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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY
REVIEW(S)

Office of Clinical Pharmacology Review

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Submission Date	12/31/2019
Submission Type	505(b)(1); Priority review
Brand Name	VILTEPSO
Generic Name	Viltolarsen
Dosage Form and Strength	250 mg in 5 mL solution in a single-dose vial
Dosing Regimen and Route of Administration	80 mg/kg administered once weekly as IV infusion over 60 minutes
Proposed Indication	Treatment of Duchenne muscular dystrophy (DMD) in (b) (4) patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping
Applicant	Nippon Shinyaku Co., Ltd.
Associated IND	IND 127474
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1. EXECUTIVE SUMMARY

Nippon Shinyaku Co., Ltd. submitted a New Drug Application (NDA 212154) for viltolarsen (VILTEPSO) for the treatment of Duchenne Muscular Dystrophy (DMD) in patients with a confirmed DMD mutation amenable to exon 53 skipping. DMD is a rare genetic neuromuscular disease affecting males and is resulting from a genetic mutation causing disruption in the dystrophin mRNA reading frame that prevents the production of functional dystrophin. Approximately 8% of these males have a deletion mutation that is amenable to correction by exon 53 skipping.

Viltolarsen is synthetic anti-sense oligonucleotide that was designed to bind to a specific sequence in exon 53 of the dystrophin pre-mRNA transcript and block the exon/intron splicing of exon 53 leading to mature mRNA transcripts that lack exon 53. This transcript translates into a truncated functional form of dystrophin.

The applicant is seeking accelerated approval of VILTEPSO based on the reported increase in dystrophin protein levels in muscle biopsies in the registration trial (NCNP-01-201, hereafter referenced as “Study 201”). This was a Phase 2, multicenter, 2-period study conducted in the United States and Canada. The initial 4 weeks of the study were a randomized, double-blind, placebo-controlled period to evaluate the acute safety of VILTEPSO. All patients then received 20 weeks of VILTEPSO 40 mg/kg/week (N=8) or 80 mg/kg/week (N=8) treatment. Muscle biopsies were collected from patients at baseline and following 24 weeks of VILTEPSO treatment. The primary endpoint was induction of dystrophin protein in muscle after 20-24 weeks of treatment measured by Western blot when normalized to myosin heavy chain. Based on dystrophin Western blot data, the applicant reported an induction of dystrophin expression, with mean values of approximately 6% of normal control levels in both dose groups (40 and 80 mg/kg/week). Secondary outcome measures of dystrophin including mass spectrometry, immunofluorescence staining, and RT-PCR were also measured to support the primary endpoint. The applicant is seeking approval for the 80 mg/kg/week dose.

The application included other supportive studies in DMD patients amenable to exon 53 skipping (NCNP-01-P1/2 and NCNP-DMT01). Data from an ongoing open label 144-week safety study was also submitted (Study NCNP-01-202). In addition, a Phase 3 confirmatory efficacy/safety study in patients with DMD mutation amenable to exon 53 skipping is currently ongoing with 80 mg/kg dose (NCNP-01-301).

The primary objectives of this review are (1) to evaluate the need for dose optimization based on intrinsic and extrinsic factors and (2) to evaluate the effect of viltolarsen on all mutations in the *DMD* gene amenable to exon 53 skipping.

1.1 Recommendations

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The proposed evidence of effectiveness is based on results from Study NCNP-01-201 in patients with a mutation in the DMD gene amenable to exon 53 skipping. The primary endpoint to support accelerated approval was the reported induction after 24 weeks in

	dystrophin protein levels using Western blot after weekly 40 or 80 mg/kg IV infusion dosing.
General dosing instructions	The recommended dose for the general population is 80 mg/kg administered by intravenous (IV) infusion once weekly over 60-minutes. The drug should be combined with normal saline to a minimum volume of 100 ml.
Dosing in patient subgroups (intrinsic and extrinsic factors)	<ul style="list-style-type: none"> • No dose adjustment is needed based on intrinsic or extrinsic factors. There was no drug interaction potential for viltolarsen with major CYP enzymes or drug transporters in vitro. Viltolarsen was not studied in patients with renal or hepatic impairment. Hepatic impairment is not expected to affect the exposure of viltolarsen. Patients with known renal impairment are expected to have higher exposure of viltolarsen and should be monitored closely. • Restoration of the reading frame by viltolarsen is assumed to be beneficial for all DMD mutations amenable to exon-53 skipping and thus can be indicated for all mutations amenable to exon-53 skipping
Labeling	The proposed labeling concepts are generally acceptable. The review team recommends close monitoring of patients with known impaired renal function during treatment with viltolarsen.
Bridge between the to-be-marketed and clinical trial formulations	There is no difference between the clinical trial formulation and the to be marketed formulation.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

Pharmacokinetics of viltolarsen was evaluated in patients with DMD in three clinical studies (i.e. DMT01, NCNP01-p1/2, NCNP01-201). Details of the design characteristics of the studies are described in Section 4.2. The studies were conducted in DMD patients following administration of doses ranging from 1.25 mg/kg/week to 80 mg/kg/week (i.e. the recommended clinical dose). Viltolarsen showed a proportional increase in exposure over the tested dose range.

Mechanism of Action: Viltolarsen is an antisense oligonucleotide for the treatment of DMD in patients amenable to exon 53 skipping. It has a morpholino backbone that interacts with dystrophin pre-messenger ribonucleic acid (pre-mRNA) and alters the exon/intron splicing patterns. Exon 53 skipping restores the mRNA reading frame and induces production of an internally shortened functional dystrophin protein in patients with genetic mutations that are amenable to exon 53 skipping.

Absorption: Viltolarsen is administered as an IV infusion over 60 minutes. Bioavailability is assumed to be 100% and median Tmax was around 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 indicated 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 dose.

Specific Population: N/A

Hepatic and Renal Impairment: Viltolarsen was not tested in patients with renal or hepatic impairment. The urinary excretion of the unchanged form was the predominant route of elimination for viltolarsen (up to 75%). In addition, hepatic metabolism of viltolarsen was not evident during in vitro testing. This was further supported by scientific literature suggesting that Phosphorodiamidate Morpholino Oligomers (PMOs) such as viltolarsen is generally resistant to enzymatic degradation¹. No dose adjustments are required for patients with hepatic impairment.

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.

2.1 Pharmacology and Clinical Pharmacokinetics

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dose of viltolarsen is 80 mg/kg administered by intravenous (IV) infusion once weekly over 60-minutes. The drug should be combined with normal saline to provide a minimum volume of 100 mL before infusion. This regimen was tested in the registration trial NCNP-01-201.

2.2.2 Therapeutic individualization

Drug Interaction with CYP Enzymes and Transporters: Viltolarsen has low potential for drug-drug interactions with CYP enzymes and drug transporters based on in vitro studies. No meaningful inhibition of cytochrome P450 enzyme activity was observed in human hepatic microsomes at concentrations that exceeded the free C_{max} from the recommended dose of 80 mg/kg by more than 100-fold. No inhibition

¹ Arora V, et al. Curr Pharm Biotechnol. 2004. PMID: 15544491; Neutrally Charged Phosphorodiamidate Morpholino Antisense Oligomers: Uptake, Efficacy and Pharmacokinetics

was detected for major transporters at clinically relevant concentrations. Also, viltolarsen was not a substrate of major CYP enzymes or drug transporters in vitro.

Renal and Hepatic Impairment: No therapeutic individualization is required for patients with renal or hepatic impairment. Viltolarsen was found to be metabolically stable and hepatic metabolism is not contributing to the elimination of viltolarsen. Accordingly, no dose adjustment is required for patients with hepatic impairment.

Renal clearance seems to be the major elimination pathway of viltolarsen. However, dose adjustment recommendations cannot be made based on creatinine clearance in DMD patients because of the DMD disease characteristics (i.e. excessively high serum creatinine concentrations). The estimated creatinine clearance values derived using the Cockcroft-Gault equation and the threshold definitions for mild, moderate and severe renal impairment in otherwise healthy subjects cannot be generalized to DMD patients. Monitoring of changes in renal function in DMD needs further scientific research. The review team recommends patients with known renal function impairment be closely monitored during the treatment with viltolarsen.

Exon 53 Genetic Mutations: There are various deletion mutations that are amenable to exon-53 skipping (e.g. 42-52, 45-52, 47-52, 48-52, 49-52, 50-52, 52, 54-58) however, only five (45-52, 47-52, 48-52, 49-52, 50-52) were enrolled in the clinical registration trial for viltolarsen. In theory, each DMD mutation amenable to exon-53 skipping will produce a different internally-shortened dystrophin. It seems likely that any amenable mutation could respond to treatment with viltolarsen. Given the heterogeneity in disease phenotype in DMD mutations and available sample size of the clinical study, it is difficult to ascertain whether differences in DMD mutation affected efficacy. While there may be some differences in the functionality of the exon-53 skipped transcripts, restoring the reading frame to produce dystrophin, even if there may be differences between DMD mutations, is warranted. Based on this, the review team recommends extending the approval to all mutations amenable to exon 53 skipping.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

Patients with known renal function impairment should be closely monitored during treatment with viltolarsen.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

DMD is a rare but lethal X-linked recessive neuromuscular disorder caused by mutations in the dystrophin gene that result in the absence or near absence of functional dystrophin protein. Most of the current pharmacologic treatments focus on the alleviation of symptoms, but do not address the underlying cause of the disease. Treatment with oral glucocorticoid (GC) medication is the only

pharmacological intervention that has been shown to slow the decline of strength and function in DMD patients. Deflazacort (EMFLAZA®) is the only GC approved for DMD in the USA.

Two anti-sense oligonucleotide (ASOs) have been approved for the treatment of DMD. Eteplirsen (EXONDYS 51®) was the first ASO approved by the FDA under the accelerated approval pathway in 2016 for DMD patients amenable to exon 51 skipping. The second is golodirsen (VYONDYS 53™) and was approved in 2019 for the treatment of DMD patients amenable to exon 53 skipping.

VILTEPSO is another ASO that was submitted in December 2019 and is being reviewed under a priority review clock. VILTEPSO received orphan designation and is seeking approval via the accelerated approval pathway to treat DMD patients amenable to exon 53 skipping.

VILTEPSO is supplied as a preservative-free solution in single-dose vials. Each vial contains 250 mg of viltolarsen dissolved in 5 mL (50 mg/mL). The recommended dose of VILTEPSO should be administered as a 60-minute IV infusion after combining with normal saline to a minimum volume of 100 mL.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Viltolarsen is designed to restore dystrophin function and halt muscle damage by binding to the exon 53 sequence of the target dystrophin pre-mRNA, allowing removal of exon 53 by alternative splicing and enabling translation of a shorter, internally truncated but partially functional version of the dystrophin protein.
Active Moieties	Viltolarsen, an antisense oligonucleotide is the active moiety. It has a morpholino backbone that interacts with dystrophin pre-messenger ribonucleic acid (pre-mRNA) and alters the exon/intron splicing patterns.
QT Prolongation	While the existing nonclinical and clinical data do not suggest a concerning proarrhythmic risk for viltolarsen, available clinical data are not adequate for the characterization of drug effect on QTc interval. The QT-IRT recommended modifications to the confirmatory Phase 3 study protocol to include additional PK measurements and high quality 12-lead ECG recordings around Tmax following the first dose in all patients. Please refer to the QT-IRT consult review in DARRTS on May 14, 2020.
General Information	
Bioanalysis	Bioanalytical methods for viltolarsen were developed and validated in human plasma and urine. Samples were extracted by a solid-phase extraction procedure and analyzed by LC-MS/MS, with (b) (4) as an internal standard.
Dose Proportionality	Viltolarsen has dose proportional pharmacokinetics over a dose range of 1.25-80 mg/kg.

Accumulation	There was no evidence of accumulation after multiple once weekly dosing. This is expected given the short elimination half-life (T _{1/2}) of ~2.5 hrs.
Variability	Inter-subject variability based on %CV for viltolarsen C _{max} and AUC was 16% and 27% respectively.
Bioavailability	
Bioavailability	Viltolarsen is administered by IV infusion and the bioavailability is expected to be 100%.
T_{max}	T _{max} is at end of infusion (i.e. 60 minutes)
Food effect (high-fat meal) GMR relative to fasted state for tablets	Viltolarsen is administered through IV infusion and food is not expected to affect the exposure.
Volume of Distribution	
Volume of Distribution	The mean viltolarsen steady-state volume of distribution was 300 mL/kg (CV%=14.4) at the approved recommended dosage of 80 mg/kg.
Plasma Protein Binding	39% to 43% and is independent of concentration.
Substrate transporter systems	Viltolarsen is not a substrate or an inhibitor of major transporters at clinically relevant concentrations.
Elimination	
Mean Terminal Elimination half-life	Approximately 2.5 (CV%=8) hours.
Metabolism	
Primary metabolic pathway(s)	Viltolarsen is not metabolized and is eliminated unchanged in the urine.
Inhibitor/Inducer [<i>in vitro</i>]	viltolarsen is not an inhibitor or inducer of major CYP enzymes or transporters at clinically relevant concentrations.
Excretion	
Primary excretion pathways	Viltolarsen is excreted unchanged in the urine. The mean total recovery of unchanged viltolarsen from PK studies ranged from 60-70%. No mass balance study was conducted for viltolarsen.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The evidence of efficacy to support accelerated approval for viltolarsen is from the pivotal Phase 2 Study (Study NCNP-01-201) that evaluated the effect of viltolarsen injection on the induction of dystrophin protein expression (a pharmacodynamic biomarker in DMD).

Study 201 was a Phase 2, multicenter, 2-period, randomized, placebo-controlled study of viltolarsen injection administered by IV infusion once weekly for 20 or 24 weeks in ambulant boys ages 4 to <10 years with mutations in the dystrophin gene amenable to exon 53 skipping. Sixteen boys were enrolled; 8 each to 40 and 80 mg/kg/week dose groups.

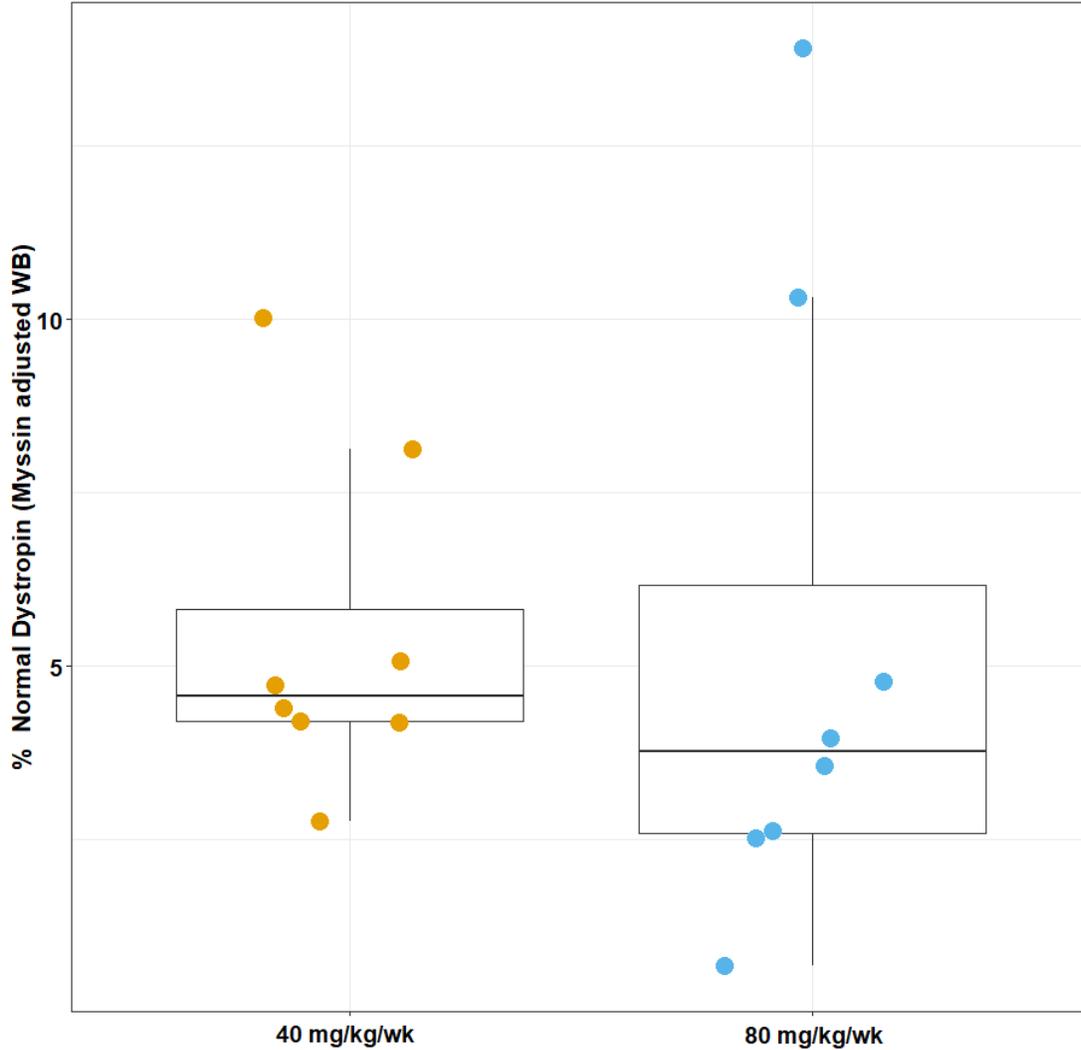
Dosing was initiated at 40 mg/kg with a 3:1 viltolarsen: placebo ratio. After 4 weeks of treatment in Cohort 1, a separate 80 mg/kg Cohort 2 began with the same 3:1 viltolarsen: placebo ratio. Following 4 weeks of randomized, double-blind treatment in both cohorts, all patients received viltolarsen injection at their dose level (40 mg/kg/week or 80 mg/kg/week) for the remaining 20 weeks of the study. Muscle biopsies (left or right tibialis anterior or biceps brachii) were collected from patients at baseline and following 24 weeks. All patients completing Study 201 enrolled in an open label extension safety Study 202.

The primary outcome measure was dystrophin protein level measured by Western blot, and secondary outcomes were dystrophin expression detected by mass spectrometry (MS) for quantitation, immunofluorescence (IF) protein staining, and alteration of dystrophin mRNA splicing measured by reverse-transcriptase polymerase chain reaction (RT-PCR).

The dystrophin myosin adjusted Western blot data (primary endpoint) showed an increased level of viltolarsen-induced dystrophin expression, with mean values between 5% to 6% of normal control levels in both dose groups (40 and 80 mg/kg/week) Figure 1. Details about other secondary endpoint assessments are discussed in the clinical review for Dr. Veneta Tandon. Please refer to the Office of Biotechnology Products (OBP) review for details regarding dystrophin assessments.

In general, treatment with viltolarsen 40 and 80 mg/kg/week appeared safe and well-tolerated in study 201. No dose-dependent safety trends were observed. At the time of Week 73 data cut for safety study (study 202), treatment with viltolarsen 40 and 80 mg/kg/week was reported as safe and well-tolerated. No dose-dependent safety trends were observed. Please refer to the clinical and OBP reviews for more information on efficacy and safety assessments.

Figure 1VILTEPSO-Induced Dystrophin Expression Following 20 to 24 Weeks of Treatment



Source: figure generated by FDA reviewer (Dataset: ADMI.XPT from study 201)

The applicant also submitted other supportive studies in patients with DMD who are amenable to exon 53 skipping (i.e. Study P1/2 & study DMT01). Study P1/2 was an open-label study performed in Japan in DMD exon 53 skipping-amenable patients 5 to <18 years of age. While the duration of dosing of viltolarsen 40 and 80 mg/kg/week was 24 weeks as in Study 201, biopsies in Study P1/2 were taken pre-treatment in all patients, then at Week 12 in half of the patients at each dose and at Week 24 in the other half of the patients at each dose to assess a time course for dystrophin expression. Western blot (WB) results were considered not adequate due to issues with bioanalytical method of dystrophin protein. Study DMT01 was 12-week exploratory, open-label, uncontrolled, single-center, dose-escalation study performed in Japanese boys with DMD. Patients used in the study were non-ambulatory patients with DMD aged 6 to 16 years who were exon 53-skipping-amenable. The objectives of this study were to assess safety and tolerability, efficacy and dose-response by evaluating the expression of dystrophin and PK after IV administration of viltolarsen at multiple dose levels (PK population: 1.25 mg/kg [N=3], 5

mg/kg [N=3] and 20 mg/kg [(N=4)] administered weekly for 12 weeks. Evaluation by WB indicated dystrophin expression in only 1 patient (Patient (b) (6) 20 mg/kg), in whom the reported extent of dystrophin expression relative to normal control was 8.1%. Dystrophin expression was not detected using this method in any of the remaining patients. WB results from this study can't be considered also due to issues with the bioanalytical method. No serious adverse events were reported in this study. Please refer to the clinical review for details. Brief description of the clinical studies supporting the development program is listed in section 4.2.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The recommended dosing regimen (80 mg/kg/week) was the highest dose tested in the registration study (Study 201), which supports the accelerated approval for this NDA based on reported increase in dystrophin levels (See Section 3.3.1 for details). This dose was also the maximum dose ever tested in humans with viltolarsen.

Two dosing regimens were evaluated in study 201, 40 mg/kg/week and 80 mg/kg/week (Figure 1). No significant dose or exposure-response (expressed by dystrophin expression) was observed and both dosing regimens resulted in a comparable induction levels of dystrophin protein according to the western blot analysis. The review team conducted additional PK/PD analysis to correlate the exposure (i.e. AUC) of viltolarsen with dystrophin expression as measured by Western blot. However, given the small sample size (n=16) an effective PK/PD assessment was not possible. There was also no significant difference in the safety profile for the two dosing regimens. Therefore, the review team agrees with the applicant's proposal to select the maximum tolerated dose (MTD). The MTD approach is usually applied for serious and fatal diseases like DMD.

There is no information available currently on the efficacy/safety of viltolarsen at doses higher than 80 mg/kg/week in DMD patients. A confirmatory efficacy/safety study in DMD patients amenable to exon 53 skipping study will be evaluated using the same dosing regimen of 80 mg/kg/week in the ongoing Phase 3 study (Study NCNP-01-301) with clinically accepted endpoints.

Finally, the body-weight based dosing was mainly based on clinical practice with ASOs drugs and is not necessarily based on exposure matching in DMD patients with different body weights (please see section 3.3.3 for details).

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No dose adjustment is recommended for patients based on intrinsic factors. The review team evaluated the effect of various deletion mutations amenable to exon 53 skipping and reported dystrophin levels and are detailed below. The impact of renal/hepatic function, body weight, on viltolarsen exposure is also discussed below.

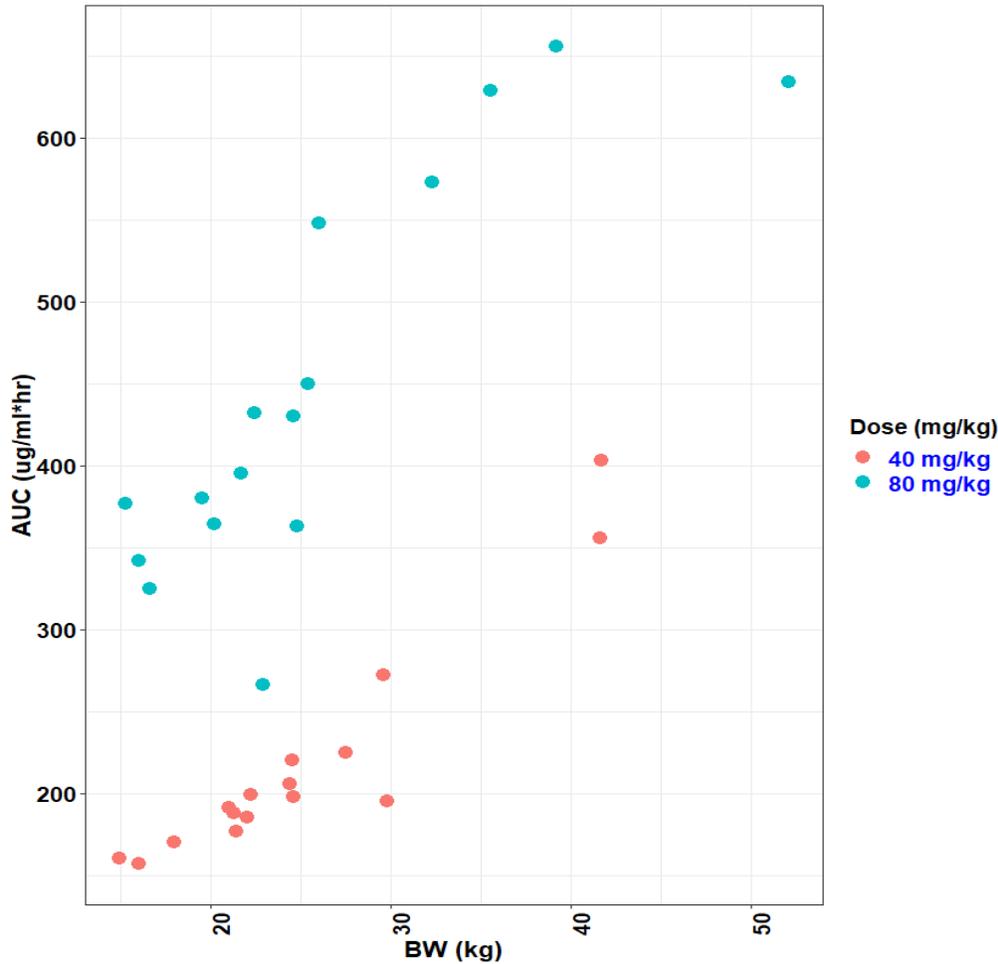
Dosing in patients with renal/hepatic impairment: No dedicated renal or hepatic impairment study were conducted for viltolarsen. However, no dose adjustment is required based on the following rationale. Viltolarsen was found to be metabolically stable and hepatic metabolism is not contributing to

the elimination of viltolarsen. In addition, viltolarsen was mainly excreted unchanged (60-70%) in the urine. Accordingly, no dose adjustment is required for patients with hepatic impairment.

Viltolarsen is eliminated renally, and renal impairment is expected to result in increasing exposure of viltolarsen. However, it is unclear how the renal function would be measured in DMD patients. Formulae such as Cockcroft-Gault, or Schwartz that use serum creatinine are not applicable in DMD setting due to changes in serum creatinine associated with disease progression. Alternate formulas have been proposed in literature but have some limitations. Hence, no formula can be proposed for estimating renal function in DMD patients and this aspect needs further investigation. Therefore, the review team concluded that dose optimization based on creatinine clearance is not feasible in DMD. However, the review team recommends that patients with known renal function impairment be closely monitored when treated with viltolarsen.

Age, Sex and Body Weight: The pharmacokinetics of viltolarsen have been evaluated in male pediatric DMD patients only because this disease is only manifested in young males. This is also why there is no experience with the use of VILTEPSO in patients 65 years of age or older. In the registration trial and the supportive P1/2 study, viltolarsen was tested in pediatric male patients with an age range of (4-12 years) and a body weight range of (15.5-51 kg). The applicant did not submit a population PK analysis to evaluate the effect of these covariates on the exposure. However, the review team correlated viltolarsen exposure as expressed by AUC with body weight from pooled data of study 201 and study P1/2 (Figure 2). Patients with higher body weight have higher exposures compared to those with lower body weight. This can be because of the body-weight based dosing scheme in addition to potential changes in distribution as the patients advance in their disease and have lesser muscle mass.

Figure 2 Relationship Between Viltolarsen Exposure (AUC ng/ml.hr) And Body Weight (kg).

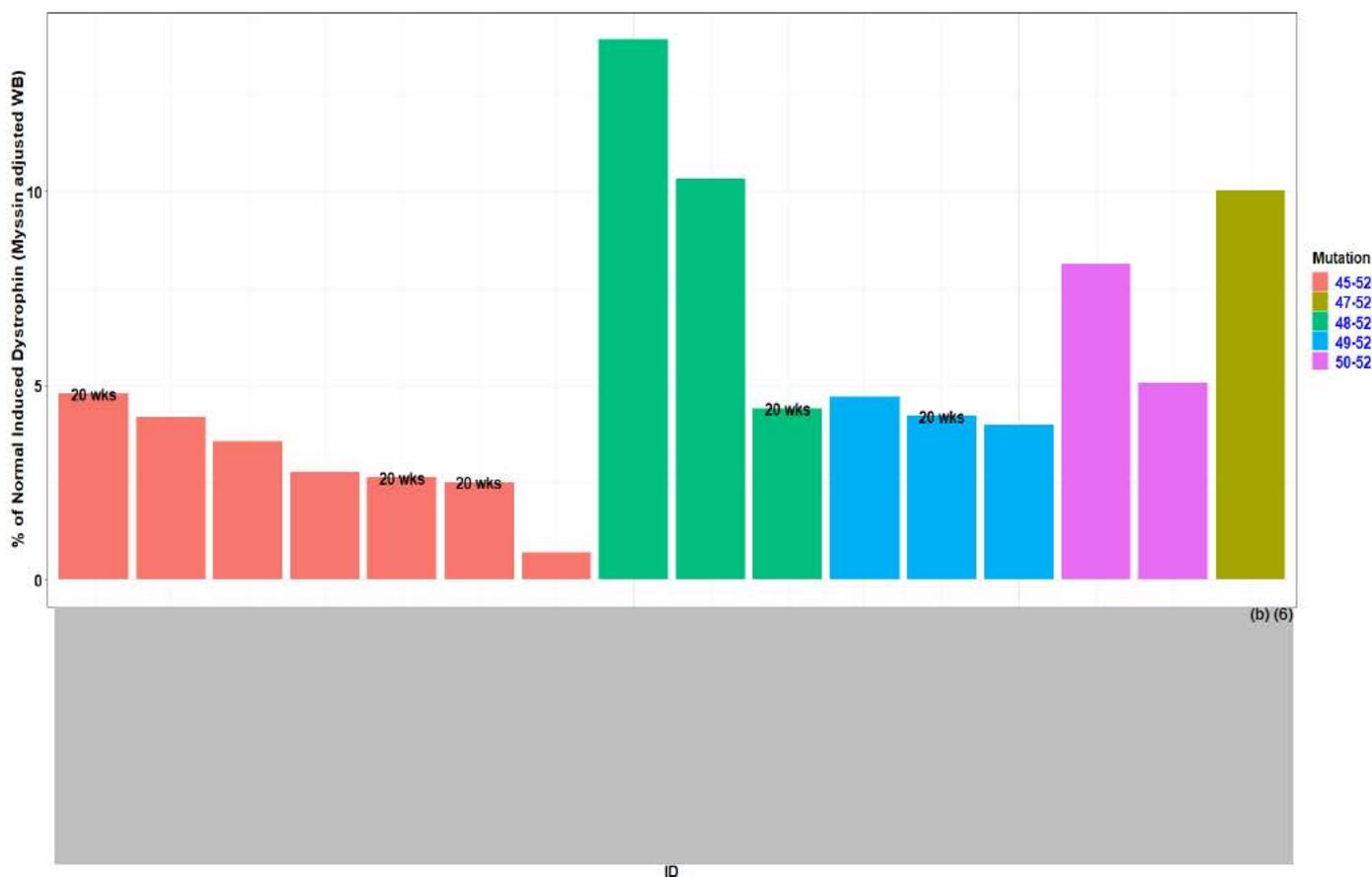


Source: figure generated by FDA reviewer (Dataset: ADPP.XPT, ADVS.XPT from study 201 & study P12)

Effect of different deletion mutations on dystrophin protein level expression and extension of the indication to all mutations amenable to exon-53 skipping:

The review team evaluated the relationship between these amenable mutations available from Study 201 and the primary endpoint represented by % induced dystrophin protein level relative to normal levels (Figure 3). Based on the results, no apparent relationship between type of deletion mutation and the primary endpoint was observed. It should be also noted that sample size of this trial is small (n=16) and 5 of these patients were in the placebo groups before treatment with viltolarsen for 20 weeks. As a result, it is difficult to interpret this subgroup analysis with this limited sample size. Please refer to section 4.2 for more details.

Figure 3. Induced Dystrophin Levels as percentage of normal Determined by Western Blot and Stratified by Mutation type. Subjects who started on placebo for first 4 weeks are labeled in black (20 wks.)



Source: figure generated by FDA reviewer (Dataset: ADMI.XPT, ADPF.XPT from study 201)

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

No. Food is not expected to affect the exposure of viltolarsen because VILTEPSO is administered by IV infusion. Also, viltolarsen has a low potential for drug-drug interactions with CYP enzymes and drug transporters. This is based on the absence of in vitro effects on key human CYPs and transporter proteins at clinically relevant concentrations as explained below.

Viltolarsen had no significant inhibitory effects for major CYP enzymes (CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 (Study BP-065-041) and did not induce CYP1A2, CYP2B6, and CYP3A4 (study BP-065-042 & BP-065-032) at concentration as high as 3000 uM. Viltolarsen had no significant inhibitory effects to UGT2B7 or UGT1A1 (BP-065-043). In addition, viltolarsen was not a substrate of transporters (multi-drug resistance transporter 1[MDR1], breast cancer resistance protein [BCRP], organic anion transporter OAT1, OAT3, organic cation transporter OCT2, MATE1, and MATE2-K) according to study BP-065-038. It also showed weak to no inhibition to major drug transporters,

OATP1B1, OATP1B3, OAT3, and BCRP, MDR1, OAT1, OCT1, OCT2, MATE1, MATE2-K, and bile salt export pump [BSEP] at concentrations as high as 300 uM which is 10 folds higher than the Cmax concentration at the recommended dose(Study BP-065-032).

In study BP-065-044 the inhibitory effect of viltolarsen at concentrations up to 3000 uM on human transporters was tested and it was found that viltolarsen had no inhibitory effect for most transporters. Viltolarsen had no inhibitory effect for most transporters in this study also. However, viltolarsen inhibited BCRP, OATP1B1, OATP1B3 and OAT3 with an IC50 value of 1970, 485, 448 and 176 uM respectively. The risk of inhibitory effects on transporter species was tested using the Cmax value at 80 mg/kg dose and the reported IC50 values. Only for OAT3, $(1+[I]/IC50)$ slightly exceeded the guideline cut-off of 0.1 with a value of 0.16. Since viltolarsen had a short half-life and disappeared from the blood rapidly after administration, and showed no accumulation, the extent of drug interaction with OAT substrate drug by viltolarsen is unlikely.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

The bioanalytical method for viltolarsen quantification were developed and validated in human plasma. Samples were prepared and extracted by a solid-phase extraction procedure and analyzed by LC-MS/MS, with (b) (4) used as an internal standard.

The details of the bio-analytical methods used in this NDA are presented in Table 1. The method met the acceptance criteria as specified in validation protocol and showed to be selective and were robust to different lots of plasma and to dilution. The methods satisfied the criteria for method validation and application to routine analysis set by the Guidance for Industry: Bioanalytical Method Validation, and hence are acceptable.

Table 1 Summary of the bioanalytical method

Parameter	Value
Analyte	Viltolarsen
Internal Standard (IS)	(b) (4)
Lower Limit of Quantitation (ng/mL)	20.0 ng/mL
Average Recovery of Drug (%)	For low concentration range (20.0-1000 mg/ml) Recovery range: 67.5-74.3% For high concentration range (500-50000 ng/ml) Recovery range: 69-84.5%
Average Recovery of IS (%)	The IS recovery had an average of 81% for the low concentrations range and 69% for the high concentrations
Standard Curve	r^2 for the low and high concentrations ranged from 0.995 to 0.99

[C] (ng/ml) & Linearity R²	
QC Intraday Precision Range (%)	For the low concentration range intraday precision ranged from 1.7% to 9.8% For the high concentration range intraday precision ranged from 2.7% to 9.1%
QC Intraday Accuracy Range (%)	For the low concentration range intraday accuracy ranged from 1 % to 13% For the high concentration range intraday accuracy ranged from 1% to 6.4%
QC Interday Precision Range (%)	For the low concentration range inter-day precision ranged from 4.7% to 12% For the high concentration range inter-day precision ranged from 4.8% to 6.7%
QC Interday Accuracy Range (%)	For the low concentration range inter-day accuracy ranged from 0.5% to 3% For the high concentration range inter-day accuracy ranged from 1.2% to 2%
Stock Stability (Days) (Equivalent to Long-Term Stability of Analyte or Internal Standard in Solution)	Stable up to 94 days at room temperature
Processed Stability (Hrs) (Equivalent to Post-Preparative Stability)	Stable up to 48 hours at room temperature
Freeze-Thaw Stability (Cycles)	Stable up to 5 cycles at temperature down -20 C
Selectivity	No interfering peaks were observed

4.2 Genomics and Targeted Therapy Review

4.2.1 Submission Contents Related to Genomics

The sponsor submitted the following labeling language for Viltolarsen:

Indications and Usage:

Viltolarsen is (b) (4) indicated for the treatment of Duchenne muscular dystrophy (DMD) in (b) (4) patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.

The sponsor's submitted data included the underlying DMD mutation for all patients. The proposed to-be labeled population compared to the studied population will be the focus of this review. The sponsor's proposed labeling states that the drug will be indicated for subjects with mutations in the dystrophin gene that are amenable to treatment with exon 53 skipping as determined by genetic testing.

Only five (45-52, 47-52, 48-52, 49-52, 50-52) exon 53 amenable mutations were represented in the clinical studies with Viltolarsen (Table 2 DMD Mutations Present in Sponsor's Study Population Table 2).

Table 2 DMD Mutations Present in Sponsor's Study Population

Patient	Age (years) ^a	Deleted Exons Start and End	Weight (kg)	Height (cm)	BMI (kg/m ²)
Cohort 1: Viltolarsen 40 mg/kg/wk					
(b) (6)	(b) (6)	50-52	14.9	102.5	14.2
		47-52	25.3	114.6	19.3
		49-52	30.4	123.4	20.0
		50-52	27.7	119.3	19.5
		45-52	21.8	113.6	16.9
		45-52	21	119	14.8
Cohort 1: Placebo					
(b) (6)	(b) (6)	49-52	25.3	115	19.1
		48-52	23.1	109.2	19.4
Cohort 2: Viltolarsen 80 mg/kg/wk					
(b) (6)	(b) (6)	45-52	21	113.5	16.3
		45-52	16.4	99.4	16.6
		48-52	35.4	127.1	21.9
		48-52	22.5	111	18.3
		49-52	15.5	100.3	15.4
Cohort 2: Placebo					
(b) (6)	(b) (6)	45-52	22.9	116.5	16.9
		45-52	24.6	122.9	16.3
		45-52	20	106.5	17.6

Source: Summary of Clinical Efficacy

4.2.2 Key Questions and Summary of Findings

4.2.2.1 Are the studied populations in the sponsor's clinical trials representative of the to-be labeled population?

No. The sponsor has studied five different DMD mutations amenable to exon-53 skipping therapy. However, Viltolarsen is to be indicated for all mutations amenable to skipping exon 53. A search of the

Leiden DMD database (www.dmd.nl) using the known exon splicing Figure 4, identified subjects composing of additional DMD mutations such as (42-52,43-52, 52, 54-58) that may be amenable to exon-53 skipping based on the mechanism of action of Viltolarsen. Amenable mutations are those in which skipping of exon-53 would, in theory, restore the reading frame. For instance, in Figure 1, a subject with a deletion of exons 44-50 would not be amenable to exon-53 skipping as exons 43 and 52 cannot be spliced together, whereas, a deletion of exons 48-52 can be successfully spliced by exon-53 skipping.

Figure 4 Depiction of the 79 Exons of the Dystrophin Gene and Splicing



Source: PMID 19156838

Note: In-frame exons are in light blue, out-of-frame in dark blue. Deletions are considered in-frame when the exons flanking the deletion “fit.”

4.2.2.2 Should Viltolarsen be indicated for patients amenable to exon-53 skipping who were not studied in the clinical development program?

Yes. Despite not all DMD mutations amenable to exon-53 skipping being enrolled in the clinical development program, if Viltolarsen is ultimately found to be safe and effective to warrant approval, then Viltolarsen should be indicated for all exon-53 amenable mutations.

Reviewer comment: In theory, restoring the reading frame by skipping exon-53 may result in a milder form of the disease (i.e. transition from DMD phenotype towards a BMD phenotype); therefore, it has the potential to be efficacious for patients with all amenable mutations. However, given the ultra-rare occurrence of some exon-53 amenable mutations (e.g. 43-52 deletions) it is exceedingly difficult to find adequate numbers of patients for clinical studies. Moreover, given the strict inclusion criteria for the Viltolarsen clinical trials, these patients may have been ineligible to participate (e.g. non-ambulatory). Furthermore, given the inherent variability in disease, studying these ultra-rare mutation subsets may be challenging for determining efficacy or lack thereof.

Many unknowns remain in how the internally-deleted dystrophin can impact disease, both in quantity and quality. Successful exon-53 skipping in the case of each DMD deletion mutation would create a different internally-shortened dystrophin protein. For some mutations amenable to exon-53 skipping we have BMD subjects with the same internally-deleted “in-frame” mutations to infer some degree of functionality of that protein (PMID: 25633150, 22102647). BMD patients are generally less severe, however there can be a large heterogeneity in disease phenotype (PMIDs: 25633150, 2404853). While in-frame deletions in the proximal regions of the protein (exons 20-40) tend to be milder than those in the distal part (exons 40-55), it is still difficult to predict exactly what the functionality of the skipped dystrophin protein may be (PMIDs: 19156838,16770791,17041910). For example, a case report of a patient missing exons 17-48 only resulted in mild BMD, with the patient being ambulant at 61 years of

age (PMID: 2404210). Thus, it is clear that the amount of exons present isn't directly correlated with functionality. Hence, while we can infer some functionality of an exon-53 skipped product, many unknowns remain on how it can affect clinical phenotype.

Determining efficacy in single patients with a specific exon-53 skipping amenable mutation is difficult for the following reasons: a lack of available subjects for study, coupled with inherent heterogeneity in disease, along with the unknowns regarding the functionality of the internally-deleted dystrophin. Moreover, there are no reasons to believe that the safety of Viltolarsen is in any way different in these ultra-rare populations of patients. Thus, if Viltolarsen is approved, any DMD deletions amenable to exon-53 skipping (i.e., theoretical restoration of the reading frame) should be eligible to receive Viltolarsen.

4.2.2.3 Is there a difference in the functionality of the exon-skipped truncated dystrophin produced by treatment with Viltolarsen?

Potentially. Given the significant intra- and inter-subject variation in disease phenotype, it is likely that large numbers of DMD patients with different mutations would need to be studied in order to determine efficacy. Given the small numbers of subjects in the sponsor's submission with specific DMD deletions, numerical comparisons can only be made for a few of the exon-53 skipping amenable groups.

4.2.2.4 Sponsor's Analysis

The sponsor did not perform any efficacy analyses by DMD mutation type. Given the overall small numbers of subjects enrolled in their clinical program, further subgroup analysis is likely underpowered. (see section 3.3.3)

4.2.2.5 Reviewer's Analysis

The sponsor enrolled five different DMD deletion mutations that were amenable to exon-53 skipping. The goal of Viltolarsen treatment is to restore the reading frame and produce a truncated dystrophin protein similar to patients with BMD. In theory, each DMD mutation amenable to exon-53 skip will produce a different internally-shortened dystrophin. It is unlikely that an amenable mutation would not respond to treatment with Viltolarsen. Given the heterogeneity in disease phenotype DMD mutations, it is difficult to ascertain whether differences in DMD mutation affected efficacy. While there may be some differences in functionality of the exon-53 skipped transcripts; restoring the reading frame to produce dystrophin even if it may be different between DMD mutations is warranted.

4.2.3 Summary and Conclusions

Viltolarsen is being sought for the indication of the treatment of DMD in all mutations amenable to exon-53 skipping. There were five different DMD mutations represented in the sponsor's clinical trials; however, additional mutations (e.g. 42-52, 43-52, 52) were eligible for enrollment. Although Viltolarsen was not studied in all DMD mutations amenable to exon-53 skipping, it is reasonable to extrapolate efficacy to ultra-rare populations (i.e., mutations with only one or two known subjects), given the inherent variability in disease, and our understanding of the mechanism of action in restoring the reading frame. Last, there are no reasons to believe that the safety of Viltolarsen is in any way different in these ultra-rare populations of patients. Hence, given the challenges of studying these ultra-rare populations of disease, coupled with the lack of any unique safety concerns, it is reasonable to approve Viltolarsen for all DMD mutations amenable to exon-53 skipping, if found to be safe and effective in the studied population.

4.3 List of Clinical Studies in the Development Program

Table 3 Clinical Development Program for Viltolarsen

Study Phase Study Number	Study Design	Dosing Regimen and Route of Administration	Study Population
Phase 2 NS-065/NCNP-01-201 (NCT02740972) North America Completed	Multicenter, 24-week dose- finding study to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of viltolarsen injection in boys with DMD	Weekly IV administration of viltolarsen injection 250 mg (40 mg/kg and 80 mg/kg) or placebo for the first 4 weeks, followed by weekly IV administration of viltolarsen injection (40 mg/kg and 80 mg/kg) over the remaining 20 weeks	16 DMD patients amenable to Exon 53 skipping, ages 4 - <10 years
Phase 1/2 NS065/NCNP01- P1/2 (JapicCTI-163291) Japan Completed	Multicenter, 24-week, parallel- group, open-label, dose- finding study of viltolarsen injection in boys with DMD	Weekly IV administration of viltolarsen injection 250 mg (40 mg/kg and 80 mg/kg) over 24 weeks	16 DMD patients amenable to Exon 53 skipping, ages 5 - <18 years
Phase 2 NS-065/NCNP-01-202 (NCT03167255) North America Ongoing	Open-label, 2-treatment, multicenter, 144-week extension study of viltolarsen injection in boys with DMD	Weekly IV administration of viltolarsen injection 250 mg (40 mg/kg and 80 mg/kg) over 144 weeks (or until commercially available) [minimum of 73 weeks of exposure available for each patient in this submission]	DMD patients who complete Phase 2 dose- finding study NS-065/NCNP-01-201
Phase 1 NCNP/DMT01 (NCT02081625) Japan Completed	Open-label, uncontrolled, dose titration, single-center, 12- week study of viltolarsen injection in boys with DMD	Weekly IV administration of viltolarsen injection 125 mg (1.25, 5, or 20 mg/kg) for 12 weeks	10 DMD patients amenable to Exon 53 skipping, ages 5 - <18 years

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