Clinical Study Protocol: NS-065/NCNP-01-301

Study Title:	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 (DMD)
Protocol Number:	NS-065/NCNP-01-301
Study Phase:	Phase 3
Product Name:	Viltolarsen
IND Number:	127474
EudraCT Number:	2019-002076-13
Sponsor:	NS Pharma, Inc.
Original Protocol Date:	12 June 2019
Amendment 1 Global Date:	04 September 2019
Amendment 2 US-AUS Specific Date:	23 September 2019
Amendment 2 Global Date:	21 February 2020
Amendment 3 US-AUS Specific Date:	02 March 2020
Amendment 4 US-AUS Specific Date:	15 December 2020
Amendment 4 Global Date:	08 January 2021
Amendment 5 China Specific Date:	14 July 2021
Amendment 5 Global Date:	08 December 2022

Confidentiality Statement

STUDY SYNOPSIS

<table>
<tr><td>Study Title</td><td colspan="3">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 (DMD)</td></tr>
<tr><td>Protocol Number</td><td colspan="3">NS-065/NCNP-01-301</td></tr>
<tr><td>Investigative Product</td><td colspan="3">Viltolarsen</td></tr>
<tr><td>Study Phase</td><td colspan="3">Phase 3</td></tr>
<tr><td>Indication</td><td colspan="3">Treatment of Duchenne Muscular Dystrophy (DMD) with dystrophin deletion amenable to exon 53 skipping</td></tr>
<tr><td>Number of Participants</td><td colspan="3">74</td></tr>
<tr><td>Study Centers</td><td colspan="3">Approximately 53 clinical sites in approximately 19 countries, predominantly in Europe, Asia, North America, Oceania, and South America.</td></tr>
<tr><td>Objectives/Endpoints</td><td>Primary Objective(s)</td><td>Primary Endpoint(s)</td></tr>
<tr><td></td><td>• To compare the efficacy of viltolarsen administered intravenously (IV) at weekly doses of 80 mg/kg over a 48-week treatment period vs. placebo controls in ambulant boys ages 4 to <8 years with DMD using the Time to Stand Test (TTSTAND) as a measure of strength and function.</td><td>• TTSTAND at 48 weeks of treatment</td></tr>
<tr><td></td><td>Secondary Objective(s)</td><td>Secondary Endpoint(s)</td></tr>
<tr><td></td><td>• To compare the efficacy of viltolarsen administered IV at weekly doses of 80 mg/kg in ambulant boys ages 4 to <8 years with DMD over a 48-week treatment period vs. placebo controls using</td><td>• Hierarchical analysis at 48 weeks treatment of the following strength and endurance measures:
o Time to Run/Walk 10 Meters Test (TTRW)
o Six-minute Walk Test (6MWT)</td></tr>
</table>

		hierarchical strength and endurance outcomes; and	○ North Star Ambulatory Assessment (NSAA) ○ Time to Climb 4 Stairs Test (TTCLIMB) ○ Quantitative muscle strength measured by hand-held dynamometer (elbow extension, elbow flexion, knee extension, and knee flexion on the dominant side only)	
		• To evaluate the safety and tolerability of viltolarsen administered IV at weekly doses of 80 mg/kg in ambulant boys ages 4 to <8 years with DMD.	• Vital signs (blood pressure, heart rate, respiratory rate, and body temperature [modality for determining temperature should be consistent for each participant at all assessment time points throughout the study]) • Physical examination • Clinical laboratory tests: ○ Hematology and clinical chemistry ○ Urinalysis ○ Urine cytology ○ Exogenous tracer glomerular filtration rate (GFR) • Antibodies to dystrophin and viltolarsen • 12-lead electrocardiogram (ECG)	

<table>
<tr><td></td><td></td><td></td><td>• Clinical signs and symptoms (adverse events [AEs] and serious adverse events [SAEs])
• Grading of clinical and clinical laboratory AEs will be according to the Common Terminology Criteria for Adverse Events (CTCAE) v.4.03</td><td></td></tr>
<tr><td></td><td></td><td>Exploratory Objective(s)</td><td>Exploratory Endpoint(s)</td><td></td></tr>
<tr><td></td><td></td><td>• To evaluate health-related quality of life impact of viltolarsen treatment on participant’s DMD.</td><td>• Pediatric Outcome Data Collection Instrument (PODCI)</td><td></td></tr>
<tr><td></td><td></td><td></td><td>• Personal Adjustment and Role Skills Scale, 3rd edition (PARS III) Questionnaire</td><td></td></tr>
<tr><td>Study Design</td><td colspan="4">This Phase 3 study is a randomized, double-blind, placebo-controlled, multi-center study in ambulant boys ages 4 to <8 years with DMD receiving 80 mg/kg viltolarsen administered IV weekly over a 48-week treatment period. Participants are randomly assigned to either 80 mg/kg/week viltolarsen or placebo in a 1:1 ratio.
<table>
<tr><th>Group</th><th>Number of Participants</th><th>Investigational Product</th></tr>
<tr><td>1</td><td>37</td><td>Viltolarsen 80 mg/kg/week</td></tr>
<tr><td>2</td><td>37</td><td>Placebo</td></tr>
</table></td></tr>
<tr><td>Study Population</td><td colspan="4">Inclusion Criteria:
1. Participant’s parent(s) or legal guardian(s) has (have) provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization, where applicable, prior to any study-related procedures; participants will be asked to give written or verbal assent according to local requirements;
2. Participant has a confirmed diagnosis of DMD defined as:
a. Participant is male with clinical signs compatible with DMD; and</td></tr>
</table>

	b. Participant has a confirmed DMD mutation(s) in the dystrophin gene that is amenable to skipping of exon 53 to restore the dystrophin mRNA reading frame including determination of unambiguously defined exon boundaries (using techniques such as Multiplex Ligation-dependent Probe Amplification [MLPA], comparative genomic hybridization [CGH] array or other techniques with similar capability); 3. Participant is ≥4 years and <8 years of age at time of first infusion in the study; 4. Participant is able to walk independently without assistive devices; 5. Participant is able to complete the TTSTAND without assistance in <10 seconds, as assessed at the Screening Visit and the Pre-infusion Visit. (Note: The TTSTAND performed independently from the NSAA should be used to determine eligibility.); 6. Participant and parent(s)/guardian(s) are willing and able to comply with scheduled visits, study drug administration plan, and study procedures; 7. Participant must be on a stable dose of glucocorticoid (GC) for at least 3 months prior to first dose of study drug and is expected to remain on the stable dose of GC treatment for the duration of the study. **Exclusion Criteria:** 1. Participant has current or history of chronic systemic fungal or viral infections; 2. Participant has had an acute illness within 4 weeks prior to the first dose of study drug based on the Principal Investigator's judgment/discretion; 3. Participant has evidence of symptomatic cardiomyopathy. (Note: Asymptomatic cardiac abnormality on investigation would not be exclusionary.); 4. Participant has an allergy or hypersensitivity to the study drug or to any of its constituents; 5. Participant has severe behavioral or cognitive problems that preclude participation in the study, in the opinion of the investigator; 6. Participant has a previous or ongoing medical condition, medical history, physical findings, or laboratory abnormalities that could affect participant safety, make it unlikely that treatment and follow-up will be correctly completed, or impair the assessment of study results, in the opinion of the investigator;

	7. Participant has had surgery within the 3 months prior to the first anticipated administration of study drug or surgery is planned for anytime during the duration of the study; 8. Participant has positive test results for hepatitis B antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) antibody at screening. (Note: A positive hepatitis C antibody result is acceptable if accompanied by a negative hepatitis C RNA test and normal bilirubin and gamma-glutamyl transferase results.); 9. Participant is currently taking any other investigational drug or has taken any other investigational drug within 3 months prior to the first dose of study drug or within 5 times the half-life of a medication, whichever is longer; 10. Participant was previously enrolled in an interventional study of viltolarsen; 11. Participant is currently taking any other exon skipping agent or has taken any other exon skipping agent within 3 months prior to the first dose of study drug; 12. Participant has taken any gene therapy; 13. Participant is currently taking idebenone, anabolic steroids (e.g., oxandrolone), or products containing resveratrol or adenosine triphosphate, or has taken such within 3 months prior to first dose of study drug. Coenzyme Q10 or creatine are permitted only if the participant is receiving a stable dose for at least 3 months prior to the first dose of study drug and for the duration of the study; 14. Note: There is no exclusion criterion #14. This criterion was removed from the protocol with Amendment 4 (version 3.0, dated 08 January 2021); however, the numbering was maintained to avoid documentation errors; 15. Participant has hydronephrosis, hydroureter, renal or urinary tract calculi, or ureteral stenosis by medical history or renal ultrasound. **Note:** Any parameter/test may be repeated at the investigator's discretion during screening to determine sustainability and reproducibility.
Test Product, Dose, and Mode of Administration	Viltolarsen injection 250 mg aqueous solution will be supplied as a 5 mL glass vial containing 50 mg/mL of drug substance solution in saline. Participants randomized to viltolarsen will receive IV infusions of viltolarsen injection administered once weekly over a 48-week period. Participants will be dosed at 80 mg/kg/week.

Comparator, Dose, and Mode of Administration	Placebo will be supplied as a 5 mL matching glass vial of saline without the drug substance solution. Participants randomized to placebo will receive IV infusions of placebo administered once weekly over a 48-week period.

Safety Measures	• Vital signs (blood pressure, heart rate, respiratory rate, and body temperature [modality for determining temperature should be consistent for each participant at all assessment time points throughout the study])
	• Physical examination
	• Clinical laboratory tests:
	  o Hematology and clinical chemistry
	  o Urinalysis
	  o Urine cytology
	  o Exogenous tracer GFR
	• 12-lead ECG
	• Antibodies to dystrophin and viltolarsen
	• Clinical signs and symptoms (AEs and SAEs)
	• Grading of clinical and clinical laboratory AEs will be according to CTCAE v.4.03

Clinical Efficacy Measures	**Primary Outcome:** • TTSTAND at 48 weeks of treatment **Secondary Outcomes:** Hierarchical analysis at 48 weeks treatment of the following strength and endurance measures: • TTRW • 6MWT • NSAA • TTCLIMB • Quantitative muscle strength measured by hand-held dynamometer (elbow extension, elbow flexion, knee extension, and knee flexion on the dominant side only)
Exploratory Measures	• PODCI • PARS III Questionnaire
Pharmacokinetic Measures	Viltolarsen levels in plasma will be assessed at predose and 1, 3, and 6 hours after initiation of infusion at Day 1. Viltolarsen levels in plasma will be assessed at predose and 2 hours after initiation of infusion at Weeks 13, 25, 37, and 48 as well as at 6 hours after initiation of infusion at Week 48.

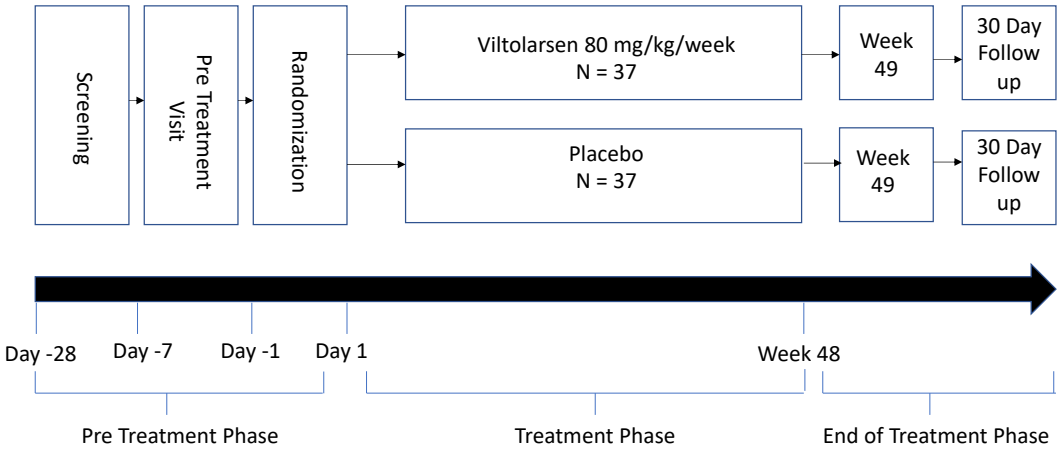
Statistical Methods	**Sample Size:** A total of approximately 74 participants: Viltolarsen 80 mg/kg/week (n=37) Placebo (n=37) **Analysis Populations:** The safety population will consist of all randomized participants who received at least 1 dose of investigational product. Participants will be analyzed as treated. This will be the primary analysis population for the evaluation of exposure and safety. The modified Intent-to-Treat (mITT) population will consist of all randomized participants who received at least 1 dose of investigational product and have a baseline assessment and at least 1 post baseline efficacy assessment. Participants will be analyzed as randomized. This will be the primary analysis population for the evaluation of efficacy. **General Statistical Considerations:** For TTSTAND (calculated as a velocity, defined as rise per second), the sample size of 74 participants has been calculated using the following values: • Mean difference = 0.05 • Standard deviation = 0.075 • Type I error level (two-sided) = 0.05 • Power level = 0.8 • Allocation ratio (N1: viltolarsen/N2: placebo) = 1 The mean difference and the SD were set based on the result of comparison between viltolarsen group and natural history control group at 25 weeks in the Phase 2 Study NS-065/NCNP-01-201 (mean difference between 2 groups: 0.0395, SD: 0.07545 and 0.07377). As the mean difference between the 2 groups at 48 weeks is expected to be larger than at 25 weeks, the mean difference was estimated to be 0.05. An unpaired t-test for analysis was used instead of mixed effect model repeat measurement for the calculation method due to lack of prior information. When approximately 90% of participants are enrolled in the study, an unblinded review will be conducted and sample size re-estimation will be considered. An additional unblinded review and re-estimation will be performed when approximately 50 participants have completed the Week 49 evaluations for the primary outcome measure.

	Efficacy Evaluation: The primary efficacy outcome of TTSTAND will be summarized descriptively at each visit using actual values and change from baseline values. The time measured for TTSTAND will be converted to a velocity expressed as rise per second. The primary efficacy outcome measure of TTSTAND velocity will be compared between participants treated with viltolarsen or placebo using mixed-effects linear models. Secondary and exploratory outcomes are detailed in the protocol and statistical analysis plan. **Safety Evaluation:** Safety analyses will be performed using the safety population. All safety assessments will be based on actual treatments received by participants and are detailed in the protocol and statistical analysis plan. **Pharmacokinetic Evaluation:** Population PK analysis will be presented in a separate report.

1 STUDY SCHEMA AND SCHEDULE OF ASSESSMENTS

1.1 Study Schema

Figure 1 Study Design



1.2 Schedule of Assessments

Table 1. Schedule of Study Assessments for Pretreatment Phase to Treatment Phase Week 24

Assessment *	Pretreatment Phase		Treatment Phase (Day 1 to Week 24) **													
	Screening Visit[a] Day -28 to Day -8	Pre-Infusion Visit Day -7 to Day -1	First Infusion Day 1	2	3	4	5	6 to 8	9	10 to 12	13	14 to 16	17	18 to 20	21	22 to 24
				± 3 days for each weekly visit												
General Procedures																
Informed consent/assent	X															
Inclusion/exclusion criteria[b]	X	X														
Confirmed diagnosis of DMD	X		X[c]													
Demographics[d]	X															
Medical and surgical history[e]	X															
Medication and treatment history[f]	X	X	X													
Medical and surgical procedure review[g]				X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication and treatment[h]				X	X	X	X	X	X	X	X	X	X	X	X	X
Height[i] and weight[j]	X	X	X								X					
Vital signs[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical and neurological examination[l]	X	X	X				X		X		X		X		X	
12-lead ECG[m]	X		X								X					
Renal ultrasound[n]	X										X					
Laboratory Assessments																
Hematology[o]	X		X		X		X		X		X		X		X	
Chemistry[o]	X		X		X		X		X		X		X		X	
First morning void urinalysis[o,p]	X[q]	X			X		X		X		X		X		X	
Urine cytology[r]		X									X					
Postdose urinalysis[o,s]			X								X					

Assessment *	Pretreatment Phase		Treatment Phase (Day 1 to Week 24) **													
	Screening Visit[a] Day -28 to Day -8	Pre-Infusion Visit Day -7 to Day -1	First Infusion Day 1	2	3	4	5	6 to 8	9	10 to 12	13	14 to 16	17	18 to 20	21	22 to 24
				± 3 days for each weekly visit												
Exogenous tracer GFR[t]		X														
Antigen and antibody testing[u]	X															
Anti-dystrophin antibody[v]			X								X					
Anti-viltolarsen antibody[v]			X								X					
Pharmacokinetic Assessment																
PK (blood)[w]			X								X					
Other Assessments																
Function and strength[x]	X	X									X					
Patient reported outcome[y]	X	X									X					
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigational Product Administration																
Study drug administration[z]			X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: DMD = Duchenne muscular dystrophy; ECG = electrocardiogram; GFR = glomerular filtration rate; IV = intravenous; PARS III = Personal Adjustment and Role Skills Scale, 3rd edition; PK = pharmacokinetics; PODCI = Pediatric Outcome Data Collection Instrument.
Note: Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, blood draws, with vital signs obtained without repositioning.

a. The informed consent/assent must be obtained prior to any study related procedures being conducted. Request for randomization will be made after all screening procedures are performed and prior to the first treatment.
b. The Time to Stand Test (TTSTAND) is performed independently and as part of the North Star Ambulatory Assessment (NSAA). The TTSTAND performed independently from the NSAA should be used to determine eligibility to satisfy inclusion criterion #5.
c. A DMD genetic test at Day 1 will be conducted in order to obtain uniform DMD mutation information for the exact intronic boundaries to be analyzed by a central laboratory.
d. Demographics will include date of birth, race, ethnicity, and hand dominance.
e. Medical history will include the following: medical and surgical history.
f. Includes prior and concomitant medication, treatment history.
g. Medical and surgical procedures will be reviewed.
h. Concomitant medication and treatments will be reviewed.
i. Height will be collected without shoes. The participant's legs should be kept as close as possible and the participant's heels should be placed back as close to the wall as possible. Participant may hold on to an object to facilitate balance.
j. Weight will be collected with the participant wearing no shoes and light-weight clothes.
k. For each visit that includes a study drug administration, vital signs will be measured at predose as well as 1 hour (up to 20 minutes following completion of the infusion) and 2 hours (± 20 minutes) after initiation of infusion. If a clinically significant change from predose is observed at

2 hours after initiation of infusion, the parameter will be measured again at 6 hours (± 20 minutes) after initiation of infusion. Vital signs will be measured prior to any blood collection scheduled at the same time point and will include systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature.

l. Physical and neurological examinations will include an assessment of the following: general appearance, head, ears, eyes, nose, and throat (HEENT), skin, lymph nodes, heart, including rhythm, heart sounds and presence of cardiac abnormalities, lungs, abdomen, extremities/joints, nervous system, and any additional assessments necessary to establish baseline status or evaluate symptoms or adverse experiences as detailed in Section 9.11.
m. ECGs will be performed with the participant having rested for at least 5 minutes, and the participant should remain in the supine or semi-recumbent position. A consistent position should be maintained for each individual participant. On Day 1, triplicate ECGs, each approximately 1 to 2 minutes apart, will be collected at predose as well as 1 hour (up to 20 minutes following completion of the infusion) and 3 hours (± 20 minutes) after initiation of infusion. At the Screening Visit and Week 13, single ECGs will be collected (predose is recommended at Week 13).
n. Renal ultrasound will include imaging of the kidneys, ureters, and bladder. Except for the screening assessment, renal ultrasound can occur up to 2 weeks prior to or after the scheduled week, as needed for scheduling purposes.
o. Refer to Table 3 for additional details on the clinical laboratory tests, including the laboratory analytes that will be measured for hematology, serum chemistry, and urinalysis.
p. Patients will collect a first morning void urine sample on the date of the specified visit and bring it to the site. Analysis of the sample will include urine dipstick protein to be performed at the site. An aliquot will also be sent to the central laboratory for urinalysis. Refer to Section 11.11.1 for details on monitoring of renal function and urine analyses.
q. First morning void urine sample collection and dipstick protein are not required at screening.
r. To be performed on a predose urine sample collected on-site.
s. To be performed on a urine sample collected within 5 hours after completion of infusion.
t. GFR will be determined using an exogenous tracer test, if available. This should be done per standard of care at the institution.
u. To include hepatitis B antigen, hepatitis C antibody, and HIV antibody.
v. To be collected predose and will be performed on serum blood samples.
w. Viltolarsen levels in plasma will be assessed at predose (within 60 minutes prior to dose) as well as 1 hour (up to 20 minutes following completion of the infusion), 3 hours (± 20 minutes), and 6 hours (± 20 minutes) after initiation of infusion at Day 1. Viltolarsen levels in plasma will be assessed at predose (within 60 minutes prior to dose) and 2 hours (± 20 minutes) after initiation of infusion at Week 13. Postdose PK should not be drawn from the cannula that was used for the infusion. These samples can be drawn from the arm opposite the infusion or can be from a separate distal access point in the same arm as the infusion. This postdose PK draw requirement is in place to prevent any contamination with viltolarsen derived from the dosing cannula.
x. Function and strength test will include the following: Time to Stand Test (TTSTAND), Time to Run/Walk 10 Meters Test (TTRW), North Star Ambulatory Assessment (NSAA), Time to Climb 4 Stairs Test (TTCLIMB), Six-minute Walk Test (6MWT), and hand-held dynamometer. The NSAA and hand-held dynamometer should be administered before the 6MWT at each visit.
y. Patient reported outcomes will include PODCI and PARS III.
z. Investigational product solution is administered every week within a ± 3-day window. A minimum of 3 days (72 hours) should elapse between treatments.

* If a participant returns to the clinic for a visit outside of the protocol evaluation time points, the visit and any assessments and/or tests performed will be recorded in the source documents and the eCRF as an Unscheduled Visit.

** If allowed per local regulations, Weeks 6 to 8, 10 to 12, 14 to 16, 18 to 20, and 22 to 24 can be completed at a non-site location via the home health vendor. NS Pharma reserves the right to require visits to be completed at the site, if needed.

Table 2. Schedule of Study Assessments for Treatment Phase from Week 25 to End-of-Treatment Phase

Assessment *	Treatment Phase (Week 25 to Week 48) ** ± 3 days for each weekly visit													End-of-Treatment Phase[a]		
Week	**25**	**26 to 28**	**29**	**30 to 32**	**33**	**34 to 36**	**37**	**38 to 40**	**41**	**42 to 44**	**45**	**46 to 47**	**48**	**49**	**Follow-Up Telephone Call[a] 30 days (± 3 days) postdose**	**ET[b]**
General Procedures																
Medical and surgical procedure review[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication and treatment[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and weight[e]	X						X							X		X
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Physical and neurological examination[g]	X						X							X		X
12-lead ECG[h]	X						X							X		X
Renal ultrasound[i]	X						X							X		X
Laboratory Assessments																
Hematology[j]	X						X							X		X
Chemistry[j]	X						X							X		X
First morning void urinalysis[j,k]	X		X		X		X		X		X			X		X
Urine cytology[l]	X						X							X		X
Postdose urinalysis[j,m]	X						X									
Exogenous tracer GFR[n]														X		X
Anti-dystrophin antibody[o]	X						X						X			X
Anti-viltolarsen antibody[o]	X						X						X			X
Pharmacokinetic Assessment																
PK (blood)[p]	X						X						X			
Other Assessments																
Function and strength[q]	X						X							X		X
Patient reported outcome[r]	X						X							X		X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Assessment *	Treatment Phase (Week 25 to Week 48) ** ± 3 days for each weekly visit													End-of-Treatment Phase[a]		
Week	**25**	**26 to 28**	**29**	**30 to 32**	**33**	**34 to 36**	**37**	**38 to 40**	**41**	**42 to 44**	**45**	**46 to 47**	**48**	**49**	**Follow-Up Telephone Call[a] 30 days (± 3 days) postdose**	**ET[b]**
Investigational Product Administration																
Study drug administration[s]	X	X	X	X	X	X	X	X	X	X	X	X	X			

Abbreviations: ECG = electrocardiogram; ET = early termination; GFR = glomerular filtration rate; IV = intravenous; PARS III = Personal Adjustment and Role Skills Scale, 3rd edition; PK = pharmacokinetics; PODCI = Pediatric Outcome Data Collection Instrument.
Note: Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, blood draws, with vital signs obtained without repositioning.

a. Participants will have a telephone call conducted by the site study staff, 30 days (± 3 days) following the last study drug administration.
b. If a participant returns to the clinic for a visit outside of the protocol evaluation time points, the visit and any assessments and/or tests performed will be recorded in the source documents and the eCRF as an Unscheduled Visit.
c. Medical and surgical procedures will be reviewed.
d. Concomitant medication and treatments will be reviewed.
e. Height will be collected without shoes. The participant's legs should be kept as close as possible and the participant's heels should be placed back as close to the wall as possible. Participant may hold on to an object to facilitate balance. Weight will be collected with the participant wearing no shoes and light-weight clothes.
f. For each visit that includes a study drug administration, vital signs will be measured at predose as well as 1 hour (up to 20 minutes following completion of the infusion) and 2 hours (± 20 minutes) after initiation of infusion. If a clinically significant change from predose is observed at 2 hours after initiation of infusion, the parameter will be measured again at 6 hours (± 20 minutes) after initiation of infusion. Vital signs will be measured prior to any blood collection scheduled at the same time point and will include: systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature.
g. Physical and neurological examinations will include an assessment of the following: general appearance, head, ears, eyes, nose, and throat (HEENT), skin, lymph nodes, heart, including rhythm, heart sounds and presence of cardiac abnormalities, lungs, abdomen, extremities/joints, nervous system, and any additional assessments necessary to establish baseline status or evaluate symptoms or adverse experiences as detailed in Section 9.11.
h. ECGs will be performed with the participant having rested for at least 5 minutes, and the participant should remain in the supine or semi-recumbent position. A consistent position should be maintained for each individual participant. At Weeks 25, 37, 49, and ET, single ECGs will be collected (predose is recommended at Weeks 25 and 37).
i. Renal ultrasound will include imaging of the kidneys, ureters, and bladder. Except for the screening assessment, renal ultrasound can occur up to 2 weeks prior to or after the scheduled week, as needed for scheduling purposes.
j. Refer to Table 3 for additional details on the clinical laboratory tests, including the laboratory analytes that will be measured for hematology, serum chemistry, and urinalysis.

k. Patients will collect a first morning void urine sample on the date of the specified visit and bring it to the site. Analysis of the sample will include urine dipstick protein to be performed at the site. An aliquot will also be sent to the central laboratory for urinalysis. Refer to Section 11.11.1 for details on monitoring of renal function and urine analyses.
l. To be performed on a predose urine sample collected on-site.
m. To be performed on a urine sample collected within 5 hours after completion of infusion.
n. GFR will be determined using an exogenous tracer test, if available. This should be done per standard of care at the institution.
o. To be collected predose and will be performed on serum blood samples.
p. Viltolarsen levels in plasma will be assessed at predose (within 60 minutes prior to dose) and 2 hours (± 20 minutes) after initiation of infusion at Week 25, Week 37, and Week 48 as well as at 6 hours (± 20 minutes) after initiation of infusion at Week 48. Postdose PK should not be drawn from the cannula that was used for the infusion. These samples can be drawn from the arm opposite the infusion or can be from a separate distal access point in the same arm as the infusion. This postdose PK draw requirement is in place to prevent any contamination with viltolarsen derived from the dosing cannula.
q. Function and strength test will include the following: Time to Stand Test (TTSTAND), Time to Run/Walk 10 Meters Test (TTRW), North Star Ambulatory Assessment (NSAA), Time to Climb 4 Stairs Test (TTCLIMB), Six-minute Walk Test (6MWT), and hand-held dynamometer. The NSAA and hand-held dynamometer should be administered before the 6MWT at each visit.
r. Patient reported outcomes will include PODCI and PARS III.
s. Investigational product solution is administered every week within a ± 3-day window. A minimum of 3 days (72 hours) should elapse between treatments.

* If a participant returns to the clinic for a visit outside of the protocol evaluation time points, the visit and any assessments and/or tests performed will be recorded in the source documents and the eCRF as an Unscheduled Visit.

** If allowed per local regulations, Weeks 26 to 36 and 38 to 47 can be completed at a non-site location via the home health vendor. NS Pharma reserves the right to require visits to be completed at the site, if needed.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

2'O-Me	2'O-methyl phosphorothioate
6MWT	Six-minute Walk Test
ADL	Activities of Daily Living
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical classification
AUC	Area under the curve
BMD	Becker muscular dystrophy
Ca	Calcium
cDNA	Complementary DNA
CGH	Comparative genomic hybridization
Cl	Chloride
CE	Clinical evaluator
CINRG	Cooperative International Neuromuscular Research Group
C_{max}	Maximum Drug Concentration
CMO	Contract manufacturing organization
CRO	Clinical Research Organization
CSR	Clinical Study Report
CK	Creatine kinase
cm	Centimeter
CTCAE	Common Terminology Criteria for Adverse Events v4.03
CVA	Central venous access
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
DMD	Duchenne muscular dystrophy
DNHS	Duchenne Natural History Study
DSMB	Data and Safety Monitoring Board
DSUR	Drug Safety Update Reports
ECG	Electrocardiogram
eCRF	Electronic case report form
EU	European Union
FDA	Food and Drug Administration
GC	Glucocorticoid
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HB	Hepatitis B
HCV	Hepatitis C Virus
HEENT	Head, ears, eyes, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug

IPIM	Investigational Product Information Manual
IRB	Institutional Review Board
IV	Intravenous(ly)
K	Potassium
kg	Kilogram
LC-MS/MS	Liquid Chromatography Tandem Mass Spectrometry
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention to treat
MLPA	Multiplex Ligation-dependent Probe Amplification
MMRM	Mixed effect model repeat measurement
mRNA	Messenger ribonucleic acid
MS	Mass spectrometry
Na	Sodium
NCNP	National Center of Neurology and Psychiatry, Japan
N/D	Not done
NOAEL	No observed adverse effect level
NSAA	North Star Ambulatory Assessment
NSP	NS Pharma, Inc.
NS-065/NCNP-01	NS-065/NCNP-01 drug substance
NS-065/NCNP-01 Injection 250 mg	NS-065/NCNP-01 investigational drug substance solution (250 mg vial strength)
PARS III Questionnaire	Personal Adjustment and Role Skills Scale, 3rd edition
PCR	Polymerase chain reaction
PHI	Protected Health Information
PK	Pharmacokinetic
PMO	Phosphorodiamidate morpholino oligomer
PODCI	Pediatric Outcome Data Collection Instrument
PT-INR	Prothrombin Time – International Normalized Ratio
QMT	Quantitative Muscle Testing
QWBA	Quantitative whole-body autoradiography
RT-PCR	Reverse transcriptase polymerase chain reaction
RBC	Red blood cell count
Ret	Reticulocyte
RIPA	Radioimmunoprecipitation assay
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SD	Standard deviation
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal Elimination Half-Life
T_{max}	Time of Maximum Drug Concentration
TEAEs	Treatment-emergent AEs

TICVAD	Totally implantable central venous access device
TK	Toxicokinetic
TNF-α	Tumor necrosis factor-alpha
TTCLIMB	Time to Climb 4 Stairs Test
TTRW	Time to Run/Walk 10 Meters Test
TTSTAND	Time to Stand Test
UPCR	Urine protein to creatinine ratio
US	United States
WBC	White blood cell count

2 INTRODUCTION

2.1 Rationale for Study Design, Control Group, and Dose Selection

2.1.1 Rationale for Dose Selection

The dose (80 mg/kg/week for 48 weeks) for this study was based on the successful treatment of participants at 80 mg/kg/week in Study NS-065/NCNP-01-201 for up to a total of 24 weeks of treatment, as well as in the Phase 1/2 Study NS-065/NCNP-01-P1/2 conducted in Japan (Japan P1/2). Results are detailed below.

Viltolarsen dystrophin levels and exon skipping ratio were assessed in Japan P1/2 (Study NS065/NCNP01-P1/2) and Study NS-065/NCNP-01-201. The results are summarized below:

1. Highest dystrophin production measured by Western Blot at 20 to 24 weeks in both Japan P1/2 (Study NS065/NCNP01-P1/2 [n = 4]) and Study NS-065/NCNP-01-201 (n = 8) studies were observed at 80 mg/kg.
2. Average dystrophin production by group measured by Western Blot at 24 weeks in Japan P1/2 (Study NS065/NCNP01-P1/2) was higher at 80 mg/kg (n = 4).
3. Average dystrophin production [redacted] measured by Western Blot at 20 to 24 weeks in both Japan P1/2 (Study NS065/NCNP01-P1/2) and Study NS-065/NCNP-01-201 (n = 3) were higher at 80 mg/kg.

   [redacted]
4. Average % of dystrophin positive fiber by group measured by immunofluorescence in Study NS-065/NCNP-01-201was higher at 80 mg/kg (n = 8).
5. Average exon skipping ratio by group measured by RT-PCR in both Japan P1/2 (NS065/NCNP01-P1/2) and Study NS-065/NCNP-01-201were higher at 80 mg/kg.
6. Safety profiles were comparable in both Japan P1/2 (NS065/NCNP01-P1/2) and Study NS-065/NCNP-01-201 studies between 40 and 80 mg/kg.

Study NS-065/NCNP-01-201 and Study NS-065/NCNP-01-202 (extension study for Study NS-065/NCNP-01-201) have enrolled a total of 16 participants. As of 28 February 2018, there have been no apparent drug-related serious adverse events (SAEs) reported, and no adverse events (AEs) led to study drug discontinuation. One SAE (left tibia/fibula fracture required hospitalization for surgery, not-related to drug) was reported in June 2018. Safety profiles were comparable for both studies at 40 mg/kg and 80 mg/kg.

In summary, the dose of 80 mg/kg/week for 48 weeks is supported, based on dystrophin production at 80 mg/kg/week and safety profile (well-tolerated for 168 weeks) in the 2 studies (Japan P1/2 (NS065/NCNP01-P1/2) and Study NS-065/NCNP-01-201) conducted to date.

2.1.2 Rationale for Study Design and Control Group

The sponsor indicated its preference to conduct a single global confirmatory trial and expressed concerns about the impact on enrolling for a placebo-controlled trial after an accelerated approval is granted in the United States (US) and Japan. The Food and Drug Administration (FDA) explained the complexity in interpreting a study with natural history as a control group due to the heterogeneity of the disease progression in Duchenne muscular dystrophy (DMD), unless the drug effect is very large. Therefore, the FDA reiterated their position that a placebo controlled study would be required.

2.1.3 Rationale for the Primary Endpoint and Age Range

The primary endpoint for this study is the Time to Stand Test (TTSTAND). The rationale for using TTSTAND as the primary endpoint is:

- TTSTAND is an objective endpoint that can be measured in a standardized way,
- TTSTAND is well validated,
- TTSTAND is clinically meaningful as a measure of patient function, and
- TTSTAND is an important prognostic factor and more generally can predict disease progression.

TTSTAND is the first functional milestone lost in DMD disease progression (McDonald et al, 2018; Arora et al, in press). The sponsor intends to use velocity rather than time (seconds)

because the velocity measure is superior to the time (seconds) measure in handling large values as patients begin to lose the ability to stand.

In consideration of boys with DMD who could perform functional tests (Arora et al, in press), age range with 4 to <8 years is selected.

2.1.4 Rationale for Study Duration of 48 Weeks

Individual participant study duration is 48 weeks, which takes into consideration the feasibility of patient enrollment and retention in the proposed placebo-controlled study.

2.2 Disease and Treatment

2.2.1 Duchenne Muscular Dystrophy– Epidemiology and Genetic/Biochemical Basis

DMD is a disorder of progressive weakness leading to severe disability and ultimately death caused by a deficiency of the dystrophin protein. The reported prevalence of DMD is 15.9 cases per 100,000 live male births in the US and 19.5 cases per 100,000 live male births in the UK (Ryder et al, 2017; Mendell et al, 2012; Moat et al, 2013). The symptoms of DMD are often first noted at about 3 to 5 years of age, although clinical manifestations may be present as early as the first year of life. Proximal leg weakness impairs mobility and precludes the ability to run or to rise from a squatting position. Complete loss of ambulation follows, with a progressive decline of upper extremity strength and function. Declines in respiratory and cardiac function contribute to morbidity later in the disease, ultimately culminating in early lethality (Bushby et al [Part 1], 2018; Birnkrant et al, 2018.) The impact of this debilitating condition on those affected by it and their families is significant.

The biochemical basis of DMD is the absence of a functional dystrophin protein in striated muscle tissue that is essential for healthy muscle function and muscle fiber integrity. In normal striated muscle the cytoplasmic dystrophin protein links intracellular actin with the extracellular matrix to provide structural stability of the muscle cell membrane. In the majority of patients with DMD, dystrophin protein is not produced because of out-of-frame mutations characterized by a deletion of one or more exons from the dystrophin gene, which is located on the short arm of the X chromosome. Dystrophin mutations in which some dystrophin protein function remains are associated with a similar, but often milder phenotype, classified as Becker muscular dystrophy (BMD). DMD and BMD exhibit X-linked recessive inheritance.

2.2.2 Current Natural History, Disease Management, and Treatment Recommendations

The Cooperative International Neuromuscular Research Group (CINRG) conducted the largest prospective multi-center natural history study to date in DMD, the CINRG Duchenne Natural History Study (DNHS) (McDonald et al, 2013; Henricson et al, 2013; McDonald et al, 2018). The study includes >400 boys and men with DMD, with variable amounts of longitudinal follow-up over the course of a decade (2006 to 2016). The study has annual follow-up visits that include timed function tests, muscle strength, questionnaire functional assessments, pulmonary function tests, and quality of life assessments.

Since there is currently no cure for DMD, the goal of care is to provide the best quality of life through all stages of the disease. To date, treatments focus on optimizing strength and function through the use of pharmacological interventions, physical therapy, and assistive and adaptive devices.

2.2.3 Glucocorticoid Treatment

At present, treatment with glucocorticoid (GC) medication is the only pharmacological intervention that has been shown to slow the decline of strength and function in DMD patients. The two main GCs used in DMD are prednisone and deflazacort (EMFLAZA™). Daily oral administration of prednisone or deflazacort stabilizes or improves strength and prolongs ambulation (Drachman et al, 1974; Brooke et al, 1987; Griggs et al, 1993; Mendell et al, 1989; Griggs et al, 1991; Fenichel et al, 1991). The mechanism by which GCs are beneficial in dystrophin deficiency is likely multifactorial, including anti-inflammatory actions. The immunosuppressive effects of GCs may not be beneficial, and other immunosuppressants have not shown benefit (Griggs et al, 1993). On February 9, 2017, the US FDA approved EMFLAZA™ for the treatment of patients 5 years of age and older with DMD.

In 2005, the American Academy of Neurology issued a practice parameter regarding GC treatment in DMD and recommended that GC should be offered as treatment, despite known side effects (Moxley et al, 2005). The significant side effects of GCs include Cushingoid features, adverse behavioral changes, obesity, growth retardation, increased risk for bone fractures, gastritis, delayed puberty, cataracts, hypertension, glucose intolerance, susceptibility to infection, and masking of response to stress (Matthews et al, 2016).

2.2.4 Dystrophin Restoring Interventions

New therapies based on specific genotypes are in development. Small molecules that can read through nonsense mutations could potentially treat approximately 13% of DMD patients (Bushby et al, 2014). Exon skipping, which uses antisense oligonucleotides to alter the splicing pattern of the genes is designed to bring out-of-frame deletions into frame. The technology of exon skipping utilizes antisense oligonucleotides that bind to a specific sequence in the messenger ribonucleic acid (mRNA) to alter splicing of exons. By this means, specific exons can be excluded from the final transcript that is exported to the cytoplasm from the nucleus; hence the term 'exon skipping'. By the design of the oligonucleotide, the out-of-frame deletion can be enlarged to include the adjacent exon such that the resulting deletion is in-frame (Kole and Krieg, 2015).

This new type of treatment could potentially treat 80% of DMD patients who have large-scale deletion or duplication mutations in the dystrophin gene (Aartsma et al, 2009). The full characterization of DMD patient mutations and further development of the technology will be crucial to fully realize these novel therapies as they are developed.

To date, 2 oligonucleotide chemistries have been brought to the stage of human clinical trial: 2'O-methyl phosphorothioate (2'O-Me) antisense oligonucleotides (Voit et al, 2014) and phosphorodiamidate morpholino oligomers (PMO) for skipping of exon 51 in the dystrophin gene (Mendell et al, 2013; Cirak et al, 2012; Cirak et al, 2011).

A 48-week study of the 2'O-Me compound drisapersen did not reach significance in the Six-minute Walk Test (6MWT), which was its primary outcome measure for this Phase 2 study (Voit et al, 2014). The PMO compound eteplirsen was tested in a 48-week study, with the number of muscle fibers showing restored dystrophin as its primary outcome measure (Mendell et al, 2013). Eteplirsen (Exondys 51®) was approved by the FDA under the accelerated approval pathway on September 19, 2016.

2.3 Background on Viltolarsen

Viltolarsen is a novel antisense oligonucleotide for the treatment of DMD, which has been discovered jointly by National Center of Neurology and Psychiatry (NCNP) which is a National Research and Development Agency in Japan and Nippon Shinyaku Co., Ltd. Details of data summarized in the following sections can be found in the Investigator's Brochure.

2.3.1 Mechanism of Action

Viltolarsen is designed to interact with the dystrophin gene ribonucleic acid (RNA) and alter the exon/intron splicing patterns. The mechanism of action is for viltolarsen to bind to a specific sequence in or near exon 53 of the dystrophin pre-RNA transcript and block the exon/intron splicing of exon 53, leading to mature mRNA transcripts that lack exon 53. Viltolarsen is thought to be effective on DMD patients with exon deletions amenable to skipping of exon 53 such as 43-52, 45-52, 47-52, 48-52, 49-52, 50-52, or 52. The loss of exon 53 restores the mRNA reading frame, thus converting a DMD (out-of-frame) deletion mutation to a Becker-like (in-frame) deletion mutation. In-frame deletion mutations are typically compatible with production of a shortened dystrophin protein, although the resulting Becker-like dystrophin protein will be smaller in molecular weight compared to the normal dystrophin protein, and likely lower in abundance (quantity) compared to normal muscle, and thus may have lower function than normal amounts of wild-type dystrophin protein.

2.3.2 Summary of Non-Clinical Findings

2.3.2.1 Pharmacology

Viltolarsen (0 to 10 μmol/L) demonstrated sustained exon 53 skipping and dystrophin protein expression for at least 2 weeks in cells from a DMD patient with deletion of exons 45–52 and in cells from a DMD patient with deletion of exons 48–52. In cynomolgus monkeys, a dose of 60 mg/kg viltolarsen resulted in exon 53 skipping in the right gastrocnemius muscles and the cardiac muscle in a 12-week intermittent intravenous (IV) toxicity study.

The potential off-target effect of viltolarsen and its n ± 1 mers among all human mRNA sequences was assessed by *in silico* and *in vitro* approaches. Taken together, while [redacted], *APCDD1*, *FUT1*, *CNTNAP2* and *MYT1* showed some predicted and statistically-significant changes on mRNA expression, the clinical relevance for these moderate differences in terms of protein expression or predicted effects on physiology *in vivo* is questionable.

Viltolarsen did not display any adverse effects in *in vitro* and *in vivo* cardiovascular, *in vivo* central nervous system, or *in vivo* respiratory safety pharmacology studies.

2.3.2.2 Pharmacokinetics

Pharmacokinetic (PK) and toxicokinetic (TK) analyses revealed no apparent species differences for viltolarsen. None of the *in vitro* or *in vivo* metabolism studies showed any distinct evidence of metabolism of viltolarsen. After IV administration, time of maximum plasma concentration (T_{max}) occurred at the first sampling time after the injection or at the end of the infusion for mice, rats, and monkeys. Maximum plasma concentration (C_{max}) and area under the curve (AUC) increased with dose, and most increases were approximately proportional to dose, with some increases being greater than dose proportional. For rats, the mean values for $t_{1/2}$ were 1.19, 1.19, and 10.5 hours for 6, 20, and 60 mg/kg. For monkeys, the mean values for $t_{1/2}$ ranged from 1.7 to 3.5 hours. For mice and monkeys, exposure did not change with 12 or 13 weeks of repeat dosing.

The fraction of viltolarsen bound to rat, monkey, and human serum proteins was low, ≤40%, for all species and was independent of concentration. The distribution of viltolarsen into red blood cells was ≤2.5%, ≤6.7%, and ≤3.5% for rat, monkey, and human, respectively, indicating low distribution of viltolarsen to red blood cells. Quantitative whole-body autoradiography (QWBA) studies showed wide tissue distribution of [^{14}C] viltolarsen in both mice and monkeys, with the highest concentrations observed in the kidney, and general distribution to muscle tissues. For both rats and monkeys, renal excretion was the major route of elimination, with less than 10% in the feces. No radioactivity was in the expired air from the rats. Most of the radioactivity was excreted within the first 24 hours. However, small measurable amounts continued to be excreted in the urine and feces throughout the seven-day collection periods.

Viltolarsen showed weak inhibition to cytochrome (CYP) 3A4 (Ki value: 1.44 mmol/L), while no inhibitory effects were observed to other CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6). Viltolarsen did not induce CYP1A2, CYP2B6 and CYP3A4. Viltolarsen showed weak inhibition to UGT1A1 (Ki value: 0.642 mmol/L), while no inhibitory effects were observed to UGT2B7. Viltolarsen was not a substrate of transporters (P-gp, BCRP, OAT1, OAT3, OCT2, MATE1 and MATE2-K). Viltolarsen showed weak inhibition to OATP1B1, OATP1B3, OAT3 and BCRP (respective IC_{50} value: 0.485, 0.448, 0.176 and 1.97 mmol/L), while no inhibitory effects were observed to other transporters (P-gp, OAT1, OCT1, OCT2, MATE1, MATE2-K and BSEP).

2.3.2.3 Toxicology

Histopathological evaluations following a single IV dose of 600 mg/kg in monkeys resulted in vacuolation of the epithelium of the proximal renal tubules. No other renal changes were noted. Repeated administration of viltolarsen via the clinically relevant route of administration (weekly IV injections) in mice, rats and monkeys resulted in decreases in red blood cell parameters, increased values for cytokines and histopathological effects in the kidney and urinary bladder. The kidney is the primary target organ in mice, rats and monkeys, as shown by increased values in clinical chemistry parameters indicative of renal effects (1000 mg/kg in 4-, 13- and 26-week mouse studies, ≥500 mg/kg in 4- and 13-week rat studies, and 600 mg/kg in a 12-week monkey study) and by histopathological findings of effects in renal tubules (≥240 mg/kg in 4-, 13- and 26-week mouse studies, ≥250 mg/kg in 4-week and 13-week rat studies ≥200 mg/kg in 12- and 39-week monkey studies) accompanied by increased kidney weight at necropsy. An additional histopathological finding in a 26-week mouse study was the presence of cytoplasmic eosinophilic material in the transitional epithelium of the urinary bladder at 60 mg/kg and above. An increase in blood urea nitrogen (BUN) was observed in all toxicity studies with all species mainly at the higher doses. The main causes of an increase in BUN are high protein diet, decrease in glomerular filtration rate (GFR) (suggestive of renal failure) and in blood volume (hypovolemia), congestive heart failure, gastrointestinal hemorrhage, fever, and increased catabolism. In the toxicity studies with viltolarsen, BUN increases were considered to be attributable to a decrease in GFR. Based on these data, the no observed adverse effect levels (NOAELs) were concluded to be 60 and 15 mg/kg in 13-week and 26-week mouse studies respectively and 60 mg/kg in 12-week and 39-week monkey studies respectively.
Results from *in vitro* and *in vivo* genotoxicity studies were negative, and studies showed no evidence of chromosomal aberrations.
In a study of the effects of viltolarsen on fertility and early embryonic development to implantation by intermittent IV administration, no toxicologically significant changes were noted in copulation rate, copulatory interval, fertility rate, necropsy, organ weights (testes or epididymis), sperm examinations, number of corpora lutea, number of implantations, implantation rate, preimplantation loss rate, number of live embryos, embryonic viability rate, number of postimplantation losses, or postimplantation loss rate. The NOAELs of viltolarsen were 240 mg/kg for general toxicity (based on increases in BUN) and 1000 mg/kg for

reproductive function and early embryonic development (no changes observed at the highest tested dose).

Viltolarsen administered to juvenile male mice (from postnatal day 7) at (SC or IV) doses up to 2000 mg/kg once-weekly (up to 4 weeks) or up to 1200 mg/kg once-weekly (up to 10 weeks) suggested tolerability up to 240 mg/kg, after which evidence of toxic effects to the kidney were observed (tubular degeneration, basophilia, and vacuolation and chronic progressive nephropathy in the kidneys at ≥ 240 mg/kg). The NOAEL for general toxicity of viltolarsen is 60 mg/kg, and for bone growth/geometry and juvenile neurotoxicity of viltolarsen is 1200 mg/kg. No toxicity specific to juvenile animals were noted.

IV injections of 200 mg/kg showed acceptable local tolerances in cynomolgus monkeys, but 600 mg/kg IV injections induced signs of inflammation at the injection site in to SC tissue. Similarly, IM injections of 100 mg/kg were not suitable for administration of viltolarsen, showing inflammation of the injection site.

No anti-viltolarsen antibodies were detected in the 4-week, 13-week or 26-week mouse studies, or in a 39-week monkey study. Anti-viltolarsen antibodies were detected in 1 male at 200 mg/kg in a 12-week monkey study and 1 male at 500 mg/kg in a 13-week rat study. However, antibody detection was not considered to affect the toxicological evaluation in this study, since skipping efficiency was confirmed in the muscle of this monkey at the end of the treatment period or no remarkable alteration in exposure to viltolarsen was observed after repeated dosing.

No toxicological differences were noted between lots of viltolarsen produced from an initial solid (SP) phase and the new liquid phase (LP2, LP2) synthetic process.

Viltolarsen was administered once weekly for 26 weeks at dose levels of 0 (vehicle: physiological saline), 50, 150, and 500 mg/kg (51 mice per group) in male CByB6F1-Tg(HRAS)2Jic mice via IV administration with a bolus injection. After the terminal necropsy, macroscopic examinations showed a mass and/or thickening in 1 side of the ureter in 1 mouse at 50 mg/kg, and in 2 mice at 150 mg/kg, and no findings at 500 mg/kg dose group. In subsequent histopathological examinations on these 3 mice, transitional cell carcinomas were noted. Histopathological examination of the ureters for the other mice was conducted and no further tumorigenic changes were identified. Additionally, no treatment-related tumors were noted in any other organs.

The blood concentration of viltolarsen in mice who received 50 mg/kg/week was lower than the blood concentration of viltolarsen expected in human patients who will receive 80 mg/kg/week.

2.3.3 Summary of Clinical Findings

A Phase 1 investigator-initiated study (Study NCNP/DMT01) (ClinicalTrials.gov NCT02081625) of viltolarsen injection was conducted in DMD patients (aged 5 to 18 years) to investigate the overall usefulness of viltolarsen injection in the treatment of DMD, based on evaluations of safety, exploration of predictive markers of treatment response, and assessment of PK. A total of 10 DMD patients were enrolled and randomized. IV administration of viltolarsen injection in doses of 1.25 mg/kg, 5 mg/kg and 20 mg/kg to DMD patients once weekly for 12 weeks was well tolerated, and no dose-limiting toxicity was observed, although all patients had at least one AE. Moreover, neither SAEs nor incidences of Common Terminology Criteria for Adverse Events (CTCAE) v4.0-JCOG (Japanese translation, published by the Japan Clinical Oncology Group [JCOG]) Grade 3 (severe) or worse were reported.

Among the mild and moderate AEs, an increase in beta-N-acetyl-D-glucosaminidase (Grade 1) was found in all patients in both cohorts 1 and 2 [Cohort 1 (n = 3) Cohort 2 (n = 3)] and in all but one patient in Cohort 3 [Cohort 3 (n = 4)].

Initially, testing appeared to reveal proteinuria in 8 of 10 patients. However, it was subsequently determined that there was a cross reaction between viltolarsen and the pyrogallol red dye-binding method, which was used for urinary protein measurement resulting in a false positive result for protein in the 24-hour pooled urine samples. To evaluate the 24-hour pooled urine samples for protein, the Coomassie brilliant blue method was used to re-measure urinary protein in the frozen urine samples. None of the retested samples showed urinary protein levels exceeding the normal range of the institution (i.e., 31.2 to 120 mg/day). [redacted]

The 24-hour pooled urine samples did not show increased levels of albumin. Spot measurements of urinary albumin were positive in 7 patients (Grade 1).

Interleukin levels were increased (Grade 1) in the serum in 6 out of 10 patients (high IL-6 level in 4 subjects, high IL-1β level in 1 subject, and high IL-2 level in 1 subject), and some level of anemia (Grade 1) was observed in 7 out of 10 patients.

Increased levels of brain natriuretic peptide (Grade 1) in serum were present in 4 patients. White blood cell count (WBC) was increased in 3 patients (Grade 1). All other mild and moderate AEs occurred in 2 or fewer patients.

The maximum plasma concentration and area under the curve (AUC_{0-t}) values increased in a dose-dependent manner, and the $t_{1/2}$ value was between 1.52 and 1.84 hours.

Distinct exon 53 skipping efficiency by reverse transcriptase polymerase chain reaction (RT-PCR), positive dystrophin fibers by immunofluorescent staining, and dystrophin protein expression by Western blot were detected in one patient in Cohort 3, who was the largest patient enrolled in the cohort and hence received a largest absolute dose of viltolarsen injection that was administered in the study.

Phase 2 Trials

Study NS065/NCNP01-P1/2, Study NS-065/NCNP-01-201, and Study NS-065/NCNP-01-202 of viltolarsen were completed. Results for all studies are detailed below.

Study NS065/NCNP01-P1/2

Study NS065/NCNP01-P1/2 is a Phase 1/2 study of viltolarsen injection conducted in Japan. This was a multi-center, parallel-group, open-label, 24-week study. Participants received weekly IV administration of viltolarsen injection 250 mg (40 mg/kg and 80 mg/kg) over 24 weeks. The primary efficacy endpoint of this study is dystrophin protein expression as measured by Western blot, immunofluorescence staining, and RT-PCR. Sixteen DMD patients amenable to exon 53 skipping, aged 5 to <18 years were enrolled.

Viltolarsen injection was well tolerated in up to the highest administered dose of 80 mg/kg; no SAEs were observed, one SAE (upper respiratory tract infection, Grade 2, not-related to drug) was reported, and no patients discontinued study drug administration as a result of an AE. Adverse events included 84 Grade 1 AEs in 10 patients, 11 Grade 2 AEs in 5 patients, and no Grade 3 AEs. The Grade 2 AEs included nasopharyngitis, and eczema, each in 2 patients, and miliaria (a common disorder of eccrine sweat glands), pharyngitis, ejection fraction decreased, ligament sprain, and urine protein present, each in 1 patient. No evidence for immunogenicity

was found in any Phase 1/2 study participants, as no anti-viltolarsen or anti-dystrophin antibodies were detected in DMD patients receiving 40 or 80 mg/kg viltolarsen injection in this study. Under the conditions of this clinical trial, viltolarsen injection was safe and well tolerated up to 80 mg/kg, the highest dose in this study.

Study NS-065/NCNP-01-201

Study NS-065/NCNP-01-201 is a Phase 2 study conducted in the US and Canada.

This was a multi-center, 24-week dose finding study to assess the safety, tolerability, PK, and pharmacodynamics of viltolarsen in boys with DMD. Participants received 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 250 mg (40 mg/kg and 80 mg/kg) over the remaining 20 weeks. The primary efficacy endpoint of this study is dystrophin protein expression as measured by Western blot. Sixteen DMD patients amenable to exon 53 skipping, aged 4 to <10 years were enrolled. There were no apparent drug-related SAEs reported, and no AEs led to study drug discontinuation. There were 59 treatment-emergent adverse events (TEAEs) with 23 TEAEs from participants in the low dose cohort and 36 TEAEs from participants in the high dose cohort. Fifty-four of the 59 TEAEs were reported as mild in severity, with 5 from the high dose cohort reported as moderate in severity. There were 55 AEs deemed unrelated to study drug and 7 as unlikely related.

Study NS-065/NCNP-01-202

Study NS-065/NCNP-01-202 was the extension study for Study NS-065/NCNP-01-201 and was conducted in the US and Canada. There were 16 DMD participants enrolled. No participants died, and no participants discontinued the study or study drug as the result of an AE (or for any other reason). No TEAEs required NS-065/NCNP-01 dose reduction or interruption.

Three participants had treatment-emergent SAEs. However, these events were assessed as not related to viltolarsen by the investigator. The most common TEAEs were cough, followed by nasopharyngitis, vomiting, pyrexia, arthropod bite, and rash. Adverse events of special interest, added in Protocol Amendment 9, were assessed upon completion of the treatment phase and did not raise drug-related safety concerns. There was no indication of treatment-related kidney toxicity. Of participants who experienced TEAEs, most experienced events of mild severity (6 participants, 37.5%) or moderate severity (8 participants, 50.0%). Two participants (12.5%) had TEAEs of maximum severity Grade 3, which were 3 of the SAEs mentioned above: lower

limb fracture, rhabdomyolysis, and lower limb fracture. No TEAEs were assessed by the investigator as CTCAE Grades 4 (life-threatening) or 5 (death). One TEAE (injection site extravasation) was assessed as drug-related by the investigator. There were no treatment-related clinically meaningful trends in laboratory parameters, vital signs, or electrocardiograms (ECGs) over time or among treatment groups. Anti-dystrophin antibodies were detected in 2 of the 16 participants (273104 at Week 145 and 273106 at Week 121). All other samples were judged anti-dystrophin antibody negative. No participants had anti-NS-065/NCNP-01 antibody results at any time. Treatment with NS-065/NCNP-01 was safe and well tolerated under the conditions of this study, for an additional 192-week time period. Preliminary evidence for clinical benefit of viltolarsen-treated participants in comparison with the CINRG DNHS population, matched for study criteria, was observed. Generally, extended improvement in performance on timed function tests was confirmed in the viltolarsen-treated participants whereas the CINRG DNHS historical control group showed deterioration. The safety profile in Study NS-065/NCNP-01-202 confirmed what was seen in the previous 24-week Study NS-065/NCNP-01-201, further supporting that viltolarsen was well tolerated. The results of this study appear to be fully aligned with the current, FDA-approved viltolarsen product labeling and prescribing information.

2.4 Risk/Benefit Assessment

2.4.1 Viltolarsen

There were no important identified risks of viltolarsen in the current clinical development program. [redacted]

No serious adverse reactions were recognized in the reporting period of the current Drug Safety Update Report (DSUR) (May 14, 2017 to May 13, 2018), and there were no actions taken for safety reasons, or any significant changes in the Investigator's Brochure (IB).

At present, none of the safety risks identified during the current reporting period were considered to be important risks. Further, nonclinical adverse effects previously identified as important potential risks have not been observed in any of the human studies conducted to date.

2.4.2 Procedures

Risks due to study-related procedures are detailed below.

Blood sample collection for hematology, chemistry, and PK is associated with the usual risks of a blood draw which include pain, bruising at the point where the blood is taken, redness and swelling of the vein, infection, and a rare risk of fainting. In order to decrease any of these possible risks the sites will employ pediatric trained staff and will use a numbing cream, if desired by the participant, to reduce the risk of pain.

Function and strength tests will be performed during this study. These include the TTSTAND, Time to Run/Walk 10 Meters Test (TTRW), Six-minute Walk Test (6MWT), North Star Ambulatory Assessment (NSAA), and Time to Climb 4 Stairs Test (TTCLIMB). All tests associated with muscle soreness, fatigue, and falls.

The 6MWT may also cause feelings of pressure or pain in the participant's chest, difficulty breathing, and shortness of breath. The 6MWT may also cause an increased risk of muscle cramping.

Quantitative muscle strength by hand-held dynamometer may cause fatigue and muscle soreness.

3 STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s)	Primary Endpoint(s)
• To compare the efficacy of viltolarsen administered IV at weekly doses of 80 mg/kg over a 48-week treatment period vs. placebo controls in ambulant boys ages 4 to <8 years with DMD using the TTSTAND as a measure of strength and function.	• TTSTAND at 48 weeks of treatment
Secondary Objective(s)	**Secondary Endpoint(s)**
• To compare the efficacy of viltolarsen administered IV at weekly doses of 80 mg/kg in ambulant boys ages 4 to <8 years with DMD over a 48-week treatment period vs. placebo controls using hierarchical strength and endurance outcomes; and	• Hierarchical analysis at 48 weeks treatment of the following strength and endurance measures: o TTRW o 6MWT o NSAA o TTCLIMB o Quantitative muscle strength measured by hand-held dynamometer (elbow extension, elbow flexion, knee extension, and knee flexion on the dominant side only)
• To evaluate the safety and tolerability of viltolarsen administered IV at weekly doses of 80 mg/kg in ambulant boys ages 4 to <8 years with DMD.	• Vital signs (blood pressure, heart rate, respiratory rate, and body temperature [modality for determining temperature should be consistent for each participant at all assessment time points throughout the study]) • Physical examination • Clinical laboratory tests: o Hematology and clinical chemistry o Urinalysis o Urine cytology o Exogenous tracer GFR • Antibodies to dystrophin and viltolarsen • 12-lead ECG • Clinical signs and symptoms (AEs and SAEs) • Grading of clinical and clinical laboratory AEs will be according to CTCAE v.4.03

Exploratory Objective(s)	**Exploratory Endpoint(s)**
• To evaluate health-related quality of life impact of viltolarsen treatment on participant's DMD.	• Pediatric Outcome Data Collection Instrument (PODCI)
	• Personal Adjustment and Role Skills Scale, 3rd edition (PARS III) Questionnaire

4 HYPOTHESIS

Viltolarsen administered at 80 mg/kg/week, in comparison to placebo, ameliorates the clinical course of ambulant boys with DMD as assessed by a muscle functional measure. The improvement in function is due to an increase in muscle tissue dystrophin expression.

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design and Plan

This Phase 3 study is a randomized, double-blind, placebo-controlled, multi-center study in ambulant boys ages 4 to <8 years with DMD receiving 80 mg/kg viltolarsen administered IV weekly over a 48-week treatment period. See Section 1.1 for study schema.

5.1.1 Number of Centers

The study will be conducted at approximately 53 clinical sites in approximately 19 countries, predominantly in Europe, Asia, North America, Oceania, and South America.

5.2 Design Implementation

5.2.1 Randomization

Participants are randomly assigned to either 80 mg/kg/week viltolarsen or placebo in a 1:1 ratio. Randomization is carried out with dynamic allocation by minimization method with the biased-coin method. The allocation factors are gene mutation and baseline values for TTSTAND, and region (North America, South America, European Union [EU], and Asia). [redacted]

The randomization schedule will be generated by an unblinded statistician and maintained by the contract manufacturing organization (CMO). All other parties will be blinded to the randomization.

5.2.2 Investigational Product Dosing

The dose per participant (in mg) will be calculated based on body weight (in kg) collected per the protocol. Details of dose preparation can be found in the study Investigational Product Information Manual (IPIM). Doses will be administered by an IV infusion over a 1 hour period. All missed or incomplete doses will be documented. The dispensed study drug vials will be stored at the research site until drug accountability is verified by the pharmacy monitor.

In the event it becomes necessary, or at the discretion of the parents/guardian, in consultation with the investigator and consulting surgeon and following adequately informed and voluntary parent/guardian consent and child assent, a totally implantable central venous access device (TICVAD) may be used, contingent upon approval by local and/or country-specific regulatory

body(ies). Implantable central venous access (CVA) ports will be considered on a case-by-case basis for participants who experience difficulty with peripheral venous access. Discussions regarding implantable ports for participants will include the study site investigator, medical monitor, and sponsor. Before final decision, NS Pharma will obtain documentation from the investigator that the consulting surgeon who will place the port holds hospital privileges as a board eligible/board certified surgeon. Implantation should not proceed without sponsor approval. Care of the TICVAD (including aseptic access and flushing) and patient monitoring must be performed by qualified personnel according to the site's standard operating procedure.

An alternative method of CVA may only be considered in the case of a documented contraindication to the placement of a TICVAD.

5.2.3 Potential Design Modifications Due to Toxicities

Dose reductions or omissions may be necessary for individual participants. The dose level will be determined jointly by the investigator and medical monitor in consultation with the sponsor.

5.2.4 Infusion Interruptions

Infusion interruptions may be necessary for individual participants. Infusion interruptions should be handled in accordance with standard procedures should an acute reaction occur during an infusion. Sites should notify the medical monitor in the event of an infusion interruption due to an acute reaction.

5.3 Study Duration and Dates

The expected study duration for each participant is approximately 48 weeks. The Pretreatment Phase will last approximately 28 days (inclusive of Screening Visit and Pre-Infusion Visit). The Treatment Phase will last approximately 48 weeks. The follow-up phase is 30 days.

5.3.1 Open-Label Extension

Participants completing the 301 study will have the option to enter an open-label extension study in which all participants will receive active study drug. Participants directly entering the extension study will not have the 30 day follow-up telephone call.

5.3.2 End of Study Definition

Primary Completion: The primary completion date is the same as the end of study date and is the date when the last participant has completed the study (i.e., last participant last visit).

If the study concludes prior to the primary completion date originally planned in the protocol (i.e., early termination of the study), then the primary completion date will be the date when the last participant is assessed or receives an intervention for evaluation in the study (i.e., last participant last visit).

End of Study: The end of study date is defined as the date when the last participant at the site is assessed or receives an intervention for evaluation in the study (i.e., last participant last visit).

5.3.3 End of Treatment

End of treatment is defined as the last assessment for the protocol specified treatment phase of the study for an individual participant.

6 STUDY POPULATION SELECTION

6.1 Study Population

Approximately 74 participants (ambulant boys, 4 to <8 years of age) with DMD that meet the eligibility criteria below will be enrolled.

6.2 Inclusion Criteria

1. Participant's parent(s) or legal guardian(s) has (have) provided written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization, where applicable, prior to any study-related procedures; participants will be asked to give written or verbal assent according to local requirements;
2. Participant has a confirmed diagnosis of DMD defined as:
    a. Participant is male with clinical signs compatible with DMD; and
    b. Participant has a confirmed DMD mutation(s) in the dystrophin gene that is amenable to skipping of exon 53 to restore the dystrophin mRNA reading frame including determination of unambiguously defined exon boundaries (using techniques such as Multiplex Ligation-dependent Probe Amplification [MLPA], comparative genomic hybridization [CGH] array or other techniques with similar capability);
3. Participant is ≥4 years and <8 years of age at time of first infusion in the study;
4. Participant is able to walk independently without assistive devices;
5. Participant is able to complete the TTSTAND without assistance in <10 seconds, as assessed at the Screening Visit and the Pre-infusion Visit. (Note: The TTSTAND performed independently from the NSAA should be used to determine eligibility.);
6. Participant and parent(s)/guardian(s) are willing and able to comply with scheduled visits, study drug administration plan, and study procedures;
7. Participant must be on a stable dose of GC for at least 3 months prior to first dose of study drug and is expected to remain on the stable dose of GC treatment for the duration of the study.

6.3 Exclusion Criteria

1. Participant has current or history of chronic systemic fungal or viral infections;
2. Participant has had an acute illness within 4 weeks prior to the first dose of study drug based on the Principal Investigator's judgment/discretion;
3. Participant has evidence of symptomatic cardiomyopathy. (Note: Asymptomatic cardiac abnormality on investigation would not be exclusionary.);
4. Participant has an allergy or hypersensitivity to the study drug or to any of its constituents;
5. Participant has severe behavioral or cognitive problems that preclude participation in the study, in the opinion of the investigator;
6. Participant has a previous or ongoing medical condition, medical history, physical findings, or laboratory abnormalities that could affect participant safety, make it unlikely that treatment and follow-up will be correctly completed, or impair the assessment of study results, in the opinion of the investigator;
7. Participant has had surgery within the 3 months prior to the first anticipated administration of study drug or surgery is planned for anytime during the duration of the study;
8. Participant has positive test results for hepatitis B antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) antibody at screening. (Note: A positive hepatitis C antibody result is acceptable if accompanied by a negative hepatitis C RNA test and normal bilirubin and gamma-glutamyl transferase results.);
9. Participant is currently taking any other investigational drug or has taken any other investigational drug within 3 months prior to the first dose of study drug or within 5 times the half-life of a medication, whichever is longer;
10. Participant was previously enrolled in an interventional study of viltolarsen;
11. Participant is currently taking any other exon skipping agent or has taken any other exon skipping agent within 3 months prior to the first dose of study drug;
12. Participant has taken any gene therapy;

13. Participant is currently taking idebenone, anabolic steroids (e.g., oxandrolone), or products containing resveratrol or adenosine triphosphate, or has taken such within 3 months prior to first dose of study drug. Coenzyme Q10 or creatine are permitted only if the participant is receiving a stable dose for at least 3 months prior to the first dose of study drug and for the duration of the study;
14. Note: There is no exclusion criterion #14. This criterion was removed from the protocol with Amendment 4 (version 3.0, dated 08 January 2021); however, the numbering was maintained to avoid documentation errors;
15. Participant has hydronephrosis, hydroureter, renal or urinary tract calculi, or ureteral stenosis by medical history or renal ultrasound.

Note: Any parameter/test may be repeated at the investigator's discretion during screening to determine sustainability and reproducibility.

6.4 Lifestyle Restrictions

6.4.1 Meals and Dietary Restrictions

Not applicable.

6.4.2 Caffeine, Alcohol, and Tobacco

Not applicable.

6.4.3 Activity

Participants are to maintain regular activities.

7 INVESTIGATIONAL PRODUCT

7.1 Description of Viltolarsen and Placebo

In this study, investigational product is defined as viltolarsen injection and placebo.

Investigational product is provided in 5 mL glass vials for dilution and IV administration.

- Viltolarsen injection 250 mg aqueous solution: 5 mL glass vial containing 50 mg/mL of drug substance solution in saline
- Placebo: 5 mL glass vial of saline without the drug substance solution

Description:

- Viltolarsen: Clear, colorless to pale yellow solution
- Placebo: Matching in clarity and color to viltolarsen

Stability: Viltolarsen injection 250 mg is stable at 5 ± 3°C. Additional stability details can be found in the IPIM.

Storage conditions: Store refrigerated at 2° to 8°C.

Investigational product will be packaged, labeled, and distributed to clinical sites by CMO. Additional details for ordering the investigational product can be found in the IPIM and the Study Reference Manual (SRM).

7.2 Dispensing Investigational Product

Participants will receive either viltolarsen injection or placebo, based on randomization.

Participants randomized to viltolarsen will receive IV infusions of viltolarsen injection administered once weekly over a 48-week period. Participants will be dosed at 80 mg/kg/week.

Participants randomized to placebo will receive IV infusions of placebo administered once weekly over a 48-week period. Participants will be dosed in an equivalent volume to viltolarsen.

Investigational products will be prepared in accordance with the IPIM by the study site pharmacy and administered by IV infusion over a 1-hour period.

7.3 Instructions for Administration of Investigational Product

Administration of prepared investigational product (diluted solution) should be completed within 6 hours of preparation and may be stored at room temperature during this time. Additional

stability details can be found in the IPIM. A minimum of 3 days (72 hours) should elapse between treatments.

7.4 Blinding

Both the investigational product and the placebo will be of equal volume and equal appearance, thus maintaining the blind.

All site investigators, coordinators, and pharmacists as well as the contract research organization (CRO) will remain blinded to treatment assignment.

7.5 Emergency Unblinding

Study sites are provided with an unblinding envelope that contains the code necessary to unblind the patient within the study IRT system. Should sites need to unblind the participant, they will follow the instructions within the envelope to log into the study IRT system, enter the code, and receive information regarding the participant's treatment assignment. Whenever possible, first contact the medical monitor to discuss.

7.6 Treatment Compliance

The participant's compliance with the treatment regimen will be monitored in terms of the participant receiving the investigational product infusion every week within a ± 3-day window. A minimum of 3 days (72 hours) should elapse between treatments. Weekly study drug treatments for this study should be calculated from the first infusion, not from the previous week's infusion. If an infusion day is rescheduled, the original scheme should be reinstated as soon as possible. Missed, delayed, or incomplete infusions will be clearly documented and considered in the analysis. The amount of solution received should be documented for all infusions.

7.7 Overdose

There is currently no experience with overdose for viltolarsen and no antidote. The investigator should treat the participant's symptoms as medically appropriate.

7.8 Packaging and Labeling

Investigational product will be packaged and shipped from CMO directly to the investigative site as a participant kit. Each participant kit consists of a single carton of 10 vials. Ancillary supplies will be provided by CMO with each participant kit. The labeling requirements comply

with Annex 13 of the EU Guideline to Good Manufacturing Practice and are in compliance with the requirements of Directive 2003/94/EC.

7.9 Storage and Accountability

Investigational Product Storage: Refrigerated (2° to 8°C), store in original packaging (10 vials in light resistant paperboard carton).

An identified, appropriate, and secure storage location will be defined at each site's pharmacy for the investigational product.

Additional details regarding proper handling of the investigational product can be found in the IPIM.

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. All unused investigational product will be returned or disposed of as defined in the IPIM. This information will be included as part of the investigational product accountability record.

8 PRIOR AND CONCOMITANT MEDICATIONS AND TREATMENTS

Glucocorticoid steroids and other pharmacological medications including over the counter medications, herbal remedies, supplements, and vitamins used within 3 months prior to the first dose of study drug will be recorded in source documents and in the electronic case report form (eCRF). The date of first glucocorticoid steroid use will also be captured. All medications taken throughout the study will be recorded in source documents and in the eCRF. The following information will be collected: the medication name, dose, unit, frequency, route, indication, start and stop dates.

Any non-pharmacological treatment the participant has received within 3 months prior to the first dose of study drug will be collected. The following information will be collected: name of treatment, indication, and start and stop date. Prior non-pharmacologic treatment will be recorded in source documents and captured in the relevant eCRF. Physical therapy schedule should not change, and no new physical therapy should be started during the study. The need for changes to physical therapy should be discussed with the medical monitor prior to implementation.

8.1 Prohibited Medications

Investigators are reminded to minimize concomitant medication or supplement use or changes to GC steroid use unless necessary for medical management.

The use of idebenone, anabolic steroids (e.g., oxandrolone), and products containing resveratrol or adenosine triphosphate is prohibited from 3 months prior to first dose of study drug and through the duration of the study. If growth hormones or supplements with a potential effect on muscle strength or function (e.g., coenzyme Q10 or creatine) are used, these should be kept stable from 3 months prior to the first dose of study drug through the duration of the study. Adjustments based on changes in body habitus are permitted. Any other experimental/investigational products are prohibited from 3 months prior to first dose of study drug or within 5 times the half-life of a medication, whichever is longer. Any other exon skipping agents and any gene therapies are prohibited. Participants who begin another investigational product will be withdrawn from the study.

8.2 Allowable Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate therapeutic and supportive care. Specifically, participants should receive full medical care during the study, including transfusions of blood and blood products, treatments with antibiotics, anti-emetics, anti-diarrheals, analgesics, topical or inhaled steroids, and other care as usual. All concomitant blood products, medications, and supplements will be recorded in source documents and in the relevant eCRF. For a stable dose of glucocorticoid, a stable dose permits weight-based adjustments (stable mg/kg).

9 STUDY PROCEDURES

9.1 Time and Events Schedule

The schedule of study assessments is described in Table 1 and Table 2; however, a participant can be seen at any time for reasons of safety. Study events are divided into the following phases:

- Pretreatment Phase:
    - From execution of the Informed Consent/HIPAA authorization/Assent until Day 1 (first infusion).
- Treatment Phase:
    - From Day 1 (first infusion) until Week 48 (last infusion).
- Post-treatment Phase:
    - The 30-day interval (including Week 49) beginning after completion of the 48-week Treatment Phase and ending after a final phone call for collection of any information about AEs and concomitant medications for all participants.

9.2 Informed Consent

Each participant's parent or legal guardian will receive an explanation of the nature and purposes of the study from the investigator or designee. The investigator or designee will ensure the study is appropriate for the participant. Consent must be obtained in accordance with the principles outlined in the current version of the Declaration of Helsinki. The participant's parent or guardian will confirm that s/he understands that the study is for research purposes only and that it may not provide any therapeutic benefit to the individual. Each participant's parent or guardian will confirm that s/he understands that the participant is free to withdraw from the study at any time without prejudice. The investigator or designee will review the elements of the HIPAA and Protected Health Information (PHI) with each participant's parent or guardian and each participant's parent or guardian will confirm that s/he understands HIPAA authorization and PHI. The investigator (or designated staff) will obtain the written informed consent and HIPAA authorization on the approved informed consent form (ICF) by the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC) at each site, from the participant's parent or guardian prior to any study-related procedures, including agreement to discontinuation

of any prohibited medications, prior to the start of the study. The written assent of children will be obtained per individual site guidelines.

The ICF must be dated and signed by the investigator or designee and the participant's legal representative and the original signed consent form must be kept by the investigator in the study participant's file. "Legal representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective study participant to the participant's participation in the procedure(s) involved in the research. The study participant's legal representative will receive a copy of the signed consent form.

If the ICF is amended during the study, the investigator must follow all applicable regulatory requirements pertaining to all new participants and repeat the consent process with the amended ICF for any ongoing participants.

9.3 Assignment of Participant Identification Number

Study NS-065/NCNP-01-301 participation begins once written informed consent/assent is obtained from the parent/legal guardian for a participant before any study-specific procedures are performed.

Following the signing of the written ICF/Assent Form, participants will be assigned a unique, site-specific, 6-digit participant identification number in sequential order of screening into the study. The participant identification number will be assigned by the site at the time of submission of the de-identified genetic test report to the central genetic counselor to confirm that the participant meets the genetic diagnostic eligibility criteria. If the de-identified genetic test report is submitted to the central genetic counselor prior to signing of the ICF (only if acceptable per local IRB/IEC), then the report will have personal health information removed prior to sending for review.

All data will be identified using the unique participant identification number. The assigned participant identification number will be retained through enrollment and throughout participation in the study. Participant identification numbers assigned to participants who fail screening may not be used again.

Each investigator will keep a Participant Identification log relating the names of the participants to their participant identification numbers to permit efficient verification of patient files, when required.

9.3.1 Screen Failures

Participants who fail to meet inclusion criteria are considered to be screen failures and are not required to return for additional visits (although a participant can be seen by the investigator at any time for safety reasons). Participants who have failed screening may be rescreened if ineligible due to a transient condition. Rescreening may be performed twice between Day -28 to Day -8. Once the rescreening has failed, the participant should repeat all screening procedures. This full re-screening may be performed up to two times, after which the participant is no longer eligible for the study.

If rescreening is more than 90 days since a current ICF/Assent form has been signed and/or the consent form has been modified from their original consent, participants should be re-consented prior to rescreening procedures.

9.4 Genetic Confirmation of Diagnosis

As part of the screening assessments the central genetic counselor will review the de-identified genetic report to confirm the participant's DMD diagnosis and presence of a mutation that is eligible for skipping of exon 53. The date of diagnosis, method of diagnosis, diagnosis results will be documented in source documents and captured in the relevant eCRF.

A DMD genetic test at Day 1 will be conducted in order to obtain uniform DMD mutation information for the exact intronic boundaries and will be analyzed by a central laboratory.

9.5 Demographics

The following information will be collected: date of birth (if allowed by local regulations), race, ethnicity, and hand dominance and documented in source documents and captured in the relevant eCRF. If local regulations do not allow collection of full date of birth, then year of birth should be collected.

9.6 Medical History

The investigator or designee will obtain detailed information regarding all past medical and surgical events. The dates and descriptions of past events will be documented in source documents and captured in the relevant eCRF.

9.7 Prior and Concomitant Treatment

The investigator or designee will review prior and concomitant treatment as indicated in Table 1 and Table 2. See Section 8 for additional details.

9.8 Weight and Height

Standing height, and weight will be collected at the visits specified in Table 1 and Table 2. Standing height will be collected with the participant barefoot (without shoes). The participant's legs should be kept as close as possible and the participant's heels should be placed back as close to the wall as possible. Participant may hold on to an object to facilitate balance. Weight will be collected with the participant wearing no shoes and light-weight clothes. Height and weight should take approximately 2 minutes. These measurements are routinely performed during standard clinical examinations of participants with DMD. Weight in kilograms (kg) and height in centimeters (cm) will be documented in source documents and captured in the relevant eCRF.

9.9 12-Lead Electrocardiograms

12-lead ECGs will be collected at the times specified in the schedule of study assessments (Table 1 and Table 2) and will be centrally read.

ECGs will be performed with the participant having rested for at least 5 minutes, and the participant should remain in the supine or semi-recumbent position. A consistent position should be maintained for each individual participant. Skin preparation should be thorough and electrodes should be placed according to standard 12-lead ECG placement. Digital ECGs will be submitted to the ECG core laboratory, which will perform the digital ECG analysis and interpretation in this study.

On Day 1, triplicate ECGs, each approximately 1 to 2 minutes apart, will be collected at predose as well as 1 hour (up to 20 minutes following completion of the infusion) and 3 hours (± 20 minutes) after initiation of infusion. At the Screening Visit; Weeks 13, 25, 37, and

49; and early termination, single ECGs will be collected (predose is recommended at Weeks 13, 25, and 37).

9.10 Vital Signs

Vital signs will be measured at each study visit as specified in Table 1 and Table 2.

Vital signs can be measured in the supine, semi-recumbent, or sitting position. A consistent position should be maintained for each individual participant. Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, blood draws, with vital signs obtained without repositioning. If the participant changes position during or after the ECG assessment, then a 5-minute rest would need to occur in the new position prior to measuring vital signs. Otherwise, vital signs can be measured immediately after the ECG is completed, and blood draws can occur immediately after vital signs. At time points after infusion when vital signs are measured but ECGs are not performed, participants should maintain the position in which they were infused. At all other times when vital signs are measured but ECGs are not performed, vital signs will be measured after a 5-minute rest.

Vital signs will be measured at predose as well as 1 hour (up to 20 minutes following completion of the infusion) and 2 hours (± 20 minutes) after initiation of infusion. If a clinically significant change from predose is observed at 2 hours after initiation of infusion, the parameter will be measured again at 6 hours (± 20 minutes) after initiation of infusion. Vital signs will be measured prior to any blood collection scheduled at the same time point and will include the following:

- Systolic blood pressure,
- Diastolic blood pressure,
- Heart rate,
- Respiratory rate,
- Temperature.

Vital signs will be documented in source documents and captured in the relevant eCRF. Any clinically significant changes noted by the investigator should be reported as an AE.

9.11 Physical and Neurological Examination

The physical and neurological examinations will be performed at the visits specified in the schedule of study assessments (Table 1 and Table 2) to assess any changes in physical presentation and symptoms.

Physical and neurological examinations will include an assessment of the following:

- General appearance;
- HEENT (head, ears, eyes, nose, and throat);
- Skin;
- Lymph nodes;
- Heart, including rhythm, heart sounds and presence of cardiac abnormalities;
- Lungs;
- Abdomen;
- Extremities/joints;
- Nervous system;
- Any additional assessments necessary to establish baseline status or evaluate symptoms or adverse experiences.

Abnormal findings will be assessed for clinical significance and details provided in the eCRF. Documentation of the physical and neurological examination findings will be included in the source documentation at the clinical site.

9.12 Renal Ultrasound

Renal ultrasound will include imaging of the kidneys, ureters, and bladder and be performed at visits specified in the schedule of study assessments (Table 1 and Table 2). Except for the screening assessment, renal ultrasound can occur up to 2 weeks prior to or after the scheduled week, as needed for scheduling purposes. Renal ultrasound will be assessed by local urologists or other appropriately trained medical professionals.

9.13 Adverse Events and Serious Adverse Events

Investigators will assess the occurrence of AEs and SAEs each study visit, or participant contact during the study. AEs and SAEs may be reported by the participant/parent, discovered upon questioning, detected during examinations or review of test and lab results. AEs and SAEs should be documented in the source documents and the relevant eCRF with a full description

including the nature, date and time of onset and resolution, determination of seriousness, severity, causality, corrective treatment, and outcome. Refer to Section 11 for safety procedures and reporting.

9.14 Clinical Laboratory Tests

Clinical laboratory assessments will be performed at visits specified in the schedule of study assessments (Table 1 and Table 2). Any blood sampling that occurs during the investigational product infusion should be collected from a location away from the investigational product infusion placement (i.e., opposite arm).

9.14.1 Sample Collection, Storage, and Shipping

Each participant will have blood drawn and urine collected for the blood and urine laboratory safety assessments as listed/described in the sections below and the schedule of study assessments (Table 1 and Table 2), including hematology, chemistry, urinalysis, 24-hour urine analysis, urine cytology, exogenous tracer GFR, anti-dystrophin antibody, anti-viltolarsen antibody, and viral antigen and antibody testing.

Blood draw volumes will be 8.5 to 24.0 mL per day at screening, Day 1, Weeks 3, 5, 9, 13, 17, 21, 25, 37, 49, and EOT, totaling up to approximately 163.5 mL over the course of the study. No more than 47.0 mL will be drawn in a 4-week period.

For post screening urinalyses, patients will collect a first morning void urine sample on the date of the specified visit and bring it to the site according to the schedule of study assessments (Table 1 and Table 2). Analysis of the sample will include urine dipstick protein to be performed at the site. An aliquot will also be sent to the central laboratory for urinalysis (see Table 3 for a list of the laboratory analytes that will be measured for all urinalyses, including the first morning void urinalysis).

If first morning void urine dipstick protein ≥2+, urine protein to creatinine ratio (UPCR) ≥0.5 mg/mg, or UPCR ≥2 × baseline, a first morning void urine dipstick protein will be repeated within 1 week. If 1 or more of these criteria are met again on the repeat test, a 24-hour urine sample will be collected within 1 week of the results to assess protein and creatinine. Caregivers will be provided a diary to enter void times during the 24-hour collection period. When obtaining this 24-hour urine, the patient will be asked to urinate in the toilet immediately after

waking up on the day of the test. This time will be recorded in the diary as the start time. Directions will be provided for collection throughout the test, and documentation of all subsequent voids will be recorded in the diary through the first sample immediately after awakening on the following morning, as close to 24-hours later as possible. Refer to Section 11.11.1 for additional details on monitoring of renal function and urine analyses.

If serum cystatin C ≥1.5 × baseline, or if serum creatinine ≥2 × baseline and ≥0.3 mg/dL, the test will be repeated within 1 week of the results. Refer to Section 11.11.1 for additional details on monitoring of renal function and urine analyses.

GFR will be determined using an exogenous tracer test, if available, at the Pre-Infusion Visit and Week 49 (or at early termination, if applicable). This should be done per standard of care at the institution.

Samples will be collected by a trained member of the study team unless otherwise noted. All blood and urine samples will be sent to the designated central laboratory for testing unless otherwise noted. The urine cytology samples will be collected predose at the site and sent to a local laboratory for analysis. The procedures for the collection, handling, and shipping of central laboratory samples will be specified in the Laboratory Manual. Clinical laboratory tests are listed in Table 3.

Table 3. Clinical Laboratory Tests

Hematology, Chemistry, Urinalysis (Screening, First Morning Void, and Postdose), 24-Hour Urine Analysis, Urine Cytology, and Glomerular Filtration Rate – Safety Labs

• Hematology
  ○ Red blood cell count
  ○ Hemoglobin
  ○ Hematocrit
  ○ Reticulocyte count
  ○ Mean corpuscular volume
  ○ Mean corpuscular hemoglobin
  ○ Mean corpuscular hemoglobin concentration
  ○ White blood cell count
  ○ White blood cell differential
  ○ Platelet count
  ○ Fibrinogen
  ○ Activated partial thromboplastin time
  ○ Prothrombin international normalization ratio
• Blood Chemistry

  - Sodium
  - Potassium
  - Chloride
  - Calcium
  - Inorganic phosphorus
  - Blood urea nitrogen
  - Creatinine
  - Cystatin C
  - Aspartate aminotransferase
  - Alanine aminotransferase
  - Gamma-glutamyl transferase
  - Alkaline phosphatase
  - Haptoglobin
  - Lactate dehydrogenase/lactate dehydrogenase isozyme
  - Creatine kinase
  - Total bilirubin (Direct/Indirect)
  - Total protein
  - Albumin
  - Albumin to globulin ratio
  - Total cholesterol
  - Triglyceride
  - Blood glucose
  - C-reactive protein
- Urinalysis (Screening, First Morning Void, and Postdose)
  - Glucose
  - Blood
  - Urobilinogen
  - Specific gravity
  - Osmolality
  - Urinary sediment (erythrocytes, white blood cells, casts, epithelial cells, crystals)
  - Protein (benzethonium chloride method)
  - Microalbumin
  - N-acetyl-beta-D-glucosaminidase
  - α1-microglobulin
  - β2-microglobulin
  - Creatinine
  - Protein to creatinine ratio
  - Protein to osmolality ratio
  - Dipstick protein (to be performed by the site on the first morning void urine samples)
- 24-Hour Urine Analysis
  - Protein (benzethonium chloride method)
  - Creatinine
- Urine Cytology
- Glomerular Filtration Rate (via Exogenous Tracer Test)

9.14.2 Anti-Dystrophin Antibody

Anti-dystrophin antibody testing will be performed on serum samples collected predose during the visits specified in the schedule of study assessments (Table 1 and Table 2). Samples will be analyzed by Shin Nippon Biomedical Laboratories, Ltd. (Japan).

9.14.3 Anti-Viltolarsen Antibody

Anti-viltolarsen antibody testing will be performed on serum samples collected predose during the visits specified in the schedule of study assessments (Table 1 and Table 2). Samples will be analyzed by Shin Nippon Biomedical Laboratories, Ltd. (Japan).

9.14.4 Antigen and Antibody Testing

Antigen and antibody testing will be performed during the screening assessment. The following tests will be performed: hepatitis B antigen, hepatitis C antibody, and HIV antibody.

9.15 Pharmacodynamics and Efficacy Assessments

9.15.1 Function and Strength

All function and strength testing will be performed by a trained site clinical evaluator (CE). The same CE should perform testing on the same participant throughout the study when possible. Instructions and further details on these tests can be found within the CE Manual.

The function and strength measures will be videotaped to ensure that they are being conducted properly and consistently by the CE, where possible and upon consent. The videotaping will only be used to standardize the assessment in the tests. The videos will be reviewed centrally by an experienced physiotherapist reviewed and will be compiled and stored confidentially in the video review portal in compliance with all ISO requirements and in compliance with data protection requirements. The video review does not affect the assessment results and adoption of the test data. The patient will be allowed to participate in the study if they meet all other criteria even if they do not agree to the recording or recording is not permitted at the site.

9.15.1.1 Time to Stand Test

TTSTAND will be performed by a CE at visits specified in the schedule of study assessments (Table 1 and Table 2). This test will assess the time it takes the participant to go from lying flat on the floor to standing and is administered as an independent test in addition to as part of the NSAA (see Section 9.15.1.4). The number of seconds required to perform the test and the

assessment of a 6-point rating scale of how the participant attains the standing position will be documented in source documents and captured in the relevant eCRF. The TTSTAND is performed independently and as part of the NSAA. The TTSTAND performed independently from the NSAA should be used to determine eligibility to satisfy inclusion criterion #5.

9.15.1.2 Time to Run/Walk 10 Meters Test

TTRW will be performed by a CE at visits specified in the schedule of study assessments (Table 1 and Table 2). This test will assess the time it takes the participant to walk/run 10 meters including a 6-point rating scale for quality of the run/walk and is administered as an independent test in addition to as part of the NSAA (see Section 9.15.1.4). The number of seconds required to perform the test will be documented in source documents and captured in the relevant eCRF. The TTRW is performed independently and as part of the NSAA.

9.15.1.3 Six-Minute Walk Test

The 6MWT will be performed by a CE at visits specified in the schedule of study assessments (Table 1 and Table 2). The 6MWT is a widely used and accepted test. The version of the 6MWT adapted for use in DMD will be used (McDonald et al, 2010). To perform the test, 2 points (cones) are set 25 meters apart and participants are asked to walk back and forth, between the cones quickly and safely for 6 minutes. The total distance in meters that the participant walks in 6 minutes is recorded. This test is considered a simple, standardized, low-technology and cost-effective means of clinically assessing 1) functional motor status and 2) integrated and global responses to exercise. The CE will measure the number of steps taken by the participant for the first 50 meters and total meters walked in 6 minutes. This test should take approximately 30 minutes.

9.15.1.4 North Star Ambulatory Assessment

NSAA will be performed by a CE at visits specified in the schedule of study assessments (Table 1 and Table 2). The NSAA is a clinician rated, 17-item, functional scale originally designed for ambulant boys with DMD who are able to ambulate at least 10 meters (Mazzone et al, 2009). This evaluation tool assesses functional activities including standing, getting up from the floor, negotiating steps, hopping, and running. The assessment is based on a 3-point rating scale of 2 = ability to perform the test normally, 1 = modified method or assistance

to perform test, 0 = unable to perform the test. Thus, total score can range from 0 (completely non-ambulant) to 34 no impairment on these assessments. Individual test item scores and total score will be recorded in source documents and in the relevant eCRF. This test should take approximately 20 minutes.

9.15.1.5 Time to Climb 4 Stairs Test

TTCLIMB will be performed by a CE at visits specified in the schedule of study assessments (Table 1 and Table 2). This test will assess the time it takes the participant to climb 4 stairs (Brooke et al, 1981) and will assess a 6-point rating scale to assess how the participant negotiates the stairs (see Section 9.15.1.4). This test should take approximately 5 minutes. The number of seconds required to perform the test will be documented in source documents and captured in the relevant eCRF.

9.15.1.6 Muscle Strength Measured with Hand-Held Dynamometer

Muscle strength will be measured for elbow extension, elbow flexion, knee extension, and knee flexion on the dominant side only using a hand-held dynamometer at visits specified in the schedule of study assessments (Table 1 and Table 2). This test should take approximately 15 minutes. The force generated for each muscle strength measure will be documented in source documents and captured in the relevant eCRF.

9.16 Pharmacokinetic Assessments

9.16.1 Collection and Assessment of Pharmacokinetic Samples

PK assessments will be performed at visits specified in the schedule of study assessments (Table 1 and Table 2). PK sampling post infusion times are measured from the start of infusion. Infusion is expected to take 1 hour to complete. Postdose PK should not be drawn from the cannula that was used for the infusion. These samples can be drawn from the arm opposite the infusion or can be from a separate distal access point in the same arm as the infusion. This postdose PK draw requirement is in place to prevent any contamination with viltolarsen derived from the dosing cannula. Blood will be drawn from participants for PK analysis at the following sampling times:

- Day 1 (first dose):
  - Predose (within 60 minutes prior to dose)
  - 1 hour (up to 20 minutes following completion of the infusion)

- 3 hours (± 20 minutes)
- 6 hours (± 20 minutes)

- Week 13:
  - Predose (within 60 minutes prior to dose)
  - 2 hours (± 20 minutes)
- Week 25:
  - Predose (within 60 minutes prior to dose)
  - 2 hours (± 20 minutes)
- Week 37:
  - Predose (within 60 minutes prior to dose)
  - 2 hours (± 20 minutes)
- Week 48:
  - Predose (within 60 minutes prior to dose)
  - 2 hours (± 20 minutes)
  - 6 hours (± 20 minutes)

Appropriate PK samples will be collected and processed by a trained member of the study team for shipment to the central laboratory who will forward to BML, Inc. (Japan) for analysis. Procedures for the collection, handling, and shipping of laboratory samples will be specified in the Laboratory Manual.

9.16.2 Shipment of Pharmacokinetic Samples

Plasma PK samples will be shipped frozen on dry ice according to instructions provided in the Laboratory Manual.

9.17 Patient Reported Outcomes

9.17.1 Pediatric Outcome Data Collection Instrument (PODCI)

The questionnaire to document health related quality of life is the Pediatric Outcomes Data Collection Instrument (PODCI). It is designed to be completed by the parent/guardian of the children aged 10 or younger. Please refer to the SRM for further details on how to administer the PODCI questionnaire.

9.17.2 Personal Adjustment and Role Skills Scale, 3rd Edition (PARS III) Questionnaire

Personal Adjustment and Role Skills Scale, 3rd edition (PARS-III) is a questionnaire designed for Duchenne muscular dystrophy young men that asks parents/guardians about their child's well-being and psychosocial adjustment (https://www.ncbi.nlm.nih.gov/pubmed/18650207). Please refer to the SRM for further details on how to administer the PARS-III Questionnaire.

10 STUDY ACTIVITIES

10.1 Pretreatment Phase

The pretreatment phase will be comprised of a minimum of 2 visits; a Screening Visit to allow the investigator to assess the participant's eligibility, and a Pre-Infusion Visit. The SRM and CE manual provides additional details on order of testing and data collection information.

10.1.1 Screening Visit (Days -28 to -8)

The ICF/assent must be obtained prior to any study related procedures being conducted. Screening will include assessments to confirm eligibility (review of inclusion/exclusion criteria and review to confirm the DMD diagnosis and appropriate mutations).

Screening activities:

- Informed consent/assent
- Review of inclusion/exclusion criteria
- Confirm DMD diagnosis
- Demographics
- Medical and surgical history
- Concomitant medication and treatment history
- Height and weight
- 12-lead ECG
- Vital signs
- Physical and neurological examination
- Renal ultrasound of kidneys, ureters, and bladder
- Function and strength
    - TTSTAND
    - TTRW
    - NSAA
    - TTCLIMB
    - Hand-held dynamometer
    - 6MWT

- Patient reported outcomes
    - PODCI
    - PARS III Questionnaire
- Antigen and antibody testing: HBs antigen, HCV antibody, HIV antibody
- Hematology
- Chemistry
- Urinalysis (random urine)
- AE review

10.1.2 Pre-Infusion Visit (Days -7 to -1)

- Review of inclusion/exclusion criteria
- Concomitant medications and treatment history; any changes will be noted
- Height and weight
- Vital signs
- Physical and neurological examination
- First morning void urinalysis

  Note: Analysis of the first morning void urine sample will include urine dipstick protein to be performed at the site.
- Urine cytology (utilizing a urine sample collected on-site)
- Exogenous tracer GFR

  Note: This should be done, if possible, per standard of care at the institution.
- Function and strength
    - TTSTAND
    - TTRW
    - NSAA
    - TTCLIMB
    - Hand-held dynamometer
    - 6MWT

- Patient reported outcomes
    - PODCI
    - PARS III Questionnaire
- AE review

10.1.3 Randomization

Randomization request will be submitted to the designated CRO and a copy to NS Pharma as described in the SRM. Request for randomization will be made after all screening procedures are performed and prior to the first treatment.

10.2 Treatment Phase

If allowed per local regulations, Weeks 6 to 8, 10 to 12, 14 to 16, 18 to 20, 22 to 24, 26 to 36, and 38 to 47 can be completed at a non-site location via the home health vendor. NS Pharma reserves the right to require visits to be completed at the site, if needed.

A ± 3 day window is permitted for each weekly visit from Weeks 2 to 48, inclusive.

10.2.1 Day 1 Dosing Visit (First Infusion)

The following assessments will occur:

- Confirmed diagnosis of DMD
- Concomitant medications and treatment history; any changes will be noted
- Height and weight
- 12-lead ECG
- Vital signs
- Physical and neurological examination
- Hematology
- Chemistry
- Postdose urinalysis (utilizing a urine sample collected within 5 hours after completion of the infusion)
- Anti-dystrophin antibody (predose)
- Anti-viltolarsen antibody (predose)
- PK blood sample (pre and postdose)
- Investigational product administration

- AE review

10.2.2 Week 2

The following assessments will occur:

- Review of medical and surgical procedures, concomitant medications, and other treatments; any changes will be noted
- Vital signs
- Investigational product administration
- AE review

10.2.3 Week 3

The following assessments will occur:

- Review of medical and, surgical procedures, concomitant medications, and other treatments; any changes will be noted
- Vital signs
- Hematology
- Chemistry
- First morning void urinalysis

  Note: Analysis of the first morning void urine sample will include urine dipstick protein to be performed at the site.
- Investigational product administration
- AE review

10.2.4 Week 4

The following assessments will occur:

- Review of medical and surgical procedures, concomitant medications, and other treatments; any changes will be noted
- Vital signs
- Investigational product administration
- AE review

10.2.5 Week 5

The following assessments will occur:

- Review of medical and surgical procedures, concomitant medications, and other treatments; any changes will be noted
- Vital signs
- Physical and neurological examination
- Hematology
- Chemistry
- First morning void urinalysis

  Note: Analysis of the first morning void urine sample will include urine dipstick protein to be performed at the site.
- Investigational product administration
- AE review

10.2.6 Weeks 6 to 8

The following assessments will occur:

- Review of medical and surgical procedures, concomitant medications, and other treatments; any changes will be noted
- Vital signs
- Investigational product administration
- AE review

10.2.7 Week 9

The following assessments will occur:

- Review of medical and surgical procedures, concomitant medications, and other treatments; any changes will be noted
- Vital signs
- Physical and neurological examination
- Hematology
- Chemistry

- First morning void urinalysis

  Note: Analysis of the first morning void urine sample will include urine dipstick protein to be performed at the site.
- Investigational product administration
- AE review

10.2.8 Weeks 10 to 12

The following assessments will occur:

- Review of medical and surgical procedures, concomitant medications, and other treatments; any changes will be noted
- Vital signs
- Investigational product administration
- AE review

10.2.9 Week 13

The following assessments will occur:

- Review of medical and surgical procedures, concomitant medications, and other treatments; any changes will be noted
- Height and weight
- 12-lead ECG
- Vital signs
- Physical and neurological examination
- Renal ultrasound of kidneys, ureters, and bladder
- Hematology
- Chemistry
- First morning void urinalysis

  Note: Analysis of the first morning void urine sample will include urine dipstick protein to be performed at the site.
- Urine cytology (utilizing a predose urine sample collected on-site)
- Postdose urinalysis (utilizing a urine sample collected within 5 hours after completion of the infusion)
- Anti-dystrophin antibody (predose)

- Anti-viltolarsen antibody (predose)
- PK blood sample (pre and postdose)
- Function and strength
    - TTSTAND
    - TTRW
    - NSAA
    - TTCLIMB
    - Hand-held dynamometer
    - 6MWT
- Patient reported outcomes
    - PODCI
    - PARS III Questionnaire
- Investigational product administration
- AE review

10.2.10 Weeks 14 to 24

The following assessments will occur:

- Review of medical and surgical procedures, concomitant medications, and other treatments; any changes will be noted
- Vital signs
- Physical and neurological examination (Week 17 and Week 21 only)
- Hematology (Week 17 and Week 21 only)
- Chemistry (Week 17 and Week 21 only)
- First morning void urinalysis (Week 17 and Week 21 only)

  Note: Analysis of the first morning void urine sample will include urine dipstick protein to be performed at the site.
- Investigational product administration
- AE review

10.2.11 Week 25

The following assessments will occur:

- Review of medical and surgical procedures, concomitant medications, and other treatments; any changes will be noted
- Height and weight
- 12-lead ECG
- Vital signs
- Physical and neurological examination
- Renal ultrasound of kidneys, ureters, and bladder
- Hematology
- Chemistry
- First morning void urinalysis

  Note: Analysis of the first morning void urine sample will include urine dipstick protein to be performed at the site.
- Urine cytology (utilizing a predose urine sample collected on-site)
- Postdose urinalysis (utilizing a urine sample collected within 5 hours after completion of the infusion)
- Anti-dystrophin antibody (predose)
- Anti-viltolarsen antibody (predose)
- PK blood sample (pre and postdose)
- Function and strength
    - TTSTAND
    - TTRW
    - NSAA
    - TTCLIMB
    - Hand-held dynamometer
    - 6MWT
- Patient reported outcomes
    - PODCI
    - PARS III Questionnaire

- Investigational product administration
- AE review

10.2.12 Weeks 26 to 36

The following assessments will occur:

- Review of medical and surgical procedures, concomitant medications, and other treatments; any changes will be noted
- Vital signs
- Investigational product administration
- AE review
- First morning void urinalysis (Week 29 and Week 33 only)

  Note: Analysis of the first morning void urine sample will include urine dipstick protein to be performed at the site.

10.2.13 Week 37

The following assessments will occur:

- Review of medical and surgical procedures, concomitant medications, and other treatments; any changes will be noted
- Height and weight
- 12-lead ECG
- Vital signs
- Physical and neurological examination
- Renal ultrasound of kidneys, ureters, and bladder
- Hematology
- Chemistry
- First morning void urinalysis

  Note: Analysis of the first morning void urine sample will include urine dipstick protein to be performed at the site.
- Urine cytology (utilizing a predose urine sample collected on-site)
- Postdose urinalysis (utilizing a urine sample collected within 5 hours after completion of the infusion)
- Anti-dystrophin antibody (predose)

- Anti-viltolarsen antibody (predose)
- PK blood sample (pre and postdose)
- Function and strength
    - TTSTAND
    - TTRW
    - NSAA
    - TTCLIMB
    - Hand-held dynamometer
    - 6MWT
- Patient reported outcomes
    - PODCI
    - PARS III Questionnaire
- Investigational product administration
- AE review

10.2.14 Weeks 38 to 47

The following assessments will occur:

- Review of medical and surgical procedures, concomitant medications, and other treatments; any changes will be noted
- Vital signs
- Investigational product administration
- AE review
- First morning void urinalysis (Week 41 and Week 45 only)

  Note: Analysis of the first morning void urine sample will include urine dipstick protein to be performed at the site.

10.2.15 Week 48

The following assessments will occur:

- Review of medical and surgical procedures, concomitant medications, and other treatments; any changes will be noted
- Vital signs
- Anti-dystrophin antibody (predose)

- Anti-viltolarsen antibody (predose)
- PK blood sample (pre and postdose)
- Investigational product administration
- AE review

10.3 End-of-Treatment Phase

10.3.1 Week 49

The following assessments will occur at the end of treatment (± 3 days) after the Week 48 dose for all participants or for a participant:

- Review of medical and surgical procedures, concomitant medications, and other treatments; any changes will be noted
- Height and weight
- 12-lead ECG
- Vital signs
- Physical and neurological examination
- Renal ultrasound of kidneys, ureters, and bladder
- Hematology
- Chemistry
- First morning void urinalysis

  Note: Analysis of the first morning void urine sample will include urine dipstick protein to be performed at the site.
- Urine cytology (utilizing a urine sample collected on-site)
- Exogenous tracer GFR

  Note: This should be done, if possible, per standard of care at the institution.
- Function and strength
  - TTSTAND
  - TTRW
  - NSAA
  - TTCLIMB
  - Hand-held dynamometer
  - 6MWT

- Patient reported outcomes
    - PODCI
    - PARS III Questionnaire
- AE review

10.3.2 Follow-Up Phone Call

Participants will have a phone call conducted with a member of the site study staff, 30 days (± 3 days) following the last investigational product infusion, to assess adverse events and medical, surgical, medication, and treatment review. Any AE(s) that is unresolved will be followed up by the site (investigator or designee) for as long as medically indicated. The CRO retains the right to request additional information for any participant with ongoing AEs at the end of the study, if judged necessary.

10.3.3 Unscheduled Visit

If a participant returns to the clinic for a visit outside of the protocol evaluation time points, the visit and any assessments and/or tests performed will be recorded in the source documents and the eCRF as an Unscheduled Visit.

10.3.4 Early Termination or Withdrawal from the Study

A participant (or the legal guardian acting on behalf of the participant) is free to withdraw consent and discontinue participation in the study at any time, without prejudice to further treatment according to standard clinical practice. Study participation may be discontinued at any time at the discretion of the investigator or sponsor. Study participation must be discontinued under the following circumstances:

- Withdrawal of consent by the participant/legal guardian;
- Failure to comply with the protocol;
- Lost-to-follow-up;
- Illness, condition, or procedural complication (including adverse events) affecting the participant's ability to participate or requiring prohibited medication;
- In the Investigator's judgment, it is deemed in the best interest of the participant to discontinue his/her participation in the study;

- The Investigator, sponsor, Data and Safety Monitoring Board (DSMB), and/or regulatory authority terminates the study; or
- Any other reason.

A Participant Completion/Discontinuation eCRF, describing the reason for discontinuation must be completed, for any discontinued or withdrawn participant regardless of reason. If a participant withdraws from the study or if the study is prematurely terminated, the investigator or designee will contact the participant or the participant's legal guardian **within 30 days** after withdrawal or termination to assess any AEs. The investigator will be asked to follow all SAEs until the event returns to baseline or until the investigator determines that follow-up is no longer medically necessary.

Participants who are withdrawn from the study may not re-enter.

The following assessments should be performed at the time of early termination:

- Review of medical and surgical procedures, concomitant medications, and other treatments; any changes will be noted
- Height and weight
- 12-lead ECG
- Vital signs
- Physical and neurological examination
- Renal ultrasound of kidneys, ureters, and bladder
- Urine cytology (utilizing a urine sample collected on-site)
- Anti-dystrophin antibody
- Anti-viltolarsen antibody
- Hematology
- Chemistry
- First morning void urinalysis

  Note: Analysis of the first morning void urine sample will include urine dipstick protein to be performed at the site.
- Exogenous tracer GFR

  Note: This should be done, if possible, per standard of care at the institution.

- Function and strength
    - TTSTAND
    - TTRW
    - NSAA
    - TTCLIMB
    - Hand-held dynamometer
    - 6MWT
- Patient reported outcomes
    - PODCI
    - PARS III Questionnaire
- AE review

If a participant is lost to follow-up, every reasonable effort must be made by the clinical site personnel to contact the participant and determine the reason for discontinuation/withdrawal (including assessment of any AEs reported by the participant/caregiver). The measures taken to follow-up must be documented in source documents.

10.3.5 Procedures for Early Termination

If a participant withdraws or is removed from the study for any reason, all early termination procedures should be completed per Table 2. Reason for withdrawal, date of the discontinuation, and date of the last dose of investigational product should be recorded in source documents and in the appropriate section of the eCRF. Investigational product assigned to the withdrawn participant may not be assigned to another participant.

The medical monitor should be consulted prior to the withdrawal of the study participant, except in the case of a medical emergency. Written notice (regardless of cause) is to be provided to the medical monitor within 48 hours of the withdrawal. At the time of discontinuation, every effort should be made to ensure all relevant procedures and evaluations scheduled for the final study visit are performed.

10.4 Participant Replacement

Participants will not be replaced.

10.5 Suspension or Termination of Study

If, in the opinion of the medical monitor, clinical observations in the study suggest that it may be unwise to continue, the study may be suspended. The medical monitor will request a DSMB meeting and consult with the sponsor. If the medical monitor, DSMB and sponsor agree that safety concerns warrant termination of the study, the sponsor will terminate the study. A written statement fully documenting the reasons for such a termination will be provided to investigators, IRBs/IECs and regulatory authorities, if required.

NS Pharma has the right to terminate an Investigator's participation in the study and remove all study materials from a clinical site. A written statement will be provided to the investigator, the IRB/IEC, and regulatory authorities, if required.

Possible reasons for termination of the study at a clinical site include, but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality,
- Inaccurate or incomplete data collection on an ongoing basis,
- Falsification of records, or
- Failure to adhere to the protocol.

If any serious or non-serious adverse events have occurred at such a clinical site, all documentation relating to the event(s) must be obtained.

11 SAFETY PROCEDURES AND PROCESSES

11.1 Definition of an Adverse Event

An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product, including control, and which does not necessarily have a causal relationship with treatment. This includes any untoward signs or symptoms experienced by the participant from the time of consent until completion of the study.

AEs may include, but are not limited to:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease or exacerbation of an existing disease.
- Any deterioration in non-protocol-required measurements of laboratory value or other clinical test (e.g., ECG) that results in symptoms, a change in treatment, or discontinuation from investigational product.

Disease signs, symptoms, and/or laboratory abnormalities already existing prior to the use of the product are not considered AEs after treatment, unless they reoccur after the participant has recovered from the preexisting condition or in the opinion of the investigator, they represent a clinically significant exacerbation in intensity or frequency. If clinically significant worsening from baseline is noted, the changes will be documented in the AE source document and the eCRF.

TEAEs are defined as any AE or worsening of an existing condition after initiation of the investigational product and through 30 days after completion of study participation.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of investigational new drug (IND) safety reporting, ‘reasonable possibility’ means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

An AE or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator’s drug brochure or is not listed at the specificity or severity that has been previously

observed. During the course of the study, the investigator brochure should be updated on an ongoing basis with new important safety information.

11.2 Definition of a Serious Adverse Event

An adverse event is serious when the participant outcome is:

- Death,
- Life-threatening (see below for expanded definition),
- Hospitalization (initial or prolonged),
- Disability or permanent damage (see below for expanded definition),
- Congenital anomaly/birth defect,
- Important medical events that, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Life-threatening Experience: Any AE that places the participant, in the view of the site investigator, at immediate risk of death from the AE as it occurred, i.e., does not include an AE that, had it occurred in a more severe form, might have caused death.

Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. However, emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

Hospitalization for an elective or outpatient procedure will not be considered to be an SAE. However, unexpected complications and/or prolongation of hospitalization that occur during elective or outpatient surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (e.g., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

Disability or permanent damage: Any AE that results in a substantial disruption of a participant’s ability to conduct normal life functions, i.e., the AE resulted in a significant, persistent or permanent change, impairment, damage or disruption in the participant's body function/structure, physical activities and/or quality of life.

Important medical events that may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above: an AE that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

11.3 Severity

It is the investigator's responsibility to assess the intensity (severity) of an AE.

The severity of the AE will be characterized and recorded as "mild, moderate, severe, life-threatening or death" according to the following definitions: The CTCAE v4.03 guidelines for severity assessments will be used to grade AEs for this trial (available at evs.nci.nih.gov/ftp1/CTCAE/About.html). The CTCAE v4.03 listed guidelines for severity assessment are:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only or intervention not indicated
- Moderate: Minimal, local or noninvasive intervention indicated or limited age-appropriate instrumental activities of daily living (ADL)
- Severe: Severe or medically significant but not immediately life-threatening; or hospitalization or prolongation of hospitalization indicated; or disabling; or limiting self-care ADL
- Life-threatening: Life-threatening consequences or urgent intervention indicated
- Death: Death related to AE

Note: A severe AE need not be serious, and an SAE need not be severe.

11.4 Relationship

It is the investigator's responsibility to assess the relationship between the investigational product and the adverse event. The degree of "relatedness" of the AE to the investigational product may be described using the following scale:

Not Related

- **Not Related**: No temporal association and other etiologies are likely the cause.
- **Unlikely**: Event or laboratory test abnormality, with a time to drug that makes a relationship improbable (but not impossible). Diseases or other drugs provide plausible explanations.

Related

- **Possible**: Temporal association, but other etiologies are likely the cause. However, involvement of the investigational product cannot be excluded.
- **Probable**: Temporal association, other etiologies are possible but unlikely. The event may respond if the investigational product is discontinued.
- **Definite**: Established temporal association with administration of the investigational product with no other more probable cause. The event should resolve when the investigational product is discontinued and recur on re-challenge.

11.5 Adverse Events of Special Interest

The following events are considered adverse events of special interest based on the route of administration and toxicology profile for viltolarsen:

- Access device complication (for participants with indwelling access devices);
- Urinary protein excretion ≥300 mg/day based on a 24-hour urine collection;
- Serum cystatin C ≥1.5 × baseline, or serum creatinine ≥2 × baseline and ≥0.3 mg/dL, confirmed with a repeat test within 1 week of the original results (i.e., meets the cystatin C or creatinine criteria for referral to a pediatric nephrologist described in Section 11.11.1);
- Any confirmed instances of hematuria or other potentially clinically significant abnormalities on urinalysis.

11.6 Disease-Related Signs and Symptoms

Reporting of disease related or DMD-related signs and symptoms as AEs are based on the investigator's clinical judgment. However, progression of symptoms and signs associated with DMD that is inconsistent to the usual course of the disease should be reported as an AE in the eCRF and source documentation.

11.7 Reporting

11.7.1 Adverse Event Reporting

All AEs occurring during the course of the study (starting from signing informed consent to study completion) will be collected on the AE eCRF. Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational product. For each AE, the following information will be recorded:

- Description of the event (e.g., headache),
- Date of onset,
- Date of resolution (or that the event is continuing),
- Action taken as a result of the event,
- Seriousness of the event,
- Severity of the event,
- Outcome of the event, and
- Investigator's assessment of relationship to investigational product.

A cluster of signs and symptoms that results from a single cause should be reported as a single AE (e.g., fever, elevated WBC, cough, abnormal chest x-ray, etc., can all be reported as "pneumonia").

The investigator will carefully evaluate the comments of the participant and the response to treatment in order that he/she may judge the true nature and severity of the AE. The question of the relationship of AE to investigational product administration should be determined by the Investigator or study physician after thorough consideration of all facts that are available.

Clinically significant changes from time of ICF will be documented as AEs on the AE eCRF. Clinically significant changes are physical findings that have medical relevance and may result in an alteration in medical care.

11.7.2 Adverse Events of Special Interest Reporting

Adverse events of special interest should be promptly recorded in the eCRF so that the DSMB and medical monitor are notified. Such events will be reviewed by the DSMB and medical monitor to enable consideration of implications for other participants.

11.7.3 Serious Adverse Event Reporting

All SAEs occurring from the time of informed consent until the follow-up telephone call, 30 days following the last administration of study drug must be reported to the designated CRO and the sponsor within 24 hours of the knowledge of the occurrence. This includes death due to any cause and whether or not the SAE is deemed drug-related or expected. After the 30-day reporting window, any SAE that the investigator considers related to study drug must also be reported.

To report the SAE, the investigator is to complete the SAE form electronically in the electronic data capture (EDC) system for the study. If the event meets serious criteria and it is not possible to access the EDC system, the investigator is to send an email, phone or fax the event to the designated CRO within 24 hours of awareness. When the EDC system becomes available, the SAE information must then be entered within 24 hours of the system becoming available.

The investigator is required to submit SAE reports to the IRB or IEC in accordance with local requirements.

11.8 Serious Adverse Event Follow-Up

SAEs will be followed by the site investigator until resolution or until the investigator determines that follow-up is no longer medically necessary.

Follow-up information, or new information regarding an ongoing SAE, must be provided promptly to the CRO within 24 hours of knowledge of the new or follow-up information. The CRO will forward the information to the sponsor, and the medical monitor.

11.9 Expedited Reporting to Regulatory Authorities

The NS Pharma designated CRO is responsible for reporting all relevant information about suspected unexpected serious adverse reactions (SUSARs) that are fatal or life-threatening as soon as possible to the applicable regulatory authorities in all the Member States concerned, and to the Central Ethics Committee, and in any case no later than 7 days after knowledge by the

CRO of such a case. All other SUSARs will be reported to the applicable regulatory authorities concerned and to the Central Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the sponsor/designee.

The NS Pharma designated CRO will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The NS Pharma designated CRO will also inform all investigators as required per local regulation. Reports of all applicable SUSARs must be communicated as soon as possible to the appropriate IRB/IEC and/or reported in accordance with local laws and regulations. Investigators should file written documentation of IRB/IEC notification for each report to the designated CRO as applicable.

The sponsor must report any suspected adverse reaction to the study drug, that is both serious and unexpected, or any SAEs suspected to be related to the CVA port, to the US FDA, Health Canada (21 CFR 312.32(c)(1)(i) and C.05.014, respectively), and other national and local health authorities.

11.10 Monitoring and Follow-Up of Adverse Events

Participants who experience AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the investigator. All follow-up results are to be reported to the medical monitor. Any actions taken and follow-up results must be recorded either on the appropriate page of the eCRF or in appropriate follow-up written correspondence, as well as in the participant's source documentation. Follow-up laboratory results should be filed with the participant's source documentation.

For all AEs that require the participant to be discontinued from the study, relevant clinical assessments and laboratory tests must be repeated at appropriate intervals until final resolution or stabilization of the event(s).

Any AEs that are unresolved at the participant's last AE assessment in the study are followed up by the investigator or designee for as long as medically indicated, but without further recording in the eCRF. The sponsor and designated CRO retain the right to request additional information for any participant with ongoing AEs/SAEs at the end of the study, if judged necessary.

11.11 General Monitoring and Management of Abnormal Clinical Laboratory Findings

It is the investigator's responsibility to review the results of all laboratory tests as they become available and to sign and date the results indicating review. For each laboratory test outside of the laboratory normal range, the investigator must ascertain if this represents a clinically significant change from baseline for the individual participant. The investigator may repeat a laboratory test or request additional tests to verify results of the original laboratory test.

If a laboratory value is determined to be an abnormal and clinically significant change from baseline for the participant, the investigator should determine if it qualifies as an AE, and if so, an appropriate eCRF will be completed. All clinically significant laboratory abnormalities occurring during the study and that were not present at baseline should be followed and evaluated with additional tests if necessary, until diagnosis of the underlying cause, or resolution.

11.11.1 Monitoring of Renal Function and Urine Analyses

All scheduled first morning void urinalyses will include urine dipstick protein to be performed at the site. If first morning void urine dipstick protein ≥2+, UPCR ≥0.5 mg/mg, or UPCR ≥2 × baseline, a first morning void urine dipstick protein will be repeated within 1 week. If 1 or more of these criteria are met again on the repeat test, a 24-hour urine sample will be collected within 1 week of the results to assess protein and creatinine. If proteinuria on a 24-hour urine sample is ≥300 mg/day, the patient will be referred to a pediatric nephrologist.

In addition, any instances of hematuria or other potentially clinically significant abnormalities on urinalysis will be confirmed at the following week's visit, or sooner at discretion of the investigator. Confirmed clinically significant treatment-emergent abnormalities will be recorded as AEs and discussed with the medical monitor. Abnormalities will be monitored and evaluated with additional tests or consultations, if necessary, until the underlying cause is determined, or the event is brought to an acceptable resolution. Additional clinical and laboratory information may be collected and documented in order to better characterize abnormalities and identify etiology and appropriate management. Potential need for interruption or discontinuation of study drug should be discussed with the medical monitor and sponsor.

If serum cystatin C ≥1.5 × baseline, or if serum creatinine ≥2 × baseline and ≥0.3 mg/dL, the test will be repeated within 1 week of the results. If either of these criteria are met again on the repeat test, the patient will be referred to a pediatric nephrologist.

To help relate creatinine and cystatin C measurements to GFR in patients with DMD, GFR will be determined using an exogenous tracer test, if available, at the Pre-Infusion Visit and Week 49 (or at early termination, if applicable). This should be done per standard of care at the institution.

11.12 Monitoring and Management of Abnormal Electrocardiograms

If a clinically significant ECG abnormality occurs that was not present at baseline (screening) and the investigator determines that the abnormality is related to investigational product, the abnormality will be discussed with the medical monitor. The ECG abnormality will be monitored and evaluated with additional tests (if necessary) until the underlying cause is determined or the event is brought to an acceptable resolution. Additional clinical and laboratory information will be collected and carefully documented in order to better characterize the ECG abnormality and rule out alternative causes. ECG findings determined to be a clinically significant change from baseline should be reported as an adverse event regardless of causality.

Unscheduled ECG assessments will be completed at the discretion of the investigator.

11.13 Intravenous (IV) Access Considerations

Investigational product dosing will be administered through IV infusion. Peripheral venous access (IV catheter that empties into a peripheral vein in the arms, hands, legs or feet) is the preferred route of investigational product administration for this study.

A CVA (IV catheter that empties into a large central vein) will be considered on a case-by-case basis for participants who have difficulty with peripheral venous access. A TICVAD is the preferred option of CVA, if necessary, for this study. The sponsor will decide whether or not to approve this option after discussions with the investigator and medical monitor have ensured mutual agreement that CVA will still maintain a positive benefit/risk ratio for the participant in this study. Before final decision, NS Pharma will obtain documentation from the investigator that the consulting surgeon who will place the port holds hospital privileges as a board eligible/board certified surgeon. The decision, rationale and conclusion regarding the maintained positive benefit/risk ratio will be detailed in writing and sent to the requesting site. CVA should not be implemented without sponsor approval.

An alternative method of CVA may only be considered in the case of a contraindication, in the opinion of the consulting surgeon for the placement of a TICVAD (port).

11.14 Data and Safety Monitoring Board

It is the responsibility of the DSMB to review data quality, relevant safety data, and AEs for all participants enrolled in the study and to make recommendations to the medical monitor, and sponsor regarding the ongoing conduct and monitoring of the study. Details are provided in the DSMB charter.

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

The statistical analyses described in this section will be performed as further outlined in the statistical analysis plan (SAP), which will be finalized prior to database lock. The SAP will supersede the protocol if there are any differences between the two documents in the plans for data analysis and the differences will be noted in the SAP. The SAP will be included as an appendix in the clinical study report for this protocol. Statistical analyses will be performed using SAS 9.2 or higher.

12.2 Determination of Sample Size

For TTSTAND (calculated as a velocity, defined as rise per second), the sample size of 74 participants has been calculated using the following values:

- Mean difference = 0.05
- Standard deviation = 0.075
- Type I error level (two-sided) = 0.05
- Power level = 0.8
- Allocation ratio (N1: viltolarsen/N2: placebo) = 1

The mean difference and the SD were set based on the result of comparison between viltolarsen group and natural history control group at 25 weeks in the Phase 2 Study NS-065/NCNP-01-201 (mean difference between 2 groups: 0.0395, SD: 0.07545 and 0.07377). As the mean difference between the 2 groups at 48 weeks is expected to be larger than at 25 weeks, the mean difference was estimated to be 0.05.

An unpaired t-test for analysis was used instead of mixed effect model repeat measurement (MMRM) for the calculation method due to lack of prior information.

When approximately 90% of participants are enrolled in the study, an unblinded review will be conducted and sample size re-estimation will be considered. An additional unblinded review and re-estimation will be performed when approximately 50 participants have completed the Week 49 evaluations for the primary outcome measure. See Section 12.8 for details.

12.3 Analysis Populations

The safety population will consist of all randomized participants who received at least 1 dose of investigational product. Participants will be analyzed as treated. This will be the primary analysis population for the evaluation of exposure and safety.

The modified Intent-to-Treat (mITT) population will consist of all randomized participants who received at least 1 dose of investigational product and have a baseline assessment and at least 1 post baseline efficacy assessment. Participants will be analyzed as randomized. This will be the primary analysis population for the evaluation of efficacy.

12.4 Demographics and Baseline Characteristics

Summaries of participant demographics (age, race, ethnicity and dominant hand), baseline safety characteristics (anthropometrics, vital signs, physical examination, hematology, chemistry, urinalysis, ECG, and antibodies), and baseline efficacy parameters will be done.

12.5 Efficacy Endpoints

All efficacy analyses will be performed using the modified intent to treat (mITT) population. In addition, additional analyses will utilize the placebo treatment group.

A hierarchical analysis, following a fixed-sequence hypothesis testing method, is used to first test TTSTAND and then TTRW, 6MWT, NSAA, TTCLIMB, and hand-held dynamometer, if the former was statistically significant.

12.5.1 Efficacy Objective

The primary efficacy outcome measure (TTSTAND) will be summarized by treatment group over time using descriptive statistics.

The TTSTAND times to perform the test will also be converted to velocities. Note that a test result that is to be converted to velocity that the participant could not perform due to disease progression will have velocity set to zero only at the first visit where this occurs. After that visit, missing observations due to disease progression will be left as missing.

The TTSTAND will be compared between the viltolarsen treated participants and the placebo treated participants using MMRM analysis with treatment group, week of the visit, and the treatment-by-week interaction as factors, and age as one covariate, and baseline performance as a second covariate. The TTSTAND times to perform the test will be converted to velocities.

The treatment comparisons of most interest will be the LS means contrasts between the viltolarsen treated participants and the placebo treated participants at Week 49.

12.5.2 Secondary Objectives

12.5.2.1 Function and Strength

TTRW, 6MWT, NSAA, TTCLIMB, and hand-held dynamometer will be summarized by treatment group over time using descriptive statistics.

The TTRW and TTCLIMB times to perform the test will also be converted to velocities. For a test that the participant could not perform, the velocity will be set to zero.

12.5.2.2 Analysis Comparing Viltolarsen to Placebo

TTSTAND, TTRW, 6MWT, NSAA, TTCLIMB, and hand-held dynamometer results will be compared between the viltolarsen treated participants and the placebo treated participants using MMRM analysis with treatment group, week of the visit, and the treatment-by-week interaction as factors, and age as one covariate, and baseline performance as a second covariate. The TTRW and TTCLIMB times to perform the test will be converted to velocities. For a test that the participant could not perform, the velocity will be set to zero.

12.6 Safety Assessments

Safety analyses will be performed using the safety population. All safety assessments will be based on actual treatments received by participants and are detailed in the protocol and statistical analysis plan.

12.6.1 Anthropometrics, Vital Signs, Laboratory Assessments, and ECG

Anthropometrics, vital signs, hematology, chemistry, urinalysis, and ECG results will be summarized by treatment over time using descriptive statistics for continuous outcomes. Actual values and change from Day 1 will be presented. Further, all laboratory abnormalities will be listed.

12.6.2 Physical Examination and Adverse Events

Physical examination results will be summarized by frequency of presence of abnormalities in body system (beyond the DMD diagnosis) and in particular any changes in the physical examination over time.

TEAEs will be summarized by treatment group. Coding will be done by system organ class and preferred term (using the Medical Dictionary for Regulatory Activities [MedDRA]). Level of severity will be assessed using the CTCAE grading system.

Summaries will include:

- Summaries at the participant level
    - How many participants had any TEAE, any SAE, highest severity of TEAE within a participant across all infusions, highest relationship level of TEAE within a participant across all infusions, highest intervention level regarding investigational product (e.g., discontinued, vs. infusion interruption vs. no interruption in infusions), and worst outcome within a participant (e.g., AE did not resolve and has a permanent effect).
- Summary at the event level
    - Summaries will be done using the MedDRA coding by events and overall, summarizing by system organ class and preferred term, by relationship to investigational product, severity, intervention, and outcome.

Listings tables will be provided for all AEs.

12.6.3 Concomitant Medications and/or Other Treatments

Glucocorticoids, which are required as part of the inclusion criteria, will be summarized by type of GC (prednisone vs. deflazacort), by schedule (daily vs. any other), and by treatment. Participants are required not to change the GC dose while on study. Any changes in doses or schedule will be listed.

Other concomitant medications will be summarized by ATC class and preferred term. Each medication will be counted once within a participant using it, regardless of the number of times it was reported on the eCRFs. The summaries will note new medications or supplements vs. those already given at baseline and study entry. Any other treatment, surgeries, will be listed and described; however, those are expected to be few without a need to be summarized using tables.

12.6.3.1 Antibodies and Pharmacokinetics

Antibodies and PK concentrations will be summarized by treatment group over time. PK concentrations may be summarized at a later date.

12.7 Pharmacokinetic Endpoints and Analysis

Population PK analysis will be presented in a separate report.

12.8 Interim Analyses

Interim analysis is planned when approximately 90% of participants are enrolled in the study. An additional unblinded review and re-estimation will be performed when approximately 50 participants have completed the Week 49 evaluations for the primary outcome measure. At these 2 time points, an unblinded data review will be conducted, which will include review by the DSMB. Based on this review, the DSMB will make a recommendation to the sponsor for possible sample size re-estimation, i.e., the additional number of participants to be enrolled to increase the conditional power to an acceptable level.

Denne (Denne, 2001) described the sample size re-estimation procedure for the group sequential test by using the conditional power without inflating the type I error rate for the interim analyses. At the point at which the sample size re-estimation is being made for the interim analyses, the test statistic z_1 is observed. The conditional power is the probability of rejection H_0 on the basis that $Z_2 \geq c_2$ given $Z_1 = z_1$, which is denoted by $CP_\theta(n_2, c_2|z_1)$. The conditional power is given by:

$$CP_\theta(n_2, c_2|z_1) = 1 - \Phi\left[\frac{c_2\sqrt{n_2} - z_1\sqrt{n_1} - \frac{(n_2-n_1)}{\sqrt{2\sigma^2}}\theta}{\sqrt{n_2 - n_1}}\right]$$

where n_1 is the sample size per treatment group at the interim analyses, the true difference in mean response θ is estimated by the current sample mean difference δ, and σ^2 is estimated by the current sample within group variance s^2. The re-estimated sample size per treatment group n_2 is obtained by solving the conditional power be at least 80% power as defined in the sample size determination. The re-estimated total sample size is given by $n^* = 2n_2$.

To preserve study integrity, a small alpha of 0.001 will be spent at the second re-estimation resulting in the overall significance level to be 0.049 at the final stage.

If the re-estimated total sample size from the interim analyses is smaller than the planned total sample size of 74, the sample size adjustment will not be needed. If the re-estimated total

sample size is larger than the planned total sample size, the sample size may be increased up to a maximum target sample size of 100.

12.9 Handling of Missing Data

Every effort will be made to collect all data. However, despite best efforts, missing or incomplete data may be reported. All missing or partial data will be presented in the participant data listing, as they are recorded on the eCRF.

Participants lost to follow-up or withdrawn will be included in statistical analyses up to the point of their last evaluation. Unless otherwise specified, no imputation of values for missing data will be performed. Of note, since participants with DMD are expected to decline over time, imputing efficacy parameters by last value carried forward mostly biases towards participants appearing stronger or faster than they are, since it carries forward potentially a better value than the value at the time of the missed observation. Therefore, for this study, we will summarize how much data are missing, but do not expect to need to impute any data to accomplish the analyses as described. Details of handling missing data will be described in the SAP.

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14 APPENDICES

Appendix 1 Sponsor Signatures

Study Title:	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 (DMD)
Study Number:	NS-065/NCNP-01-301
Final Date:	08 December 2022

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol:

[redacted]

[redacted]

[redacted]

[redacted]

Appendix 2 Investigator's Signature

Study Title:	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 (DMD)
Study Number:	NS-065/NCNP-01-301
Final Date:	08 December 2022

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Prior to the start of the study, I agree to release sufficient and accurate financial information that permits NS Pharma to demonstrate that as an investigator and all study personnel listed on the FDA Form 1572, the Health Canada Qualified Investigator Undertaking form, or similar as required by other national/local health authorities, I have no personal or professional financial incentive regarding the future approval or disapproval of the investigational product such that my research might be biased by such incentive.

Signed:_____ Date:_____

Name and credentials _____

Title _____

Affiliation _____

Address _____

Telephone number _____

Appendix 3 Administrative Considerations

Investigators

The investigator must agree to the responsibilities and obligations listed below, as specified by the appropriate FDA/Health Canada regulatory requirements or International Council for Harmonisation/Good Clinical Practices (ICH/GCP) guidelines:

- Agree to conduct the study in accordance with the relevant current protocol;
- Agree to personally conduct or supervise the described investigation(s);
- Agree to inform any participants, or persons used as controls, that the investigational products are being used for investigational purposes and ensure that the requirements relating to obtaining informed consent and IRB/IEC review and approval are met;
- Agree to report adverse experiences that occur during the course of the investigation(s);
- Read and understand the information in the Investigator's Brochure, including the potential risks and side effects of the investigational product;
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments;
- Maintain adequate and accurate records and make those records available for inspection;
- Ensure that an IRB/IEC will be responsible for the initial and continuing review and approval of the clinical investigation;
- Agree to promptly report to the IRB/IEC all changes in the research activity and all unanticipated problems involving risks to participants or others;
- Agree to not make changes in the research without IRB/IEC approval, except where necessary to eliminate apparent hazards to participants; and
- Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements.

Refer also to:

- FDA Regulations Related to Good Clinical Practice (GCP) and Clinical Trials: http://www.fda.gov/oc/gcp/regulations.html
- Guidance and Information Sheets on GCP in FDA-Regulated Clinical Trials: http://www.fda.gov/oc/gcp/guidance.html

- Guidance for IRBs and Clinical Investigators:
  http://www.fda.gov/oc/ohrt/irbs/default.htm
- Guidance for Industry - E6 Good Clinical Practice: Consolidated Guidance
  http://www.fda.gov/cder/guidance/959fnl.pdf

Informed Consent, Protected Health Information (PHI) and Confidentiality

Informed Consent

The ICF, assent form, and consent process must comply with US 21CFR Part 50 and local laws. The ICF/Assent Form will document the study-specific information provided to the participant by the investigator or designee and the participant's/legal guardian's agreement to participate in the study.

The investigator, or designee (as described on Delegation of Authority log), must explain in terms understandable to the participant, the purpose and nature of the study, the study procedures, anticipated benefits, potential risks, the possible adverse effects and any discomfort participation in the study may involve. Each participant must provide a signed and dated ICF before any study related procedures are performed. In the case of a participant who is incapable of providing informed consent, the investigator or designee must obtain a signed and dated ICF from the participant's legal guardian.

Minors, who are not legally capable of giving informed consent, may possess the ability to assent or dissent to participation in the study. The investigator, or designee should explain the study and study procedures to the minor in as much detail as the minor is able to comprehend. IRB/IEC-approved, age-appropriate Assent Forms must be obtained from minor participants as required by local laws and governing IRBs/IECs.

Confidentiality

Authority regulations (FDA, Health Canada, or other national and local health authorities) require the sponsor or the sponsor's authorized representative to inspect all study documents and records maintained by the investigator, including but not limited to medical records (office, clinic, or hospital) for the participants in this study. These regulations also allow the sponsor's records to be inspected by authorized representatives of the regulatory authorities. The names and identities of all research participants will be kept in strict confidence and will not appear on

eCRFs or other records provided to or retained by the sponsor or the sponsor's authorized representative. Participant confidentiality will be respected during review of source documents by monitors, auditors and other sponsor representatives. Review procedures will adhere to regulatory requirements and professional standards for confidentiality. Names and identities of participants can be protected by de-identifying (i.e., "blacking-out") participant's name and replacing the name with the participant's study identification number. The ICF must include appropriate statements explaining these requirements.

Protected Health Information (PHI)

Information on maintaining participant confidentiality in accordance with US and local patient privacy regulations must be provided to each participant/legal guardian as part of the informed consent process, either as part of the ICF or as a separate signed HIPAA consent. The investigator or designee must explain to each participant that for the evaluation of study results, the participant's PHI obtained during the study may be shared with NS Pharma and its designees, regulatory agencies and IRBs/IECs. As the study sponsor, NS Pharma will not use the participant's PHI or disclose it to a third party without applicable participant authorization. It is the investigator's responsibility to obtain written permission to use PHI from each participant/legal guardian. If a participant or participant's legal guardian withdraws permission to use PHI, it is the investigator's responsibility to obtain the request in writing and ensure that no further data is collected on the participant. Any data collected up to the point of HIPAA consent withdrawal may be used in analysis of the study results.

Study Administrative Structure

Institutional Review Board/Independent Ethics Committee Approval

Before initiation of the study, the investigator must obtain approval or favorable opinion of the research protocol, informed consent form, and any material related to participant recruitment from an IRB or IEC complying with the provisions specified in 21 CFR Part 56 and applicable pertinent state and federal requirements of each participating location, including ICH and GCP guidelines.

Institutional Review Boards and IECs must be constituted according to the applicable laws. It is the responsibility of each clinical site to submit the protocol, Investigator's Brochure, participant informed consent, participant recruitment materials (if applicable), and other documentation as required by the IRB/IEC for review and approval. A copy of the written approval must be provided to NS Pharma.

The documentation should clearly mention the approval/favorable opinion of the protocol, the participant informed consent form, and participant recruitment materials (if applicable), including respective version dates. The written approval and a list of the voting members, their titles or occupations, and their institutional affiliations must be obtained from the IRBs/IECs and provided to NS Pharma (or its authorized CRO) prior to the release of clinical study supplies to the clinical site and commencement of the study. If any member of the IRB/IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

Clinical sites must adhere to all requirements stipulated by their respective IRB/IEC. This includes notification to the IRB/IEC regarding: protocol amendments, updates to the participant informed consent, recruitment materials intended for viewing by participants, IND Safety Reports, serious and unexpected adverse events, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB/ IEC, and submission of final study reports and summaries to the IRB/ IEC.

It is the responsibility of each clinical site to submit information to the appropriate IRB/IEC for annual review and annual re-approval.

The investigator must promptly inform their IRB/IEC of all SAEs or other safety information reported from the participant or NS Pharma or its authorized CRO.

Protocol Amendments

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments. Protocol amendments that are deemed substantial (e.g., affecting the safety of the participant, the scope of the study, and/or the scientific quality) will be submitted to regulatory authorities and/or to the IEC/IRB as appropriate. For substantial amendments, the changes will become effective only after approval by the Sponsor, the responsible Investigator, IEC/IRB, and competent authorities. All other amendments (i.e., non-substantial or administrative amendment) will be documented in the Trial Master File.

Ethical Conduct of the Study

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in the protocol and conduct the study in accordance with the CFRs (21 CFR Parts 11, 50, 54, 56, 312, 314, and 320) and local regulations, which originate from the ethical principles laid down in the current revision of the Declaration of Helsinki, GCPs, and policies and procedures as outlined by the ethical requirements for IRB/IEC review and informed consent forms.

The investigator agrees to allow monitoring and auditing of all essential clinical study documents by NS Pharma or its authorized representatives and inspection by the FDA or other appropriate regulatory authorities. Monitoring and auditing visits by NS Pharma or authorized designee will be scheduled with the appropriate staff at mutually agreeable times periodically throughout the study.

The investigator will assure proper implementation and conduct of the study, including those study-related duties delegated to other appropriately qualified individuals. The investigator will assure that study staff cooperates with monitoring and audits and will demonstrate due diligence in recruiting and screening study participants. The investigator must sign and return to NS Pharma (or its authorized CRO) the “Study Acknowledgment” page and provide a copy of current curriculum vitae.

Study Monitoring

The investigator agrees to allow direct access to all essential clinical study documents for the purpose of monitoring and/or auditing by NS Pharma or its authorized representatives and inspection by the appropriate regulatory authorities.

NS Pharma (or its authorized CRO) has the obligation to follow this study closely to ensure that the study is conducted in accordance with the protocol, ICH and GCP regulatory requirements, the CFRs, FDA, and the current Declaration of Helsinki throughout its duration by means of personal visits to the investigator's facilities and other communications.

These visits will be conducted to evaluate the progress of the study, verify the rights and well-being of the participants are protected, and verify the reported clinical study data are accurate, complete, and verifiable from source documents. This includes review of informed consent forms, results of tests performed as a requirement for participation in this study, and any other medical records (e.g., laboratory reports, clinic notes, investigational product disbursement log, pharmacy records, participant sign-in sheets, participant-completed questionnaires, telephone logs, ECGs) required to confirm information contained in the eCRFs.

A monitoring visit should include a review of the essential clinical study documents (regulatory documents, case report forms, medical records and source documents, investigational product disposition records, participant informed consent forms, etc.) as well as discussion on the conduct of the study with the investigator and staff.

The monitor should conduct these visits as frequently as appropriate for the clinical study. The investigator and staff should be available during these visits for discussion of the conduct of the study as well as to facilitate the review of the clinical study records and resolve/document any discrepancies found during the visit.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the clinical site by signature and date on the study-specific monitoring log.

Details of monitoring procedures will be described in the study monitoring plan.

On-Site Audits

Representatives of NS Pharma or its authorized clinical quality assurance group may visit a clinical site at any time during the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs. Participant privacy must be respected. The investigator and clinical site personnel are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by NS Pharma or its authorized representative.

The clinical study may also be inspected by the FDA (or other regulatory authorities) to verify that the study was conducted in accordance with protocol requirements, as well as the applicable regulations and guidelines.

In the event the investigator is contacted by regulatory authorities who wish to conduct an inspection of the clinical site, the investigator will promptly notify NS Pharma (or its authorized CRO) of all such requests and will promptly forward a copy of all such inspection reports.

Case Report Forms

Access to eCRFs will be provided to the clinical site. As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the participants treated as part of the research under this protocol. The investigator agrees to maintain accurate source documentation and eCRFs as part of the case histories.

Study records are comprised of source documents, eCRFs, and all other administrative documents (e.g., IRB/IEC correspondence, clinical study materials and supplies shipment manifests, monitoring logs, and correspondence). A study-specific binder will be provided with instructions for the maintenance of study records.

A completed eCRF must be submitted for each participant who receives investigational product, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and participant number. Any personal information, including participant name, should be removed or rendered illegible

to preserve individual confidentiality. The eCRF should not be used as a source document unless otherwise specified by NS Pharma.

It is essential that all dates appearing on NS Pharma participant data collection forms for laboratory tests, cultures, etc., be the dates on which the specimens were obtained, or the procedures performed. The eCRFs will be electronically signed by the investigator and dated as verification of the accuracy of the recorded data. All data collection forms should be completed within 48 hours following the evaluation.

Data reflecting the participant's participation with the investigational product under investigation are to be reported to NS Pharma. The data are to be recorded on the eCRFs and/or other media provided or approved by NS Pharma.

Details for completing the eCRF are provided in the eCRF completion manual for this study.

Source Documents

Source documentation is defined as any hand written or computer-generated document that contains medical information or test results that have been collected for or in support of the protocol specifications (e.g., laboratory reports, clinic notes, investigational product disbursement log, pharmacy records, participant sign-in sheets, participant completed questionnaires, telephone logs, x-rays, and ECGs). All draft, preliminary, and pre/final iterations of a final report are also considered to be source documents (e.g., faxed and hard copy of laboratory reports, faxed and hard copy of initial results, and final report).

Authority regulations require the sponsor (or the sponsor's authorized representative) to inspect all documents and records to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. These regulations also allow the sponsor's records to be inspected by authorized representatives of regulatory authorities. The investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution agrees to retain and maintain all study records that support the data collected from each participant, as well as all study documents as specified in ICH/GCP, Section 8 Essential Documents for the Conduct of a Clinical Trial. Retention of study documents will be governed by the Clinical Study Agreement between the sponsor and Institution.

Study documents (including eCRFs, source documents, clinical drug disposition records, signed participant informed consent forms, adverse event reports, and other regulatory documents) as required by the applicable regulations, must be maintained for 15 years after a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and the FDA is notified.

It is the responsibility of NS Pharma or authorized CRO to inform the investigator/institution as to when these documents no longer need to be retained.

Publication and Disclosure Policy

All information derived from this clinical study will be used by NS Pharma (or designee) and therefore, may be disclosed by NS Pharma (or designee) as required to other clinical investigators, to the FDA, and to other government agencies, or in connection with intellectual property filings or publications. Details of disclosure of study information are provided in the investigator's written clinical study agreement with NS Pharma.

The results of the study will be reported in a clinical study report (CSR) prepared by NS Pharma (or designee), which will contain eCRF data from all clinical sites that conducted the study.

NS Pharma shall have the right to publish data from the study without approval from the investigator. All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) may only be prepared through cooperation between NS Pharma (or designee) and the study investigator(s). If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to NS Pharma for review in accordance with the provisions of such investigator's written agreement with NS Pharma (or designee) before submission for

publication or presentation. If requested by NS Pharma in writing, the investigator will withhold such publication in accordance with the provisions of such agreement.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states:
Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
Authors need to meet conditions 1, 2, 3, and 4.
When a large, multi-center group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above.