and Patisiran for Hereditary Transthyretin Amyloidosis: Effectiveness and Value

1. Disease description

Hereditary transthyretin amyloidosis (hATTR) is an autosomal dominant hereditary disease that is caused by many genetic variants, affecting a single-copy gene, but with two principal clinical manifestations – a predominantly neurologic phenotype and a predominantly cardiac phenotype. A considerable overlap in symptoms is common in many patients. As we learn more about hATTR, the disease descriptions including Familial Amyloid Polyneuropathy (FAP) and Familial Amyloid Cardiomyopathy (FAC), are being replaced by hATTR alone, or with a descriptor of the predominant clinical manifestation – e.g., hATTR with symptoms of neuropathy.

We believe that the multiplicity of symptoms that patients may experience is important to recognize and understand, and incorporate into any evaluation of new treatments, as it paints a more complete picture of the devastating nature of the disease, particularly in its advanced stages. Over time, the amyloid deposits in the peripheral nervous system can cause symptoms of polyneuropathy such as pain, loss of sensation and weakness in the hands, arms, legs or feet. In some cases, the autonomic nervous system, which controls involuntary body functions such as blood pressure, heart rate, and digestion, may also be affected by amyloidosis.

The multiple symptoms, late diagnosis and progressive nature of the disease create a disease state that has significant patient burden and reduced life expectancy. In the later stages of the disease, patients can experience devastating impacts on their functional capability and quality of life, and the disease can also take its toll on caregivers and other family members.

2. Epidemiology

While the exact prevalence of hATTR is unknown, we believe that the estimates of 10,000 people worldwide with hATTR with symptoms of polyneuropathy is reasonable. We think that this scoping document should also include an estimate of the US prevalence, as the document is intended to inform healthcare decision-makers in the US, as they prioritize their coverage policies for hATTR patients. The estimate of 1 per 100,000 in the US has been published by a leading researcher in the field, which would put the US prevalence between 3,000 and 3,500.

3. Treatment

In the scoping document, the use of diflunisal (as first-line treatment) is supported by a statement that it "significantly reduced progression of neurologic impairment at two years, and preserved quality of life compared to placebo". For fair balance you should add that these

results need to be carefully considered as the attrition rate in the study exceeded 50% in the first year. In addition, as an NSAID, diflunisal may not be suitable for patients with significant renal or cardiac impairment, both of which are common in patients with hATTR.

Regarding tafamidis, it should be noted that its approval in the European Union and several South American and Asian countries is for patients with Stage 1 (early) disease only, and it was only studied in a randomized controlled trial in patients with the Val30Met mutation.

With regard to the translation of surrogate outcomes to clinical benefit, in the pivotal NEURO-TTR study, in the Inotersen-Ionis treatment group, robust reduction in circulating TTR levels was observed throughout the 15-month treatment period and was correlated with clinical improvement measured by the two primary end-points in the study. Positive data was also demonstrated with patisiran for similar endpoints in a similar patient population thereby validating reduction of TTR as a biomarker for effectiveness of treatment in hATTR. The exact relationship between reduction in serum TTR and slowing or halting of disease progression has yet to be established, however, based on the data we have generated it is likely that there is a threshold effect rather than a direct proportionality between TTR reduction and clinical benefit.

4. Stakeholder Input

We welcome the inclusion of input from patients, their families, and patient advocates in the proposed evaluation, as the impact of the disease on patients and their families is both significant and complex. Patient advocacy groups have been a steadfast source of support for patients in the absence of any effective treatments for the disease, and have an important and valuable role to play in the current and future care of hATTR patients.

5. Analytic Framework

The inclusion of diflunisal as a comparator in the proposed analytic framework is problematic. As mentioned earlier, diflunisal is and NSAID and may not be suitable for patients with significant renal or cardiac impairment, both of which are common in patients with hATTR.

With regard to Table 1.1 – Key Outcomes and Harms, in addition to the adverse events related to the interventions themselves, the analysis should include the potential harms related to co-administered drugs, such as the pre-treatment of patients with systemic corticosteroids in advance of patisiran infusion as this was the treatment regimen in their pivotal study and will likely be included in the product label. Additionally, while “Injection Site Reactions” is listed as a potential harm, “Infusion Site Reactions” has been omitted. The types and severity of reactions can be very different between injection sites and infusion sites, and both these harms should be listed.

With regard to “Settings”, the “focus on outpatient settings in the United States” should not ignore the substantial proportion of patients who are admitted to hospital for the various complications of hATTR.

We endorse the inclusion of a societal perspective in the value framework as the impact of the disease on the patients, and their families and caregivers is significant, and very relevant to any evaluation of the treatments for the disease. The progression of the disease robs the patient of the opportunity to continue to live an independent and productive life, and often necessitates family members and caregivers giving up productive work, careers and community and social activities.