CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210922Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 210922
ONPATTRO (patisiran) Lipid Complex Injection

Addendum to Drug Product Quality Review

Recommendation: Adequate

Drug Name/Dosage Form	Patisiran Lipid Complex Injection
Strength	10 mg/5 mL (2 mg/mL)
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Alnylam Pharmaceuticals

This is an addendum to NDA 210922 Drug Product Quality Review, dated 05-11-2018 by Mariappan Chelliah. This clarifies the shelf-life to be granted to the proposed commercial batches of the drug product.

Reviewer's Assessment: ***Adequate***

In the Drug Product quality review, dated 05-11-2018, based on the available stability data for the registration stability batches, this reviewer concluded that a shelf-life of 24 months may be granted to the drug product. However, in response to the Sponsor's email query dated 08-07-2018, the Agency seeks to clarify how the shelf-life is calculated for this product.

During the review cycle, the Sponsor updated the stability data for the registration batches and stated that the existing stability data support 24 months of storage for drug product from the date of fill (see page 47 of module 1.11.1, eCTD seq. 0016, dated 04-06-2018).

However, in a subsequent clarification (see page 18 of module 1.11.1, eCTD seq. 0020, dated 04-27-2018), the Sponsor stated the following:

"In the April 06 response to the Agency's information request (drug product question 7b) we stated that the existing stability data support 24 months of storage for drug product from the day of fill.

We would like to further clarify that the claimed drug product shelf life is to be dated from the date of bulk drug product production, in line with regulatory expectations that the date of drug product manufacture be defined as the time of drug product formulation.

The stability data as shown in the original NDA (Section 3.2.P.8.3 Stability Data), and the response to the Agency on April 7 demonstrate 24-month stability from the date of vial fill.

(b) (4)

Although the shelf-life is usually assigned from the compounding date, it is typically estimated from the stability data available from the fill date. However, because of the

(b) (4)

the available long-term real time stability data, and the statistical evaluation of the stability data, the Agency deems that the following shelf-life may be granted:

Shelf-life: 24 months from the date of (b) (4) vial filling and when stored at 2°C to 8°C. (b) (4)

Mariappan Chelliah

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Wendy Wilson- Lee

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Martha Heimann

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GUID: 504f845f00000ed260627d268a8cdc9d

Recommendation: Approve

NDA 210922
Review 1

Drug Name/Dosage Form	Patisiran Lipid Complex Injection
Strength	10 mg/5 mL (2 mg/mL)
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Alnylam Pharmaceuticals
US agent, if applicable	N/A

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Monica Cooper	Charles Jewell
Drug Product	Mariappan Chelliah	Wendy Wilson-Lee
Process	Erin Kim	Nallaperumal Chidambaram
Microbiology	Denise Miller	Bryan Riley
Facility	Christina Capacci-Daniel	Derek Smith
Biopharmaceutics	Banu Zolnik	Ta-Chen Wu
Regulatory Business Process Manager	Dahlia Walters	--
Application Technical Lead	Martha Heimann	--
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental	N/A	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD-05, CMC module for rolling submission	11/15/2017	All
SD-07, Final NDA module	12/11/2017	Product, labeling
SD-10, Response to IR	03/05/2018	Biopharmaceutics, product
SD-12, Response to IR	03/08/2018	process
SD-16, Response to IR	04/06/2018	Drug substance, product
SD-17, Response to IR	04/09/2018	Microbiology
SD-20, Response to IR	04/27/2018	Biopharmaceutics, drug substance, product
SD-22, Response to IR	05/01/2018	Microbiology

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	IV		(b) (4)	Adequate	05/04/2018	
	V			Adequate	05/08/2018	
	V			Adequate [1]	02/03/2017	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	

[1] Adequate information in application or no changes to information since previous adequate reviews.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	117395	Development of patisiran for treatment of hereditary transthyretin mediated amyloidopathy (hATTR)

2. CONSULTS

None

Executive Summary

I. Recommendations and Conclusion on Approvability

The OPQ review team recommends APPROVAL of NDA 210922 for Onpattro™ (patisiran lipid complex injection) for intravenous infusion. A (b) (4)-month retest date is granted for the drug substance when stored at (b) (4)C in the proposed commercial container closure system, and a 24-month expiration dating period is granted for the drug product when stored refrigerated in the commercial packaging. ***The CMC post-marketing commitment (PMC) and post-approval quality agreements between OPQ and Alnylam listed below should be included in the action letter.***

PMC

Description: Development and validation of a new in vitro drug release method and setting of the drug release acceptance criteria for the finished drug product

Milestones: Submission of the Interim PMC Report within 6 months from NDA's action date (Type B WRO)
2/12/2019

Submission of the Final PMC Report within 12 months from NDA's action date (as Prior Approval CMC Supplement to the NDA)
8/12/2019

Post-approval Quality Agreements

We would like to remind you of the following post-approval quality agreements included in the amendment dated April 27, 2018 (SD-20).

- To provide the full-scale commercial manufacturing process data to support the in-process (b) (4) by December 31, 2019.
- To validate the (b) (4) method for the representative (b) (4) impurities [(b) (4)] for both strands of the patisiran drug substance and to provide the data to FDA by December 31, 2018. Per FDA's '*Guideline for Industry: Text on Validation of Analytical Procedures*,' quantitative test methods for impurities should include validation of specificity, linearity, precision (repeatability), intermediate precision, accuracy, range, and LOD/LOQ.
- To provide the validation data with respect to impurities for the drug product (b) (4) methods post approval by December 31, 2018.

III. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	Treatment of adults with hereditary transthyretin-mediated amyloidosis
Duration of Treatment	Chronic
Maximum Daily Dose	0.3 mg/kg up to 30 mg maximum every three weeks.
Alternative Methods of Administration	None

Patisiran is a synthetic small interfering ribonucleic acid (siRNA) formulated as lipid nanoparticle (LNPs) containing 2 mg/mL patisiran and lipid excipients in phosphate buffered saline for slow IV infusion. It is indicated for treatment of hereditary transthyretin (TTR) mediated amyloidopathy (hATTR), a rare disease with a median survival time of 4.7 years following onset of symptoms. The proposed dosage is 0.3 mg/kg administered every three weeks. Patisiran was granted orphan drug, fast track, and breakthrough therapy designations, in 2012, 2013, and 2017, respectively.

TTR is a homotetrameric transport protein synthesized primarily in the liver, and is a carrier for retinol (vitamin A) and thyroxine. In individuals with a mutated copy of the gene encoding for TTR, the tetramer containing wild type and mutant TTR is less stable. Breakdown of TTR results in protein misfolding and aggregation to form amyloid fibrils that deposit in tissue, peripheral nervous system, and CNS. Depending on the location of the mutation, disease symptoms include polyneuropathy, cardiomyopathy, nephropathy, and gastrointestinal dysfunction. In the two principal phenotypes, the patients present with either polyneuropathy or cardiomyopathy.

Patisiran is a double-stranded oligonucleotide comprising sense and antisense strands. The sense and antisense strands both contain 21 nucleotides. Nineteen nucleotides of the sense strand hybridize with the complementary 19 nucleotides of the antisense strand, forming 19 nucleotide base pairs, and leaving two 3'-terminal nucleotides on each strand as un-hybridized overhangs. Following IV infusion and targeted delivery of the lipid nanoparticles to hepatocytes in the liver, patisiran is released into the cytoplasm, where it can bind to and activate the RNA-induced silencing complex (RISC). The duplex then unwinds and the antisense strand binds to a genetically conserved sequence in the 3′ untranslated region of mutant and wild type TTR mRNA, resulting in degradation of the mRNA and reduction of wild type and mutant TTR protein synthesis.

B. Quality Assessment Overview

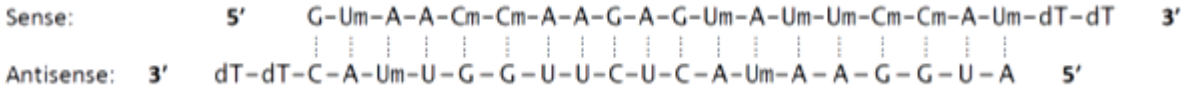
Factors critical to the OPQ evaluation of the submission were the route of administration (intravenous), the absence of any approved products for treatment of a life-threatening rare disorder, and the complexity of the active ingredient and product formulation. Approval of

the application would be the first approval for a duplex siRNA, and the first approval for an siRNA lipid nanoparticle formulation.

Drug Substance

Patisiran is a chemically synthesized, double-stranded oligonucleotide comprising 21-residue sense and antisense strands hybridized across 19 nucleotide base pairs. The structure can be represented as shown in Figure 1, where hyphens represent the sodium form of a 3′ – 5′ phosphodiester linkage and the dotted lines represent the base pairs.

Figure 1: Structural Formula of Patisiran Drug Substance



A, C, G, and U represent adenosine, cytidine, guanosine, and uridine r bonucleotide residues, respectively.
Cm and Um represent 2′-O-methylcytidine and 2′-O-methyluridine residues, respectively.
dT represents thymidine deoxyr bonucleotide residues.

The patisiran drug substance is a white to off-white powder. The double-stranded oligonucleotide is manufactured by (b) (4)

Regulatory controls for patisiran drug substance include multiple orthogonal tests for identity and purity of the duplex siRNA. Identity of the duplex is confirmed by size exclusion chromatography (SE-HPLC UV) retention time, melting temperature, and molecular mass of the identity of the sense and antisense strands. Purity is determined (b) (4) . The controls also include appropriate tests for appearance, sodium content, pH, water content, elemental impurities, residual solvents, endotoxins, and bioburden.

The drug substance is stored in a (b) (4) The applicant's proposed (b) (4) month retest date can be granted to the drug substance when stored at (b) (4) °C in the proposed commercial container closure system.

Critical issues for the drug substance include: (b) (4) The applicant has adequately addressed concerns identified during the review.

Drug Product

Patisiran lipid complex injection is a sterile, preservative- free, white to off-white, opalescent, homogeneous liquid for intravenous infusion. It is supplied as a 5-mL liquid containing 10 mg patisiran (2 mg/mL) in a 10-mL, single dose, Type (b) (4) glass vial. In the product formulation, the patisiran siRNA is encapsulated in novel lipid nanoparticles (LNPs). The nanoparticles are suspended in a PBS buffer.

The lipid components of the formulation include two novel excipients, DLin-MC3-DMA[1] ((b) (4) and PEG2000-C-DMG[2] ((b) (4) DSPC[3] (b) (4) and cholesterol. (b) (4)

Patisiran lipid complex injection is manufactures in (b) (4) drug product is compounded at the Alnylam Pharmaceuticals facility in Cambridge, MA. The drug substance is (b) (4)

The regulatory specification for the drug product includes tests for physical parameters (i.e., siRNA encapsulation, particle size, and in vitro siRNA release) that are critical for protection of the siRNA in plasma and delivery to the liver. Assay, purity, and identity test methods for patisiran are similar to those for the bulk drug substance. The specification includes identity and assay for the individual lipid components, residual (b) (4) (process aids), and all compendial testing (sterility, bacterial endotoxins, particulate matter, etc.) appropriate for a parenteral product.

[1] DLin-MC3-DMA: (6*Z*,9*Z*,28*Z*,31*Z*)-heptatriaconta-6,9,28,31-tetraen-19-yl-4-(dimethylamino)butanoate

[2] PEG2000-C-DMG: (R)-2,3-bis(tetradecyloxy)propyl 1-(methoxypoly(ethyleneglycol)2000)propyl carbamate, or α-(3'-{[1,2-di(myristyloxy)propanoxy}carbonylamino}propyl)-ω-methoxy polyoxyethylene

[3] DSPC: 1,2-distearoyl-*sn*-glycero-3-phosphocholine

It is noted that the review team and the applicant have identified concerns related to the robustness of the siRNA in vitro release method. The current method is considered acceptable on an *interim basis*. The Applicant has agreed to develop a new validated and robust in vitro drug release method as part of Post Marketing Commitment within 12 months from the NDA's action date. If, however, the Application receives a Complete Response action based on deficiencies raised by other disciplines, then the recommendation/requirement to develop a new and optimal in vitro drug release method will be included in the CR letter as CR issues.

It is also noted that the acceptance criterion for product appearance (b) (4) During the Phase 3 trial, the drug product was filtered through 0.2 µm sterile polyethersulfone (PES) filters. However, the entire maximum dose volume could not be filtered through a single 0.2 µm filter. Therefore, the applicant evaluated PES filters with larger pore sizes. Patisiran drug product filtered through 0.2 µm, 0.45 µm, (b) (4) filters had comparable quality and complied with the product specification. Product labeling will specify use of a sterile 0 45 µm (PES) during dose preparation. The review team considers this an acceptable mitigation approach.

Patisiran lipid complex injection is packaged in a single-dose Type (b) (4) glass vial with (b) (4) stopper and an aluminum flip-off cap. Based on stability data provided in the application, a 24-month shelf life is granted for product stored at 2°C – 8°C.

Critical issues for the drug product include use of two novel synthetic lipid excipients (DLin-MC3-DMA and PEG2000-C-DMG), complexity of the manufacturing, sterilization and filling processes, stability of the drug product during manufacturing, shelf-life, and under in-use conditions, potential leachables from the vial and closure, and potential delamination of the glass vial. The applicant has adequately addressed concerns identified during the review.

Methods Verification

Verification of the drug substance and drug product (b) (4) methods (identity, assay, and purity) and the (b) (4) method (percentage of duplex form and total impurities) by the Division of Pharmaceutical Analysis (DPA) was requested; however, methods verification is not complete. As the methods verification process is ongoing, standard language regarding cooperation with methods verification should be included in the action letter.

Facilities

All facilities that will be involved in commercial manufacture and testing of patisiran and patisiran lipid complex injection are currently acceptable. The PMC to develop a more robust in vitro release method addresses some of the inspectional concerns noted at the drug product facility inspection and is in agreement with corrective actions proposed by the firm.

C. Special Product Quality Labeling Recommendations

The product should be stored at 2°C – 8°C and labeled "Do Not Freeze."
The product should be filtered through a sterile 0.45 µm polyethersulfone (PES) syringe filter during dose preparation.

D. Final Risk Assessment for Patisiran Lipid Complex Injection

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Appearance	• Formulation • Container closure • Raw materials • Process parameters • Scale • Equipment • Site	**L**	(b) (4)	Adequate	
Assay (active), stability		**L**		Adequate	
Lipid component assay		**L**		Adequate	Currently 24-month expiry granted based on real time primary stability data
Lipid entrapment efficiency (bound vs. free drug)		**H**		Adequate	
In vitro release		**H**		Adequate	Post-marketing commitment
Particle size distribution		**H**		Adequate	
Sterility		**H**		Adequate	
Endotoxin, pyrogen		**M**		Adequate	
Fill volume/delivered volume		**L**		Adequate	

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Osmolality		**L**	(b) (4)	Adequate	
pH (high)		**L**		Adequate	
pH (low)		**L**			
Particulate matter		**M**		Adequate	
Leachable/Extractables		**L**		Adequate	

LABELING

I. Package Insert

The following assessment is based on the Applicant's labeling submissions in eCTD seq. 0007, dated 12-11-2017 and eCTD seq. 0011, dated 02-14-2018.

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	**ONPATTRO (patisiran) lipid complex injection****
Dosage form, route of administration	lipid complex, injection**
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	**Lipid Complex Injection: 10 mg/5 mL (2 mg/mL) in a single-dose vial

**Edit proposed by the Agency and yet to be accepted by the Sponsor (see the assessment section below for further information).

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	The drug product must be filtered into a sterile container through a 0.45µm sterile syringe filter. The required volume, based on patient weight, is drawn and diluted into a saline bag to give the intravenous infusion solution.

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Lipid Complex Injection**
Strengths: in metric system	10 mg/5 mL (2 mg/mL)
Active moiety expression of strength with equivalence statement (if applicable)	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	…white to off-white, opalescent, homogeneous solution in a single-dose vial.

**Edit proposed by the Agency and yet to be accepted by the Sponsor (see the assessment section below for further information).

4. *Section 11 Description*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Yes
Dosage form and route of administration	Yes
Active moiety expression of strength with equivalence statement (if applicable)	Yes
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Yes
Statement of being sterile (if applicable)	Yes
Pharmacological/ therapeutic class	Yes
Chemical name, structural formula, molecular weight	Yes
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	pH ~7.0

5. *Section 16 How Supplied/Storage and Handling*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	10 mg/5 mL (2 mg/mL)
Available units (e.g., bottles of 100 tablets)	Single vial per container
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	…white to off-white, opalescent, homogeneous solution for intravenous infusion…
Special handling (e.g., protect from light)	Do not freeze
Storage conditions	Store at 2°C to 8°C (36°F to 46°F).
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Yes

Reviewer's Assessment of Package Insert: *Adequate*

Per labeling submitted in eCTD seq. 0011, the drug product is named as 'ONPATTRO (patisiran) injection, for intravenous use'. However, during the review cycle the Agency determined that the appropriate dosage form designation for this formulation is 'lipid complex injection". This reviewer has edited the product name in the prescribing information in the SharePoint to 'ONPATTRO (patisiran) lipid complex injection, for intravenous use'. The Agency will be recommending the Sponsor to use this name throughout the labeling.

II. Labels:

1. *Carton Labels (from eCTD seq. 0011)*

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Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Onpattro (patisiran) injection	Onpattro (patisiran) lipid complex injection**
Dosage strength	10 mg/5 mL	10 mg/5 mL
Net contents	Missing – but acceptable for small container.	Single dose vial
"Rx only" displayed prominently on the main panel	Yes	Yes
NDC number (21 CFR 207.35(b)(3)(i))	Yes	Yes
Lot number and expiration date (21 CFR 201.17)	Yes	Yes
Storage conditions	Missing – but acceptable for small container.	Store refrigerated at 2°C to 8°C (36°F to 46°F). Do not freeze.
Bar code (21CFR 201.25)	Yes	Yes
Name of manufacturer/distributor	Manufactured for: Alnylam Pharmaceuticals, Inc. Cambridge, MA 02142	Manufactured for: Alnylam Pharmaceuticals, Inc. Cambridge, MA 02142 Manufactured by: Ajinomoto Althea, Inc. San Diego, CA 92121
And others, if space is available	--	--

**Edit proposed by the Agency and yet to be accepted by the Sponsor (see the assessment section below for further information).

Reviewer's Assessment of Labels: ***Adequate***

The carton and container labels meet the appropriate rules and regulations. As discussed above, the Agency will be recommending the Applicant to revise the name in the carton and container labels to 'Onpattro (patisiran) lipid complex injection'. Therefore, the labeling will likely change further.

List of Deficiencies: None

Overall Assessment and Recommendation: Adequate

Primary Drug Product Reviewer: Mariappan Chelliah (see below for date)

Secondary Reviewer: Wendy Wilson-Lee (see below for date)

Mariappan Chelliah

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Date: 5/11/2018 11:09:43AM
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Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 5/11/2018 11:54:53AM
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BIOPHARMACEUTICS

Application No: NDA 210922

Drug Product Name / Strength: Onpattro (patisiran) Injection, 10 mg/5 mL (2 mg/mL)

Route of Administration: Injection; via intravenous infusion

Applicant Name: Alnylam Pharmaceuticals, Inc.

List of Submissions reviewed:

eCTD Seq.0005 (5) dated 11/15/2017 (Rolling NDA Part 1 of 2)
eCTD Seq.0010 (11) dated 03/05/2018 (In Response to Biopharmaceutics IR dated 02/20/2018)
eCTD Seq.0020 (20) dated 04/27/2018 (In Response to Biopharmaceutics IR dated 04/17/2018)

Background:

Alnylam Pharmaceuticals Inc is seeking approval for Onpattro (patisiran) injection as a treatment for adults with hereditary transthyretin-mediated amyloidosis via 505 (b)(1) of Federal Food, Drug and Cosmetic Act.

Review Summary:

This Biopharmaceutics Review evaluated the overall in vitro drug release data supporting the 1) proposed in vitro drug release method, 2) in vitro drug release acceptance criteria, as well as the need for 3) bridging of formulations, and 4) biowaiver request.

Based on the review of the provided information/data, the Division of Biopharmaceutics has the following conclusions and recommendations:

1) **In Vitro Drug Release Method and Acceptance Criteria**
   The proposed in vitro drug release method and the proposed acceptance criteria are acceptable for batch release and stability testing of the finished product on an **interim basis.** The Applicant agreed to develop a validated and robust in vitro drug release method within 12 months from the NDA's action date as part of the Post Marketing Commitment. The details of the PMC are found in Appendix 1 of this review.

2) **Bridging the Formulations**
   Bridging data are not necessary between the clinical and the proposed commercial formulations because there were no changes in the formulation or manufacturing process throughout the drug product development.

3) **Biowaiver Request**
   Biowaiver Request is not submitted nor required. The Applicant characterized the pharmacokinetic profile of patisiran injection in the following studies: ALN-TTR02-001, ALN-TTR02-005 (Phase 1 SAD studies in healthy volunteers) and ALN-TTR02-002,

ALN TTR02-003 (Phase 2 multiple ascending dose studies in patients). These studies are reviewed by OCP reviewers (refer to OCP review in DARRTS dated 5/21/2018).

- ***OVERALL REVIEW RECOMMENDATION***

  From the Biopharmaceutics perspective, NDA 210922 for Onpattro (patisiran) injection, 2 mg/mL is recommended for **APPROVAL.** The Applicant agreed to develop a new validated and robust in vitro drug release method as part of Post Marketing Commitment within 12 months from the NDA's action date. If, however, the Application receives a Complete Response action based on deficiencies raised by other disciplines, then the recommendation/requirement to develop a new and optimal in vitro drug release method will be included in the CR letter as CR issues.

- ***SIGNATURES***

Primary Biopharmaceutics Reviewer Name and Date:

Banu S. Zolnik, PhD 6/11/2018
Biopharmaceutics Reviewer
Division of Biopharmaceutics-Branch 1
Office of New Drug Products

Secondary Reviewer Name and Date:

Gerlie Gieser, PhD (for Ta-Chen Wu, Ph.D.) 6/11/2018
Acting Biopharmaceutics Lead
Division of Biopharmaceutics-Branch 1
Office of New Drug Products

BIOPHARMACEUTICS ASSESSMENT

- **DRUG SUBSTANCE:**

Patisiran is a double stranded small interfering RNA(siRNA) consisting of two single stranded RNA molecules (the sense and antisense strands).

- **DRUG PRODUCT:**

The proposed drug product is formulated as patisiran containing lipid nanoparticles in phosphate buffered saline. The pictorial representation of the nanoparticles, as provided by the Applicant, is shown in Figure 1.

(b) (4)

(b) (4)

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MICROBIOLOGY

Product Background: This is a parenteral drug product for the treatment of adults with hereditary transthyretin-mediated amyloidosis. This drug is to be administered by intravenous infusion via an ambulatory infusion pump over 80 minutes once every three weeks.

NDA: 210-922

Drug Product Name / Strength: Onpattro (patisiran) at 2 mg/mL, 5 mL fill in a 10 mL vial

Route of Administration: Intravenous

Applicant Name: Alnylam Pharmaceuticals, Inc.

Manufacturing Site:

Bulk Drug Product Manufacture
Alnylam Pharmaceuticals, Inc.
665 Concord Avenue
Cambridge MA 02138
FEI: 3013754451

Finish and Fill Manufacturer
Ajinomoto Althea, Inc.
11040 Roselle Street
San Diego CA 92121
FEI: 3004575449

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): N/A

Review Summary: **The information supporting the** (b) (4) **filling of the vials at the contract manufacturing facility was reviewed under the facilities DMF (DMF** (b) (4)**) and found to be acceptable. The product specific information supporting the sterility assurance of the proposed drug product is the subject of this review. There were two information requests (IR) sent in the course of this review for which the applicant submitted acceptable responses. The information provided was adequate and supports the** (b) (4) **for the drug product.**

List Submissions Being Reviewed:
06 Nov 2017 Original NDA submission
09 Apr 2018 IR Response amendment
01 May 2018 IR Response amendment

Highlight Key Outstanding Issues from Last Cycle: NA

Remarks: NA

Concise Description Outstanding Issues Remaining: None

Supporting Documents:

DMF (b) (4) (b) (4) LOA dated 07/20/17 for the (b) (4). The DMF is adequate per DMA review (b) (4) dated 03 Feb 2017. The DMF has not added new information for the (b) (4) since this review.

DMF (b) (4) (b) (4) *Facility in San Diego CA*, Ajinomoto Althea Inc. LOA 11/01/2017. DMA review ((b) (4).docx) dated 05/08/18 was adequate.

List Number of Comparability Protocols (ANDA only): NA

S Drug Substance: drug substance is not sterile.

There is a bioburden and endotoxin release specification. The bioburden is NMT (b) (4) cfu/gram and the endotoxin is NMT (b) (4) EU/mg.

Note: The chemistry reviewer requested that DMA look at the excipients to determine if the ML and endotoxin limits are appropriate. There a 5 excipients, two are novel, one is not novel but does not have a USP monograph and two have a USP monograph; non are sterile.
The novel excipients are DLin-MC3-DMA and PEG_{2000}-C-DMG. The DLin-MC3-DMA is a lipid and the release specifications include bioburden (NMT (b) (4) cfu/gr for both TAMC and TYMC), specified microorganism (absence of *Salmonella, E. coli, S. aureus* and *P. aeruginosa*) and has an endotoxin limit of NMT (b) (4) EU/mg. The PEG_{2000}-C-DMG release specifications includes bioburden (NMT (b) (4) cfu/g for both TAMC and TYMC) with an endotoxin limit of NMT (b) (4) EU/mg.

A third excipient which is not novel is 1, 2-Distearoyl-sn-glucero-3-phosphocholine (DSPC). The release specifications for this excipient include bioburden (NMT (b) (4) cfu/g for TAMC, NMT (b) (4) cfu/g for TYMC, and absence of E. coli) with an endotoxin limit of NMT (b) (4) EU/g.

The two USP monographed excipients are cholesterol and Phosphate Buffered Saline.

(b) (4)

Reviewer's Assessment: ***Adequate;*** The information provided is acceptable. The bioburden and endotoxin of the bulk drug product is tested (b) (4) .

P Drug Product

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – patisiran sodium is a double-stranded small interfering ribonucleic acid formulated as a lipid nanoparticle in phosphate buffered saline. The particle size is (b) (4) nm. The final drug product is a sterile, preservative free, white to off-white opalescent liquid.
- **Drug product composition** – the composition below was copied from 3.2.P.1 Table 1 of the submission.

Table 1: Quantitative Composition of Patisiran Drug Product

Component	Content per Volume (mg/mL)	Content per Vial (mg)	Function	Quality Standard
Patisiran drug substance (patisiran sodium)	2.0 patisiran (equivalent to 2.1 patisiran sodium)	Patisiran 10.0 (equivalent to 10.5 patisiran sodium)	Active ingredient	Manufacturer's specifications
DLin-MC3-DMA	13.0	65.0	(b) (4)	Manufacturer's specifications
PEG_{2000}-C-DMG	1.6	8.0		Manufacturer's specifications
DSPC	3.3	16.5		Manufacturer's specifications
Cholesterol	6.2	31.0		USP/NF, Ph. Eur., JP
PBS[a]				
Sodium phosphate, dibasic, heptahydrate	2.3	11.7		USP, Ph. Eur.
Potassium phosphate, monobasic, anhydrous	0.2	0.9		NF
Sodium chloride	8.8	44.0		USP, Ph. Eur.
Water for injection	qs	qs		USP, Ph. Eur.

a values for content per volume have been rounded to two significant figures; content per vial is calculated using non-rounded values
Abbreviations: JP=Japanese Pharmacopeia; LPN=lipid nanoparticles; NF=National Formulary; PBS=phosphate buffered saline; Ph. Eur.=European Pharmacopoeia; quantum sufficient; USP=United States Pharmacopoeia

Sodium content is 3.99 mg/mL and 20.0 mg/vial.

- **Description of container closure system –**
  - **Vial:** 10 mL Type (b) (4) glass vial
  - **Stopper:** 20 mm gray (b) (4)).

Reviewer's Assessment: ***Adequate,*** the information provided is a sufficient description for review.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure Integrity Testing (CCIT)

CCIT studies were provided using both a microbial ingress testing and helium leak testing.

(b) (4)

[redacted]

Reviewer's Assessment: ***Adequate;*** The CCIT studies provided support the integrity of the primary container closure system for the proposed drug product.
The shelf life container closure integrity is assessed in the stability program.

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