

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212154Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: July 21, 2020

To: Teresa Burrachio, M.D.
Division of Neurology 1 (DN1)

Annie Nguyen, PharmD, Regulatory Project Manager, (DN1)

Tracy Peters, PharmD, Associate Director for Labeling, (DN1)

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

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

Subject: OPDP Labeling Comments for VILTEPSO™ (viltolarsen) injection, for intravenous use

NDA: 212154

In response to the DN1 consult request dated October 23, 2019, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for VILTEPSO™ (viltolarsen) injection, for intravenous use (Viltepsa).

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DN1 (Annie Nguyen) on July 20, 2020 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 April 6, 2020 and our comments are provided below.

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

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/s/

SAPNA P SHAH
07/21/2020 06:12:33 PM



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOLOGY AND NEPHROLOGY

Date: June 17, 2020

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, Pharm.D.
Clinical Analyst, DCN

To: Anhtu Nguyen, RPM
DN1

Subject: IRT Consult to IND-127474 and NDA-212154

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo is an addendum to our previous reviews dated 05/14/2020 (under IND-127474) and dated 04/01/2020 (under NDA-212154), which evaluated the sponsor's request for substitution of thorough QT study and our recommendation to characterize the effects of viltolarsen on the QTc interval using alternate design.

1 IRT Response

After reviewing the data from the Phase 1/2 and Phase 2 studies, we maintain our previous recommendation that the sponsor amends their Phase-3 study protocol (Study # NS-065/NCNP-01-301) to collect additional PK measurements and high quality 12-lead ECG recordings (see ICH E14 and Q&A #1) around T_{max} (e.g., at 1 and 3 h the from start-of-infusion) following the first dose in all patients. The data from the sponsor's Phase-1/2, Phase-2 studies and the amended Phase-3 study would be adequate to characterize the effects of viltolarsen on the QTc interval as per ICH E14 Q&A (R3) 6.1.

2 Background

Nippon Shinyaku Pharm Inc. submitted an NDA for viltolarsen injection for the treatment of Duchenne muscular dystrophy (DMD; in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping). Viltolarsen (NDK-65, NS-065, NCNP-01; MW: 6924.82 da) is an antisense (morpholino) oligonucleotide and the sponsor claims that it designed to modify dystrophin protein expression and expected to reduce muscle damage by restoring dystrophin function. The product is formulated as injection (Viltepsa, single dose 5 mL vial) containing 250 mg viltolarsen (50 mg/mL and 9 mg NaCl) for intravenous injection (to be

administered as infusion over 60 min). The proposed dose is 80 mg/kg once weekly and the peak concentrations of 329000 ± 91000 ng/mL (T_{max} ~1 h; half-life: ~2.5 h) are expected at steady-state with the proposed maximum therapeutic dose (W24; Study # NS065/NCNP01-P1/2). The sponsor's hERG assay (hERG transfected CHO cells) indicates no effects on tail peak currents at viltolarsen concentrations up to 3000 μ g/mL (433.2 μ mol/L, 5.2% inhibition) (Study # TX10836).

Recently, the IRT reviewed the sponsor's waiver request for thorough QT study and recommended to characterize the drug effects on the QTc interval in alternate study designs to exclude large mean increases in QTc (i.e., >20 msec) as per ICH E14 Q&A (R3) 6.1 (Dt: 04/01/2020). In our previous review we incorrectly stated the sponsor does not have access to the raw datasets.

- During the late cycle meeting, the sponsor commented that they had access to the raw datasets and, after the meeting, highlighted that the data were submitted in the original submission. The IRT identified that although the programs were not submitted by the sponsor, the submission included the ECG data. The IRT reviewed the submitted data and concluded that the available data is not adequate to characterize the effects of viltolarsen on the QTc interval as per ICH E14 Q&A (R3) 6.1. In the Phase 1/2 study, the ECGs were collected on Day 1 and Day 162 at 60, 40, and 20 min before the start of infusion and immediately after end of infusion, and 1, 2, and 4 hours after the end of infusion. However, the study evaluated limited number of subjects at the maximum therapeutic dose (80 mg/kg/wk; n=8). In addition, the ECGs collected in other Phase-2 studies (Studies # NS-065/NCNP-01-201 and 202) were also not adequate. The ECG data are available from only few subjects receiving the therapeutic dose (80 mg/kg/wk) and these data were not collected at the end-of-infusion (T_{max}).
- Since the sponsor is conducting Phase-3 confirmatory study in DMD patients (pediatric population) and intends to collect ECGs (Study # NS-065/NCNP-01-301), the IRT recommended that the sponsor amends their study protocol to collect additional PK measurements and high quality 12-lead ECG recordings (see ICH E14 and Q&A #1) around T_{max} (e.g., at 0.5, 1, 3 h post dose) following the first dose in all patients. With modifications to the Phase-3 protocol for NS-065/NCNP-01-301, the study could be used to characterize the drug effects on the QTc interval as per ICH E14 Q&A (R3) 6.1 (Dt: 05/14/2020).

The available data from the sponsor's Phase-1/2, Phase-2 studies and the planned Phase-3 study would be adequate to characterize the effects of viltolarsen on the QTc interval as per ICH E14 Q&A (R3) 6.1.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrpqt@fda.hhs.gov.

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/s/

GIRISH K BENDE
06/17/2020 09:03:42 AM

JOSE VICENTE RUIZ
06/17/2020 09:09:48 AM

CHRISTINE E GARNETT
06/17/2020 09:27:08 AM

Clinical Inspection Summary

Date	5/27/2020
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 Veneeta Tandon, Ph.D., Clinical Reviewer Division of Neurology 1 Office of Neuroscience
NDA #	212154
Applicant	Nippon Shinyaku Co., Ltd.
Drug	Viltolarsen injection
NME	Yes
Proposed Indication	Treatment of Duchenne Muscular Dystrophy amenable to exon 53 skipping
Consultation Request Date	12/18/2019
Summary Goal Date	6/12/2020
Priority/Standard Review	Priority
Action Goal Date	8/12/2020
PDUFA Date	8/12/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigators Drs. Harper, Rao, and Smith were inspected in support of this NDA (Protocols NS-065/NCNP-01-201 and NS-065/NCNP-01-202). The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

For Protocol NS-065/NCNP-01-201, the primary efficacy endpoint supporting accelerated approval was dystrophin expression (a biological endpoint) at baseline and Week 25. With regard to this endpoint, the inspections focused on verifying whether the protocol was followed with respect to obtaining muscle biopsy samples as well as the preparation and processing of biopsy samples at the clinical site. The clinical investigator inspections were not intended to verify dystrophin protein production since the muscle biopsy samples were sent to the vendor, (b) (4) where they were analyzed for dystrophin protein.

OSI received a consult from the Division of Neurology 1 (DN1) on 12/18/2019 that identified the clinical investigators listed above as well as Dr. Mah (Site 23/Canada) for Good Clinical Practice (GCP) inspections. An inspection assignment was issued on 12/31/2019, and the requested GCP inspections were scheduled by the Office of Regulatory Affairs (ORA).

However, at the current time, the COVID-19 global pandemic has significantly limited our ability to conduct on-site GCP inspections. As a result, and in an effort to protect the health, safety, and welfare of FDA employees and study staff, the need for planned inspections in support of this NDA was reevaluated. At that time, the domestic clinical inspections already had been completed, and the foreign inspection in Canada was pending. Following discussions between OSI and DN1, a decision was made that assessment of the application could proceed without the inspection of the clinical site of Dr. Mah.

II. BACKGROUND

Viltolarsen injection is being developed under NDA 212154 (IND 127474) for the treatment of Duchenne Muscular Dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.

The sponsor has submitted one Phase 2 study, Protocol NS-065/NCNP-01-201, and an open-label extension study, Protocol NS-065/NCNP-01-202, to support the accelerated approval of viltolarsen for the treatment of DMD amenable to exon 53 skipping. Accelerated approval is based on a biological endpoint, dystrophin expression, from Protocol NS-065/NCNP-01-201.

Protocol NS-065/NCNP-01-201

Title: "A phase II, dose finding study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of NS-065/NCNP-01 [viltolarsen] in boys with Duchenne Muscular Dystrophy"

Subjects: 16

Sites: 5 sites in the U.S., 1 site in Canada

Study Initiation and Completion Dates: 12/16/2016 to 2/26/2018

This was a 2-period, randomized, placebo-controlled, dose-finding study of viltolarsen injection administered for 20 or 24 weeks to subjects with Duchenne Muscular Dystrophy (DMD). Main inclusion criteria were boys, 4 to <10 years of age, with a confirmed diagnosis of DMD. DMD diagnosis included clinical signs compatible with DMD and confirmed mutation(s) in the dystrophin gene that was amenable to skipping of exon 53.

The study included three phases:

Screening Phase – 2 to 4 weeks; included a Screening Visit Day (Day -21) to assess eligibility and a Pre-Infusion Visit Day -7 to obtain a baseline muscle biopsy.

Treatment Phase – comprised of two separate periods

- Period 1:
 - 4 weeks (Weeks 1 to 4); double-blind
 - Subjects were randomized (3:1) to viltolarsen or placebo
 - Low-Dose Cohort: viltolarsen 40 mg/kg/week or placebo
 - Safety results were reviewed by the Study Chair, Medical Monitor, and Data and Safety Monitoring Board (DSMB). If the low-dose cohort was deemed safe, dosing continued for the high-dose cohort.
 - High-Dose Cohort: viltolarsen 80 mg/kg/week or placebo

- Period 2:
 - 20-weeks (Weeks 5 to 24); open label.
 - Subjects in the Low-Dose Cohort in Period 1 received open label viltolarsen 40 mg/kg/week.
 - Subjects in the High-Dose Cohort in Period 1 received open label viltolarsen 80 mg/kg/week.

The dose of investigational product (IP) was calculated based on the most recent body weight in kg collected per protocol and not including the current visit. Per the schedule of events, body weight was obtained at screening (Day -7) and Weeks 1, 5, 9, 13, 17, and 21 during the treatment phase. IP was administered via IV infusion over a 1-hour period.

Post-Treatment Phase – 30 days; beginning after completion of the 24-week Treatment Phase and ending after the final phone call for AEs and concomitant medications. The Post-Treatment Phase was only for subjects who did not enter the open-label extension study.

Muscle biopsies were obtained from the biceps muscle by a trained surgeon at baseline and at Week 25. Muscle biopsy samples were processed at the clinical site under supervision of personnel from (b) (4) the vendor responsible for analyzing the samples for dystrophin protein. Clinical site personnel shipped the samples to (b) (4) who then shipped the samples to (b) (4). Accelerated approval is based on the primary biological endpoint, dystrophin expression at Week 25 compared to baseline.

Protocol NS-065/NCNP-01-202

Title: "A phase II, open-label, extension study to assess the safety and efficacy of NS-065/NCNP-01 [viltolarsen] in boys with Duchenne Muscular Dystrophy"

Subjects: 16 subjects who participated in Study 201

Sites: 5 sites in the U.S., 1 site in Canada

Study Initiation and Completion Dates: 6/28/2017 and ongoing

Database Cut-Off Date: 1/29/2019

This is an ongoing Phase 2, open-label study to assess the safety and efficacy of viltolarsen in subjects with DMD who completed Protocol NS-065/NCNP-01-201. Protocol NS-065/NCNP-01-202 is a 24-week extension study in which subjects continue to receive weekly viltolarsen infusions at the same dose level they received in Protocol NS-065/NCNP-01-201.

Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of enrolled subjects and site efficacy.

III. RESULTS**1. Amy Harper, M.D.**

Site #02

1000 East Broad Street, 5th Floor

Richmond, VA 23298

Inspection Dates: 2/11/2020 – 2/14/2020

At this site for Protocol NS-065/NCNP-01-201, 3 subjects were screened, all of whom were randomized and completed the study. These three subjects then enrolled in Protocol NS-065/NCNP-01-202, the open label extension study, and were continuing in this study at the time of the inspection.

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, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, and protocol deviations.

With regard to the primary efficacy endpoint data, dystrophin protein expression (a biological endpoint), the inspection focused on verifying whether the protocol was followed with

respect to obtaining muscle biopsies as well as the preparation and processing of the samples at the clinical site per applicable manuals. The clinical investigator inspections were not intended to verify dystrophin protein production since the muscle biopsy samples were sent to the vendor, (b) (4) where they were analyzed for dystrophin protein.

(b) (4) was the vendor performing the dystrophin protein analyses. Documentation was available at the site confirming the presence of (b) (4) personnel for oversight of muscle biopsy freezing and processing of samples. (b) (4) completed Clinical Site Audit reports documenting their observations during the muscle biopsy freezing procedures as well as general compliance with the Flash Freezing of Muscle Biopsy SOP (CL004SOP). The Clinical Site Audit Reports were reviewed and identified one temperature excursion (-26°C vs. -160 to -140 °C per SOP) that occurred during the flash freezing process of the baseline muscle biopsy sample obtained on (b) (6) from Subject (b) (6).

For the 25-week muscle biopsy performed on (b) (6) for Subject (b) (6) two samples of right biceps muscle were excised rather than one piece as specified in the protocol. The FDA field investigator asked about the extra biopsy sample and was told that, during the procedure, the surgeon observed a second tray and assumed that a second biopsy sample was being requested without confirming with study staff. This extra muscle biopsy sample was noted in the (b) (4) Clinical Site Audit Reports. (b) (4) the CRO responsible for clinical monitoring, was also aware of this error as they mentioned the second muscle biopsy sample via email correspondence with the clinical investigator. This deviation was also recorded in a protocol deviation log available at the site, although it was entered, in error, on the log for Protocol NS-065/NCNP-01-202, the open label protocol. However, this protocol deviation was not included in the sponsor data listings for either protocol.

Otherwise, there was no evidence of underreporting of adverse events, and no SAEs occurred at this site.

Reviewer's comments: Review of the (b) (4) Clinical Site Audit Reports for this site noted one instance of a temperature excursion in muscle biopsy sample preparation. OSI cannot determine whether this temperature excursion would have impacted the integrity of this muscle biopsy sample.

*One extra muscle biopsy sample was taken from one of three enrolled subjects at this site. This subject experienced "swelling of incision site" which the clinical investigator considered to be related to the biopsy procedure and possibly related to the additional sample that was obtained. This **adverse event** was included in sponsor data listings for Protocol NS-065/NCNP-01-202 since the onset occurred when the subject was enrolled in the open-label protocol. However, the **protocol deviation** was not included in the sponsor data listings.*

2. Vamshi Rao, M.D.

Site #31

225 E Chicago Ave

Chicago, IL 60611

Inspection Dates: 1/30/2020 – 2/5/2020

At this site for Protocol NS-065/NCNP-01-201, 9 subjects were screened, and 5 subjects were randomized, all of whom completed the study. These five subjects then enrolled in Protocol NS-065/NCNP-01-202, the open label extension study, and were continuing in this study at the time of the inspection.

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, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, and protocol deviations.

With regard to the primary efficacy endpoint data, dystrophin protein expression (a biological endpoint), the inspection focused on verifying whether the protocol was followed with respect to obtaining muscle biopsies as well as the preparation and processing of the samples at the clinical site per applicable manuals. The clinical investigator inspections were not intended to verify dystrophin protein production since the muscle biopsy samples were sent to the vendor, (b) (4) where they were analyzed for dystrophin protein.

(b) (4) was the vendor performing the dystrophin protein analyses. Documentation was available at the site confirming the presence of (b) (4) personnel for oversight of muscle biopsy freezing and processing of samples. (b) (4) Site Visit Follow-Up Letters were reviewed, and no significant issues (e.g., deviations from biopsy processing procedures), were described. (b) (4) personnel noted that for two subjects, a larger than required muscle biopsy sample was obtained. These two muscle biopsy samples measured 2cm x 1 cm x 1 cm rather than the 1cm x 0.5cm x 0.5cm size required for processing as noted in the Flash Freezing of Muscle Biopsy Samples SOP (CL004SP). The Manual of Operations for Protocol NS-065/NCNP-01-201 included a Muscle Biopsy Manual describing the surgical procedure for obtaining the muscle biopsy specimen. The manual stated that one muscle sample 1 cm in length and 0.5 cm in diameter should be obtained. (b) (4) recommended that the site confirm the biopsy size with the surgeons before the procedure.

Otherwise, there was no evidence of underreporting of adverse events, and no SAEs occurred at this site.

Reviewer's comments: (b) (4) noted that larger than SOP-specified muscle biopsy

samples were obtained in two of five enrolled subjects. No adverse events were reported that appear related to the muscle biopsy procedures. These errors were not included in the sponsor protocol deviation log.

3. Edward Smith, M.D.

Site #34

2301 Erwin Road, T Level, Suite 0913

Durham, NC 27710

Inspection Dates: 3/2/2020 – 3/6/2020

At this site for Protocol NS-065/NCNP-01-201, 2 subjects were screened, all of whom were randomized and completed the study. These two subjects then enrolled in Protocol NS-065/NCNP-01-202, the open label extension study, and were continuing in this study at the time of the inspection.

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, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, and protocol deviations.

With regard to the primary efficacy endpoint data, dystrophin protein expression (a biological endpoint), the inspection focused on verifying whether the protocol was followed with respect to obtaining muscle biopsies as well as the preparation and processing of the samples at the clinical site per applicable manuals. The clinical investigator inspections were not intended to verify dystrophin protein production since the muscle biopsy samples were sent to the vendor, (b) (4) where they were analyzed for dystrophin protein.

(b) (4) was the vendor performing the dystrophin protein analyses. Documentation was available at the site confirming the presence of (b) (4) personnel for oversight of muscle biopsy freezing and processing of samples. (b) (4) completed Clinical Site Audit reports documenting their observations during the muscle biopsy freezing procedures as well as general compliance with the Flash Freezing of Muscle Biopsy SOP (CL004SOP).

For this site, (b) (4) personnel noted that for both enrolled subjects, three muscle biopsy samples were collected for the baseline assessment rather than one sample. These baseline biopsies were performed on (b) (6) for Subject (b) (6) and (b) (6) for Subject (b) (6). After observing the first muscle biopsy freezing and processing on (b) (6), (b) (4) personnel noted that the “first muscle biopsy was of an appropriate size, therefore the second and third tissue samples were not necessary” and recommended that (b) (4) the CRO, follow-up with the site to confirm before the procedure the amount of biopsy tissue to collect. After

observing the second muscle biopsy freezing and processing on 8/8/17, (b) (4) again noted that three muscle samples were obtained. (b) (4) recommended that (b) (4) follow-up with the surgical team to confirm that they read the surgery protocol and that they were willing to follow it to the best of their ability. Although it is unclear when these recommendations were communicated to (b) (4) the site had to be aware of these errors since site personnel prepared the muscle biopsy samples. These deviations were not mentioned in the (b) (4) site monitoring visit reports and are not included in the sponsor's protocol deviations listing. Of note, the appropriate amount of muscle tissue was obtained for the 25-week biopsies for these two subjects.

On three occasions, this site did not use the correct weight for determining the dose of study drug to be infused for Protocol NS-065/NCNP-01-201 (see Table 1). The protocol states that the dose (40 mg/kg or 80 mg/kg) should be calculated based on the most recent weight obtained per protocol. Weights were obtained at screening, pre-infusion visit (Day -7), Week 1 (Day 1), Weeks 5, 9, 13, 17, 21, and 25. These dosing errors appear to be minor; the largest error was administration of viltolarsen 1672 mg (which would be 82 mg/kg if using the per protocol weight of 20.4 kg to calculate the administered dose) for Subject (b) (6)

Table 1. Study Drug Dosing Deviations

Subject	Infusion Week/Study Drug	Per Protocol Weight to be Used for Dose Calculation	Actual Weight Used by Site for Dose Calculation	Dose Administered*	Correct Dose	Included in Protocol Deviation Log
(b) (6)	Week 1/ Placebo	PreInfusion (19.7 kg)	Screening (19.5 kg)	1560 mg	1576 mg	Yes
	Week 7/ Viltolarsen 80 mg/kg	Week 5 (20.4 kg)	Week 7 (20.9 kg)	1672 mg	1632 mg	Yes
(b) (6)	Week 4/ Viltolarsen 80 mg/kg	Week 1 (15.5 kg)	Week 4 (15.6 kg)	1248 mg	1240 mg	No

*Study drug provided as 25 mg/mL

Otherwise, there was no evidence of underreporting of adverse events. One SAE occurred in Protocol NS-065/NCNP-01-202. Subject (b) (6) experienced a left tibia/fibula fracture requiring hospitalization for pin placement. This SAE was included in the sponsor data listings.

Reviewer comment: The surgeon at this site excised more than the needed amount of muscle for the baseline muscle biopsies for both subjects enrolled at this site. These additional samples were unnecessary and could have increased the risk of biopsy-related adverse events in these subjects who were each around 5 years old. However, no biopsy-related adverse events were reported. These protocol deviations were not included in the sponsor data listings.

Of note, the appropriate amount of muscle tissue was obtained for the 25-week biopsies for both subjects.

The dosing errors that were noted during the inspection were due to the calculation of dose based on a different weight than that specified by the protocol. For this site, these errors appear to be relatively minor and are unlikely to impact the efficacy or safety data for this site.

{See appended electronic signature page}

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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CONCURRENCE:

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Division of Neurology 1/Medical Team Leader/Teresa Buracchio
Division of Neurology 1/Clinical Reviewer/Veneeta Tandon
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OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Reviewer/Cara Alfaro
OSI/GCPAB Program Analyst/Yolanda Patague

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/s/

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Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOLOGY AND NEPHROLOGY

Date: May 14, 2020

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, Pharm.D.
Clinical Analyst, DCN

To: Anhtu Nguyen, RPM
DN1

Subject: IRT Consult to IND # 127474 / NDA-212154 (SDN # 058)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 4/2/2020 regarding your question on the sponsor's study protocol. We reviewed the following materials:

- Previous IRT review dated 04/01/2020 under NDA-212154 in DARRTS ([link](#)); and
- Sponsor's clinical study protocol # NS-065/NCNP-01-301 (SN0055 / SDN058; [link](#)).

1 IRT Response to the Division

With modifications to the phase 3 protocol for NS-065/NCNP-01-301, the study could be used to characterize the drug effects on the QTc interval as per ICH E14 Q&A (R3) 6.1. For this purpose, we recommend that the protocol is amended to collect additional PK measurements and high quality 12-lead ECG recordings (see ICH E14 and Q&A #1) around Tmax (e.g., at 0.5, 1, 3 h post dose) following the first dose in all patients. We request that the sponsor submits their QT assessment plan for our review.

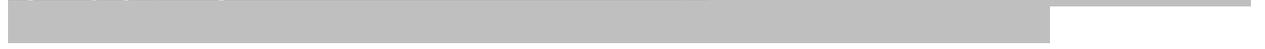
2 Background

Nippon Shinyaku Pharm Inc. submitted an NDA for viltolarsen injection for the treatment of Duchenne muscular dystrophy (DMD; in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping). Viltolarsen (NS-065/NCNP-01; MW: 6924.82 da) is an antisense (morpholino) oligonucleotide and the sponsor claims that it designed to modify dystrophin protein expression and expected to reduce muscle damage by restoring dystrophin function. The product is formulated as injection (Viltepsol, single dose 5 mL vial) containing 250 mg viltolarsen (50 mg/mL and 9 mg NaCl) for intravenous injection (to be administered as infusion

over 60 min). The proposed dose is 80 mg/kg once weekly and the peak concentrations of 329000 ± 91000 ng/mL (T_{max} ~1 h; half-life: ~2.5 h) are expected at steady-state with the proposed maximum therapeutic dose (W24; Study # NS065/NCNP01-P1/2).

Recently, the IRT reviewed the sponsor's waiver request for thorough QT study and recommended to characterize the drug effects on the QTc interval in alternate study designs to exclude large mean increases in QTc (i.e., >20 msec) as per ICH E14 Q&A (R3) 6.1. Refer to the previous IRT review dated 04/01/2020 under NDA-212154 in DARRTS ([link](#)).

The sponsor is conducting Phase-3 confirmatory study in DMD patients (pediatric population) and intends to collect ECGs. This is a randomized, double-blind, placebo-controlled, multi-center study to assess the efficacy and safety of viltolarsen in ambulant patients with Duchenne muscular dystrophy (Study # NS-065/NCNP-01-301; Ver 2.1). (b) (4)

 (b) (4)

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrpqt@fda.hhs.gov.

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CHRISTINE E GARNETT
05/14/2020 11:59:24 AM

351(k) BLA IMMUNOGENICITY REVIEW

Application Type	NDA
Application Number	212145
Submit Date	December 12, 2019
Received Date	December 12, 2019
BsUFA Goal Date	August 12, 2020
Division/Office	Division IV / OBP/ OPQ
Review Completion Date	5/12/2020
Product Code Name	NS-065
Proposed Proper Name¹	viltolarsen
Proposed Proprietary Name¹	Viltepso
Pharmacologic Class	oligonucleotide
Applicant	Nippon Shinyaku Co., Ltd.
Applicant Proposed Indication(s)	treatment of Duchenne Muscular Dystrophy (DMD) in patients amenable to Exon 53 skipping
Recommended Regulatory Action	Approval with PMCs

Immunogenicity Reviewers

Primary Reviewer(s)	Frederick Mills, PhD., OPQ, OBP, Division IV
Secondary Reviewer(s)	Gerald Feldman, Ph.D., OPQ, OBP, Division IV, Chief, Laboratory of Immunobiology

Table of Contents

Immunogenicity Reviewers	1.
Table of Contents.....	2
1. Summary Basis of Recommendation/Executive Summary.....	3
1.1 Immunogenicity Executive Summary and Recommendation	3
1.3 Deficiencies and Other Recommended Comments to Applicant.....	3
2. Review	4
2.1 Immunogenicity Risk Assessment.....	4
2.2 Validation of Anti-Drug Antibody Assay	4
2.2.1 Method Principle	4
2.2.2 Validation Exercises.....	4
2.3 Qualification of anti-dystrophin Antibody Assay	7
2.3.1 Method Principle	7
2.3.2 Qualification data	7
2.5 Clinical Immunogenicity Results	9
2.6 Information Requests Sent During Review.....	9

1. Summary Basis of Recommendation/Executive Summary

1.1 Immunogenicity Executive Summary

The anti-viltolarsen (N-065) antibody assay sensitivity, as stated by the Sponsor and independently calculated by this reviewer from titer data, is in the range of 500 ng/ ml, which is consistent with FDA's 2009 immunogenicity assay guidance. The assay also is appropriately validated for precision, drug tolerance, and stability for critical reagents. Therefore, the validation supports the interpretation of clinical the immunogenicity results, for which no patients were found to be ADA positive for treated subjects evaluated from a Phase II study. However, important recommended aspects of assay validation are either only retrospectively evaluated, or not provided, including a statistical evaluation of distribution and outlier exclusion for cutpoint samples, system suitability specifications for negative and positive controls, and effects of hemolysis. Moreover, the 2019 FDA guidance for immunogenicity assays (<https://www.fda.gov/regulatory-information/search-fdaguidancedocuments/immunogenicity-testing-therapeutic-protein-productsdevelopingand-validating-assays-anti-drug>) recommends assay sensitivity in the range of 100 ng/ml. Therefore, I recommend a PMC to provide appropriate validation of, and improved sensitivity for the ADA assay.

The Sponsor's qualitative anti-dystrophin antibody assay has only been shown to be capable of detecting high levels of antibody; i.e. detection of a PC at 50 µg/ ml, or with rough interpolation between negative and positive controls, two patient samples at 5.7 µg/ml and 10.3 µg/ ml. Nonetheless, from their Phase II study, the Sponsor was able to detect one out of 16 patients as being positive for anti-dystrophin antibodies. This finding suggests that there may be other patients with anti-dystrophin antibody levels below the detection limit of the assay. Therefore, I recommend that the sponsor should improve the sensitivity of the assay. Whether or not this recommendation rises to the level of requesting a PMC is a subject for discussion with the clinical division.

1.2 Deficiencies and Other Recommended Comments to Applicant

Your anti-viltolarsen (N-065) antibody assay sensitivity has a sensitivity in the range of 500 ng/ ml, consistent with FDA's 2009 immunogenicity assay guidance. The assay is also appropriately validated for precision, drug tolerance, and stability of critical reagents. Therefore, your validation supports the interpretation of your clinical immunogenicity results, for which no patients were found to be ADA positive for treated subjects evaluated from your Phase II study (Clinical Study Number: NS-065/NCNP-01-201). However, important recommended aspects of assay validation are either only retrospectively evaluated, or not provided, including a statistical evaluation of distribution and outlier exclusion for cutpoint samples, selectivity, system suitability specifications for negative and positive controls, and effects of hemolysis. Moreover, the 2019 FDA guidance for immunogenicity assays (<https://www.fda.gov/regulatory-information/search-fdaguidancedocuments/immunogenicity-testing-therapeutic-protein-productsdevelopingand-validating-assays-anti-drug>) recommends sensitivity in the range of 100 ng/ml or lower. Therefore, you should submit a PMC to provide the appropriate validation as well as improve the sensitivity for your current ADA assay, or develop and validate an alternative assay with better sensitivity.

Your qualitative anti-dystrophin antibody assay has only been shown to be capable of detecting high levels of antibody (detection of a PC at 50 µg/ ml, or two patient samples judged to be 5.7 µg/ml and 10.3 µg/ ml). Nonetheless, from your NS-065/NCNP-01-201 Phase II study, you were able to detect one out of 16 patients as being positive for anti-dystrophin antibodies. This finding suggests that there may be other patients with anti-dystrophin antibody levels below the detection limit of the current assay. Therefore you should submit a PMC to improve the sensitivity of this assay, or develop an alternative assay with better sensitivity.

Approach to be discussed with the clinical division

2 Review

2.1 Immunogenicity Risk Assessment

Evaluation of Anti-Drug Antibodies (ADA) is an important part of the clinical assessment of biologics, including therapeutic oligonucleotides such as viltolarsen (NS-065), as ADA may contribute to loss of efficacy due to altered PK and abrogation of uptake into cells. ADA to viltolarsen do not pose a high safety risk, as there is no endogenous counterpart.

For DMD treatment, successful viltolarsen therapy will lead to production of low levels of dystrophin in treated DMD patients. Because these subjects do not express endogenous dystrophin, dystrophin resulting from exon skipping mediated by viltolarsen can be seen by the patient's immune systems as a foreign protein, potentially leading to antibody formation and immune reactions against the dystrophin-expressing muscle cells. Therefore, it is important to monitor anti-dystrophin antibodies, in addition to ADA levels.

2.2 Validation of Anti-viltolarsen Antibody Assay

An ELISA method for determining anti-NS-065 (viltolarsen) antibody in human serum was validated. Pooled blank human serum was prepared and validation was assessed for precision, specificity, cut point and normalization factor, specificity cut point, antibody titer, drug tolerance limit, room temperature stability, freeze and thaw stability, and frozen storage.

2.2.1 Method Principle

The NS-065 oligonucleotide is used to coat an ELISA plate. After blocking and washing, samples are added to wells, followed by a 60 minute incubation. Following washing, peroxidase-conjugated protein A/G detection reagent is added, binding to antibody-antigen complexes in the wells. After washing, TMB solution is added; any peroxidase in the wells catalyzes conversion of the TMB to a product whose OD is read with a plate-reading spectrophotometer.

2.2.2 Validation Exercises

Table 2.1: Validation Result-s and Reviewer Assessment for anti-NS-065 antibody method used in Phase 2 study NS-065/NCNP-01-201

Validation Parameter	Study PBC 119-036	Reviewer Comment
Contract Research Org	(b) (4)	CRO established (b) (4) preclinical, clinical pharmacology, and clinical testing
Assay principle	ELISA	Standard approach
Positive control (PC)	Anti-NS-065 rabbit IgG 6.47 mg/mL	Appropriate polyclonal Ab, as the patient responses are polyclonal
PC Dose Curve and Hook Effect	No data	Should be part of PMC, consistent with FDA guidance
PC1 (LPC)	500 ng / ml	For the titer determination, 1/1600 or 1/3200 dilutions of PC3 (8000 ng/ ml) were the last dilutions to give an absorbance signal above background. Thus these samples contained 5 or 2.5 ng/ ml PC. In

		<i>assay practice, the MRD is 1/100, so using PC1 (LPC) in the assay format will yield a sample at 5 ng/ml concentration, which is similar to the highest detectable dilutions in the titer assessment. Therefore, the LPC is appropriately at or near this empirically determined sensitivity of the assay.</i>
PC2	2000 ng / ml	<i>Adequate for controlling assay in high ADA range</i>
PC3 (HPC)	8000 ng/ ml	<i>Adequate for controlling assay in high ADA range</i>
PC4	100000 ng / ml	<i>Adequate for controlling assay in high ADA range</i>
Matrix and NC	Pooled sera from cutpoint determination that did not exceed the cutpoint.	<i>Acceptable-corresponds to pooled normal serum, which is a standard matrix for ADA assay</i>
MRD	1/100	<i>Within guidance, but as part of a PMC, the Sponsor should justify the MRD.</i>
NC system suitability range	In the response to the 3/20/2020 IR The sponsor used the data from the PBC119-036 validation study is a 99% confidence interval for absorbance of negative control samples to be < 0.1401	<i>The Sponsor also provided data for 13 runs from Study PBC411-002, which was the study for assessment of clinical samples. These data have per-run mean NC values of 0.0502-0.0906, from which I calculated an overall mean of 0.073, SD 0.0088, 12.2 %CV, providing further support for adequate control of the NC during actual assay practice</i>
LPC system suitability range	From the response to the 3/20/2020 IR for 13 runs in additional study PBC411-002, there is a 99% confidence interval for absorbance of positive control samples (500 ng/ml) to be between 0.0508 and 0.2030	<i>From the data in the response for Study PBC411-002 there are per-run mean LPC values of 0.091-0.124, from which I calculated an overall mean of 0.116, SD 0.014, 12.4 %CV, providing further support for adequate control of the LPC during actual assay practice</i>
HPC system suitability range	From the response to 3/20/2020 IR for 13 runs in additional study PBC411-002, there is a 99% confidence interval for absorbance data of positive control samples (8,000 ng/ml) to be between 0.4126 and 1.0755	<i>From the data in the response for Study PBC411-002 there are per-run mean HPC values of 7.21-13.23 from which I calculated an overall mean of 0.74, 0.14 SD, 18.7% CV indicating adequate control of the HPC during actual assay practice</i>
Screening cut- point (SCP) Floating CP: Mean NC response ×	50 individuals, with equal Caucasian, Asian, and African ancestry Calculated from mean for CPs determined on three separate days. The CP on each day was	<i>This approach is consistent with FDA guidance standard for floating CP. However, the sponsor did not provide a statistical assessment of the distribution of cutpoint samples</i>

normalization factor [1.15]	Median + 1.645 (1.483 x MAD) Median Absolute Deviation CP factor = mean / mean of neg. controls across days =1.1462	<i>and outlier exclusion. These evaluations should be part of a PMC.</i>
Confirmatory cut-point (CCP) Floating	Specificity cut point samples (n=1) from 25 individuals (Caucasian: 9 people, Negroid: 8 people, and Mongoloid: 8 people) and positive control sample (PC3) were analyzed once a day for three days (All the samples prepared from an individual were analyzed on the same plate.). % Inhibition and confirmation cut point were calculated from sample values of specificity cut point samples that were pretreated with diluent or diluent for confirmatory on each analysis day. Mean of confirmation cut points obtained in a three-day analysis was used as specificity cut point.	<i>Consistent with FDA guidance, The specificity / confirmatory cutpoint is 15.9%. which is a modest required inhibition, helping to ensure that weakly reactive samples are nonetheless confirmed.</i> <i>However, the Sponsor did not provide a statistical assessment of the distribution of cutpoint samples and outlier exclusion. These evaluations should be part of a PMC.</i>
Titer Cut Point (TCP)	Employed screening cutpoint	<i>Adequate, as the titer determination simply needs to detect an ADA signal on samples that have already been confirmed.</i>
Assay Drug tolerance	12.5 µg/ml	<i>Adequate, as serum concentrations are < 250 ng /ml</i>
Target tolerance	NA	<i>There is no soluble target</i>
Sensitivity	Not provided, calculated by reviewer from titer data to be in the 500 ng / ml range	<i>The Sponsor will need to formally evaluate assay sensitivity as part of PMC.</i>
Repeatability/Intra-assay variability	NC %CV 1.2 -9.1% PC1 %CV 0.23-1.30 PC2 %CV 1.94 – 9.26 PC3 %CV 0.44- 2.01	<i>Adequate as per Guidance</i>
Intermediate Precision (IP)/inter-assay variability	NC %CV 18.6 LPC %CV 14.9 HPC %CV 13.83	<i>Adequate as per Guidance</i>
Selectivity	Not assessed	<i>Should be included as part of PMC consistent with FDA guidance</i>
Stability	PC1, PC3, and Negative control assessed in triplicate	<i>Adequate stability demonstrated for RT, freeze-thaw, and frozen storage</i>
Lipemia	In their response to the 3/20/2020 IR, the sponsor states that because there was no correlation observed between patients	<i>I have examined the data on assay responses for lipemic patients, as provided by the Sponsor in their</i>

	with high cholesterol or triglycerides and absorbance measured In ELISA for ADA assay in Study NS-065/NCNP-201, an effect of lipidemia is unlikely. `	<i>response to the 3/20/2020 IR, and agree with their statement that there is no correlation with lipemic status.</i>
Hemolysis	In their response to the 3/20/2020 IR, the Sponsor indicates that effects of hemolysis and lipemia are unlikely because of the 1/100 MRD.	<i>The Sponsor should formally evaluate hemolysis as part of a PMC, consistent with FDA guidance</i>
ADA Assay Assessment	Suitable for Intended purpose	<i>Assay validation allows interpretation of existing clinical immunogenicity data, but a PMC is required to make the assay consistent with current FDA guidance.</i>

2.3 Qualification of Anti-dystrophin Antibody Assay

2.3.1 Method Principle

This is a qualitative Western blot assay. Normal human muscle lysate is run on polyacrylamide gel, blotted, and incubated with patient sera or positive control antibody. IgG reactive bands in lysate are detected by luminescence using labeled protein A/G. Samples that give a reactive band of same size as the putative dystrophin band in positive control lane are scored as anti-dystrophin positive.

Sample	Negative control	Precision sample				Mean	SD	CV
Anti-dystrophin antibody in serum (µg/mL)	0	50						
Image								
Luminescence intensity	3157	3970	4356	4641	4322	337	7.8	
Normalized luminescence intensity	0	813	1199	1484	1165	337	28.9	

From response to 3/30/2020 IR, Intra-assay precision

2.3.2 Qualification

This assay is not directly related to assessing antibodies against the viltolarsen / NS-065 product. Because the DMD patients do not produce dystrophin, clinical efficacy is manifested as expression of low levels of dystrophin protein, which may be seen as a foreign protein by the patient's immune system. Therefore, it may be useful from a clinical standpoint to determine if patients are producing anti-dystrophin antibodies. This assay has been reviewed as a qualified assay that may provide some useful information but need not follow recommendations of current FDA guidance for immunogenicity assay validation.

Table 2.1: Results and Reviewer Assessment for qualification of anti-dystrophin antibody assay used for Phase 2

Assay Parameter	Qualification Parameters	Reviewer Comment
Contract Research Organization	(b) (4)	CRO established (b) (4) preclinical, clinical pharmacology, and clinical testing
Assay principle	Reactivity of dystrophin-sized band on Western blot	<i>The intent of this design is reasonable, given the large size of dystrophin, and therefore the potential difficulty in handling the protein in a traditional ELISA format.</i>
HPC	HPC (50 µg/ ml anti-dystrophin)	<i>Controls assay at high anti-dystrophin levels</i>
Sensitivity	50 µg/ ml as judged by reactivity of the positive control	<i>This sensitivity will only allow detection of very high anti-dystrophin antibody levels, and will likely not be informative about early development of antibody responses, as well as antibodies at sustained low levels.</i>
Intra-assay precision	HPC (50 µg/ ml anti-dystrophin) In the response to the March 20, 2020 IR, data provided across one run yielded a 28.9% CV	<i>This intra-assay precision is somewhat high relative to guidance, but the inter-assay precision (below) is tighter, indicating adequate control</i>
Intermediate Precision (IP)/inter-assay variability	HPC (50 µg/ ml anti-dystrophin) In the response to the March 20, 2020 IR, data provided across 3 runs yielded a 19.1 %CV	<i>This %CV indicates adequate control of the assay at high anti-dystrophin antibody levels.</i>
Stability	In their response to the 3/20/2020 IR The Sponsor states : In analysis of patient samples from Study NS-065/NCNP-201, it was confirmed that positive controls of anti-dystrophin antibody consistently detected dystrophin protein and negative controls did not. The Sponsor believes that it means there was no issue on stability of critical reagents including muscle tissue lysates, positive control of anti-dystrophin antibody, HRP-Protein A/G and ECL Western blot detection reagent.	<i>Because it may be necessary to perform additional evaluation of anti-dystrophin antibodies in subsequent clinical studies, the Sponsor will be advised that they should evaluate the stability of critical reagents</i>
Anti-dystrophin Assay Assessment	Assay capable of detecting high levels of anti-dystrophin antibody	

2.4 Clinical Immunogenicity Results

A study was performed to detect anti-NS-065/NCNP-01 antibody in human serum samples obtained in the clinical study “A Phase II, Dose Finding Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of NS-065/NCNP-01 in Boys with Duchenne Muscular Dystrophy(DMD) (Clinical Study Number: NS-065/NCNP-01-201)”. Samples at all time points from 15 of the 16 patients were judged negative in the screening test. In one patient, all samples [Day 1 (pre-dose), Week 5, Week 13, and Week 24] were judged to be positive in the screening test. In the absorption test, however, they were judged to be negative. Antibody titer calculation test was not performed. All samples from 16 patients were judged anti-NS-065/NCNP-01 antibody negative.

Reviewer comments

Because important validation parameters of sensitivity, precision, and drug tolerance were appropriately assessed, these ADA data are interpretable.

For the same Phase II study (Clinical Study Number: NS-065/NCNP-01-201), serum samples collected from 16 patients at the clinical study sites were analyzed for anti-dystrophin antibodies. Anti-dystrophin antibodies were detected in 1/16 patients (80 mg/kg dose group, patient ID: (b) (6) blood collection time point: Weeks 13 and 24). All other samples were judged anti-dystrophin antibody negative.

Reviewer comments

The anti-dystrophin antibody assay has only been shown to detect high anti-dystrophin antibody levels. The finding of one positive patient out of 16 treated subjects raises the possibility that there are other patients with antibodies at levels undetectable by the assay.

2.5 Information Requests Sent During Review

FDA 3/20/2020 IR requests are shown in italic bold face text, Sponsor responses are in standard type, and reviewer comments in italics

Immunogenicity:

1. The validation report for your ADA assay lacks important information (see <https://www.fda.gov/regulatory-information/search-fdaguidancedocuments/immunogenicity-testing-therapeutic-protein-productsdevelopingand-validating-assays-anti-drug>). For this assay, you should provide data regarding sensitivity, allowed ranges of negative and positive control values for system suitability, and effects of hemolysis and lipidemia. Without this information, your ADA results for Study NS-065/NCNP-201 cannot be meaningfully interpreted

Sensitivity

The ADA assay to determine anti-NS-065 antibody in human serum was developed based on the FDA draft guidance (Assay Development for Immunogenicity Testing of Therapeutic Proteins, December 2009, [Appendix 1-1](#)) and a scientific literature¹) authored by [Gopi Shankar, et al \(J Pharma Biomed Anal, 48 \(2008\) 1267-81\)](#). The ADA method validation study [PBC119-036](#) was completed in 2014. It employed ELISA (Enzyme-linked Immuno Sorbent Assay) which was generally used for ADA assay with intention to test and analyze samples as semi-quantitative assay. Our multi-tiered approach to conclude a positive result is:

1. Screening Assay

Calculate and establish cut point from pooled blank human serum from 50 individuals (Caucasian: 17 people, Negroid: 17 people, and Mongoloid: 16 people) and screen study samples.

2. Confirmatory Assay

Calculate and establish specificity cut point, assess study samples testing reactive in screening assay and determine whether study samples are positive or negative for ADA in absorption test.

3. Titration Assay

Analyze study samples testing positive in confirmatory assay and determine antibody titer.

All three assays above are validated in the study (PBC119-036). Serial dilutions of antiviltolarsen rabbit IgG were used as positive controls in the validation study and 500 ng/ml of anti-viltolarsen rabbit IgG was minimum amount that was confirmed in the study. Although the Sponsor did not assess lower concentration than 500 ng/ml, 500 ng/ml could be considered as the lowest concentration at which the anti-viltolarsen rabbit IgG dilution consistently produces a positive result numerically in our ADA assay. It was also consistent with the FDA draft guidance (Assay Development for Immunogenicity Testing of Therapeutic Proteins, December 2009, [Appendix 1-1](#)) recommending sensitivity of approximately 250 -500 ng/ml as such antibody concentrations had been associated with clinical events. Our ADA validation study had been basis for anti-viltolarsen antibody analysis in the investigator-initiated Phase 1 study (Study NCNP/DMT01). Considering it informative to continue assessment in the same methodology for ADA in Phase 2 study, the Sponsor decided not to add changes in methodology.

As a result, clinical samples from only one patient in Study NS-065/NCNP-201 were tested as reactive in the screening assay but determined as negative in the following confirmatory assay. Results of all other samples were negative under the cut point. No study sample from Study NS-065/NCNP-201 was determined as positive in the confirmatory assay.

Reviewer comments

The Sponsor states that they have not evaluated responses lower than 500 ng/ml, and I have confirmed this as a nominal sensitivity from their tier results. However, as recommended by FDA guidance, sensitivity should be formally evaluated as part of a PMC.

Allowed ranges of negative and positive control values for system suitability

The Sponsor performed additional analysis on the range of negative and positive control values using the data for precision in the validation study (PBC119-036) in reference to the literature¹) to confirm the system suitability. It was confirmed;

1. 99% confidence interval for absorbance data of negative control samples was reported less than 0.1401 ([Appendix 1-2](#)).
2. 99% confidence interval for absorbance data of positive control samples (500 ng/ml) was confirmed between 0.0508 and 0.2030 ([Appendix 1-3](#)).
3. 99% confidence interval for absorbance data of positive control samples (8,000 ng/ml) was confirmed between 0.4126 and 1.0755 ([Appendix 1-3](#)).

It was also confirmed that the absorbance data of negative and positive control samples (500 and 8,000 ng/ml) which were measured in the same plates with patient samples from Study NS-065/NCNP-201 were all within each confidence interval confirmed in the validation study. Therefore, system suitability for analysis of patient samples from Study NS-065/NCNP-201 was retrospectively confirmed.

Reviewer comments

In their IR response the Sponsor provided NC and PC data from 13 runs in Study PBC411-002, which represents actual assay practice vis a vis assessment of Phase 2 ADA samples. From these data I calculated the following statistics for the controls

<i>control</i>	<i>Range absorbance</i>	<i>mean</i>	<i>SD</i>	<i>%CV</i>
<i>NC (pooled serum)</i>	<i>0.0502-0.0906</i>	<i>0.072731</i>	<i>0.008883</i>	<i>12.21377</i>
<i>LPC (500 ng/ml)</i>	<i>0.091-0.124</i>	<i>0.1116</i>	<i>0.013847</i>	<i>12.40799</i>
<i>HPC (8000 ng/ml)</i>	<i>7.21-13.23</i>	<i>0.738508</i>	<i>0.138063</i>	<i>18.69492</i>

These statistics for NC and PCs during actual assay practice show acceptable variability (< 20% CV) across runs. Taken together with the Sponsor's estimates of the confidence intervals for the controls, these data indicate adequate control of the NC and PCs. However, as part of a PMC, and consistent with FDA guidance, the Sponsor should prospectively define acceptance criteria for the controls.

Effects of hemolysis and lipidemia

Those effects were not evaluated in the validation study, however the Sponsor believes they can be considered minimum and not to affect the result of patient samples reported as positive vs. negative, even if possible, by the following reasons:

1. The value of 100 which was recommended as maximum within typical MRD range in the FDA draft guidance (Assay Development for Immunogenicity Testing of Therapeutic Proteins, December 2009, [Appendix 1-1](#)) was employed as an MRD in our ADA assay to ensure both of reproducibility and sensitivity.
2. There was no correlation observed between patients with high cholesterol or triglycerides and absorbance measured in ELISA for ADA assay in Study NS-065/NCNP-201 ([Appendix 1-4](#)).

Reviewer comments

I have examined the data on assay responses for lipemic patients and agree with the Sponsor's statement that there is no correlation with lipemic status. However, an MRD of 100 does not mean in and of itself that there is no effect of hemolysis. Therefore, I recommend that as part of PMC, the effect of hemolysis be assessed, consistent with FDA guidance.

2. We recognize the qualitative nature of your anti-dystrophin antibody assay. However, in order to allow interpretation of the results from Study NS-065/NCNP-201 using this assay, you will need to provide an estimate of the minimum amount of anti-dystrophin antibody that can be detected, as well as data on assay precision, and the stability of any critical reagents.

Estimate of the minimum amount of anti-dystrophin antibody that can be detected

Our anti-dystrophin antibody assay was developed for the purpose of detection of dystrophin protein in muscle tissue lysates by Western blot. In the validation study (SBL 119-083), dystrophin protein was consistently and reproducibly detected using 400 ng/ml of rabbit polyclonal anti-dystrophin antibody dilution as a positive control sample, which meant that 50 ug/ml of anti-dystrophin antibody was detected in original human serum sample prior to dilution and was the minimum amount which could be consistently detected in our anti-dystrophin antibody assay. The Sponsor did not assess lower concentrations than 50 ug/ml of anti-dystrophin antibody in human serum in the validation study. However, bands showing less amount of anti-dystrophin antibody were detected in patient samples from Study NS-065/NCNP-201, and the Sponsor performed additional analyses to estimate the amount of anti-dystrophin antibody by extrapolating intensity of the detected bands using negative and positive controls ([Appendix 2-1](#)).

1. Patient sample from (b) (6) at Week 13
Estimated at 5.7 ug/ml of anti-dystrophin antibody in original serum sample (45.6 ng/ml in dilution sample)
2. Patient sample from (b) (6) at Week 24
Estimated at 10.3 ug/ml of anti-dystrophin antibody in original serum sample (82.4 ng/ml in dilution sample)

As mentioned, our anti-dystrophin antibody assay was originally validated as a qualitative assay, those two data are considered as estimation calculated based on available data of positive and negative controls.

Reviewer comments

The sensitivity, as defined by the 50 µg/ml PC, as well as the interpolated values of 5.7 µg/ml and 10.3 µg/ml, will only allow detection of high anti-dystrophin antibody levels, and will likely not be informative about early development of antibody responses, as well as antibodies at sustained low levels.

Assay precision

The Sponsor performed additional analysis of the data from the validation study (SBL 119-083) and provided data on assay precision as follows.

1. Intra-assay precision ([Appendix 2-2](#))

CV: 28.9%

2. Inter-assay precision ([Appendix 2-3](#))

CV: 19.2%

Reviewer comments

The %CV values indicate adequate control of the assay at high anti-dystrophin antibody levels.

Stability of critical reagents

In analysis of patient samples from Study NS-065/NCNP-201, it was confirmed that positive controls of anti-dystrophin antibody consistently detected dystrophin protein and negative controls did not. The Sponsor believes that it means there was no issue on stability of critical reagents including muscle tissue lysates, positive control of anti-dystrophin antibody, HRP-Protein A/G and ECL Western blot detection reagent.

Reviewer comment

The Sponsor should evaluate the stability of critical reagents to support subsequent use of this assay.

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/

FREDERICK C MILLS
05/15/2020 03:43:01 PM

GERALD M FELDMAN
05/15/2020 04:36:59 PM

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: May 11, 2020

TO: Eric Bastings, M.D.
Director (Acting)
Division of Neurology Products 1
Office of New Drugs

FROM: Arindam Dasgupta, Ph.D.
Deputy Director
Division of New Drug Bioequivalence Evaluation (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm.D.
Director
DNDSI/OSIS

SUBJECT: Surveillance inspection of [REDACTED] (b) (4)
[REDACTED]

Inspection Summary

OSIS inspected the bioanalytical portion of Study NS-065/NCNP-01-201 (NDA 212154, Viltolarsen) conducted at [REDACTED] (b) (4)
[REDACTED] (b) (4)

I observed objectionable conditions and issued Form FDA 483 at the inspection close-out. The objectionable conditions included documentation and reporting issues. The final inspection classification is Voluntary Action Indicated (VAI).

Recommendation

Based on my review of the inspectional findings, I conclude the data from the audited studies are reliable to support a regulatory decision. However, the review division should consider the impact of Observation 2b on the study results.

Inspected Studies

NDA 212154

Study Number: NS-065/NCNP-01-201 ([REDACTED] (b) (4))

Study Title: "A Phase II, Dose Finding Study to Assess the Safety, Tolerability, Pharmacokinetics, and

Pharmacodynamics of NS-065/NCNP-01 in Boys with Duchenne Muscular Dystrophy (DMD)

Bioanalytical

Study report: 010-CSR-049: Western Blot, RT-PCR and Immunostaining Analysis of the Clinical Samples for Dystrophin Protein from NS-065/NCNP-01-201 (b) (4) Trial (Dated June 28, 2019)

Sample Analysis Period: (b) (4)

Analytical Site: (b) (4)

(Note: (b) (4) moved to suite (b) (4) since the studies were conducted)

Scope of Inspection

OSIS scientist Arindam Dasgupta, Ph.D. conducted the analytical inspection of study **NS-065/NCNP-01-201** (b) (4) at (b) (4) from (b) (4)

This was the first FDA and BIMO inspection of (b) (4)

The bioanalytical portion of the current inspection audited records related to western blotting analytical bioassays reported in study reports "010-CSR-049: Western Blot, RT-PCR and Immunostaining Analysis of the Clinical Samples for Dystrophin Protein from NS-065/NCNP-01-201 (b) (4) Trial" and "Study report 010-MVR-081: Method Validation Report for Dystrophin Quantification by Western Blot Analysis or NS Pharma Program 2019-244 (Dated Dec 11, 2019)". The inspection evaluated the firm's adherence to the blinding procedure, tissue specimen receipt and storage, and conduct of the western blot (WB) analyses performed. The inspection included, but was not limited to, record review of the following: tissue sample receipt, storage, and handling, western blotting analytical procedures, positive and negative controls used in the WB procedures, and the randomization and blinding scheme associated with the subject tissue samples. During the inspection, I requested the (b) (4) analyst to quantitate the dystrophin bands, actinin bands and myosin heavy chain bands with Image Lab software for images that are acquired by ChemiDoc XRS+ system for dystrophin, Alpha-actinin and myosin. I reviewed the generated data and compared it with the data in the study report submitted to FDA.

Inspectional Findings

At the conclusion of the inspection, I observed objectionable findings and issued Form FDA 483 to (b) (4). The Form FDA 483 observations (**Attachment 1**), (b) (4) response dated March 23, 2020 (**Attachment 2**) and my evaluation are presented below.

(b) (6)

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V. 2.6 Last Revised Date 9-26-2019

Conclusion

After review of the inspectional findings, I conclude that data from the audited study are reliable for agency review. However, the review division should evaluate if Observation 2b has any impact on the study results.

Arindam Dasgupta, Ph.D.
Deputy Director, DNDSI

Final ClassificationAnalytical Site

VAI -

(b) (4)

cc:

OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Benson/Choi/Skelly/Au

Draft: AD 05/05/2020

Edit: CB 05/08/2020

ECMS: Cabinets/CDER OTS/Office of Study Integrity and
Surveillance/INSPECTIONS/BE Program/ANALYTICAL/

(b) (4)

[REDACTED]
(b) (4)

OSIS File#: [REDACTED] (b) (4)

FACTS: [REDACTED] (b) (4)

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/s/

ARINDAM DASGUPTA
05/11/2020 06:32:31 AM

CHARLES R BONAPACE
05/11/2020 02:23:07 PM

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)

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

Date of This Review:	April 9, 2020
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 212154
Product Name and Strength:	Viltepso ^a (viltolarsen) injection, 250 mg/5 mL (50 mg/mL)
Applicant/Sponsor Name:	Nippon Shinyaku Co., Ltd. (NS Pharma)
OSE RCM #:	2019-2016-1
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

^a DMEPA review of the proposed proprietary name, Viltepso, concluded that the name could result in medication errors due to confusion with another product that is also under review. Thus, the ultimate acceptability of the proprietary name, Viltepso, is dependent upon which underlying application is approved first.

1 PURPOSE OF MEMORANDUM

NS Pharma submitted revised container label and carton labeling received on April 7, 2020 for Viltepso. The Division of Neurology 1 (DN 1) requested that we review the revised container label and carton labeling for Viltepso (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations we made during a previous label and labeling review.^b

2 CONCLUSION

NS Pharma implemented all our recommendations, and we have no additional recommendations at this time.

Morris, C. Label and Labeling Review for Viltepso (NDA 212154). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 17. RCM No.: 2019-2016.

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/

JOHN C MORRIS
04/09/2020 10:16:24 AM

BRIANA B RIDER
04/09/2020 10:20:12 AM



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOLOGY AND NEPHROLOGY

Date: April 1, 2020

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst
Division of Cardiology and Nephrology

To: Annie Nguyen, RPM
DN1

Subject: QT Consult to NDA # 212154 (SDN # 0002)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 1/9/2020 regarding the Division's QT related question. We reviewed the following materials:

- Sponsor's proposed product label (SN0002; [link](#));
- Sponsor's summary of clinical safety (SN0002; [link](#)); and
- Highlights of clinical pharmacology and cardiac safety (SN0013; [link](#)).

1 QT-IRT's response to the Division

The sponsor did not conduct a thorough QT study for viltolarsen. The sponsor is requesting a waiver for a thorough QT study based on the severe nature of Duchenne muscular dystrophy (DMD), the unmet medical need, and the extreme difficulty in recruiting patients for such studies. We note that other development programs for DMD treatments (*e.g.*, (b) (4)) have not conducted a thorough QT study and instead characterized the drug effects on the QTc interval in alternate study designs to exclude large mean increases in QTc (>20 msec) as per ICH E14 Q&A (R3) 6.1.

While the existing nonclinical and clinical data do not suggest a concerning proarrhythmic risk for viltolarsen, the data are not adequate for the characterization of drug effect on the QTc interval. The ECG data collected in the Phase 1/2 study (# NS065/NCNP01-P1/2) could be adequate; however, the sponsor does not have access to the raw datasets, and we are not able to confirm the safety findings in the study. As with other programs for DMD, we recommend that sponsor characterizes the drug effect on the QTc interval in an alternative study design to exclude large

mean increases (ICH E14 Q&A (R3) 6.1). This could be accomplished by including replicate 12-lead ECGs in ongoing or future clinical trials in patients.

2 BACKGROUND

2.1 Product Information

Nippon Shinyaku Co, Ltd has submitted an NDA for viltolarsen injection for the treatment of Duchenne muscular dystrophy (DMD; in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping). Viltolarsen (NS-065/NCNP-01; MW: 6924.82 da) is an antisense (morpholino) oligonucleotide and the sponsor claims that it designed to modify dystrophin protein expression and expected to reduce muscle damage by restoring dystrophin function.

The product is formulated as injection (Viltepsa, single dose 5 mL vial) containing 250 mg viltolarsen (50 mg/mL and 9 mg NaCl) for intravenous injection (to be administered as infusion over 60 min). The proposed dose is 80 mg/kg once weekly and the peak concentrations of 329000 ± 91000 ng/mL (Tmax ~1 h; Half-life: ~2.5 h) are expected at steady-state with the proposed maximum therapeutic dose (W24; Study # NS065/NCNP01-P1/2).

Viltolarsen exhibits dose proportional pharmacokinetics between 1.25 and 80 mg/kg doses. The sponsor indicates that viltolarsen has a low drug interaction (CYP-mediated, as a victim drug) potential and it is mainly excreted in the urine as an unchanged parent (>90% in patients). Expected high clinical exposure scenario is not identified at this stage in development and clinical pharmacology studies characterizing potential worst-case scenario for the parent drug and metabolites due to organ impairment (i.e., renal and hepatic) are pending.

2.2 Sponsor's position related to their QT assessment

Since there is currently no cure for DMD, the goal of care is to provide the best possible quality of life through all stages of the disease.

Developing Drugs for Treatment, the Sponsor does not plan to conduct clinical pharmacology studies in special populations (i.e., viltolarsen will not be studied in patients with hepatic/renal impairment or in patients to evaluate QTc interval effects). A waiver of such studies will be requested, largely based on the severe nature of DMD, the unmet medical need, and the extreme difficulty in recruiting patients for such studies.

Reviewer's comment: *The sponsor did not include a formal request for substitution of thorough QT study in this submission. The Sponsor claims that they do not plan to conduct clinical pharmacology studies in special populations (i.e., viltolarsen will not be studied in patients with hepatic/renal impairment or in patients to evaluate QTc interval effects).*

2.3 Nonclinical Cardiac Safety

Refer to the sponsor's highlights of clinical pharmacology and clinical safety.

Effects on the Cardiovascular System in Conscious Monkeys, IV, dose escalation (Study TX10834): Four male cynomolgus monkeys were injected IV with doses of 0 (vehicle), 60, 200 and 600 mg/kg of viltolarsen (10 mL/kg). Blood pressure, heart rate and electrocardiograms (ECG) parameters (heart rate, PR interval, QRS duration, QT interval and QTc [Bazett's formula]) were recorded prior to dosing, immediately after dosing, and at intervals up to 24 h post-dose.

Viltolarsen had no adverse effect on blood pressure, heart rate, ECG parameters, or clinical signs at dose levels up to 600 mg/kg and no specific effects on QT/QTc interval or clinical signs potentially suggestive of a pro-arrhythmic effect were observed at dose levels up to 600 mg/kg.

Reviewer's comment: *The expected peak concentrations of 329000 ± 91000 ng/mL (Free: ~ 28 μ M; PPB: $\sim 40\%$) at steady-state with once weekly dosing of 80 mg/kg offers > 15 -fold margin ($hERG IC50 > 433$ μ M; Study # TX10836).*

2.4 Clinical Cardiac Safety

One patient in Study 202 had a TEAE associated with cardiac function (sinus arrhythmia; see Study 202 section below for details); no other patient in Studies P1/2, 201, or 202 had a TEAE associated with cardiac function.

2.5 Summary results of QTc assessments

2.5.1 Study 201: 40 mg/kg/wk (8 patients) and 80 mg/kg/wk (8 patients)

12-lead ECGs were performed after the patient had rested for 10 minutes in the supine position at screening, Day 1, Week 13, and Week 25/ET.

Relatively small mean changes from baseline were observed for PR, QRS, QT, QTcB, QTcF, and RR at Weeks 13 and 25. No patient had a QTcF value higher than 432 msec or a change from baseline of >33 msec. None of these changes from baseline were considered to be clinically meaningful. No patient had a cardiac rhythm or interpretation value at Week 13 or 25 that was considered abnormal-clinically significant by local cardiologist.

2.5.2 Study 202: 40 mg/kg/wk (8 patients) and 80 mg/kg/wk (8 patients)

12-lead ECGs are scheduled at Weeks 25, 37, 49, 73, 97, 121, 146, and 169 (or early termination) and were performed as described for Study 201.

For the Week 96 data cut, no patient had a QTcF value higher than 434 msec or a change from Week 25 of >46 msec. None of these changes from baseline were considered to be clinically meaningful. No patient had a cardiac rhythm or interpretation value that was considered abnormal-clinically significant by the local cardiologist.

2.5.3 Study P1/2: 40 mg/kg/wk (8 patients) and 80 mg/kg/wk (8 patients)

Intensive ECGs were performed on Days 1 and 162 at 60, 40, and 20 minutes before the start of infusion; 30 minutes after the start of infusion; immediately after the end of infusion; and 1, 2, and 4 hours after the end of infusion. Electrocardiography will be performed using the electrocardiograph provided by the sponsor, and the ECG parameters will be measured by the central ECG laboratory.

On standard ECG, no clinically meaningful abnormal findings were observed in either group. The worst post-treatment QTcF interval was ≤ 450 msec and worst post-treatment QTcB interval was ≤ 480 msec in all subjects. In addition, the change from baseline to the worst value after treatment was ≤ 30 msec QTcF and QTcB.

Table 12.5.3-1 Summary of significant abnormal resting standard 12-lead ECG (post-treatment value)

Item	Treatment group	N	Worst value after treatment							
			≤450 msec		450< ≤480 msec		480< ≤500 msec		500 msec<	
			n	%	n	%	n	%	n	%
QTc interval (Fridericia correction)	All patients	16	16	100.0	0	0.0	0	0.0	0	0.0
	40 mg/kg group	8	8	100.0	0	0.0	0	0.0	0	0.0
	80 mg/kg group	8	8	100.0	0	0.0	0	0.0	0	0.0
QTc interval (Bazett correction)	All patients	16	9	56.3	7	43.8	0	0.0	0	0.0
	40 mg/kg group	8	5	62.5	3	37.5	0	0.0	0	0.0
	80 mg/kg group	8	4	50.0	4	50.0	0	0.0	0	0.0

Source: Clinical Study Report: NS065/NCNP01-P1/2

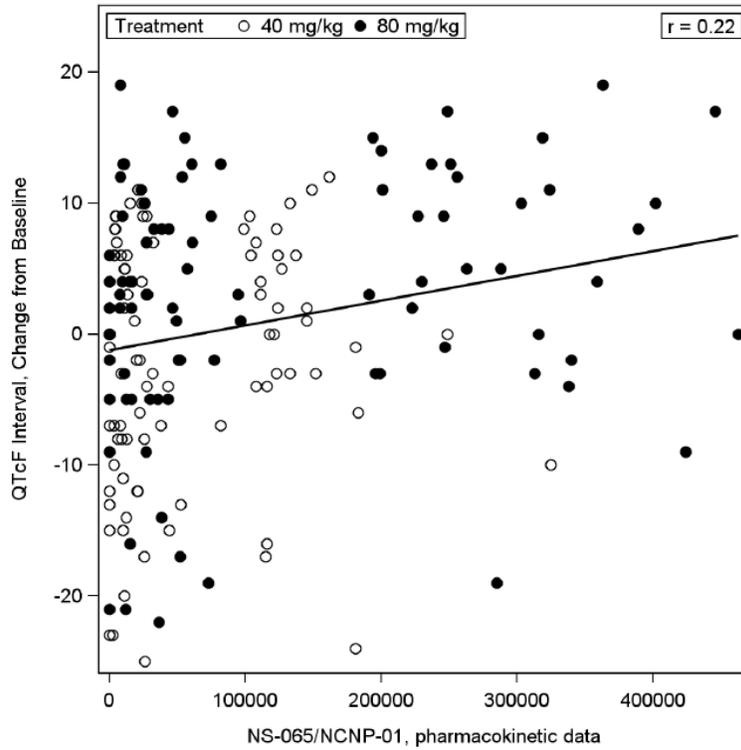
14.3.6-13 Resting 12-Lead Electrocardiogram

Change in Descriptive Statistics Values

Item	Treatment Group / Visit / Timepoint	N	Mean (SD)	Median	Min~Max	Difference			
						Mean (SD)	Median	Min~Max	
QTc Interval Fridericia's Correction (msec)	All Patients	V1a / 1 hr pre-dose	16	399.6 (23.2)	404	352~438	-	-	-
		V1a / 40 min pre-dose	16	397.9 (22.4)	399	350~432	-	-	-
		V1a / 20 min pre-dose	16	402.6 (22.5)	406	366~443	-	-	-
		V1a / Average of 3 pre-dose	16	400.1 (22.4)	403.5	356~438	-	-	-
		V1a / 30 min after the start	16	404.9 (21.5)	410.5	363~435	4.8 (6.1)	4.5	-3~17
		V1a / 0 hr post-dose	16	405.7 (21.8)	407.5	358~444	5.6 (6.3)	4	-4~19
		V1a / 1 hr post-dose	16	405.1 (20.1)	407	366~445	4.9 (8.3)	7	-15~17
		V1a / 2 hrs post-dose	16	402.1 (19.1)	402.5	366~439	1.9 (8.1)	4	-14~11
		V1a / 4 hrs post-dose	16	401.4 (17.3)	403	365~430	1.3 (10.2)	4	-16~19
		V24 / 1 hr pre-dose	16	394.1 (17.6)	397.5	352~419	-6.0 (11.7)	-4	-28~9
		V24 / 40 min pre-dose	15	394.3 (20.0)	396	347~426	-7.9 (8.5)	-7	-27~4
		V24 / 20 min pre-dose	16	394.6 (20.3)	398.5	347~430	-5.5 (8.9)	-6	-19~8
		V24 / 30 min after the start	16	399.2 (19.2)	398	352~432	-0.9 (11.4)	-1	-24~14
		V24 / 0 hr post-dose	16	402.3 (20.5)	403.5	349~438	2.2 (9.8)	2	-16~17
		V24 / 1 hr post-dose	16	397.9 (20.6)	399.5	354~434	-2.3 (10.6)	-2	-19~13
		V24 / 2 hrs post-dose	16	394.7 (17.2)	393	362~436	-5.4 (10.7)	-5	-25~8
	V24 / 4 hrs post-dose	16	398.6 (16.5)	399.5	364~435	-1.6 (10.7)	-0.5	-23~13	
	40 mg/kg	V1a / 1 hr pre-dose	8	399.4 (28.0)	408.5	352~438	-	-	-
		V1a / 40 min pre-dose	8	399.0 (29.2)	411.5	350~432	-	-	-
		V1a / 20 min pre-dose	8	404.8 (26.8)	411.5	366~443	-	-	-
		V1a / Average of 3 pre-dose	8	401.1 (27.8)	411	356~438	-	-	-
		V1a / 30 min after the start	8	404.6 (26.1)	418	363~435	3.5 (5.1)	3	-3~11
		V1a / 0 hr post-dose	8	405.0 (28.4)	414.5	358~444	3.9 (4.8)	2.5	-4~12
		V1a / 1 hr post-dose	8	403.4 (26.1)	404.5	366~445	2.3 (8.9)	5.5	-15~10
		V1a / 2 hrs post-dose	8	400.6 (24.6)	401	366~439	-0.5 (7.9)	1.5	-12~10
		V1a / 4 hrs post-dose	8	400.1 (22.1)	399	365~430	-1.0 (9.9)	-0.5	-15~9
		V24 / 1 hr pre-dose	8	390.6 (21.3)	391.5	352~419	-10.5 (12.5)	-12	-28~9
		V24 / 40 min pre-dose	8	391.8 (25.9)	393	347~426	-9.4 (8.6)	-8.5	-27~3
		V24 / 20 min pre-dose	8	392.4 (25.6)	398	347~430	-8.8 (5.8)	-8.5	-17~0
		V24 / 30 min after the start	8	396.4 (24.6)	395.5	352~432	-4.8 (11.1)	-3.5	-24~9
		V24 / 0 hr post-dose	8	399.0 (26.9)	402.5	349~438	-2.1 (8.6)	-1.5	-16~10
		V24 / 1 hr post-dose	8	397.5 (26.7)	399	354~434	-3.6 (9.7)	-5	-17~11
V24 / 2 hrs post-dose		8	393.8 (21.9)	393	362~436	-7.4 (12.0)	-7	-25~6	
V24 / 4 hrs post-dose	8	397.3 (22.0)	395	364~435	-3.9 (10.7)	-5	-23~8		
80 mg/kg	V1a / 1 hr pre-dose	8	399.9 (19.0)	400.5	365~425	-	-	-	
	V1a / 40 min pre-dose	8	396.8 (14.9)	398	373~419	-	-	-	
	V1a / 20 min pre-dose	8	400.5 (18.9)	400.5	372~434	-	-	-	
	V1a / Average of 3 pre-dose	8	399.1 (17.3)	400.5	370~426	-	-	-	
	V1a / 30 min after the start	8	405.3 (17.5)	404.5	381~432	6.1 (7.0)	5.5	-3~17	
	V1a / 0 hr post-dose	8	406.4 (14.6)	405.5	389~430	7.3 (7.5)	4.5	-2~19	
	V1a / 1 hr post-dose	8	406.8 (13.3)	410.5	385~424	7.6 (7.1)	8	-2~17	
	V1a / 2 hrs post-dose	8	403.5 (13.1)	405.5	381~422	4.4 (8.1)	7.5	-14~11	
	V1a / 4 hrs post-dose	8	402.8 (12.3)	405	388~424	3.6 (10.7)	4	-16~19	
	V24 / 1 hr pre-dose	8	397.6 (13.4)	400	369~412	-1.5 (9.6)	1	-22~8	
	V24 / 40 min pre-dose	7	397.1 (11.4)	396	384~413	-6.1 (8.6)	-2	-22~4	
	V24 / 20 min pre-dose	8	396.9 (14.7)	399	374~416	-2.3 (10.6)	2.5	-19~8	
	V24 / 30 min after the start	8	402.0 (12.9)	402.5	379~420	2.9 (11.0)	7	-19~14	
	V24 / 0 hr post-dose	8	405.6 (12.3)	403.5	385~424	6.5 (9.4)	9.5	-9~17	
	V24 / 1 hr post-dose	8	398.3 (14.0)	399.5	368~417	-0.9 (11.9)	0.5	-19~13	
	V24 / 2 hrs post-dose	8	395.6 (12.2)	393.5	377~412	-3.5 (9.7)	-5	-22~8	
V24 / 4 hrs post-dose	8	399.9 (9.7)	402.5	383~410	0.8 (10.9)	2.5	-21~13		

Source: Clinical Study Report: NS065/NCNP01-P1/2

14.3.5-17 Change from Baseline in Resting 12-Lead Electrocardiogram QTcF Values and Blood Drug Concentration (naïve pooled analysis)



Source: Clinical Study Report: NS065/NCNP01-P1/2

Reviewer's comment: Overall, the ECGs collected in Study NS065/NCNP01 do not show large mean increases in QTc according to the sponsor's analysis. We cannot confirm these results because the sponsor does not have access to the associated datasets.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderderpqt@fda.hhs.gov.

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/

GIRISH K BENDE
04/01/2020 02:29:42 PM

CHRISTINE E GARNETT
04/01/2020 02:35:03 PM

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:	March 17, 2020
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 212154
Product Name and Strength:	Viltepso ^a (viltolarsen) injection, 250 mg/5 mL (50 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Nippon Shinyaku Co., Ltd.
FDA Received Date:	September 30, 2019
OSE RCM #:	2019-2016
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

^a DMEPA review of the proposed proprietary name, Viltepso, concluded that the name could result in medication errors due to confusion with another product that is also under review. Thus, the ultimate acceptability of the proprietary name, Viltepso, is dependent upon which underlying application is approved first.

1 REASON FOR REVIEW

As part of the approval process for Viltepsa (viltolarsen) injection, the Division of Neurology 1 (DN 1) requested that we review the proposed Viltepsa Prescribing Information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS 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
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

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 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted PI, container label, and carton labeling our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

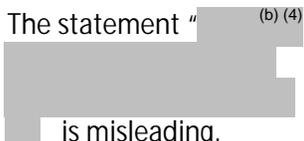
Table 2. Identified Issues and Recommendations for DN 1			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	Diluent description does not follow USP naming convention for Normal Saline.	Per USP, the correct terminology utilized for Normal Saline should be: 0.9% Sodium Chloride Injection, USP.	We recommend replacing the terminology “normal saline” with “0.9% Sodium Chloride Injection, USP”.
Highlights of Prescribing Information - Dosage and Administration			
1.	The statement “  (b) (4) is misleading.	The reader may inaccurately assume that:	We recommend this statement be revised to clarify that if the volume of Viltepsa is less than 100 mL, it must be diluted with

Table 2. Identified Issues and Recommendations for DN 1			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		<ul style="list-style-type: none"> The product must always be combined with normal saline. They can dilute to a total volume that is more than 100 mL. 	0.9% Sodium Chloride Injection, USP" to 100 mL.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Use of the confusing symbol "≥".	This symbol may be mistaken as opposite of intended.	Replace the symbol "≥" with its intended meaning (that is, greater than or equal to).
2.	Section 2.2, Step d. contains several actions, which decreases readability.	May increase the risk for preparation errors.	We recommend Step d. be split into 2 sub-steps. (See Appendix F2)
3.	In Section 2.2, Step e. use of the description (b) (4) " is unclear.	At this point, the drug is contained within an infusion bag.	We recommend replacing the description (b) (4) with "infusion bag containing the solution".

Table 3. Identified Issues and Recommendations for Nippon Shinyaku Co., Ltd. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The format for expiration date is not defined.	We are unable to assess the proposed expiration date format from a medication safety perspective (for example, risk for deteriorated drug medication errors).	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to

Table 3. Identified Issues and Recommendations for Nippon Shinyaku Co., Ltd. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	It is unclear whether the linear barcode on the container label and carton labeling contains, at a minimum, the appropriate National Drug Code (NDC) number.	The NDC number must be contained within the linear barcode per 21 CFR 201.25.	Ensure the linear barcode on the container (vial) label and carton labeling contains, at a minimum, the NDC number, in accordance with 21 CFR 201.25.
3.	The storage statement contains the symbol “-” and the overall prominence can be improved.	May increase the risk for degraded drug medication errors.	Revise and bold the statement “Refrigerate at 2°C-8°C (36°F-46°F)” to read as follows on the container label and carton labeling: Carton labeling: “Must be refrigerated, store at 2°C to 8°C (36°F to 46°F).” Container label: “Refrigerate at 2°C to 8°C (36°F to 46°F).”
4.	The strength statement lacks not prominence.	May increase the risk for wrong dose medication errors.	Increase the prominence of the strength, taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.15(a)(6).
Carton Labeling			
1.	The usual dose statement is not present.	The usual dose statement is required per 21 CFR 201.55.	Add the following usual dosage statement to the carton labeling: “Recommended Dosage: See prescribing information.”

4 CONCLUSION

Our evaluation of the proposed Viltepso PI, container label, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Nippon Shinyaku Co., Ltd. so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Viltepso that Nippon Shinyaku Co., Ltd. submitted on September 30, 2019.

Table 4. Relevant Product Information for Viltepso	
Initial Approval Date	N/A
Active Ingredient	viltolarsen
Indication	treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping
Route of Administration	Intravenous
Dosage Form	Injection
Strength	250 mg/5 mL (50 mg/mL)
Dose and Frequency	80 mg/kg once weekly
How Supplied	Single dose vials
Storage	Store at 2°C to 8°C (36°F to 46°F). Do not freeze. (b) (4)
Container Closure	Clear USP (b) (4) Glass Vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 6, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, viltolarsen and NDA 212154. Our search did not identify any previous reviews.

APPENDIX F. LABELS AND LABELING

F.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 Viltepso labels and labeling submitted by Nippon Shinyaku Co., Ltd. on September 30, 2019.

- Container label
- Carton labeling
- Prescribing Information (Excerpt containing recommendations for Section 2.2 Preparation Instructions)

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

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/s/

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