CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212154Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION: Approval

NDA 212154
Review #1

Drug Product Name	Viltolarsen Injection
Dosage Form	Injection
Strength	250 mg/5 mL (50 mg/mL)
Route of Administration	Intravenous (IV)
Rx/OTC Dispensed	Rx
Applicant	Nippon Shinyaku Co., Ltd.
US agent, if applicable	NS Pharma, Inc.

QUALITY TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Rohit Tiwari	Su (Suong) Tran
Drug Product	Mariappan Chelliah	Julia Pinto
Manufacturing	Tianhong Tim Zhou	Aditi Thakur
Microbiology	Avital Shimanovich	John Metcalfe
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Dahlia Walters / Florence Aisida	
Application Technical Lead	Martha Heimann	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

Submissions	Document Date	Disciplines Affected
SD-02, CMC/Clinical [1]	9/30/2019	All
SD-15, Response to IR	2/14/2020	Microbiology
SD-18, Response to IR	2/30/2020	Drug Substance
SD-19, Response to IR	3/25/2020	Manufacturing
SD-21, Response to IR	4/1/2020	Drug Product
SD-22, Labeling/Container	4/7/2020	Drug Product
SD-27, Response to IR	4/16/2020	Drug Substance

Submissions	Document Date	Disciplines Affected
SD-29, Response to IR	4/22/2020	Manufacturing
SD-32, Response to IR	4/30/2020	Manufacturing
SD-34, Response to IR	5/29/2020	Manufacturing

[1] The 9/30/20119 submission was intended to be the final section of a rolling NDA; however, the clinical section was deemed incomplete final section was received and NDA filed on 2/12/2019.

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessed	Comments
(b) (4)	III		(b) (4)	N/A [1]	--	
	III			N/A [1]	--	
	III			N/A [1]	--	

[1] Adequate information in NDA

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

Document	Application Number	Description
IND	12754	Development of viltolarsen for treatment of DMD

2. CONSULTS

Not applicable.

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The Office of Product Quality (OPQ) review team recommends that the Agency **APPROVE** NDA 212154 for Viltolarsen Injection. From a quality perspective, the application, as amended, provides adequate information to ensure that the Applicant can consistently manufacture a product that is suitable to treat the intended patients.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The Applicant, Nippon Shinyaku Co. (NS) has developed viltolarsen, a novel anti-sense oligonucleotide (ASO), as a treatment for Duchenne muscular dystrophy (DMD) in patients with mutations of the *DMD* gene that are amenable to exon 53 skipping (8% – 10% of DMD patients). Viltolarsen is a 21-base ASO with a phosphorodiamidate morpholino oligomer (PMO) backbone. Viltolarsen is designed to bind to exon 53 of dystrophin pre-mRNA, resulting in exclusion of the exon (exon skipping) during mRNA processing and production of an internally shortened dystrophin protein. If approved, it would be the third ASO for treatment of DMD. Two ASOs developed by Sarepta Therapeutics, eteplirsen and golodirsen, which target exon 51 and exon 53 of the *DMD* gene, respectively, are currently approved.

Proposed indication(s) including intended patient population	Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.
Duration of treatment	Chronic, weekly
Maximum daily dose	80 mg/kg
Alternative methods of administration	None

B. Quality Assessment Overview

(b) (4)

The product is a sterile, preservative-free, solution of viltolarsen (250 mg/mL) in 0.9% saline. Key review concerns included:

- adequacy of the drug substance (b) (4) process and control strategy,
- Sterility and stability of the drug product during manufacturing, at release, and over the proposed shelf-life,

- characterization of the extractables/leachables profile for the primary packaging and potential for delamination of the vial, and
- quality of the drug product for the proposed in-use period and condition.

Drug Substance: **Adequate**

Viltolarsen is a 21-mer PMO (base sequence: 5'-CCTCCGGTTCTGAAGGTGTTC-3'). It is manufactured using (b) (4) The Applicant provided detailed descriptions of the manufacturing process, the critical process parameters, and critical in process controls. It is noted that in-process controls include (b) (4)

The proposed specification for viltolarsen includes tests are appropriate for quality control of oligonucleotides. These include multiple orthogonal identity tests, assay, related substances, pH, residual solvents, bioburden and bacterial endotoxins. (b) (4) . The Applicant used several reference standards for specified and other related substances as representatives in their analytical method validation studies. This use of reference sample gives assurance that the identification and physicochemical characterization of the impurities by the Applicant is appropriate. The Applicant's risk assessment, and data provided, support omission of testing for elemental impurities. All noncompendial analytical procedures are adequately described and validated.

The drug substance is stored (b) (4) . The provided stability data support an initial (b) (4) *-month retest period*.

Drug Product: **Adequate**

Viltolarsen injection 250 mg/5 mL is a sterile, colorless, clear solution formulated in 0.9% sodium chloride and adjusted to pH 7.0 – 7.5 with hydrochloric acid or sodium hydroxide. The drug product is packaged in clear (b) (4) glass vials with

elastomeric closures and flip-off aluminum seals. The drug product is intended for IV administration over 60 minutes. Doses lower than 5000 mg (100 mL) should be diluted with 0.9% saline to 100 mL before administration. Doses 5000 mg or higher do not require dilution. The Applicant has demonstrated that the drug product is compatible with the container closure system and commonly used infusion components.

The proposed specification is consistent with ICH guidances and USP requirements for parenteral products. The specification does not include testing for elemental impurities, which is supported by the Applicant's risk assessment. Noncompendial analytical procedures and acceptance criteria for impurities are the same as for the drug substance and are adequately validated.

The drug product can form soluble physical aggregates (b) (4) upon storage, especially at higher temperatures. (b) (4) can be quantitated by size exclusion chromatography (SEC); however, only trace levels (b) (4)% each) were detected in long term stability studies (5°C ± 3°C) and low levels were (b) (4)% maximum) were observed after 6 months under accelerated storage conditions. Per the nonclinical reviewer, (b) (4) are not a safety concern based on nonclinical toxicology studies. The Applicant proposes to continue monitoring the product by SEC post-approval but exclude the test from the commercial specification. The provided stability data support omission of the test.

The Applicant has provided up to 18 months of long-term stability data (5°C ± 3°C) and 6 months of accelerated stability data (25°C/60%RH) for the primary stability batches. None of the attributes tested showed any trending under the long-term storage conditions. The proposed *18-month shelf life for drug product stored at 2°C to 8°C (36°F to 46°F)* is acceptable.

Labeling: **Adequate**

Information in the package insert and container labels is acceptable from a product quality perspective.

Manufacturing: **Adequate**

The manufacturing process for Viltolarsen Injection consists of: (b) (4)

(b) (4)

(b) (4) Based on the information provided in the original submission and in response to information requests, all equipment used to manufacture the drug product is compatible with the formulation and suitable for

manufacture of sterile products. The proposed commercial manufacturing process and in-process controls are deemed adequate to ensure product quality and patient safety.

All facilities that will be used for commercial manufacture and testing of viltolarsen and Viltolarsen Injection have been evaluated and are currently acceptable. Facility status should be verified prior to final action on the NDA.

Microbiology: **Adequate**

The drug product is a sterile aqueous solution for IV administration. (b) (4) Based on the information provided in the original submission and in response to information requests, the environmental controls, sterilization processes, and in-process controls are adequate to ensure sterility. The drug product specification includes appropriate test methods and acceptance criteria, per USP requirements, for sterility and bacterial endotoxins testing. All test methods are validated.

The product will be administered by warming the correct number of vials for the calculated dose to room temperature and inverting the vials to mix. The dose withdrawn from the vial(s) and transferred to a 100 mL 0.9% saline infusion bag from which the corresponding amount of saline has been withdrawn. The solution should not be held at room temperature for more than 5 hours and infusion should be completed within 6 hours of preparation. The solution can be held for 24 hours at 2°C – 8°C after dilution. The in-use period is supported by data from a hold time study.

Environmental: **Adequate**

The Applicant submitted a claim of categorical exclusion under 21 CFR 25.31(b) and a statement of 'no extraordinary circumstances' was included. The claim is appropriate for the estimated amount of drug to be produced for direct use.

C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQAs**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Comments**
Assay, stability	Formulation Container Closure Raw materials Process parameters Scale/equipment/site	**L**	(b) (4)	**Adequate**	
Fill volume		**L**		**Adequate**	
Osmolality		**L**		**Adequate**	
pH		**L**		**Adequate**	
Leachables		**L**		**Adequate**	
Particulate matter		**M**		**Adequate**	
Endotoxins		**M**		**Adequate**	
Sterility		**H**		**Adequate**	

D. List of Deficiencies for Complete Response

Not applicable.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
CMC Lead
Office of New Drug Products
Division of New Drug Products II

6/15/2020

Martha Heimann

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	VILTEPSO	adequate
Established name(s)	Viltolarsen	adequate
Route(s) of administration	intravenous use	adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	250 mg/5 mL (50 mg/mL) in a single-dose vial	adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	n/a
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	single-dose vial	adequate

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	If the volume of VILTEPSO required is ≥100 mL, it is administered from an infusion bag. Otherwise, it is diluted in normal saline. The diluted solution may be stored for up to 5 hours at room temperature and up to 24 hours at 2°C to 8°C (36°F to 46°F).	The dosage preparation and administration are adequately described. The in-use storage time for the admixture is supported by the in-use stability data.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Injection	adequate
Strength(s) in metric system	250 mg/5 mL (50 mg/mL)	adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	n/a	n/a
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	clear and colorless solution	adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	n/a
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	single-dose vial	adequate

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	VILTEPSO (viltolarsen)	adequate
Dosage form(s) and route(s) of administration	Injection; intravenous administration	adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	n/a	n/a
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Each mL contains 9 mg sodium chloride.	adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Each mL contains 9 mg sodium chloride. Hydrochloric acid and/or sodium hydroxide are used for adjusting the pH.	adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	n/a
Statement of being sterile (if applicable)	Sterile	adequate

Pharmacological/ therapeutic class	Viltolarsen is an antisense oligonucleotide drug substance for the treatment of DMD in patients amenable to exon 53 skipping. It has a morpholino backbone that interacts with dystrophin premessenger ribonucleic acid (pre-mRNA) and alters the exon/intron splicing patterns. Viltolarsen contains 21 linked subunits.	adequate
Chemical name, structural formula, molecular weight	Nucleotide sequence is included. MF: $C_{244}H_{381}N_{113}O_{88}P_{20}$ MW: 6924.82 daltons.	adequate
If radioactive, statement of important nuclear characteristics.	n/a	n/a
Other important chemical or physical properties (such as pKa or pH)	pH: 7.0 to 7.5	adequate

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	n/a	n/a
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	n/a	n/a

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Injection	adequate
Strength(s) in metric system	250 mg/5 mL (50 mg/mL)	adequate
Available units (e.g., bottles of 100 tablets)	single-dose vials	adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	The solution is clear and colorless.	adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	n/a	n/a
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	single-dose vials	adequate

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	n/a	n/a
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	n/a	n/a

Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	2°C to 8°C (36°F to 46°F).	adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	n/a	n/a
Include information about child-resistant packaging	n/a	n/a

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured for: NS Pharma, Inc. Paramus, NJ 07652	adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): n/a

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

3.2 Carton Labeling

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	Viltepso (viltolarsen)	adequate
Dosage strength	250 mg/5 mL (50 mg/mL)	adequate
Route of administration	For intravenous infusion	adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	n/a	n/a
Net contents (e.g. tablet count)	1 vial	n/a
"Rx only" displayed on the principal display	Yes	adequate
NDC number	73292-011-01	adequate
Lot number and expiration date	Yes	adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Must be refrigerated, store at 2°C-8°C (36°F-46°F) Do not freeze	adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Single dose	adequate
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	n/a	n/a
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	n/a	n/a
Bar code	Yes (2D barcode)	adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	NS Pharma, Inc. 140 East Ridgewood Avenue, Suite 280S Paramus, NJ 07652 Tel. 1-866-677-4276	adequate
Medication Guide (if applicable)	n/a	n/a
No text on Ferrule and Cap overseal	n/a	n/a
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	n/a	n/a
And others, if space is available	n/a	n/a

Assessment of Carton and Container Labeling: *Adequate*
The container and carton labels comply with all the regulatory requirements from a product quality perspective.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor: Mariappan V. Chelliah

Secondary Assessor Name: Julia Pinto

Mariappan Chelliah

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Julia Pinto

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	212154
Assessment Cycle Number	01
Drug Product Name/ Strength	Viltolarsen, 250 mg/5 mL
Route of Administration	Intravenous infusion
Applicant Name	Nippon Shinyaku Co., Ltd.
Therapeutic Classification/ OND Division	Division of Neurology Products
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
CMC information	09/30/2019
Quality responses to IR	02/14/2020
Quality responses to IR	03/25/2020

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The drug product is for the treatment of Duchenne Muscular Dystrophy in patients amenable to Exon 53 skipping. The application received an orphan drug and Fast Track Designation. The application was received on a rolling status by the Agency; CMC information was included in the second wave. (b) (4)

Concise Description of Outstanding Issues: None

Supporting Documents: N/A

S DRUG SUBSTANCE

The drug substance (DS) is not-sterile. The DS microbiological specification is (b) (4) The drug product is (b) (4) Therefore, the microbiological quality of the DS will not be assessed in this review.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of the drug product** – The drug product (DP) is a clear, colorless, single-dose, sterile solution.

- **Composition of the drug product –** The following table provides the composition of the DP:

Ingredient	Quantity	Function
Viltolarsen	250 mg/5 mL	API
Sodium Chloride	45 mg/5 mL	(b) (4)
(b) (4) Hydrochloric Acid	q.s.	pH adjustor
Sodium Hydroxide	q.s.	pH adjustor
Water for Injection	q.s. to 5 mL	Vehicle

- **Description of the container closure system –** The following table provides a description of the container closure system (CCS):

Component	Description	Supplier
Vial	5 mL/20 mm clear (b) (4) Glass Vial	(b) (4)
Stopper	(b) (4) (b) (4) ubber Stopper,	
Seal	20 mm aluminum seal with white plastic cap	

Assessment: ***Adequate***

The applicant provided a description of the DP and CCS.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

(b) (4)

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