

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210922Orig1s000

OTHER REVIEW(S)



**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)**

**Epidemiology: ARIA Sufficiency Memo: Onpattro (patisiran)
Version: 2018-01-24**

Date: July 31, 2018

Reviewer: Elisa Braver, PhD
Division of Epidemiology I

Team Leader: Kira Leishear, PhD, MS
Division of Epidemiology I

Associate Division Director: Wei Hua, PhD, MHS, MS
Division of Epidemiology I

Subject: Active Risk Identification and Assessment (ARIA) Sufficiency
Memo for Pregnancy Safety Concerns

Drug Name: Onpattro (patisiran)

Application Type/#: NDA 210922

Applicant/Sponsor: Alnylam Pharmaceuticals, Inc.

OSE RCM #: 2018-877

Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Hereditary transthyretin amyloidosis, known as hATTR, is one of a group of diseases characterized by deposition of an abnormal protein, amyloid, made by the liver into various organs of the body, including the central nervous system, heart, kidneys, and gastrointestinal tract.^a hATTR results from mutations to the transthyretin (TTR) gene that in turn cause abnormal folding of the protein. One form of this disease causes sensorimotor peripheral neuropathy (with symptoms of numbness, pain, and weakness), focal nerve lesions (such as carpal tunnel syndrome), autonomic dysfunction (such as orthostatic hypotension), vitreous opacity of the eye, and glaucoma. This disease can be fatal.^b Amyloid deposits in the heart can cause heart failure, chest pain, fluid overloads, and shortness of breath. There currently are no FDA-approved treatments; existing treatments aim at alleviating symptoms rather than addressing the underlying mutation or amyloid deposition.

Onpatro (patisiran) is a new molecular entity with a proposed indication for treating polyneuropathy (PN) among adult patients with hATTR-PN. Patisiran is a small interfering ribonucleic acid that targets TTR messenger ribonucleic acid (mRNA) in order to suppress the production of TTR. It has been designated an Orphan drug and received a Fast Track designation.

During the clinical trials, the most commonly observed ($\geq 10\%$) adverse events associated with the use of patisiran in the 18-month placebo-controlled study were peripheral edema (30%); infusion-related reaction (19%); and back pain (14%). The adverse event that caused the most patients to stop taking patisiran across all clinical studies was cardiac failure (2 patients in the placebo-controlled study, 1.4%). The cardiac failures were considered as due to the underlying disease rather than attributed to patisiran. Patisiran depletes serum vitamin A levels, but supplementation with vitamin A may help.

1.2. Describe the Safety Concern – Pregnancy Risk

There are no available data in humans concerning the effects of patisiran use during pregnancy. Among Sprague-Dawley rats, no drug effects were observed on mating, sperm parameters, drug-related fetal malformations, or pregnancy/uterine parameters following administration of

^a National Center for Advancing Translational Science, National Institutes of Health. Familial Transthyretin Amyloidosis. Available: <https://rarediseases.info.nih.gov/diseases/656/transthyretin-amyloid-neuropathy>

^b National Institute for Health And Care Excellence, United Kingdom. Available: <https://www.nice.org.uk/guidance/gid-hst10013/documents/draft-scope-pre-referral>

patيسان.^c Development studies did not observe drug effects on physical, neurobehavioral, or reproductive development of offspring following weekly infusions of patيسان to pregnant rats. Fetal exposure was not detectable among rats. As observed in humans, suppression of TTR and decreases in vitamin A levels were observed among female rats. The doses in rats were up to 2.4 times the recommended human dose.

Among New Zealand White rabbits, administration of patيسان resulted in loss of litters that was thought to be secondary to maternal toxicity (i.e., weight loss and liquid feces) at doses that were greater than 3.2 times the recommended human dose.^d In the embryofetal development study in rabbits, administration of patيسان on gestational days 7, 13, and 19 resulted in weight loss among the fetuses, but fetal exposure was not detectable among rabbits. No evidence of drug-related fetal malformations or effects on pregnancy or uterine parameters was observed in the rabbits.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- Specific FDA-approved indication in pregnant women exists and exposure is expected
- No approved indication, but practitioners may use product off-label in pregnant women
- No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
- No approved indication, but use in women of childbearing age is a general concern

2.2. Regulatory Goal

- Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
- Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.
- Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

^c David Carbone. Pharmacology/Toxicology NDA Review and Evaluation for Patيسان, July 11, 2018. Division of Neurology Products, Office of New Drugs (CDER/FDA).

^d Ibid.



2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

- Pregnancy registry with internal comparison group
- Pregnancy registry with external comparison group
- Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- Electronic database study with chart review
- Electronic database study without chart review
- Other, please specify:

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

- Study Population
- Exposures
- Outcomes
- Covariates
- Analytical Tools

For any checked boxes above, please describe briefly:

Study Population and Outcomes: ARIA is insufficient to identify the study population (babies that experienced in utero exposure or postpartum exposure through lactation) because the mother and baby records are not currently linked in Sentinel. Thus, the exposure corresponding to the mother and potential outcomes corresponding to the infant cannot be connected. This lack of linkage between mother and baby records renders ARIA insufficient for both the study population and outcome identification.

Analytical Tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

We did not formally assess the other parameters given that the mother-infant linkage is not currently available in ARIA.

2.5. Please include the proposed PMR language in the approval letter.



The following language (still in draft form) has been proposed for PMRs related to pregnancy outcomes:

Establish a worldwide Pregnancy Surveillance Program to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes in women exposed to Onpattro (patisiran) during pregnancy. Provide a complete protocol which includes details regarding how you plan to encourage patients and providers to report pregnancy exposures (e.g. telephone contact number and/or website in prescribing information), measures to ensure complete data capture regarding pregnancy outcomes and any adverse effects in offspring, and plans for comprehensive data analysis and yearly reporting.

The finalized PMR language will be issued upon approval.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ELISA R BRAVER
07/31/2018

KIRA N LEISHEAR
07/31/2018

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07/31/2018

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08/02/2018

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08/02/2018

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08/02/2018

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: July 31, 2018

To: Teresa Buracchio, M.D.
Division of Neurology Products (DNP)

Annie Nguyen, PharmD, Regulatory Project Manager, (DNP)

Tracy Peters, PharmD, Associate Director for Labeling, (DNP)

From: Sapna Shah, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Acting Team Leader, OPDP

Subject: OPDP Labeling Comments for ONPATTRO™ (patisiran) lipid complex injection, for intravenous use

NDA: 210922

In response to the DNP consult request dated January 8, 2018, OPDP has reviewed the proposed product labeling (PI) for the original NDA submission for ONPATTRO™ (patisiran) lipid complex injection, for intravenous use (Onpattro).

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DNP (Annie Nguyen) on July 17, 2018, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 16, 2018, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Sapna Shah (240) 402-6068 or Sapna.Shah@fda.hhs.gov.

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SAPNA P SHAH
07/31/2018

Clinical Inspection Summary

Date	07/10/2018
From	Cara Alfaro, Pharm.D., Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Anhtu (Annie) Nguyen, Regulatory Project Manager Rainer Paine, M.D., Medical Officer Division of Neurology Products
NDA #	210922
Applicant	Alnylam Pharmaceuticals, Inc.
Drug	Patisiran
NME	Yes
Proposed Indication	Treatment of adults with hereditary transthyretin-mediated amyloidosis
Consultation Request Date	1/12/2018, amended 4/10/2018 to add CRO
Summary Goal Date	6/11/2018, Extension granted to 7/11/2018
Action Goal Date	8/11/2018
PDUFA Date	8/11/2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Adams and O’Riordan, the sponsor, Alnylam Pharmaceuticals, and the CRO, Medpace, were inspected in support of this NDA. Although objectionable conditions or practices that are significant deviations from Good Clinical Practice (GCP) were noted at the sponsor and CRO inspections, the findings are unlikely to significantly impact data reliability.

The final compliance classification of the inspection of Drs. Adams and O’Riordan was No Action Indicated (NAI). The final compliance classification of the inspections of Alnylam Pharmaceuticals and Medpace was Voluntary Action Indicated (VAI).

NOTE: The European Medicines Agency (EMA) had received the same marketing authorization application. The FDA and EMA conducted joint inspections of the sponsor, Alnylam Pharmaceuticals, and the CRO, Medpace. Additionally, two clinical investigator sites enrolling subjects in Protocol ALN-TTR02-004 were inspected by EMA: Dr. Juan Buades Reines (Site #61) of Mallorca, Spain and Dr. Maria Gonzalez-Duarte Briseno (Site #110) of Mexico. The EMA inspectional findings/results for these two clinical site inspections were communicated to OSI.

EMA identified critical inspectional findings at Site #61 including deficiencies in the informed consent process, in preserving the confidentiality of subjects, in the management of investigational product, and in source document management. Major findings included lack of GCP training documentation, some ICF versions lacking signature option of legal representative of the subject or a witness, protocol deviations, and late reporting of SAEs.

Based on these findings, EMA considered the data from Site #61 to be suboptimal and recommended that these data be excluded from analyses.

EMA identified protocol violations as a critical inspectional finding at Site #110 as well as a major finding of late SAE reporting. The EMA concluded that despite the findings, the data generated at Site #110 was reliable and suitable for assessment. The findings are unlikely to adversely affect safety or efficacy assessments.

With the exception of Site #61, the EMA inspectional findings support the validity of data as reported by the sponsor under this NDA. We therefore recommended that DNP consider conducting a sensitivity analysis excluding the data from Site #61. Exclusion of Site #61 did not significantly impact the primary efficacy analysis.

II. BACKGROUND

Patirisan injection is being developed, under NDA 210922, for the treatment of adults with hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis). Under IND 117395, the sponsor was granted Orphan Drug designation (6/2012), Fast Track designation (10/2013), and Breakthrough Therapy designation (11/2017). The sponsor has submitted one Phase 3 study, ALN-TTR02-004 (APOLLO), to support the efficacy and safety of patisiran for the treatment of hATTR amyloidosis.

Protocol ALN-TTR02-004 (APOLLO)

Title: “A phase 3 multicenter, multinational, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of patisiran-LNP (ALN-TTR02) in transthyretin (TTR)-mediated polyneuropathy (familial amyloidotic polyneuropathy-FAP)”

Subjects: 225 enrolled and randomized

Sites: 43 sites in 19 countries; Western Europe (19 sites), North America (12 sites, 11 sites in the United States), Asia/Pacific (6 sites), Latin America (4 sites), Middle East/Central Asia (1 site), Eastern Europe (1 site)

Study Initiation and Completion Dates: 12/23/2013 – 8/17/2017

Database Lock: 9/14/2017

This was a randomized, double-blind, placebo-controlled study in adults with hereditary transthyretin-mediated amyloidosis (hATTR) with polyneuropathy. The protocol consisted of a Screening/Baseline Phase (Day -42 to Day -1), an On-Treatment Phase (Day 0 to Week 79/80), and a Follow-up Phase (Weeks 81 to 86). Eligible subjects were randomized, in a 2:1 ratio, to the following:

- Patisiran 0.3 mg/kg by intravenous infusion every 21 days for up to 78 weeks
- Placebo by intravenous infusion every 21 days for up to 78 weeks

The primary efficacy endpoint was the difference between patisiran and placebo in the change from baseline to 18 months in the Neurologic Impairment Score (mNIS+7).

Rationale for Site Selection

The clinical sites were chosen primarily based on risk ranking in the site selection tool, numbers of enrolled subjects, enrollment in multiple pivotal clinical studies, and prior inspectional history. The sponsor, Alnylam Pharmaceuticals, was also inspected. Based on findings from the sponsor inspection, which indicated potential issues with overall clinical trial monitoring, the CRO, Medpace, was inspected.

III. RESULTS

Site #/ Name of CI/ Address	Protocol #/ # of Enrolled Subjects	Inspection Dates	Compliance Classification
Site #50 David Adams CHU Bicetre Service de neurologie adultes du Pr D. ADAMS Centre de Référence des Maladies Rares 78 rue du Général Leclerc Le Krenlin Bicêtre cedex 94275 France	ALN-TTR02-004 Subjects: 22	12-16 Mar 2018	NAI
Site #85 William O’Riordan 5565 Grossmont Center Drive Building 2, Suite 1 La Mesa, CA 91942	ALN-TTR02-004 Subjects: 12	5-9 Mar 2018	NAI
Sponsor Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142	ALN-TTR02-004	2 – 25 Apr 2018	VAI

Site #/ Name of CI/ Address	Protocol #/ # of Enrolled Subjects	Inspection Dates	Compliance Classification
CRO Medpace 5375 Medpace Way Cincinnati, OH 45227	ALN-TTR02-004	16-20 Apr 2018	VAI

Compliance Classifications

NAI = No Action Indicated, no deviation from regulations.

VAI = Voluntary Action Indicated, deviation(s) from regulations.

OAI = Official Action Indicated, significant deviations from regulations. Data may be unreliable.

1. David Adams, M.D.

At this site for Protocol ALN-TTR02-004, 24 subjects were screened, 22 subjects were randomized, and 20 subjects completed the study. Two subjects discontinued the study: one subject withdrew due to the adverse event ischemia of the right lower limb and the other was withdrawn due to “physician decision” (progressive decline in the subject’s general health).

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, training documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, protocol deviations, and primary efficacy data (mNIS+7). Medpace was responsible for clinical monitoring of Protocol ALN-TTR02-004. Monitoring visits were conducted prior, during, and after active subject participation at intervals of every one to two months.

Modified NIS (mNIS) +7 total scores were not available at the site for verification against data listings. Assessments for the mNIS + 7 are completed by blinded investigators, and the assessment booklets/pages are then faxed to Mayo Clinic for scoring. The FDA field investigator reviewed random baseline and 18 month NIS individual item scores for the weakness (NIS-W) and reflexes (NIS-R) components, which are part of the total score for the mNIS+7. The FDA field investigator also reviewed secondary efficacy data, including the 10 meter walk and the Composite Autonomic Symptom Scores (COMPASS). No discrepancies were noted for these primary and secondary efficacy data. As part of a data integrity check, this reviewer verified NIS-W and NIS-R individual item scores by comparing source documents with data listings for 12 of 24 enrolled subjects. Two relatively small discrepancies were noted for NIS-W data (*refer to Alnylam inspection summary for further details regarding data integrity check and data discrepancies*).

There was no evidence of under-reporting of adverse events. The FDA field investigator noted that some SAEs were not reported within 24 hours from the time that site personnel first learned of the event, as required in the protocol. The study coordinator stated that the Medpace study monitor initially specified that SAEs related to disease progression should not be reported. During the sponsor inspection, it was noted that 19 of 33 SAEs occurring at this site were reported late and that 12 of those were reported at least one year after occurrence. However, after May 2016, the site began reporting all SAEs within the 24-hour timeframe.

Reviewer Comments: Two relatively small discrepancies were noted in NIS-W data for Subject # (b) (6). It is unlikely that these discrepancies would impact the overall efficacy analyses (refer to discussion in Alnylam inspection summary). SAEs were reported late, email communications included with the EIR verify that the Medpace monitor had instructed the site not to report SAEs that were related to disease progression (see further discussion of late SAE reporting in Alnylam and Medpace inspection summaries). Though reported late, there is no evidence of unreported SAEs. These SAEs were related to disease progression and are considered unlikely to have impacted subject safety unless these SAEs were related to the drug's lack of efficacy in treating the disease.

2. William O'Riordan, M.D.

At this site for Protocol ALN-TTR02-004, 22 subjects were screened, 12 subjects were randomized, and 10 subjects completed the study. Two subjects discontinued the study due to SAEs: sudden cardiac death occurring approximately one year after randomization to patisiran (Subject # (b) (6)) and acute renal failure in a subject randomized to placebo (Subject # (b) (6)).

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all subjects enrolled was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, study personnel training, IRB/sponsor communications, financial disclosure, test article storage and accountability, inclusion/exclusion criteria, adverse event reports, protocol deviations, and primary efficacy data (mNIS+7). Medpace was responsible for clinical monitoring of Protocol ALN-TTR02-004. Monitoring visits were conducted prior, during, and after active subject participation at intervals of every one to two months.

There was no evidence of under-reporting of adverse events. As part of a data integrity check, this reviewer verified NIS-W and NIS-R individual item scores by comparing source documents with data listings for 11 of 12 enrolled subjects (source documents for efficacy for Subject # (b) (6) not available). No discrepancies were noted (*refer to Alnylam inspection summary for further details regarding data integrity check*).

3. Alnylam Pharmaceuticals, Inc.

This was a joint inspection conducted by FDA and EMA. The inspection covered sponsor practices related to Protocol ALN-TTR02-004 and focused on six clinical investigator sites: #s 50, 51, 61, 81, 90, and 91.

Records reviewed included, but were not limited to, organizations charts, SOPs, monitoring plans and reports, transfer of responsibilities, correspondence, training records, Form FDA 1572s, financial disclosure forms, Clinical Operations Plans, eCRFs, protocol deviations, serious adverse events, and test article accountability. Study specific records were reviewed for 50% of subjects enrolled at each of the six clinical investigator sites selected.

Clinical monitoring and data management for Protocol ALN-TTR02-004 was conducted by the CRO, Medpace. (Medpace subcontracted three regional CROs for monitoring services in Portugal, Bulgaria, Cyprus, Turkey, and Japan). (b) (4) performed co-monitoring visits on behalf of the sponsor, and an independent consultant, (b) (4) performed as-needed clinical site audits. (b) (4) was the central laboratory for neurological impairment assessment (the primary efficacy endpoint), including staff training and certification.

A Form FDA 483 was issued at the conclusion of the inspection. Inspection observations included the use of electronic records that were not 21 CFR Part 11 compliant and inadequate study oversight, as outlined below.

Electronic Records

From January 2014 to August 2016, data captured by (b) (4) for calculating the primary endpoint was recorded in REDCap EDC and manipulated in Microsoft Excel. The REDCap EDC was not Part 11 compliant for electronic signatures. The information in Excel does not include tracked changes, version controls, or other measures to prevent potential modification or deletion of data. REDCap data were transferred into the Part 11 compliant ClinTrak EDC in August 2016, but audit trails could not be transferred into ClinTrak and were not otherwise recoverable. Based on the vendor audits performed for the sponsor in October 2013 and 2015, the sponsor was aware that (b) (4) was using systems that were not Part 11 compliant.

Reviewer Comments: The sponsor acknowledged the inspectional findings and the implementation of their CAPAs appear acceptable to prevent future recurrence of this finding.

Due to the use of electronic databases that were not Part 11 compliant to handle the primary efficacy endpoint data for much of the study, OSI requested source data from the sponsor to verify primary efficacy endpoint data. Specifically, OSI requested these source data for 6 sites identified in the Alnylam and Medpace inspections as having some continuing compliance issues (Sites 50, 51, 61, 81, 85, and 87). The sponsor provided a USB 3.0 device containing certified electronic copies of the source records that were used to derive the mNIS+7 scores, the primary efficacy endpoint. Due to time constraints, only the NIS-W and NIS-R individual item scores were verified. The NIS-W and NIS-R are components of the overall mNIS+7. Per

protocol, the NIS-W and NIS-R scores were assessed at baseline, Month 9, and Month 18, with two assessments for each time point. NIS-W and NIS-R scores were checked for all 17 subjects enrolled at Sites 51, 61, 81, and 87; 11 of 12 subjects enrolled at Site 85 (data for one subject was not included in sponsor submission); and 12 of 24 subjects enrolled at Site 50. Of note, Sites #s 50 and 85 were the clinical sites that OSI inspected for this NDA submission.

In reviewing NIS-W and NIS-R individual item scores for baseline, Month 9, and Month 18, there were three instances of data discrepancies for the NIS-W when comparing the source data to the data listings (refer to Table 1). Note that the discrepancies listed were noted only for one of two assessments performed for each timepoint.

Table 1. Discrepancies in NIS-W Data During Data Verification

Subject	Treatment Arm	Timepoint	NIS-W	
			Source Data	Data Listing
(b) (6)	Patisiran	Baseline	33	32.5
	Placebo	Baseline	62.5	66.5
	Placebo	Month 18	73	69

The most significant data discrepancy noted was for Subject # (b) (6). Since two assessments were performed for every timepoint, the mean of the two assessments for baseline were 65.5 (source) vs. 67.5 (data listing) and for Month 18 were 70.5 (source) vs. 68.5 (data listing). For this subject, the mean change from baseline to Month 18 would be 5 (source) vs. 1 (data listing); both are in the direction of worsening. Since these appear to be small differences, and the NIS-W is only one component of the mNIS+7, it is unlikely that this discrepancy would impact the overall efficacy analyses.

Study Oversight

Based on the sponsor records, the field investigator noted some continuing noncompliance of clinical investigators at Site #s 61, 81, and 91. Examples of noncompliance included laboratory reports not signed by the clinical investigator, missing laboratory reports, incomplete documentation of adverse events in CRFs, late SAE reporting, and lack of source documentation. Alnylam did not ensure proper follow up at clinical sites to mitigate continued noncompliance.

The CRO, Medpace, was responsible for study monitoring. The first subject was enrolled in December 2013. In June 2014, Alnylam hired (b) (4) to perform co-monitoring. Alnylam also hired an independent consultant, (b) (4), to perform as-needed site audits. Despite monitoring by Medpace, co-monitoring, and audit activities, issues with noncompliance continued and were not resolved in a timely manner.

Reviewer Comments: Protocol ALN-TTR02-004 was initiated in 12/2013 and completed in 8/2017. It is unclear when Alnylam became aware of inadequate monitoring of clinical sites and/or continuing noncompliance of clinical investigators. (b) (4) Consulting was hired in June 2014 to conduct co-monitoring of clinical sites. For the sites with continuing noncompliance (#s 61, 81, 91) co-monitoring visits were conducted between 3/2015 and 11/2016, with three

co-monitoring visits for Site 091 and two co-monitoring visits for Site 081. It appears that issues identified in monitoring visits were eventually resolved, though some took more than one year for resolution. No study sites enrolling subjects in this study were terminated

As for the late SAE reporting, the protocol stated that adverse events related to disease progression should not be reported as adverse events. However, the protocol also outlined the standard definition of a SAE, which included hospitalization, requiring them to be reported within 24 hours from the time that site personnel first learned of the event. This caused confusion with some CRAs and clinical sites (number not stated), who thought that SAEs related to disease progression did not have to be reported. It is unknown when Medpace and Alnylam became aware of this SAE reporting issue. This issue does not appear to have been addressed until June 2016 when an email was sent from Clinical Trial Management Medpace to Medpace CRAs to advise them that SAEs should be reported regardless of relationship to disease progression. Alnylam stated that all of these SAEs were captured and are in the NDA submission.

Potential Unblinding Event (also see Medpace inspection summary)

Although not listed on the Form FDA 483 as an inspectional finding, the field investigator noted an issue of potential study unblinding.

Urine and plasma PK concentration results were blinded data sources for Protocol ALN-TTR02-004. Due to an error by (b) (4) the laboratory vendor, urine PK concentrations for all 225 subjects were transferred to Medpace (the CRO), which subsequently transferred the data to Alnylam and (b) (4) (the statistics vendor).

Reviewer Comments: This reviewer agrees with the sponsor's assessment that the urine PK results would unlikely unblind the study since 98% of samples were below the lower limit of quantitation. We also conferred with the OCP reviewer for this application, who agreed that, based on the types and levels of metabolites found in the urine, the urine PK results should not lead to unblinding.

4. Medpace

This was a joint inspection conducted by FDA and EMA. The inspection covered CRO practices related to Protocol ALN-TTR02-004 and focused on the same six clinical investigator sites as the Alnylam inspection: #s 50, 51, 61, 81, 90, and 91.

Records reviewed included, but were not limited to, organizations charts, SOPs, monitoring plans and reports, transfer of responsibilities, correspondence, training records, Clinical Operations Plans, meeting minutes, Safety Plans, eCRFs, protocol deviations, serious adverse events. Study specific records were reviewed for 50% of subjects enrolled at each of the six clinical investigator sites selected.

A Form FDA 483 was issued at the conclusion of the inspection. Inspection observations included failure to ensure proper monitoring of the study, including potential unblinding of the

study, as outlined below.

Clinical Monitoring

As discussed in the Alnylam inspection summary, there was continued noncompliance of clinical investigators at Sites 61, 81, and 91. Examples of noncompliance included laboratory reports not signed by clinical investigator, missing laboratory reports, incomplete documentation of adverse events in CRFs, late SAE reporting, and lack of source documentation. For Site 50, 19 of 33 (57%) SAEs were reported late; 12 of those were reported at least one year after occurrence. Medpace performed frequent monitoring visits at these sites and documented continuing noncompliance with the protocol. For two of these sites, 81 and 91, Site Corrective Action Plans were implemented to improve site compliance. However, noncompliance continued, and it is not clear when, or if, these issues were escalated to the sponsor in a timely manner.

As discussed in the Alnylam inspection summary, Alnylam hired (b) (4) to perform co-monitoring activities and (b) (4) to perform periodic audits of the clinical sites. These visits also documented continued noncompliance. At Site 61, for example, an audit in February 2017 noted the critical finding that “electronic medical records were not contemporaneous with the date of subject visits, lacked detail, and the source of the data entered post visits could not be determined.” This same audit report, however, also concludes with an overall impression that the clinical investigator conducted the study in a satisfactory manner.

Reviewer Comments: Issues of continuing noncompliance of clinical investigators at Sites 61, 81, and 91 was problematic. Medpace appeared to document the issues, but many remained unresolved at multiple follow-up monitoring visits, co-monitoring visits, and audits. For some sites, Site Corrective Action Plans were implemented to address continuing issues but did not appear to be effective.

The issue of late reporting of SAEs is discussed in the Alnylam inspection summary. Medpace CRAs were advising some sites (e.g. Site 50) not to report SAEs if they were related to progression of the disease. It is unclear whether Medpace did not appropriately train the CRAs regarding SAE reporting or if they were not aware that these events were not being reported. This issue should have been identified and addressed much earlier. Although all SAE data were ultimately included in the NDA submission, these safety data may not have been available to the Data Monitoring Committee in real time in order to monitor the progress of the clinical study and the safety of the study participants.

Because of the critical finding from the audit of Site 61, in conjunction with findings from the EMA inspection of this site, we had recommended to the review division to perform a sensitivity analysis excluding data from this site.

Potential Unblinding Event

As discussed in the Alnylam inspection summary, urine and plasma PK concentration results were blinded data sources for Protocol ALN-TTR02-004. Due to an error by (b) (4) the

laboratory vendor, urine PK concentrations for all 225 subjects were transferred to Medpace (the CRO), which subsequently transferred the data to Alnylam and (b) (4) (the statistics vendor). This reviewer and the OCP reviewer for this application agreed that, based on the types and levels of metabolites found in the urine, the urine PK results should not lead to unblinding.

Reviewer Comments: Since Medpace had responsibility for data management, it seems reasonable that they should have had some responsibility to ensure that the data transfer files from (b) (4) did not contain unblinded data. However, this expectation may not have been outlined in the Data Transfer Agreement. Although Medpace did not take any responsibility for this inspectional finding, according to information from Alnylam, Medpace has instituted additional QC steps to address this finding.

5. EMA Findings

The European Medicines Agency (EMA) had received the same marketing authorization application. The FDA and EMA conducted joint inspections of the sponsor, Alnylam Pharmaceuticals, and the CRO, Medpace, as noted above. The EMA selected two clinical sites enrolling subjects in Protocol ALN-TTR02-004 to inspect independently: Dr. Juan Buades Reines (Site #61/Spain) and Dr. Maria Gonzalez-Duarte Briseno (Site #110/Mexico). The EMA inspectional findings/results were communicated to OSI. The EMA summarized the inspections noting that there were critical, major and minor findings.

The inspectional findings for Site #61 included several critical and major findings. Critical findings included deficiencies in the informed consent process, in preserving the confidentiality of subjects, in the management of investigational product, and in source document management. Major findings included lack of GCP training documentation, some ICF versions lacking signature option of legal representative of the subject or a witness, protocol deviations, and late reporting of SAEs. Based on these findings, EMA considered the data from Site #61 to be suboptimal and recommended that these data be excluded from analyses.

The inspectional findings for Site #110 included a critical finding of protocol violations and a major finding of late SAE reporting. The EMA concluded that despite the findings, the data generated at Site #110 was reliable and suitable for assessment. The findings are unlikely to adversely affect safety or efficacy assessments.

With the exception of Site #61, the EMA inspectional findings support the validity of data as reported by the sponsor under this NDA. We therefore recommended that DNP consider conducting a sensitivity analysis excluding the data from Site #61. Exclusion of Site #61 did not significantly impact the primary efficacy analysis.

{See appended electronic signature page}

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/s/

CARA L ALFARO
07/10/2018

PHILLIP D KRONSTEIN
07/10/2018

KASSA AYALEW
07/10/2018

MEMORANDUM OF REVIEW

STN: NDA 210922

Subject: Immunogenicity assessment for original application.

RECEIPT DATE:

REVIEW DATE: 7/2/2018

PRIMARY REVIEWER: Susan Kirshner, Ph.D.

APPLICANT: Alnylam Pharmaceuticals Inc.

PRODUCT: Patiseran (TTR02, patisiran-lnp)

INDICATION: Treatment of adults with hereditary transthyretin-mediated amyloidosis.

I. SUMMARY BASIS OF RECOMMENDATION:

a. Recommendation:

Appropriate validation studies were performed to establish the suitability of the assay. Overall the assay is suitable for its intended purpose. Depending on the actual concentration of free PEG in patient serum samples effective assay sensitivity may range from 250 – 1000 ng/ml.

II. REVIEW OF SUBMISSION:

Reviewer note: The FDA Draft Guidance for Industry Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products (2016) will be referred to as FDA Guidance in this memo.

Documents Reviewed:

303458 – Validation of an Enzyme-linked Immunosorbent Assay (ELISA) for the detection of Anti-PEG IgG/IgM Antibodies Present in Human Serum – contains original validation exercise plus 4 amendments.

1. Background:

TTR02, patisiran-lnp, is a pegylated lipid nanoparticle containing a double stranded siRNA against the untranslated region of wild-type and mutant transthyretin. Patisiran-LNP is being developed for the treatment of adults with hereditary transthyretin-mediated amyloidosis.

Patisiran-LNP is comprised of patisiran (2 mg/ml), a double stranded siRNA, formulated as a nanoparticle using the lipid excipients Dlin-MC3-DMA, DSPC, cholesterol, and PEG2000-C-DMG. To address immunogenicity concerns the company was advised by FDA's clinical pharmacology group to develop an assay to assess for anti-PEG antibodies.

This memo provides OBP's evaluation of the ELISA used by the Sponsor to detect anti-PEG IgG and IgM in human serum.

Controls:

Plates were coated with PEG2000-C-DMG

Drug tolerance material – Dlin-MC3-DMA lot X076 – component of the pegylated nanoparticle lipid (LNP); ALN-TTR02 lot IC118 and XAP13001 – an LNP with siRNA against transthyretin, Patisiran-LNP; ALN-18328 lot A05AC12001N – patisiran (siRNA unformulated); Tafamidis (ALY-SAN-086) lot RRN/1104 – small molecule drug used to delay the loss of peripheral nerve function in adults with familial amyloid polyneuropathy by stabilizing transthyretin.

Positive control: Anti-PEG methoxy group Rabbit Monoclonal Antibodies (Epitomics catalog number 2061-1) concentration 0.97 mg/ml neat lot YI101708PS and 0.803 mg/ml lot GR175680-15). This Ab can detect linear and branched PEG molecules.

Low low positive control (LLPC) 200 ng/ml; LPC 250 ng/ml; MPC 1000 ng/ml and HPC 2000 ng/ml

Ig positive control: Human IgG whole molecule (Rockland) and Human IgM (myeloma) whole molecule (Rockland)

Secondary reagents: Goat anti-human IgG+M (H+L) HRP (Jackson ImmunoResearch Laboratory); Goat anti-rabbit IgG-HRP (Fc fragment specific)

Matrices: Pooled Normal Human Serum (Bioreclamation); Individual lots of Normal Human Serum (Bioreclamation)

Summary Description of the Method:

Plates are coated (10 ug/well) with PEG2000-C-DMG. Serum samples diluted 1/40 (Blocker Casein in PBS) are added to the plate. Captured anti-PEG antibodies are detected with horseradish peroxidase (HRP) conjugated goat anti-human IgM+IgG. After addition of trimethylbenzidine (TMB) absorbance (A_{450nm}) is determined.

Method validation:

Reviewer note: The Table below was copied from the Sponsor's submission, 303458: Validation of an Enzyme-linked Immunosorbent Assay (ELISA) for the detection of Anti-PEG IgG/IgM Antibodies Present in Human Serum pg 427 – 430.

Text Table 1
Summary of the Validation Data

Experimental Procedure	Acceptance Criteria	Results
Validation Parameter: Screening Cut-point (CP) and Cut-point Factor (CF)		
<p>50 individual lots of normal human serum (25 males and 25 females) were analyzed on a total of three occasions, performed by three different analysts.</p> <p>For the statistical analyses, please refer to the Biometry report "Cut-Point (CP), Correction Factor (CF) and Confirmatory Cut-Point (CCP) Determination."</p>	N/Ap	<p>The global cut-point factor (CF) = 2.325</p> <p>The normalized CP (PSCP) will be calculated for each assay using the following formula: PSCP = Blank TS global Mean A_{450nm} x 2.325</p>
Validation Parameter: Confirmatory Cut-point (CCP)		
<p>50 individual human serum (25 males and 25 females) (the same sera used for the CP determination), on a total of three occasions, were spiked with PEG2000-C-DMG at a final concentration of 5 µg/mL (spiked samples).</p> <p>The CCP was determined to be the mean % Signal Inhibition value (when comparing the mean A_{450nm} of the PEG2000-C-DMG spiked lot to the corresponding mean A_{450nm} of the unspiked lot) plus $2.33 \times SD$, which represents the 99th percentile of a normal distribution.</p>	N/Ap	<p>The global CCP, calculated as the average of the three CCP values = 58.1%. However, the lowest CCP, 46.5%, was selected in deviation as a CCP value (refer to Section 10.13, Deviations).</p>
Validation Parameter: Confirmatory Cut-Point (CCP) Controls		
<p>PCs (LLPC, LPC and HPC) and PNMS (Blank TS) were spiked with PEG2000-C-DMG at a final concentration of 5 µg/mL (spiked samples).</p> <p>The % signal inhibition was determined for each PC and PNHS sample, using the following formula: % Signal Inhibition = $[1 - (\text{spiked sample mean } A_{450nm} / \text{control unspiked sample mean } A_{450nm})] * 100$.</p>	<p>% signal inhibition of each PC \geq CCP</p> <p>% signal inhibition of Blank < CCP</p>	<p>100% of HPC and LPC samples have the % signal inhibition \geq CCP</p> <p>100% of Blank samples have the % signal inhibition < CCP</p>

Reviewer comments on SCP: This approach is consistent with FDA Guidance to use results from at least 2 analysts on at least 3 days for cut point determination. Cut point determination included appropriate removal of outliers and use of the 5% false positive rate as recommended by FDA Guidance. The cut point determination results were reviewed and the cut point is acceptable.

Reviewer comments on CCP: The Sponsor's approach is acceptable because using the lower CCP is a more conservative approach to identifying ADA positive serum samples. Cut point determination included appropriate removal of outliers and use of a 1% false positive rate as recommended by FDA Guidance. The assay cut point performed acceptably because the LPC was always positive and the negative control negative. The LPC is 250ng/ml, which is within the recommended sensitivity range of FDA Guidance (2009) available in 2012 when this assay was validated.

Text Table 1
Summary of the Validation Data (Cont'd)

Experimental Procedure	Acceptance Criteria	Results
Validation Parameter: Intra- and Inter-assay Precision		
PCs (LLPC: 200 ng/mL, LPC: 250 ng/mL, MPC: 1000 ng/mL and HPC: 2000 ng/mL) were assayed in replicates of 3 (n = 3), each one in duplicate on 6 occasions, performed by 3 analysts on 6 days, using a balanced design.	<p>Mean A_{450nm} of PCs (3 replicates at each PC level, on each occasion) should be \geq PSCP.</p> <p>The global mean LLPC $A_{450nm} <$ global mean LPC $A_{450nm} <$ global mean MPC $A_{450nm} <$ global mean HPC A_{450nm}.</p> <p>Intra-assay precision: % CV \leq 25 % at all PC levels.</p> <p>Inter-assay precision: % CV \leq 25 % at all PC levels.</p>	<p>Two outlier precision assays were excluded from the precision assessment in deviation (refer to Section 10.13, Deviations).</p> <p>LPC, MPC and HPC had mean A_{450nm} values \geq PSCP on all 6 occasions.</p> <p>LLPC had mean A_{450nm} values \geq PSCP on 5 out of 6 occasions.</p> <p>The global mean A_{450nm} of LLPC $<$ global mean A_{450nm} of LPC $<$ global mean A_{450nm} of MPC $<$ global mean A_{450nm} of HPC.</p> <p>Intra-assay precision: % CV \leq 25 % at all PC levels.</p> <p>Inter-assay precision: % CV \leq 25% at LLPC, LPC, MPC and HPC levels.</p>
Validation Parameter: Assay Sensitivity		
PCs (LLPC: 200 ng/mL and LPC: 250 ng/mL) were assayed in replicates of 3 (n = 3), each one in duplicate on 6 occasions, performed by 3 analysts on 6 days, using a balanced design.	Lowest PC concentration consistently positive (i.e., \geq PSCP on all occasions) and whose intra- and inter-assay %CV is \leq 25%.	<p>LPC (250 ng/mL) was positive on all 6 occasions.</p> <p>No false-positive samples were identified among the serum lots used for the determination of cut-point and assay sensitivity.</p>
Validation Parameter: Specificity		
10 individual lots of normal human serum (5 males and 5 females) were analyzed on one occasion.	At least 80% of the unspiked normal human serum lots should be $<$ PSCP.	10 lots were $<$ PSCP.
Validation Parameter: Selectivity		
10 individual lots of normal human serum (5 males and 5 females), were spiked with the PC at 200 ng/mL (LLPC), 250 ng/mL (LPC) and 2000 ng/mL (HPC).	80% lots within \pm 25% mean A_{450nm} of the same PC level prepared in pooled normal human serum.	100% serum lots were within \pm 25% at LLPC, LPC and HPC levels.

Reviewer comment on precision: Assay precision is within industry standard for this type of assay and is acceptable. The precision of blank test sample was noted in the report to be 20.9% and is acceptable.

Reviewer comment on sensitivity: The assay consistently detected antibodies at 250 ng/ml which is below the 2009 FDA Guidance recommendation of 500 ng/ml. The ADA are to PEG, which is not endogenous to humans and so there is low risk of patients developing deficiency syndromes. Therefore, the sensitivity of the assay is acceptable.

Reviewer comment on specificity: The assay does not non-specifically provide signal. The confirmatory cut point study indicates that the assay can specifically detect positive control. Assay specificity is acceptable.

Reviewer comment on selectivity: Testing of selectivity could have been more robust with the sponsor investigating other interfering matrix factors such as lipids. However, these results support a conclusion that the assay can detect the analyte of interest in the test article matrix. No further action required.

Text Table 1
Summary of the Validation Data (Cont'd)

Experimental Procedure	Acceptance Criteria	Results
Validation Parameter: Precision of Titers		
Titration was evaluated using the PC at HPC level. The PC was spiked into neat pooled human serum at 40X HPC, was diluted 1/40 (MRD) in Blocker Casein in PBS buffer and then serially diluted for the titration assessment. .	For the titration results to be acceptable, the titer of each sample should remain within \pm one 2-fold dilution for all analyses (e.g., 1/40, 1/80, 1/160).	The inter- and intra-assay titer precision met AC.
Validation Parameter: Stability		
<p>The stability assessment was performed with the PC spiked into neat pooled human serum at 3 PC levels: HPC (2000 ng/mL), LPC (250 ng/mL), and LLPC (200 ng/mL). Stability samples were submitted to the following stability treatments:</p> <ol style="list-style-type: none"> 1. Stability samples were stored in a freezer set to maintain -80°C for at least 24 hours, thawed unassisted and kept at ambient room temperature for at least 4, 6, and 24 hours to determine bench top (BT) stability. 2. Stability samples were stored in a freezer set to maintain -80°C for at least 24 hours and thawed unassisted at ambient room temperature. When completely thawed (at least 1 hour), the samples were re-frozen for at least 12 hours. This cycle of freezing and thawing was done 2, 4, 6 times and the samples were analyzed after the set of cycles. 3. Aliquots of stability samples, stored in a freezer set to maintain -80°C, were analyzed after 1 month period. The LTS stability of 3 and 6 month periods is ongoing. 	<p>Mean A_{450nm} values of the PC stability samples at the minimum required dilution \geq PSCP, and if the titer of HPC samples is within the acceptable range of titers defined during assessment of titration precision.</p> <p>At least 67% of the stability aliquots, at each PC level, should meet the acceptance criteria.</p>	<p>All LLPC, LPC and HPC BT stability samples (4, 6 and 24 hrs) met AC.</p> <p>All LLPC, LPC and HPC FT stability samples (2, 4 and 6 freeze/thaw cycles) met AC.</p> <p>LLPC, LPC and HPC LTS (1 month) met AC.</p>

Reviewer comment on precision of titers: Precision of titers is consistent with FDA Guidance and is acceptable.

Reviewer comment on stability: Results of the stability studies show that that PCs are suitable for use in the assay. In amendment 4 of the assay validation long term stability data were updated to include stability data through 4.2 years.

Drug interference assessment with PEG

<p>PC samples (LLPC: 200 ng/mL, LPC: 250 ng/mL, MPC: 1000 ng/mL and HPC: 16000 ng/mL) were spiked with PEG at 8 selected concentrations (10, 50, 100, 250, 500, 1000, 2500 and 4000 ng/mL final concentration in neat serum).</p> <p>All drug interference samples were tested n=1 in duplicate on 1 occasion.</p> <p>The % difference between the PC samples with and without the addition of PEG was calculated for information purposes.</p>	<p>The drug interference was defined as the lowest concentration of PEG that interferes with the detection of PC samples and brings the mean A_{450nm} values below the PSCP.</p>	<p>All HPC drug interference samples had mean A_{450nm} values \geq PSCP.</p> <p>MPC drug interference samples had mean A_{450nm} values \geq PSCP in the presence of ≤ 100 ng/mL of PEG in neat serum.</p> <p>LPC drug interference samples had mean A_{450nm} values \geq PSCP in the presence of ≤ 10 ng/mL of PEG in neat serum.</p> <p>All LLPC drug tolerance samples had mean $A_{450nm} < PSCP$.</p> <p>In conclusion, PEG concentrations ≤ 10 ng/mL did not interfere with the detection of anti-PEG antibodies at the LPC (250 ng/mL) level.</p>
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From amendments 1 and 2
Reviewer comments on PEG interference:
 According to the PK reports, which needs to be confirmed by the Clinical Pharmacology reviewer, trough levels of PEG-2000-C-DMG are 0.024 ug/ml. Therefore, trough levels are expected to be higher than drug tolerance at 250 ng/ml antibody but lower than drug tolerance at 1000 ng/ml antibody (MPC). Therefore, the effective sensitivity of the assay is between 250 and 1000 ng/m in the presence of free PEG. Free PEG is expected to interfere with the assay because it directly competes for binding with the positive controls.

Drug interference assessment with MC3

PC samples (LPC: 250 ng/mL, MPC: 1000 ng/mL and HPC: 16000 ng/mL) were spiked with MC3 at 7 selected concentrations ((1, 10, 25, 50, 100, 150, and 200 µg/mL in neat serum final concentration in neat serum).

The drug interference was defined as the lowest concentration of MC3 that interferes with the detection of PC samples and brings the mean A_{450nm} values below the PSCP.

All HPC, MPC and LPC drug interference samples had mean A_{450nm} values \geq PSCP.

In conclusion, MC3 did not interfere with the detection of anti-PEG antibodies at the 1 to 200 µg/mL concentrations in neat serum.

From Amendment 3

Reviewer comment: MC3 did not interfere with ADA detection. Assessment of MC3 is relevant because it is a component of Patisiran-LNP.

Drug interference assessment with ALN-TTR02

PC samples (LPC: 250 ng/mL, MPC: 1000 ng/mL and HPC: 16000 ng/mL) were spiked with ALN-TTR02 at 8 selected concentrations (0.01, 0.05, 0.1, 1, 10, 50, 100 and 200 µg/mL final concentration in neat serum).

The drug interference was defined as the lowest concentration of ALN-TTR02 that interferes with the detection of PC samples and brings the mean A_{450nm} values below the PSCP.

0.10 µg/mL HPC and MPC drug interference samples had mean A_{450nm} values \geq PSCP.

0.05 µg/mL LPC drug interference samples had mean A_{450nm} values \geq PSCP.

In conclusion, ALN-TTR02 did not interfere with the detection of anti-PEG antibodies at concentrations 0.01 to 0.05 µg/mL in neat serum.

From Amendment 3

Reviewer comment: ALN-TTR02 is another name for Patisiran-LNP and does not interfere with the detection of the low positive control at 0.05 ug/ml. According to the Sponsor trough concentrations of Patisiran-LNP are 0.021 ug/ml with interpatient variability of 210%. Therefore, the effective sensitivity of the assay may be slightly worse than 250 ng/ml.

Drug interference assessment with ALN-18328		
<p>PC samples (LPC: 250 ng/mL, MPC: 1000 ng/mL and HPC: 16000 ng/mL) were spiked with ALN-18328 at 8 selected concentrations (0.01, 0.05, 0.1, 1, 10, 50, 100 and 200 µg/mL final concentration in neat serum).</p>	<p>The drug interference was defined as the lowest concentration of ALN-18328 that interferes with the detection of PC samples and brings the mean A_{450nm} values below the PSCP.</p>	<p>All HPC, MPC and LPC drug interference samples had mean A_{450nm} values \geq PSCP.</p> <p>In conclusion, ALN-18328 did not interfere with the detection of anti-PEG antibodies at concentrations 0.01 to 200 µg/mL in neat serum.</p>

From Amendment 3

Reviewer comment on ALN-18328 interference: ALN-18328 is unformulated patisiran. Assessment of ALN-18328 interference is relevant because it is a component of Patisiran-LNP. ALN-18328 did not interfere with detection of anti-PEG antibodies.

Drug interference assessment with Tafamidis		
<p>PC samples (LPC: 250 ng/mL, MPC: 1000 ng/mL and HPC: 16000 ng/mL) were spiked with Tafamidis at 8 selected concentrations (0.01, 0.05, 0.1, 1, 10, 50, 100 and 200 µg/mL final concentration in neat serum).</p>	<p>The drug interference was defined as the lowest concentration of Tafamidis that interferes with the detection of PC samples and brings the mean A_{450nm} values below the PSCP.</p>	<p>All HPC, MPC and LPC drug interference samples had mean A_{450nm} values \geq PSCP.</p> <p>In conclusion, Tafamidis did not interfere with the detection of anti-PEG antibodies at concentrations 0.01 to 200 µg/mL in neat serum.</p>

From Amendment 3

Reviewer comment on Tafamidis interference: Tafamidis is a small molecule drug used to delay loss of peripheral nerve function in adults with familial amyloid polyneuropathy. Assessment of Tafamidis interference is relevant because it may be a component of serum samples from Patisiran-LNP treated subjects. Tafamidis did not interfere with detection of anti-PEG antibodies.

Prozone Effect		
<p>A prozone sample was prepared by diluting the Rabbit Anti-PEG monoclonal antibody in neat pooled human serum at a concentration 10 times greater than the HPC. This sample was diluted 1/40 (MRD) in Blocker casein in PBS buffer and then serially diluted using 2-fold dilutions in pooled human serum previously diluted 1/40 in Blocker casein in PBS buffer to reach the PSCP. The prozone samples were analyzed n=1 in duplicate on one occasion.</p>	<p>The mean A_{450nm} value of each PC dilution above HPC should be \geq mean HPC A_{450nm}</p>	<p>The mean A_{450nm} values of prozone sample dilutions 1/40, 1/80 and 1/160 were \geq mean HPC A_{450nm}</p> <p>The dilution 1/320 (62.5 ng/mL) produced mean A_{450nm} (1.899) < mean HPC A_{450nm} (1.970) and thus, it did not meet AC.</p>

Reviewer comment: I concur there is no prozone effect.

Precision of Titers		
<p>Titration was evaluated using the PC at HPC level. The PC was spiked into neat pooled human serum at 40X HPC, was diluted 1/40 (MRD) in Blocker Casein in PBS buffer and then serially diluted for the titration assessment. The HPC samples were diluted using at least six 2-fold serial dilutions. The 2-fold serial dilutions were prepared using pooled human serum diluted 1/40 in Blocker Casein in PBS buffer. Titration samples was analyzed n=1, on three occasions (inter-assay precision), and n = 3 on 1 occasion (intra-assay precision). The final titer reported is the highest dilution factor that produced a mean A_{450nm} value \geq PSCP.</p>	<p>For the titration results to be acceptable, the titer of each sample should remain within \pm one 2-fold dilution for all analyses (e.g.: 1/40, 1/80, 1/160).</p>	<p>The inter- and intra-assay titer precision met AC.</p>

Reviewer comment on titer precision: Titer precision is consistent with FDA expectations of \pm one twofold dilution and is acceptable.

III. REVIEWER CONCLUSIONS:

Appropriate validation studies were performed to establish the suitability of the assay. Overall the assay is suitable for its intended purpose. Depending on the actual concentration of free PEG in patient serum samples effective assay sensitivity may range from 250 – 1000 ng/ml.

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/s/

SUSAN L KIRSHNER
07/02/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: June 8, 2018
Requesting Office or Division: Division of Neurology Products (DNP)
Application Type and Number: NDA 210922
Product Name and Strength: Onpattro^{***a} (patisiran) lipid complex injection
10 mg/5 mL (2 mg/mL)
Applicant/Sponsor Name: Alnylam Pharmaceuticals, Inc
FDA Received Date: May 16, 2018
OSE RCM #: 2017-2349-1
DMEPA Safety Evaluator: Chad Morris, PharmD, MPH
DMEPA Team Leader: Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Neurology (DNP) requested that we review the revised trade and sample carton labeling and container labels for Onpattro^{***} (Appendix A) to determine they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^b

2 ASSESSMENT

We reviewed the revised trade and sample carton labeling and container labels for Onpattro^{***}. In addition to the revisions DMEPA recommended, we note 4 other revisions were made to the carton and or container labels, and include the revision of the dosage form to lipid complex injection, addition of placeholders for the lot number and expiration date, addition of component numbers and 2D barcodes, and one spelling correction.

^a ***The proposed proprietary name, Onpattro, was conditionally approved in OSE RCM: 2017-19668675 (NDA 210922) on 03/09/2018.

^b Morris, C. Label and Labeling Review for Onpattro (NDA 210922). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 06. RCM No.: 2017-2349.

As part of our review of the revised labels and labeling, we considered whether the aforementioned revisions would impact the safe use of the product. We did not identify new vulnerabilities that may increase the risk for medication errors.

3 CONCLUSION

The revised trade and sample carton labeling and container labels for Onpattro*** are acceptable from a medication error perspective. We have no further recommendations at this time.

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/s/

JOHN C MORRIS
06/08/2018

LOLITA G WHITE
06/08/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: April 6, 2018
Requesting Office or Division: Division of Neurology Products (DNP)
Application Type and Number: NDA 210922
Product Name and Strength: Onpattro^{***a} (patisiran) injection
10 mg/5 mL (2 mg/mL)
Product Type: Single ingredient product
Rx or OTC: Rx
Applicant/Sponsor Name: Alnylam Pharmaceuticals, Inc.
Submission Date: December 11, 2017
OSE RCM #: 2017-2349
DMEPA Safety Evaluator: Chad Morris, PharmD, MPH
DMEPA Team Leader: Lolita White, PharmD

^a ***The proposed proprietary name, Onpattro, was conditionally approved in OSE RCM: 2016-12105251 (IND 117395) on 06/16/2017.

1 REASON FOR REVIEW

This review evaluates the proposed trade and sample carton labeling and container labels, and prescribing information for Onpattro*** (patisiran) injection (NDA 210922) for areas of vulnerability that may increase the risk for medication errors. This review is written in response to a request from the Division of Neurology Products.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed carton labeling and container labels, and prescribing information identified the following areas that can be improved to decrease risk of medication error:

Carton labeling and container labels

- The usual dose statement is not consistent with 21 CFR 201.55.
- The format of the expiration date is not clearly defined, which may lead to a degraded drug product medication error.

Prescribing Information

- Section 2.1 contains the error prone symbol “≥,” which may increase the risk for wrong dose medication errors.
- The recommended dose is presented with inconsistent units of measure, which may increase the risk for wrong dose medication errors.

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the proposed carton labeling and container labels, and prescribing information that can be improved to reduce the potential for confusion and increase the

prominence, clarity, and readability of important product information to mitigate the potential for medication errors and promote the safe use of Onpattro***. We provide recommendations in Sections 4.1 and 4.2 to address our concerns. We advise these recommendations are implemented prior to the approval of this NDA.

4.1 RECOMMENDATIONS FOR THE DIVISION OF NEUROLOGY PRODUCTS

Prescribing Information

- In Section 2.1 the error prone symbol “≥” is used, which may increase the risk for wrong dose medication errors. We recommend replacing the symbol “≥” with its intended meaning to prevent misinterpretation and confusion.
-
- In the HPI and Section 2.1 the units for the recommended dose is expressed as mg/kg, but in Section 2.3 the dosing units are expressed as (b) (4)/kg. This may increase the risk for wrong dose medication errors. We recommend you consider changing the following two statement from:
 - “Calculate the required (b) (4) of ONPATTRO based on the recommended weight-based dosage (b) (4) [see Dosage and Administration (2.1)]”
 - Withdraw the entire contents of one of more vials into a single sterile syringe.to read:
 - “Calculate the required dose of ONPATTRO based on the recommended weight-based dosage [see Dosage and Administration (2.1)]”.
 - Withdraw the entire contents of one of more vials into a single sterile syringe (b) (4).

4.2 RECOMMENDATIONS FOR ALNYLAM

We recommend the following be implemented prior to approval of this NDA:

Carton labeling and container labels

As currently presented:

- The usual dose statement does not comply with 21 CFR 201.55. We recommend you update your usual dose statement to read “See package insert for dosage and administration information.”
- The format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format like either:

DDMMMYYYY (e.g., 31JAN2013)

MMMYYYY (e.g., JAN2013)

YYYY-MMM-DD (e.g., 2013-JAN-31)

YYYY-MM-DD (e.g., 2013-01-31)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Onpattro*** that Alnylam submitted on December 11, 2017.

Table 2. Relevant Product Information for Onpattro***	
Initial Approval Date	N/A
Active Ingredient	patisiran
Indication	treatment of adults with hereditary transthyretin-mediated amyloidosis
Route of Administration	IV infusion
Dosage Form	injection
Strength	10 mg/5 mL (2 mg/mL)
Dose and Frequency	0.3 mg/kg every 3 weeks by intravenous infusion over approximately 80 minutes. For patients weighing ≥ 100 kg the recommended dose is 30 mg
How Supplied	Preservative-free, Single use, 5 mL vial per carton
Storage	Store at 2°C to 8°C (36°F to 46°F). Do not freeze. Discard vial if it has been frozen. If refrigeration is not available, ONPATTRO can be stored at room temperature up to 25°C (up to 77°F) for up to 14 days. The diluted solution should be administered immediately after preparation. If not used immediately, store in the infusion bag at room temperature (up to 30°C [86°F]) for up to (b) (4) hours (including infusion time). Do not freeze.
Container Closure	Glass vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 12, 2017, we searched DMEPA's previous reviews using the terms, Onpattro and patisiran. Our search did not identify any previous reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Onpattro*** labels and labeling submitted by Alnylam on December 11, 2017.

- Trade Carton labeling
- Trade Container label
- Sample Carton labeling
- Sample Container label
- Prescribing Information (Image not shown)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page

^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN C MORRIS
04/06/2018

LOLITA G WHITE
04/09/2018

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	117395
Request Receipt Date	9/29/2017
Product	patisiran
Indication	treatment for adults with hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) with polyneuropathy
Drug Class/Mechanism of Action	ribonucleic acid interference (RNAi)
Sponsor	Alnylam Pharmaceuticals
ODE/Division	ODE I/ Division of Neurology Products
Breakthrough Therapy Request(BTDR) Goal Date (within <u>60 days</u> of receipt)	11/28/2017

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

- 1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

Hereditary transthyretin- mediated amyloidosis (hATTR amyloidosis) is a life-threatening autosomal dominant disorder (>120 TTR gene mutations known) due to slowly progressive buildup of amyloid protein in the peripheral and central nervous systems, heart, kidneys, eyes, bone, and gastrointestinal tract. The disease is caused by misfolding of the transthyretin (TTR) protein leading to protein aggregation and the formation of amyloid fibrils.

There are three general forms of the disease, although patients can have overlapping symptoms from all three forms. The neuropathic form includes peripheral neuropathy, autonomic dysfunction, vitreous opacity of the eye, and glaucoma. The leptomeningeal form includes stroke, intracranial hemorrhage, hydrocephalus, ataxia, spastic paralysis, seizures, dementia, psychosis, and vision impairment. The cardiac form includes arrhythmia, cardiomegaly, heart failure, and death.

The incidence of hATTR is 1/538 in northern Portugal and about 1/100,000 in the U.S.

Symptom onset occurs between 20 and 70 years of age. Death usually occurs within 5-12 years after onset, most often due to cardiac dysfunction, infection, or cachexia.

The disease is often misdiagnosed if there is no family history to increase clinical suspicion. The diagnosis can be confirmed by histopathology and genetic analysis.

Treatment options include liver transplant. There is no approved drug for the treatment of hATTR in the United States.

- 2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?**

YES NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. Consideration of Breakthrough Therapy Criteria:

- a. Is the condition serious/life-threatening¹? YES NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
- YES the BTDR is adequate and sufficiently complete to permit a substantive review
 - Undetermined
 - NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):
 - i. Only animal/nonclinical data submitted as evidence
 - ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])
 - iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)
 - iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)
 - v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

¹ For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

² For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

- *Information regarding the disease and intended population for the proposed indication.*
 - See Section I, (1).
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*
 - See Section I, (1).

Patisiran was granted orphan drug designation on 6/14/2012 and Fast Track on 10/31/2013.

The mechanism of action of patisiran is via ribonucleic acid interference (RNAi). RNAi is a biological process by which siRNA, typically 21-23 nucleotides in length, can direct sequence-specific degradation of mRNA. When synthetic siRNAs are introduced into cells, the net effect is the binding of the siRNA to its complementary mRNA sequence, the cleavage of this target mRNA, and the suppression of the target protein encoded by the mRNA. Thus, patisiran suppresses the production of TTR (both wild type and mutated type).

Since unformulated siRNAs are rapidly eliminated and do not achieve significant tissue distribution, siRNA targeting TTR mRNA are delivered to target tissue in lipid nanoparticle (LNP) formulations intravenously. The target tissue is primarily the liver.

7. Information related to endpoints used in the available clinical data:

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The following endpoints were used for the Patisiran-LNP Phase 3 (ALN-TTR02-004, APOLLO) Trial.

- Primary efficacy endpoint
 - Change from baseline in the mNIS+7 composite neurologic impairment score at 18 months.
- Secondary endpoints
 - Norfolk QOL-DN quality of life score
 - motor strength (NIS-W)
 - disability (R-ODS)
 - gait speed (10-meter walk test)
 - nutritional status (mBMI)
 - autonomic symptoms (COMPASS-31)

The primary endpoint, mNIS+7, is composed of a clinical exam-based neuropathy impairment score (NIS) combined with electrophysiologic measures of small and large nerve fiber function (+7) such as nerve conduction studies (NCS), quantitative sensory testing (QST), and measurement of autonomic function (postural blood pressure). Many of the individual components of the score, such as nerve conduction studies, are clearly biomarkers that do not, of themselves, represent direct clinical benefit. Other components of the score, such as

motor and sensory function by neurological exam, also are not direct measures of clinical benefit, as differences detected by the physician might not be perceptible to the patient or result in improved function in daily activities.

The Norfolk Quality of Life – Diabetic Neuropathy (QOL-QN) is a 47-item questionnaire that assesses neuropathy symptoms and physical functioning, activities of daily living (ADL), symptoms of small and large-fiber neuropathy, and autonomic neuropathy.

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

There are no established endpoints for clinical trials in TTR-FAP. The Division had previously indicated to the sponsor that positive results on the mNIS+7, if supported by positive results on the Norfolk QOL-DN, would be an acceptable approach to demonstrating a clinically meaningful treatment effect in the APOLLO trial.

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

There is limited evidence to conclude the degree to which any observed reduction in the TTR protein could be considered to predict clinical benefit.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

Treatment options for hATTR include liver transplant and Diflunisal, which is a non-steroidal anti-inflammatory drug (NSAID) (off-label use). There is no approved drug for hATTR in the United States. The following table summarizes the clinical study that was completed with diflunisal.

Rx Name	Endpoints	Treatment Effect Magnitude	Intended Population
<i>Diflunisal</i> (Off-label use)	Neuropathy Impairment Score plus 7 nerve tests (NIS+7) quality-of-life questionnaire (36-Item Short-Form Health Survey [SF-36])	The NIS+7 score increased by 25.0 (95% CI, 18.4-31.6) points in the placebo group and by 8.7 (95% CI, 3.3-14.1) points in the diflunisal group, a difference of 16.3 points (95% CI, 8.1-24.5 points; P < .001). Mean SF-36 physical scores decreased by 4.9 (95% CI, -7.6 to -2.2) points in the placebo group and increased by 1.5 (95% CI, -0.8 to 3.7) points in the diflunisal group (P < .001).	Adults with familial amyloid polyneuropathy exhibiting clinically detectable peripheral or autonomic neuropathy

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

None.

10. Information related to the preliminary clinical evidence:

The patisiran-LNP (ALN-TTR02-004, APOLLO) trial was a randomized, double-blind, placebo-controlled Phase 3 trial in adult patients with hATTR amyloidosis with polyneuropathy. The APOLLO trial enrolled 225 patients (148 on patisiran-LNP and 77 on placebo). 193 patients completed the study. The following table summarizes the design of the trial.

Study ID	Phase	Design	Endpoints	Treatment groups	Number of subjects enrolled
ALN-TTR02-004, APOLLO	3	Randomized, double-blind, placebo-controlled	<ul style="list-style-type: none"> • Primary efficacy endpoint <ul style="list-style-type: none"> • Change from baseline in the mNIS+7 composite neurologic impairment score at 18 months. • Secondary endpoints <ul style="list-style-type: none"> • Norfolk QOL-DN quality of life score • motor strength (NIS-W) • disability (R-ODS) • gait speed (10-meter walk test) • nutritional status (mBMI) • autonomic symptoms (COMPASS-31) 	Patisiran Placebo	225 adult patients with hATTR amyloidosis with polyneuropathy

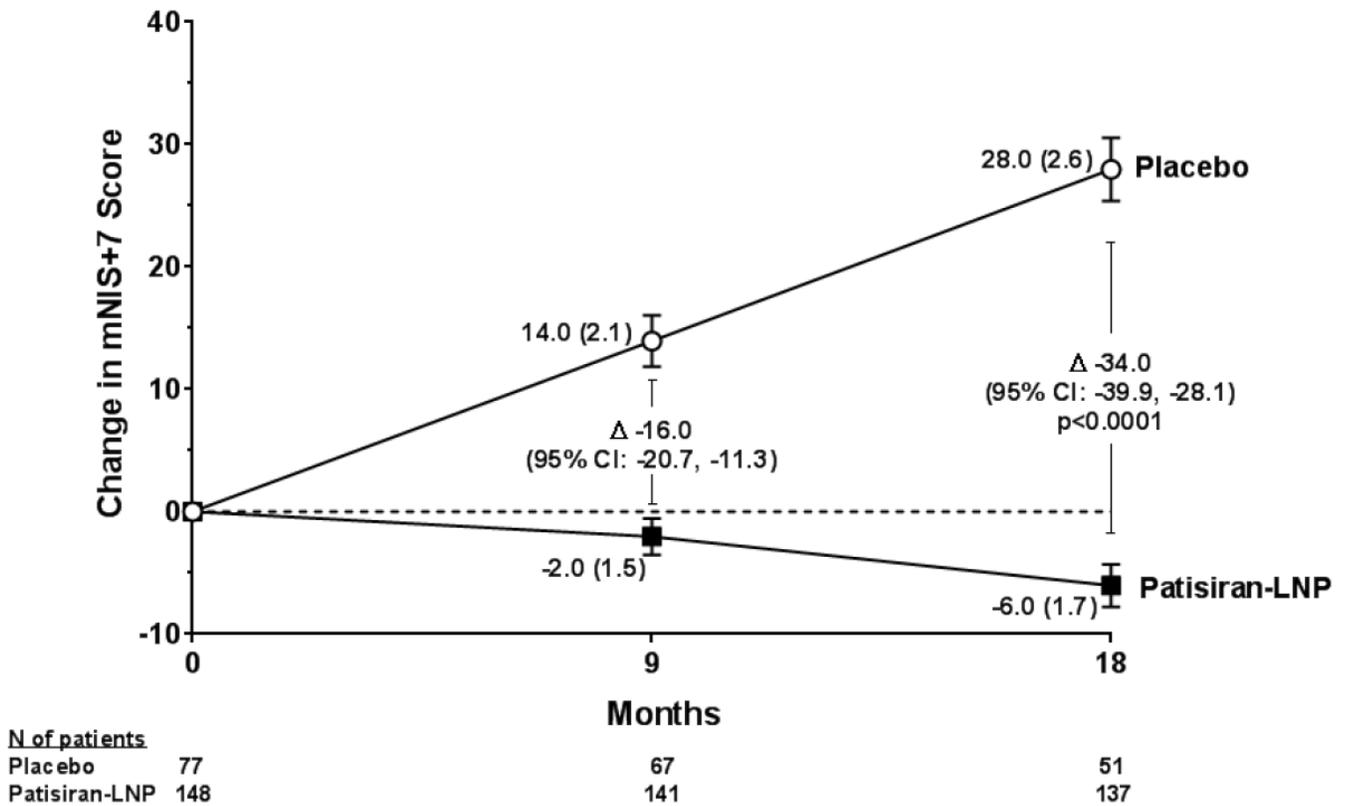
The tables/figure below, copied from the sponsor’s submission, summarize the APOLLO study results. Highly statistically significant results are present across all key efficacy endpoints. Further, as the sponsor’s figure 4 indicates, there appears to be a numerical improvement in the primary endpoint over the course of the trial.

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

Study 004: mNIS+7 Change from Baseline at 18 Months, MMRM Analysis (mITT)

mNIS+7	Placebo (N=77)	Patisiran-LNP (N=148)
Month 18 Change from Baseline		
N	51	137
LS Mean (SEM)	27.96 (2.60)	-6.03 (1.74)
Difference (Patisiran – Placebo)	-33.99	
95% CI	-39.86, -28.13	
p-value	9.26x10 ⁻²⁴	

Study 004: Change in mNIS+7 at 9 and 18 Months, MMRM Analysis (mITT)



Study 004: Summary of Secondary Endpoint Analyses, MMRM Analysis (mITT)

Secondary Endpoint	Baseline, Mean (SD)		Change from Baseline at 18 months, LS Mean (SEM)		Treatment Difference, LS Mean (95% CI) (Patisiran-LNP – Placebo)	p-value
	Patisiran-LNP N=148	Placebo N=77	Patisiran-LNP	Placebo		
Norfolk QoL-DN ^a	59.6 (28.2)	55.5 (24.3)	-6.7 (1.8)	14.4 (2.7)	-21.1 (-27.2, -15.0)	<0.0001
NIS-W ^a	32.7 (25.2)	29.0 (23.0)	0.05 (1.3)	17.9 (2.0)	-17.9 (-22.3, -13.4)	<0.0001
R-ODS ^b	29.7 (11.5)	29.8 (10.8)	0.0 (0.6)	-8.9 (0.9)	9.0 (7.0, 10.9)	<0.0001
10-meter walk test (m/sec) ^b	0.80 (0.40)	0.79 (0.32)	0.08 (0.02)	-0.24 (0.04)	0.31 (0.23, 0.39)	<0.0001
mBMI ^c	970 (211)	990 (214)	-3.7 (9.6)	-119 (14.5)	116 (82, 149)	<0.0001
COMPASS-31 ^a	30.6 (17.6)	30.3 (16.4)	-5.3 (1.3)	2.2 (1.9)	-7.5 (-11.9, -3.2)	0.0008

Abbreviations: QOL-DN, Quality of Life – Diabetic Neuropathy; NIS-W, Neuropathy Impairment Score – Weakness; R-ODS, Rasch-built Overall Disability Scale; mBMI, modified body mass index; COMPASS – Composite Autonomic Symptom Scale

All endpoints analyzed using the mixed effect model repeated measures method (MMRM).

^aA lower number indicates less impairment/less disability/fewer symptoms

^bA higher number indicates less impairment

^cmBMI: BMI (kg/m²) multiplied by serum albumin (g/L); a higher number indicates better nutritional status

- b. Include any additional relevant information. Consider the following in your response:

These data provide clear preliminary clinical evidence of a substantial improvement over available therapies. No drug is approved for hATTR in the U.S.

The safety data for patisiran suggest an acceptable safety profile. There are no safety considerations that would affect the consideration of this request.

11. Division’s recommendation and rationale (pre-MPC review):

GRANT :

Provide brief summary of rationale for granting:

The APOLLO trial results show a clinically meaningful difference in neurological impairment favoring the drug group, as supported by highly statistically significant results for all primary and secondary endpoints. No drug is approved for the treatment of hATTR in the U.S.

DENY:

Provide brief summary of rationale for denial:

Not applicable.

12. Division's next steps and sponsor's plan for future development:

There is a pre-NDA meeting scheduled for November 13, 2017. The sponsor's NDA is already under a rolling review with a planned submission during December 2017. No additional development advice is necessary at this time. The Division has and will continue to work closely with the sponsor to expeditiously finalize and review its application.

13. List references, if any:

Berk, J., et al., Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. JAMA, 2013. 310(24): p. 2658-67.

Adams, D., et al., First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy. Current Opinion in Neurology, 2016. 29(S1): p. S14-26

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES NO

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation
Deny Breakthrough Therapy Designation

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 8/4/17/M. Raggio

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/s/

RAINER PAINE
01/16/2018

NICHOLAS A KOZAUER
01/16/2018