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RESEARCH**

APPLICATION NUMBER:

212154Orig1s000

SUMMARY REVIEW

Summary Memorandum

Date	August 12, 2020
From	Teresa Buracchio, M.D. Eric Bastings, M.D. Billy Dunn, M.D.
Subject	Summary Memorandum
NDA/BLA # and Supplement#	212154
Applicant	Nippon Shinyaku Co., Ltd.
Date of Submission	December 31, 2019
PDUFA Goal Date	August 12, 2020
Proprietary Name	Viltepso
Established or Proper Name	Viltolarsen
Dosage Form(s)	Single-use vial for intravenous infusion
Applicant Proposed Indication(s)/Population(s)	Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping
Applicant Proposed Dosing Regimen(s)	80 mg/kg once weekly
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping
Recommended Dosing Regimen(s) (if applicable)	80 mg/kg once weekly

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Duchenne muscular dystrophy (DMD) is a rare progressive X-linked neuromuscular disorder caused by mutations in the dystrophin gene. Lack of dystrophin results in degeneration of muscle fibers, inflammation, and ultimately replacement of muscle by fibrotic and adipose tissue. The disease causes progressive and profound muscle weakness and degeneration. Muscle weakness typically begins between ages 3 to 5 years, with loss of ambulation usually occurring by 12 years of age. Death typically occurs before age 30 years, generally from respiratory and/or cardiac muscle involvement. The disease prevalence is estimated to be 1.4 per 10,000 males ages 5 to 24 years. Approximately 8% of those patients have a deletion mutation that is amenable to correction by exon 53 skipping.

Viltolarsen is an antisense oligonucleotide (ASO) with a phosphorodiamidate morpholino oligomer (PMO) backbone that was designed to bind to exon 53 of dystrophin premessenger ribonucleic acid (mRNA) in the nucleus of a cell to alter the splicing process that creates a mature mRNA. Viltolarsen targets a region in exon 53 to restore the mRNA reading frame and induce the production of de novo truncated dystrophin protein. Viltolarsen has been developed as an intravenous (IV) infusion at a dose of 80 mg/kg once weekly.

There are three FDA-approved treatments for DMD. Deflazacort (Emflaza) is a glucocorticoid approved for treatment of DMD in patients 2 years of age and older. Deflazacort is purported to have anti-inflammatory and immunosuppressive properties and has been shown to improve muscle strength in DMD patients. Eteplirsen (Exondys 51) received a biomarker-based accelerated approval in September 2016, for the treatment of a subset of DMD patients with mutations in the dystrophin gene that are amenable to exon 51 skipping. Golodirsen (Vyondys 53) also received a biomarker-based accelerated approval in December 2019 for the treatment of a subset of DMD patients with mutations in the dystrophin gene that are amenable to exon 53 skipping, the same population as proposed for viltolarsen. Both eteplirsen and golodirsen were based on the demonstration of increases in truncated dystrophin protein; any clinical benefit of these changes has not been established and must be confirmed by a clinical study for each product.

This submission contains biomarker and safety data from Study NS-065/NCNP-01-201 that assessed dosages of either 40 or 80 mg/kg/week in 16 DMD patients 4 to <10 years of age on stable doses of corticosteroids for ≥ 3 months. Additional safety data are provided from an ongoing long-term extension study (202) in those same patients.

Truncated dystrophin quantification by western blot in Study NS-065/NCNP-01-201 showed the following:

- For viltolarsen 40 mg/kg/wk, there was an increase in relative dystrophin levels from 0.3% of normal at baseline to 5.7% (mean change 5.4%, $p,0.001$; median 4.6%) after 20 to 24 weeks of treatment.

- For viltolarsen 80 mg/kg/wk, there was an increase in relative dystrophin levels from 0.6% of normal at baseline to 5.9% (mean change 5.3%, $p=0.01$; median 3.8%) after 20 to 24 weeks of treatment.

Increases in dystrophin on western blot were supported by nominally statistically significant increases from baseline in dystrophin on mass spectroscopy after 20 to 24 weeks of treatment with both 40 mg/kg and 80 mg/kg dosages of viltolarsen. The mean change from baseline was greater for the 80 mg/kg/wk dosage (3.7%; $p<0.01$) than for the 40 mg/kg/wk dosage (1.5%; $p=0.03$); however, the difference between the two dosages was not nominally statistically significant.

The dystrophin biomarker data are proposed by the applicant as a surrogate endpoint that is reasonably likely to predict a clinical benefit, in support of the approval of viltolarsen under the accelerated approval pathway. The accelerated approval pathway is appropriate for viltolarsen because DMD is clearly a serious and life-threatening disease, and viltolarsen has the potential to address an unmet medical need and provide an advantage over available therapy (deflazacort) in some patients. Deflazacort has a modest response rate, and there is evidence that a substantial proportion of DMD patients are not using steroids, in part because of their safety profile. Viltolarsen has a novel mechanism of action that has a well-understood relationship to the disease pathophysiology, and has been shown to increase dystrophin levels in DMD patients with a genetic mutation amenable to exon 53 skipping, thereby potentially improving muscle function. Although there remains uncertainty regarding the level of dystrophin that would be likely to confer clinical benefit, the increase in dystrophin levels demonstrated for viltolarsen is similar in size or may be slightly greater to that established for eteplirsen and golodirsen, drugs that received accelerated approval based on a previous conclusion by CDER that the increase in dystrophin level was reasonably likely to predict clinical benefit. Based on these precedents, and barring any evidence to suggest otherwise, the statistically significant increase in de novo (truncated) dystrophin protein demonstrated in Study NS-065/NCNP-01-201 supports accelerated approval of viltolarsen for the treatment of DMD in patients with a genetic mutation amenable to exon 53 skipping. A confirmatory study intended to confirm clinical benefit is ongoing.

There was no difference in the increase in dystrophin as measured by western blot between the 40 mg/kg/week and 80 mg/kg/week dosages; however, there were slightly greater increases in dystrophin as measured by mass spectrometry at the 80 mg/kg/week dosage compared to the 40 mg/kg/dosage, although the difference was not nominally statistically significant. As there was no notable difference in safety between the 40 mg/kg/week and 80 mg/kg/week dosages, and considering the marginally greater increases in dystrophin seen on mass spectrometry with the 80 mg/kg/week dosage, that dosage appears the most appropriate to recommend for use in patients.

Although limited in size, the safety database is adequate to support the safety of viltolarsen for DMD, given its rarity. Overall, the most frequent adverse events observed with viltolarsen were upper respiratory tract infection, injection site reaction, cough, and pyrexia. Kidney is a target organ for ASOs, and viltolarsen is primarily distributed to the kidney. Renal toxicity was the primary toxicity observed in nonclinical studies, and nonclinical data suggest the potential for serious renal toxicity in humans. No serious renal adverse reaction, however, was reported in viltolarsen clinical studies. The seriousness of the indication along with the unmet medical need make the risk for renal toxicity acceptable, and manageable through labeling and enhanced pharmacovigilance. PMRs will be issued for assessments of QT prolongation (see Section 5) and immunogenicity.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> • DMD is a rare progressive X-linked neuromuscular disorder caused by mutations in the dystrophin gene. Lack of dystrophin results in degeneration of muscle fibers, inflammation, and ultimately replacement of muscle by fibrotic and adipose tissue. • The disease causes progressive and profound muscle weakness and degeneration. Muscle weakness typically begins between ages 3 to 5 years, with loss of ambulation usually occurring by 12 years of age. Death typically occurs before age 30 years, generally from respiratory and/or cardiac muscle involvement. The disease prevalence is estimated to be 1.4 per 10,000 males ages 5 to 24 years. Approximately 8% of those patients have a deletion mutation that is amenable to correction by exon 53 skipping. 	<p>DMD is a serious and life-threatening disease. The loss of muscle strength in DMD is progressive, leading to loss of ambulation in the teens, followed by decline in respiratory and cardiac function, resulting in death typically in the third decade.</p>
Current Treatment Options	<ul style="list-style-type: none"> • Emflaza (deflazacort) is a glucocorticoid approved for treatment of Duchenne muscular dystrophy (DMD) in patients 2 years of age and older. • Exondys 51 (eteplirsen) is approved for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping, under the accelerated approval pathway. • Vyondys 53 (golodirsen) is approved 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, under the accelerated approval pathway. 	<p>Deflazacort, the only drug with full approval for the treatment of DMD, has a modest response rate, and there is evidence that a substantial proportion of DMD patients are not using steroids, in part because of their safety profile.</p> <p>Eteplirsen and golodirsen were approved under the accelerated approval pathway, and clinical benefit has not yet been confirmed for both drugs.</p>
Benefit	<ul style="list-style-type: none"> • Truncated dystrophin quantification by western blot in Study NS-065/NCNP-01-201 showed a mean increase in relative dystrophin levels from 0.6% of normal at baseline to 5.9% after 20 to 24 weeks of treatment with viltolarsen 80 mg/kg once weekly, with a mean change from baseline of 5.3% (p=0.01). The median change from baseline in dystrophin level was 3.8%. • Increases in dystrophin on western blot were supported by nominally 	<p>The applicant has demonstrated a small, but statistically significant, increase in de novo (truncated) dystrophin protein in DMD patients with a genetic mutation amenable to exon 53 skipping. Although there remains uncertainty regarding the level of dystrophin that would be likely to</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>statistically significant increases from baseline in dystrophin on mass spectrometry after 20 to 24 weeks of treatments with both 40 mg/kg and 80 mg/gk dosages of viltolarsen. The mean change from baseline (3.7%; p<0.01) was greater for the 80 mg/kg/wk dosage than for the 40 mg/kg/wk dosage (1.5%;p=0.03); however, the difference between the two doses was not nominally statistically significant.</p> <ul style="list-style-type: none"> • Exon 53 skipping was confirmed by measurement and sequence verification of exon 53 skipped mRNA. 	<p>confer clinical benefit, the increase in dystrophin levels demonstrated for viltolarsen is similar in size or slightly greater to that established for eteplisen and golodirsen, drugs that received accelerated approval based on a previous conclusion by CDER that the increase in dystrophin level was reasonably likely to predict clinical benefit.</p>
<p>Risk and Risk Management</p>	<ul style="list-style-type: none"> •At the time of the NDA submission, there were 32 patients exposed to viltolarsen, with 16 patients with >12 months of exposure (8 patients at 40 mg/kg/wk and 8 patients at 80 mg/kg/wk). •The most common adverse reactions (incidence ≥15%) were upper respiratory tract infection, injection site reaction, cough, and pyrexia. There was no notable dose-response for adverse reactions between the 40 mg/kg and 80 mg/kd dosages. •Renal toxicity was the primary toxicity observed in nonclinical studies, and nonclinical data suggest the potential for serious renal toxicity in humans. However, no serious renal adverse reaction or concerning renal abnormalities were observed in clinical studies. •There is a potential risk of infection and other complications related to the indwelling catheters that may be used to administer viltolarsen, but this risk is not specific to viltolarsen. •Current immunogenicity data do not suggest a strong immunogenicity risk for viltolarsen; however, immunogenicity assays should be improved for increased sensitivity. •There are inadequate data to assess the potential for QT prolongation. 	<p>Overall, the most frequent adverse events observed were mild; none caused substantial or permanent harm to patients. Upper respiratory tract infection, injection site reaction, cough, and pyrexia were the most common adverse reactions. There was no apparent dose-response for adverse reactions between the 40 mg/kg and 80 mg/kd dosages, although the safety database was too limited to allow for informative comparisons.</p> <p>Nonclinical studies indicate a potential for serious renal toxicity in humans, but no serious renal adverse reaction have been observed in human. The seriousness of the indication, along with the unmet medical need, make the risk for serious renal toxicity acceptable. It will be important to inform patients and prescribers about the risk, and a warning regarding the potential for renal toxicity will be included in labeling. Enhanced pharmacovigilance for renal toxicity will also be requested.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		<p>Because of limitations due to the small number of patients exposed and duration of exposure in the clinical trials, it is likely that adverse reactions not identified to date, or of a magnitude not observed to date, will occur in the postmarketing setting.</p> <p>Risk management can be achieved through clear product labeling and routine postmarketing surveillance, plus enhanced pharmacovigilance for renal toxicity.</p> <p>The applicant will be required to evaluate the potential for QT prolongation with viltolarsen and improve the sensitivity of the immunogenicity assays of viltolarsen as postmarketing requirements.</p>

2. Background

DMD is a rare progressive X-linked neuromuscular disorder caused by mutations in the dystrophin gene. Lack of dystrophin results in degeneration of muscle fibers, inflammation, and ultimately replacement of muscle by fibrotic and adipose tissue. The disease causes progressive and profound muscle weakness and degeneration. Muscle weakness typically begins between ages 3 to 5 years, with loss of ambulation usually occurring by 12 years of age. Death typically occurs before age 30 years, generally from respiratory and/or cardiac muscle involvement. The disease prevalence is estimated to be 1.4 per 10,000 males ages 5 to 24 years.¹ Approximately 8% of these patients have a deletion mutation that is amenable to correction by exon 53 skipping.

Viltolarsen (also referred to as NS-065 in this memorandum) is an antisense oligonucleotide (ASO) with a phosphorodiamidate morpholino oligomer (PMO) backbone that was designed to bind to exon 53 of dystrophin pre-messenger ribonucleic acid (mRNA) in the nucleus of a cell to alter the splicing process that creates a mature mRNA. Viltolarsen targets a region in exon 53 to restore the mRNA reading frame and induce the production of de novo truncated dystrophin protein. Viltolarsen has been developed as an intravenous (IV) infusion at a dosage of 80 mg/kg once weekly.

This application provides dystrophin biomarker data proposed as a surrogate endpoint that is reasonably likely to predict clinical benefit in support of the accelerated approval of viltolarsen for the treatment of Duchenne muscular dystrophy (DMD) in patients with a confirmed DMD mutation amenable to exon 53 skipping. Viltolarsen (proprietary name Viltepso) is a new molecular entity (NME) and has not previously been the subject of any marketing application.

There are three FDA-approved treatments for DMD. Deflazacort (Emflaza) received full approval in February 2017 for the treatment of DMD. Deflazacort is a glucocorticoid, a member of the corticosteroid class of medications, that is purported to have anti-inflammatory and immunosuppressive properties and has been shown to improve muscle strength in DMD patients. Eteplirsen (Exondys 51) received a biomarker-based accelerated approval in September 2016 for the treatment of a subset of DMD patients with mutations in the dystrophin gene that are amenable to exon 51 skipping. Golodirsen (Vyondys 53) also received a biomarker-based accelerated approval in December 2019 for the treatment of a subset of DMD patients with mutations in the dystrophin gene that are amenable to exon 53 skipping, the same population as proposed for viltolarsen. Eteplirsen and golodirsen were both approved based on the demonstration of increases in levels of truncated dystrophin protein; any clinical benefit of these changes has not been established and must be confirmed by a clinical study for each product.

¹ Romitti et al. *Pediatrics*. 2015; 135. <https://pediatrics.aappublications.org/content/135/3/513>

This submission contains biomarker and safety data from Study NS-065/NCNP-01-201, which assessed dosages of either 40 or 80 mg/kg/week in 16 DMD patients 4 to <10 years of age on stable doses of corticosteroids. Additional safety data are provided from an ongoing long-term extension study (202) in those same patients.

A summary of the regulatory history of viltolarsen is provided in the combined clinical and statistical review.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann. Dr. Heimann's review lists the entire OPQ team that was involved with the review of this application.

The product is a sterile, preservative-free, solution of viltolarsen (250 mg/mL) in 0.9% saline. 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 OPQ team has determined that the specifications for viltolarsen drug substance include appropriate tests for oligonucleotides. 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.

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.

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

There were no outstanding issues identified in the OPQ review, and all manufacturing facilities for this product were found to be acceptable. OPQ recommends approval of this NDA. Please refer to the OPQ review for details of the product quality assessment.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application was Dr. David Carbone, with Dr. Lois Freed performing a secondary review.

Dr. Carbone concludes that the application is approvable from a pharmacology/toxicology standpoint.

Following are the key findings from the nonclinical studies:

- In vitro proof-of-concept studies conducted in DMD patient fibroblasts demonstrated viltolarsen-induced exon 53 skipping and production of dystrophin protein.
- Potential off-target effects of viltolarsen were evaluated, and the *APCCDD1* gene was the only potential target that was thought to have possible relevance to humans. Mutations at this locus are associated with hereditary hypotrichosis that can cause hypopigmented hair shafts. It was noted that one patient in clinical trials experienced an event of “hair color changes” that were considered possibly drug related.
- In both 13-week and 26-week mouse studies, the primary toxicity was observed in the kidney. There were deaths in two high-dose males. Kidney findings included basophilic material in the distal tubule and/or collecting duct, dilatation of the distal tubules and/or collecting duct, vacuolation of the epithelium of the distal tubule and/or collecting duct, and fibrosis. Clinical pathology findings consistent with nephrotoxicity included increased BUN, creatinine, and cystatin C, as well as increases in C-reactive protein. The NOAEL for viltolarsen-induced toxicity is 60 mg/kg/week IV, which, in the 26-week study, was associated with plasma exposures (AUC(0-24 hr)) of 67.47 $\mu\text{g}\cdot\text{hr}/\text{mL}$ on Day 175. (Plasma levels were <LLOQ by 4 hrs post dose.) For comparison, plasma exposure (AUC(0-24hr)) in humans (Study 201) at the recommended dose of 80 mg/kg/week IV is 387375 ng $\cdot\text{hr}/\text{mL}$ or 387 $\mu\text{g}\cdot\text{hr}/\text{mL}$; $t_{1/2} = 8$ hrs.
- In 12-week and 39-week monkey studies, the primary drug-related toxicity was also observed in kidney. Histopathology findings in kidney (accompanied by increases in BUN only at 600 mg/kg) were similar to those in mouse but of lesser severity; renal fibrosis was not detected, and no deaths occurred. The NOAEL for viltolarsen-induced toxicity is 60 mg/kg, which, in the 39-week study, was associated with plasma exposures ((AUC(0-24hr)) of 261.1 $\mu\text{g}\cdot\text{hr}/\text{mL}$ on Day 259.
- No adverse effects were observed in fertility studies.
- In the pivotal juvenile toxicology study, viltolarsen (0, 15, 60, 240, or 1200 mg/kg) was administered to juvenile male mice by subcutaneous injection on postnatal day (PND) 7 and by intravenous injection weekly from PND 14 to PND 70. The highest dose resulted in deaths because of renal toxicity. In surviving animals at 240 and 1200 mg/kg, there was a dose-dependent increase in the incidence and severity of renal tubular effects (including degeneration), which were not accompanied by clinical pathology correlates.

Delayed sexual maturation was observed at the high dose. The NOAEL of 60 mg/kg, based on kidney toxicity, was associated with plasma exposure (AUC(0-24hr)) of 542.4 µg*hr/mL.

- Viltolarsen was negative in a standard battery of in vitro (Ames, chromosomal aberration in CHL cells) and in vivo (mouse micronucleus) genotoxicity assays.

Dr. Freed concludes that the nonclinical studies of viltolarsen are adequate to support approval for the proposed indication, although the data suggest the potential for serious renal toxicity in humans. Dr. Freed notes that, as previously agreed to by the Division, carcinogenicity studies in two species may be conducted post approval (as PMRs), based on the seriousness of the indication.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Drs. Bilal AbuAsal (the primary reviewer), Hobart Rogers, Atul Bhattaram, Christian Grimstein, and Sreedharan Sabarinath (the clinical pharmacology team leader). The final signatory for the OCP review was Dr. Mehul Mehta.

Table 1 below summarizes the key findings of the OCP review with respect to the pharmacologic and clinical pharmacokinetic (PK) properties of viltolarsen.

Table 1: Summary of OCP Review Findings

Absorption	Viltolarsen is administered as an IV infusion and bioavailability is assumed to be 100%. Median Tmax was approximately 1 hour (end of infusion).
Distribution	The mean viltolarsen steady-state volume of distribution was 300 mL/kg (%CV=15) at a dose of 80 mg/kg. Viltolarsen plasma protein binding ranged from 39% to 43% and is not concentration dependent.
Metabolism and Elimination	Data from in vitro metabolism indicate that viltolarsen is metabolically stable and is mostly excreted unchanged in urine. No metabolites were detected in plasma or urine. Viltolarsen elimination half-life was 2.5 (CV% 8) hours, and plasma clearance was 217 mL/hr/kg (CV%=22) at the 80 mg/kg dosage.
Renal Impairment	Viltolarsen was not tested in patients with renal impairment. Urinary excretion is the predominant route of elimination of viltolarsen. Since viltolarsen is predominantly renally cleared, impairment in renal function is expected to increase its systemic exposure. Therefore, patients with known renal function impairment should be closely monitored during treatment with viltolarsen. Creatinine clearance is not considered as a reliable metric to measure renal function in DMD

	population because of the disease characteristics predominantly affecting muscles. Therefore, no dose adjustment recommendations based on creatinine clearance can be provided for viltolarsen.
Hepatic Impairment	Viltolarsen was not tested in patients with hepatic impairment. Urinary excretion is the predominant route of elimination of viltolarsen. In addition, hepatic metabolism of viltolarsen was not evident during in vitro testing. No dose adjustments are required for patients with hepatic impairment.
Drug Interactions	Viltolarsen has low potential for drug-drug interactions with CYP enzymes and drug transporters based on in vitro studies.
QT Prolongation	There is insufficient information to assess the effects of viltolarsen on QT prolongation.

Dosing Regimen:

The recommended dosage of viltolarsen is 80 mg/kg administered by intravenous (IV) infusion once weekly over 60 minutes. This regimen was tested in trial NS-065/NCNP-01-201.

Genetic mutations:

Of the eight deletion mutations (42-52, 45-52, 47-52, 48-52, 49-52, 50-52, 52, 54-58) amenable to exon 53 skipping, only five (45-52, 47-52, 48-52, 49-52, 50-52) were enrolled in the clinical studies with viltolarsen. It is reasonable to conclude that the restoration of the reading frame by viltolarsen should be beneficial for all DMD mutations amenable to exon 53 skipping. Hence, the OCP team recommends that viltolarsen should be indicated for patients with any of the mutations amenable to exon 53 skipping.

QT prolongation:

The applicant submitted a request for a waiver for a QT study based on ECG data from NCNP-01-P1/2. The QT-IRT determined that there is not adequate information to assess the effects of viltolarsen on QT prolongation due to the small sample size of the study, and notes that ECGs were not collected at Tmax. The ongoing confirmatory trial (Study NCNP-01-301) will collect additional ECG assessments. The QT-IRT team recommends that a new request for QT waiver request be submitted once these data are available. A postmarketing requirement (PMR) will be issued for the collection of additional ECG data in the confirmatory study to assess the effects of viltolarsen on the QT interval.

OCP recommends approval of this application.

6. Clinical Microbiology

Not applicable.

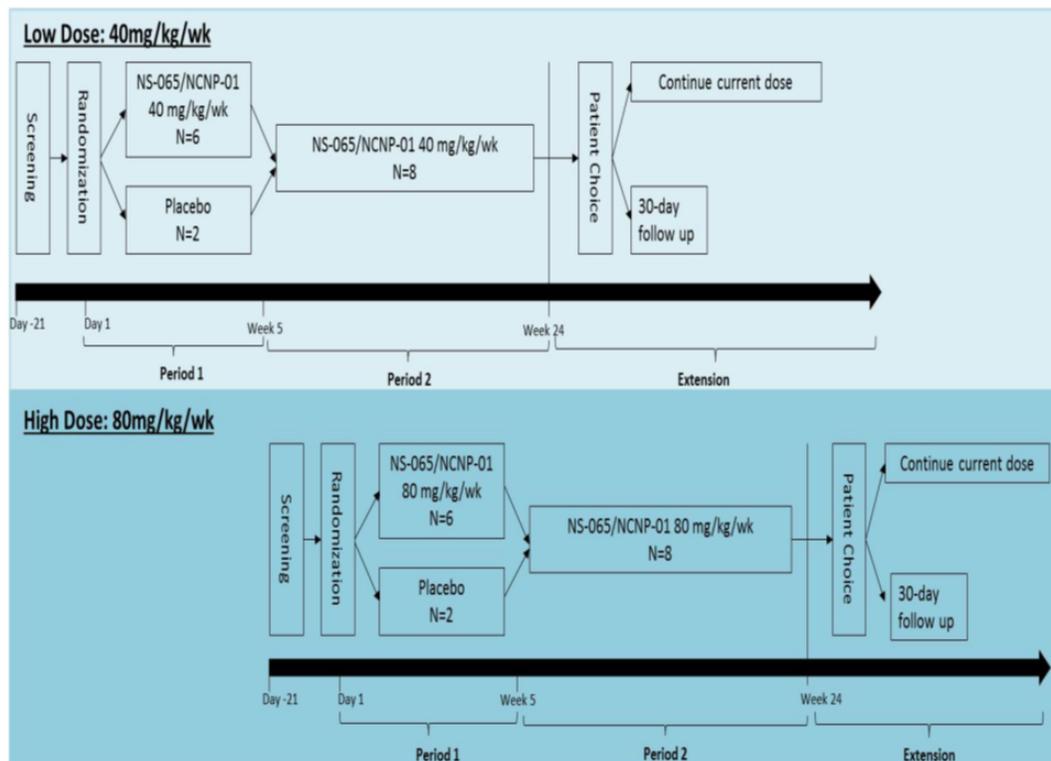
7. Clinical/Statistical - Efficacy

Dr. Veneeta Tandon was the clinical reviewer for this application. Dr. Xiang Ling was the biometrics reviewer, and Dr. Kun Jin was the biometrics team leader. Dr. Baikuntha Aryal and Dr. Ashutosh Rao (lead) from the Office of Biotechnology Products (OBP) reviewed the dystrophin assays.

Study NS-065/NCNP-01-201

Study NS-065/NCNP-01-201 (also referred to as Study 201 in this review) was a multicenter, 2-period, dose-finding study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of viltolarsen in patients with genotypically confirmed DMD with a deletion amenable to exon 53 skipping. The study was conducted in the United States and Canada. The initial 4 weeks were a randomized, double-blind, placebo-controlled period to study the safety of IV viltolarsen in 8 patients (3:1 randomization; 6 on viltolarsen and 2 on placebo) in two sequentially-enrolled dose cohorts of 40 mg/kg/week (n=8) or 80 mg/kg/week (n=8). After 4 weeks of treatment with no safety concerns for the entire 40 mg/kg/wk cohort, the 80 mg/kg/wk cohort was initiated. After Week 24, all patients continued in an open-label extension study (Study NS-065-202) at their previously randomized dose of either 40 mg/kg/wk or 80 mg/kg/wk. The study design schematic is shown in Figure 1.

Figure 1: Study 201 Schematic



The study enrolled male patients aged 4 to <10 years, inclusive, with an established clinical diagnosis of DMD and a genetic mutation amenable to exon 53 skipping (e.g., deletions of exons, such as 42 to 52, 45 to 52, 47 to 52, 48 to 52, 49 to 52, 50 to 52, 52, or 54 to 58), taking a stable dose of corticosteroids for at least 3 months, no evidence of symptomatic cardiomyopathy, the ability to walk independently without assistive devices, and the ability to complete all performance-based assessments.

The primary endpoint for the study was the change from Baseline to Week 25 (corresponding to 24 weeks of treatment in patients randomized to viltolarsen or 20 weeks of treatment in patients randomized to placebo) in dystrophin protein levels (in biceps muscle biopsy samples) determined by western blot analysis.

Secondary endpoints for the study include the change from Baseline to Week 25 for the following:

- Induction of dystrophin protein in muscle measured by mass spectrometry (MS)
- Induction of dystrophin protein in muscle measured by immunofluorescence (IF)-labeled antibody detection on tissue sections
- Induction of dystrophin mRNA in muscle measured by reverse-transcriptase-polymerase chain reaction (RT-PCR)

Several additional assessments were collected as secondary endpoints, including the muscle strength, mobility, and functional exercise capacity, as measured by Time to Stand From Supine (TTSTAND), Time to Run/Walk 10 meters (TTRW), Time to Climb 4 Stairs (TTCLIMB), North Star Ambulatory Assessment (NSAA), 6-Minute Walk Test (6MWT), and Quantitative Muscle Testing (QMT) compared to a matched natural history control group.

Data Quality and Integrity

OBP reviewed the assays used to analyze the muscle biopsies and determined that the western blot method was appropriately validated and conducted to reliably measure relative dystrophin content in the patient samples. OBP notes that the western blot method was validated using myosin heavy chain and alpha actinin as housekeeping proteins for normalization; however, there is some residual variability in dystrophin results in this method using either normalization control protein. The degree of variability was less when dystrophin intensities were normalized with myosin heavy chain compared to alpha-actinin; therefore, the dystrophin protein results obtained by myosin heavy chain normalization may be relatively more reliable than alpha-actinin normalization.

OBP found that the MS method appears to be reliable technique to accurately measure dystrophin content in the gel-extract of clinical samples and can be used to support the Western blot data.

The validated IF method is only recommended to be used qualitatively for the co-localization. It may not be appropriate for use as quantitative measures to make any conclusion for dose or efficacy.

OPB states that due to concerns for the potential of overestimation of drug-induced effects, RT-PCR data should only be used to confirm the mechanism of action and to qualitatively support dystrophin production measured by western blot as a treatment effect.

Statistical Analysis

For each of the western blot tests, immunoblot dystrophin was normalized to to each alpha-actin and to myosin. Three responses from 3 triplicate gels run were averaged to attain a single result for summarizing and analyzing. If any responses were missing, then the available non-missing responses were averaged.

Efficacy analyses were based on the modified intent-to-treat (mITT) population, consisting of all randomized patients who received at least 1 dose of investigational product and had a baseline assessment and at least 1 post baseline efficacy assessment. Patients were grouped by the two dose groups for efficacy analyses.

Western blot within-patient change in percentage of normal dystrophin production was tested using a paired t-test within each dose level. A two-sample t-test was used to compare change across the two dose levels. The two doses were also combined and

tested using a paired difference t-test. Normality of change in percentage of normal dystrophin at post-baseline was to be assessed and if needed, a nonparametric test or a transformation to achieve normality would be performed.

There was no planned formal multiple-testing procedure for secondary endpoints.

Patient Demographics

The viltolarsen-treated population (n=16) had the following characteristics: mean age of 7 years (range 4 to 9), 94% White. The study enrolled patients with the following exon deletions: 45-52 (7), 47-52 (1), 48-52 (3), 49-52 (3), 50-52 (2).

Patient Disposition

A total of 16 ambulatory patients participated in the study. There were no discontinuations in the study.

Results

Primary endpoint

To control for differences in capillary loading and or muscle content in western blot analyses, a housekeeping protein (e.g., myosin or α -actinin) that has presumed constant expression in muscle cells regardless of the disease state was used for normalization. Results for both methodologies are presented; however, as discussed in the prior section on assay quality, Drs. Baikuntha and Rao conclude that analytical methodology for normalization with myosin heavy chain is relatively more reliable due to lesser variation in quantitation.

A statistically significant increase in dystrophin from baseline was observed after 20 to 24 weeks of treatment with once-weekly IV viltolarsen at 40 mg/kg and 80 mg/kg, based on western blot (Table 2). Dr. Ling notes that there were four primary analyses, as western blot analysis included normalization to both myosin heavy chain and α -actinin and there were 2 doses. Although a formal multiple-testing procedure was not planned, the analysis results remain nominally statistically significant for any reasonable adjustment for multiplicity control. The results were also supported by a sensitivity analysis. There was no statistically significant difference between the 40 mg/kg and 80 mg/kg dosages (p=0.94).

Table 2: Dystrophin Levels Determined by Western Blot in Study 201

Visit/Statistics	Treatments							
	Normalized to Myosin (% of Normal)				Normalized to α -Actinin (% of Normal)			
	40 mg/kg/wk (N=8)		80 mg/kg/wk (N=8)		40 mg/kg/wk (N=8)		80 mg/kg/wk (N=8)	
	Obs	CFB	Obs	CFB	Obs	CFB	Obs	CFB
Baseline								
Mean (SD)	0.3 (0.1)	--	0.6 (0.8)	--	0.2 (0.2)	--	0.4 (0.7)	--
Median	0.3	--	0.4	--	0.1	--	0.2	--
Min, Max	0.1, 0.4	--	0.1, 2.6	--	0.0, 0.6	--	0.0, 2.1	--
Week 25								
Mean (SD)	5.7 (2.4)	5.4 (2.4)	5.9 (4.5)	5.3 (4.5)	5.4 (2.8)	5.2 (2.8)	3.7 (2.4)	3.3 (2.5)
Median	4.9	4.6	4.0	3.8	4.5	4.3	3.3	2.7
Min, Max	3.2, 10.3	2.8, 10.0	1.1, 14.4	0.7, 13.9	2.0, 10.4	1.7, 10.2	0.7, 8.0	0.3, 8.0
95% CI	--	(3.4, 7.4)	--	(1.6, 9.0)	--	(2.8, 7.6)	--	(1.2, 5.3)
P-value (Paired T-Test)*	--	0.0004	--	0.0123	--	0.0012	--	0.0074
95% CI (80-40 mg)*	--	--	--	(-3.9, 3.7)	--	--	--	(-4.8, 0.9)
P-value (2-Sample Test)*	--	--	--	0.94	--	--	--	0.17

CFB=change CI=confidence interval; Max=maximum; Min=minimum; mITT=modified intent-to-treat; Obs=observed; SD=standard deviation

For each visit where a biopsy was performed, up to 3 planned responses for each test were averaged to attain a single result for summarizing and analyzing.

* Within-patient change from baseline was tested using a paired t-test within each dose level to test whether change from baseline was different than 0. A two-sample t-test was used to test whether the change from baseline with the 80 mg/kg/wk dosage was different from the change from baseline with the 40 mg/kg/wk dosage.

Source: Statistics Reviewer Analysis (copied from Clinical/Statistical review)

Secondary endpoints

Mass spectrometry (MS)

Statistically significant increases in dystrophin from baseline were observed after 20 to 24 weeks of treatments with both 40 mg/kg and 80 mg/gk dosages of viltolarsen on MS, which supports the findings observed on western blot (Table 3). The mean change from baseline (3.7%) was numerically greater for the 80 mg/kg/wk dosage than for the 40 mg/kg/wk dosage (1.5%); however, the difference did not reach nominal statistical significance (p=0.16). The values for the post-treatment dystrophin

levels with MS are also lower than those reported with the western blot method, but the reason for this is unclear.

Table 3: Dystrophin Production by MS (mITT Population)

Dystrophin (%) Visit/ Statistic	40 mg/kg/wk (N=8)		80 mg/kg/wk (N=8)	
	Obs	CFB	Obs	CFB
Baseline				
Mean (SD)	0.5 (0.15)	--	0.6 (0.19)	--
Median	0.6	--	0.6	--
Min, Max	0.2, 0.8	--	0.2, 0.9	--
Week 25				
Mean (SD)	2.1 (1.1)	1.5 (1.1)	4.2 (3.7)	3.7 (3.8)
Median	2.1	1.7	2.6	1.9
Min, Max	0.0, 3.3	-0.7, 2.7	1.3, 10.8	0.8, 10.5
95% CI	--	(0.6, 2.4)	--	(0.5, 6.8)
P-value* (Paired T-Test)	--	0.0061	--	0.0300
95% CI (80 mg – 40 mg)	--	--	--	(-1.08, 5.37)
P-value (2-Sample T-Test)	--	--	--	0.16

CFB=change from baseline; CI=confidence interval; Max=maximum; Min=minimum; Obs=observed; SD=standard deviation

*Note: all p-values in the table are nominal

Source: verified by the reviewer (Copied from Clinical/Statistical review)

Immunofluorescence

There were nominally statistically significant mean increases from baseline in dystrophin-positive myofibers measured by IF in both the 40 and 80 mg/kg/wk groups at Week 25.

RT-PCR

Baseline muscle biopsies did not show any detectable skipped RT-PCR product. At Week 25, all patient biopsies showed both skipped and unskipped RT-PCR bands. The RT-PCR products obtained were consistent with each patient's deletion mutation and showed exon 53-specific skipping by DNA sequence analysis, supporting target engagement. The 80 mg/kg/day group showed greater increases in exon skipping measured by RT-PCR compared with the 40 mg/kg/wk group, although it is noted in the OBP review that RT-PCR should be used qualitatively rather than for quantitative assessments.

Clinical outcomes

The application included clinical data for change from baseline on functional outcomes (TTSTAND, TTCLIMB, TTRW, 6MWD, and NSAA) and strength assessments (QMT) at 25 weeks. The applicant provided a comparison of these changes to matched patients from the CINRG network natural history database. The

applicant's analysis did not show any clinically meaningful difference in clinical function at the end of 24 weeks of treatment with viltolarsen 40 and 80 mg/kg/wk, compared to natural history. Additionally, as discussed in Dr. Tandon's review, given the variability in the natural history of the DMD, comparisons to a natural history cohort, even when matched controls are utilized, does not appear reliable.

Study NS065/NCNP01-P1/2

Study NS065/NCNP01-P1/2 was a multicenter, parallel-group, open-label 24-week study that assessed two dosages of viltolarsen, 40 or 80 mg/kg once weekly, in 16 DMD patients ages 5 to < 18 years of age. Muscle biopsies were taken from the left or right tibialis anterior muscle or biceps brachii muscle at baseline and Week 12 from 8 subjects, and at Week 24 from 8 subjects, in both dose groups. The primary endpoint of the study was the change in dystrophin from baseline as assessed by western blot, immunofluorescence and exon skipping efficiency by RT-PCR. The study was conducted in Japan and was intended to be a supportive study.

OBP reviewed the method validation for each of the dystrophin methodologies and found them to be inadequate for dystrophin quantification. Specifically, they noted the following:

(b) (4)

OBP concludes that: "overall, the quality of the dystrophin data from Japanese Phase 1/2 study are considered not robust and inconclusive to make any claims (b) (4)

Therefore, this study will not be discussed further in support of efficacy.

Efficacy Conclusions

Study NS-065/NCNP-01-201 has rigorously established that viltolarsen is able to produce statistically significant increases in truncated dystrophin at dosages of 40 mg/kg and 80 mg/kg administered once weekly.

As measured by western blot:

- For viltolarsen 40 mg/kg/wk, there was an increase in relative dystrophin levels from 0.3% of normal at baseline to 5.7% (mean change 5.4%, $p < 0.001$; median 4.6%) after 20 to 24 weeks of treatment.
- For viltolarsen 80 mg/kg/wk, there was an increase in relative dystrophin levels from 0.6% of normal at baseline to 5.9% (mean change 5.3%, $p = 0.01$; median 3.8%) after 20 to 24 weeks of treatment.

The increases observed on western blot were supported by nominally statistically significant increases in dystrophin from baseline with both dosages of viltolarsen on mass spectrometry. The mean change from baseline observed with mass spectrometry was greater for the 80 mg/kg/wk dosage (3.7%; $p < 0.01$) than for the 40 mg/kg/wk dosage (1.5%; $p = 0.03$); however, the difference between the two dosages did not reach statistical significance.

Exon 53 skipping was confirmed by measurement and sequence verification of exon 53 skipped mRNA. The immunofluorescence data qualitatively support the increases in dystrophin observed with other methods. The 80 mg/kg/day dosage led to greater increases in exon skipping compared with the 40 mg/kg/wk dosage; however, it is noted that RT-PCR methodology is acceptable for qualitative support but is not reliable for quantitative assessments. Overall, the positive and highly statistically persuasive results, with support across both dose levels and secondary endpoints, make reliance on a single efficacy study appropriate to support approval.

The accelerated approval provisions of FDASIA in section 506(c) of the FD&C Act provide that FDA may grant accelerated approval to: . . . a product for a serious or life-threatening disease or condition . . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. We will review the efficacy results in the context of these criteria for accelerated approval.

DMD clearly meets the criteria of a serious and life-threatening condition.

There are currently three drugs approved for the treatment of DMD: eteplirsen, golodirsen, and deflazacort. The indication for eteplirsen is for patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping, i.e., a population distinct from that proposed for viltolarsen. The indication for golodirsen is for patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. This population is the same as that proposed for viltolarsen. However, both eteplirsen and golodirsen were approved under the accelerated approval pathway based on a surrogate endpoint and clinical benefit has not yet been verified for either product; therefore, as described in the Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics,² they are not considered “available therapies” for the purposes of determining unmet need. Deflazacort is indicated for a broad DMD population, irrespective of genetic mutation. However, deflazacort has a modest response rate, and there is evidence that a substantial proportion of DMD patients are not using steroids, in part because of their safety profile.

² <https://www.fda.gov/media/86377/download>

As described in the Guidance for Industry: Expedited Programs for Serious Conditions Drugs and Biologics,³ a drug may address an unmet need where there is available therapy, if “a drug with a novel mechanism of action (but comparable safety and effectiveness) could have the potential to provide an advantage over available therapy in some patients. In such a case, the novel mechanism of action should have a well-understood relationship to the disease pathophysiology. In addition, there should be a reasonable basis for concluding that a significant number of patients may respond differently to the new drug compared with available therapy.” The role of dystrophin is well-characterized in the pathophysiology of DMD. Viltolarsen has a novel mechanism of action of skipping exon 53 in the dystrophin gene compared to deflazacort, leading to increased production of truncated dystrophin, with the potential to improve muscle function. While a clinical benefit remains to be confirmed, the safety of viltolarsen does not appear worse than that of steroids.

Additionally, the expedited programs guidance describes that benefit compared to existing therapy can be demonstrated when a drug is used “in combination with available therapy (i.e., as demonstrated in an add-on study)”. In the clinical study, all patients were taking background therapy with steroids, including deflazacort. Therefore, viltolarsen offers the potential to provide a benefit additional to that of steroids.

The applicant has demonstrated a statistically persuasive, albeit small, increase in de novo (truncated) dystrophin protein in DMD patients with a genetic mutation amenable to exon 53 skipping with weekly intravenous administration of viltolarsen 80 mg/kg, in a study with a scientifically-sound design, and using rigorous analytical methods. Although there remains uncertainty regarding the level of dystrophin that would be likely to confer clinical benefit, the increase in dystrophin levels demonstrated for viltolarsen is similar in size or may be larger to that established for eteplirsen and golodirsen, drugs that received accelerated approval based on a previous conclusion by CDER that the increase in dystrophin level was reasonably likely to predict clinical benefit. Based on this precedent, and barring any evidence to suggest otherwise, the statistically significant increase in de novo (truncated) dystrophin protein demonstrated in Study NS-065/NCNP-01-201 supports accelerated approval of viltolarsen for the treatment of DMD in patients with a genetic mutation amenable to exon 53 skipping.

The applicant is seeking approval of the 80 mg/kg/week dosage of viltolarsen. Although there were no clear differences in changes from baseline in levels of truncated dystrophin production between the 40 mg/kg/week and 80 mg/kg/week dosages of viltolarsen based on the western blot analyses, dystrophin quantification based on mass spectrometry showed a numerically greater increase in dystrophin with the 80 mg/kg/week dosage: the increase from baseline in dystrophin levels was 1.5% \pm 1.1% (mean \pm SD) and 1.7% (median) for the 40 mg/kg/week dosage, vs. 3.7%

³ <https://www.fda.gov/media/86377/download>

±3.8% (mean±SD) and 1.9% (median) for the 80 mg/kg/week dosage. The IF and RT-PCR data may also suggest greater effects for the 80 mg/kg/week dosage; however, those methodologies are not reliable for quantitative assessments. There is no observed difference in the safety profile between the two dosages, or greater safety concern with higher dosage; however, the safety database is limited. . Therefore, we agree with the applicant's proposal to have 80 mg/kg/week be the recommended dosage. It must also be noted that the applicant is currently only investigating the 80 mg/kg/week dosage in an ongoing confirmatory clinical study, so that there would not be a way to clinically confirm the benefit of the 40 mg/kg/week dosage using the results from that study.

The confirmatory randomized, double-blind, placebo-controlled study (Study NS-065/NCNP-01-301) intended to confirm clinical benefit of the 80 mg/kg once weekly dosage of viltolarsen is ongoing.

8. Safety

Dr. Tandon conducted the safety review of this application.

Studies 201, 202, and P1/2 are the primary sources of safety data and were described in Section 7. Additionally, safety data were submitted from a Phase 1 study (DMT101) in 10 patients that evaluated dosages of 1.25-20 mg/kg/wk.

Dr. Tandon's review indicates that 32 DMD patients were exposed to viltolarsen at the time of the NDA submission, with 16 patients exposed for more than 12 months (8 at 40 mg/kg/wk, and 8 at 80 mg/kg/wk). In the 90-day safety update, the total number of patients with 24 or more months of exposure was 8. The safety database is adequate in the context of a rare disease such as DMD.

Dr. Tandon reviewed the coding of the adverse event terms in the submission and pooled similar terms for the safety analyses. Please refer to Dr. Tandon's review for a description of her pooling methods.

The following are the principal conclusions of Dr. Tandon's safety review of the application:

Deaths. No deaths occurred in the viltolarsen clinical development program.

Discontinuations. No patient in the viltolarsen clinical development program discontinued study treatment due to a treatment-emergent adverse event (TEAE).

Serious Adverse Events. Two patients experienced a serious adverse event in the viltolarsen clinical development program: one upper respiratory tract infection, and one limb fracture. Neither event appears related to treatment.

All Adverse Events (serious plus non-serious). For the analysis of incidence of TEAEs, Dr. Tandon initially analyzed the 4-week controlled portion of Study 201.

However, given the small sample size, short duration of the controlled period, and low incidence of AEs, the analysis was not informative (please refer to Table 24 in the Clinical/Statistical review).

Dr. Tandon then performed a pooled analysis of Studies 201 and P1/2, which were both 24 weeks long and included both dosages (40 mg/kg/wk and the 80 mg/kg/wk). The most frequently occurring adverse events (>10%) in this pooled analysis are presented in Table 4 below.

Table 4: TEAEs in ≥10% of the patients during 20-24 weeks of treatment with either 40 or 80 mg/kg/week viltolarsen (Pooled Studies 201 and P1/2)

Treatment Emergent Adverse Event n (%)	40mg/kg/wk (n=16)	80 mg/kg/wk (n=16)
Upper respiratory tract infection	4 (25)	10 (62.5)
Injection site reaction	2 (12.5)	4 (25)
Contusion	3 (18.75)	2 (12.5)
Cough	2 (12.5)	3 (18.75)
Pyrexia	0 (0)	3 (18.75)
Nasal congestion	3 (18.75)	0 (0)
Arthralgia	1 (6.25)	2 (12.5)
Dermatitis	2 (12.5)	1 (6.25)
Diarrhea	1 (6.25)	2 (12.5)
Influenza	2 (12.5)	1 (6.25)
Pain in extremity	2 (12.5)	1 (6.25)
Rash	2 (12.5)	1 (6.25)
Vomiting	1 (6.25)	2 (12.5)
Abdominal pain	0 (0)	2 (12.5)
Ejection fraction decreased	0 (0)	2 (12.5)
Urticaria	0 (0)	2 (12.5)

Source: Analysis by clinical reviewer, Dr. Tandon.

There was not a clear dose-response for adverse events between the 40 mg/kg and 80 mg/kg dosages, although the database is too small to draw any firm conclusions.

Dr. Tandon also performed an analysis of the data from long-term extension Study 202. TEAEs that occurred during the long-term extension were similar to that observed in the 24 weeks of treatment period of Studies 201 and P1/2.

Laboratory and clinical assessments and vital signs. Dr. Tandon evaluated the clinical laboratory assessments for mean change and for outliers by treatment and visit. Analyses of markers of renal injury are discussed below under adverse events of interest. No other findings regarding laboratory values, vital signs, or electrocardiograms (ECGs) were identified as being of clinical concern.

See Section 5 for a discussion of the QT assessment.

Adverse Events of Interest

Infusion related reactions/Hypersensitivity Reactions. Dr. Tandon reviewed the safety dataset for terms related to infusion reactions or hypersensitivity reactions and did not identify any concern.

Injection site Reactions/Infections. There is a potential risk of infection and other complications related to the indwelling catheters that may be used to administer viltolarsen. Dr. Tandon reviewed the safety dataset for terms that were related to injection site reaction, catheter site reactions, or infections related to indwelling catheters. There were no infections related to injections or indwelling catheters. In general, reactions were mild and local reactions were related to pain, swelling, or bruising. Injection-site reaction will be included in the adverse events table in the prescribing information.

Renal adverse events. Kidney is a target organ for ASOs, and viltolarsen is primarily distributed to the kidney and excreted intact in urine following parenteral administration. As renal toxicity was identified as a potential risk in nonclinical studies, FDA nephrologists from the Division of Cardiology and Nephrology (DCN) were consulted to review the renal data and provide advice for labeling.

There was no clear signal for renal toxicity in the clinical studies based on the laboratory data on the adverse events; however, the safety database is very limited in size and treatment duration. Given these limitations, the DCN consultants felt that it would be reasonable to include a Warning for renal toxicity with recommendation for monitoring, and describe the relevant nonclinical findings in Section 8.4.

Immunogenicity

The immunogenicity assays were reviewed by Fred Mills, PhD (primary reviewer), and Gerald Feldman, PhD (secondary reviewer), from the Office of Biotechnology Products (OBP).

OBP found the anti-drug-antibody (ADA) assay to be appropriately validated for precision, drug tolerance, and stability for critical reagents, based on FDA's 2009 immunogenicity assay guidance. The current validation supports the interpretation of clinical the immunogenicity results, for which no patients were found to be ADA-positive in Study 201. However, OBP notes that certain aspects of the assay validation are either retrospectively evaluated or not provided, and assay sensitivity can be improved to be aligned with the 2019 FDA guidance for immunogenicity assays. Therefore, OBP recommends a postmarketing study to provide appropriate validation of, and improved sensitivity for, the ADA assay.

The 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). However, the assay was capable of detecting 1 out of 16 patients (6.25%) from the 80 mg/kg dosage group in Study 201. Due to sensitivity of the anti-dystrophin antibody assay, the possibility of additional positive patients with lower levels of antibody cannot be ruled out. Therefore, OBP recommends that the applicant improve the sensitivity of the assay. PMRs will be issued in order to improve the sensitivity of the immunogenicity assays.

Safety conclusions

The safety experience with viltolarsen supports an acceptable risk/benefit profile. Overall, the most frequent adverse events observed with viltolarsen were upper respiratory tract infection, injection site reaction, cough, and pyrexia. There was no clear dose-response for adverse events between the 40 mg/kg and 80 mg/kg dosages, although the database is small, making it difficult to draw any firm conclusions in this regard. Although no serious renal adverse events were reported in viltolarsen clinical studies, renal toxicity was the primary toxicity observed in nonclinical studies, and nonclinical data suggest the potential for serious renal toxicity in humans.. The seriousness of the indication, along with the unmet medical need, make the risk for renal toxicity acceptable, and manageable through labeling (as a warning) and enhanced pharmacovigilance. Additionally, although not observed in the safety database for this submission, it is noted that there is also a possible risk of infection and other complications related to the indwelling catheters that may be used to administer viltolarsen. This risk, however, is not specific to viltolarsen.

PMRs will be issued for assessments of QT prolongation (see Section 5) and improvement of immunogenicity assays for increased sensitivity.

9. Advisory Committee Meeting

This application was not referred for review to an advisory committee because the safety profile of viltolarsen is acceptable for the intended population, the clinical trial designs were acceptable, and the findings on the surrogate marker were clear.

10. Pediatrics

This application contains pediatric data described in Sections 7 and 8. Pediatric Research Equity Act (PREA) requirements were not triggered for this orphan indication.

11. Other Relevant Regulatory Issues

No Good Clinical Practice (GCP) issues were identified in Dr. Tandon's review.

Dr. Tandon concludes that the applicant has adequately disclosed financial interests and arrangements with clinical investigators.

Inspections were performed by the Office of Scientific Investigations (OSI) for clinical sites and the Office of Study Integrity and Surveillance (OSIS) for bioanalytical issues. OSI determined that the study data generated are acceptable and may be used in support of this NDA. OSIS determined that the bioanalytical data are reliable to support a regulatory decision.

Prior to the NDA submission, the Controlled Substance Staff (CSS) determined that there was no abuse potential of viltolarsen.

12. Labeling

Please refer to the final negotiated product labeling. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

13. Postmarketing Recommendations

The Division of Risk Management (DRISK) reviewer for the application was Ingrid Chapman, who concluded that a risk evaluation and mitigation strategy (REMS) is not necessary for viltolarsen.

The following will be postmarketing requirements:

- In order to verify the clinical benefit of viltolarsen, complete Study NS-065/NCNP-01-301 (“a Phase 3 Randomized, Double-blind, Placebo-controlled, Multi-center Study to Assess the Efficacy and Safety of Viltolarsen in Ambulant Boys with Duchenne Muscular Dystrophy”). The study will assess treatment with viltolarsen 80 mg/kg over 48 weeks. The primary endpoint will be Time to Stand.
- A 26-week carcinogenicity study of viltolarsen, administered by a clinically relevant route, in an appropriate transgenic mouse model.
- A two-year carcinogenicity study of intravenously administered viltolarsen in rat.
- Amend 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 hours the from start-of-infusion) following the first dose in all patients. Submit data and analyses from your Phase-1/2, Phase-2 studies, and the amended Phase-3 study to characterize the effects of viltolarsen on the QT_c interval as per ICH E14 Q&A (R3) 6.1. If these data do not support a TQT study waiver, the effect of viltolarsen on the QT_c interval will need to be evaluated in a dedicated study as per the ICH E14 guideline.

- Provide the appropriate validation as well as improve the sensitivity for the current anti-drug antibody (ADA) assay to at least 100 ng/ml, or develop and validate an alternative assay with this level of sensitivity. Include in the assay validation a statistical evaluation of distribution and outlier exclusion for cutpoint samples, selectivity, system suitability specifications for negative and positive controls, and effects of hemolysis. Use the anti-viltolarsen antibody assay with improved sensitivity provided for in PMR 5 to re-evaluate samples from the Phase 3 confirmatory study.
- Use the anti-viltolarsen antibody assay with improved sensitivity provided for in PMR 5 to re-evaluate samples from the Phase 3 confirmatory study.
- Improve the sensitivity of the qualitative anti-dystrophin antibody assay compared to the current assay or develop an alternative assay with an increased level of sensitivity.
- Use the anti-dystrophin antibody assay with improved sensitivity provided for in PMR 7 to re-evaluate samples from the Phase 3 confirmatory study.

14. Recommended Comments to the Applicant

We request that you perform postmarketing surveillance for serious renal toxicity events. Provide expedited reporting of serious renal toxicity events and provide comprehensive summaries and analyses of these events as part of your required postmarketing safety reports [e.g., periodic safety update reports (PSURs)]. In the analysis of each case, provide an assessment of causality, with documentation of risk factors and results of all assessments that support the diagnosis or the causality, along with duration of Viltepso therapy, the time from first Viltepso dose to adverse event onset, the time from last Viltepso dose prior to the event onset, concomitant therapies, treatment given for the event, and outcome. Include a comparison of the rates of renal failure and glomerulonephritis to background rates of those events in the general population (overall and stratified by age), as well as background rates (if available) for patients with Duchenne muscular dystrophy (DMD) (overall and stratified by age).

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/s/

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