Clinical Study Protocol: NS-065/NCNP-01-211

Study Title:	A Phase 2 Open-label Study to Assess the Safety, Tolerability, and Efficacy of Viltolarsen in Ambulant and Non-Ambulant Boys with Duchenne Muscular Dystrophy (DMD) Compared to Natural History Controls
Protocol Number:	NS-065/NCNP-01-211
Study Phase:	Phase 2
Product Name:	Viltolarsen
IND Number:	127474
EudraCT Number:	2020-003653-30
Sponsor:	NS Pharma, Inc.
Original Protocol Date:	21 January 2021
Global Amendment 1 Date:	21 March 2022

Confidentiality Statement

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STUDY SYNOPSIS

<table>
<tr><td>Study Title</td><td colspan="2">A Phase 2 Open-label Study to Assess the Safety, Tolerability, and Efficacy of Viltolarsen in Ambulant and Non-Ambulant Boys with Duchenne Muscular Dystrophy (DMD) Compared to Natural History Controls</td></tr>
<tr><td>Protocol Number</td><td colspan="2">NS-065/NCNP-01-211</td></tr>
<tr><td>Investigative Product</td><td colspan="2">Viltolarsen</td></tr>
<tr><td>Study Phase</td><td colspan="2">Phase 2</td></tr>
<tr><td>Indication</td><td colspan="2">Treatment of DMD with dystrophin deletion amenable to exon 53 skipping</td></tr>
<tr><td>Number of Patients</td><td colspan="2">20</td></tr>
<tr><td>Study Centers</td><td colspan="2">The study will be conducted at approximately 10 study sites in approximately 6 countries, including China, Italy, Russia, Spain, Turkey, and the United States.</td></tr>
<tr><td>Objectives/Endpoints</td><td>Primary Objective</td><td>Primary Endpoints</td></tr>
<tr><td></td><td>• To evaluate the safety and tolerability of viltolarsen administered intravenously (IV) at weekly doses of 80 mg/kg in ambulant and non-ambulant boys ≥8 years of age with DMD</td><td>• Vital signs
• Physical examination
• Renal ultrasound
• Echocardiogram
• Clinical laboratory tests
  ○ Hematology and clinical chemistry
  ○ Urinalysis
  ○ Urine cytology
• 12-lead electrocardiogram (ECG)
• Anti-viltolarsen antibodies
• Anti-dystrophin antibodies
• Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)</td></tr>
<tr><td></td><td>Secondary Objective</td><td>Secondary Endpoints</td></tr>
<tr><td></td><td>• To compare the efficacy of viltolarsen administered IV at weekly doses of 80 mg/kg over a 48-week Treatment Period versus natural history controls in</td><td>• Peak Expiratory Flow (PEF)
• Forced Vital Capacity (FVC)
• Forced expiratory volume in 1 second (FEV1)</td></tr>
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<tr><td></td><td>
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<tr><td>ambulant and non-ambulant boys ≥8 years of age with DMD</td><td>• Performance of Upper Limb (PUL)
• Brooke scale
• Vignos scale
• Hand-held dynamometer
• North Star Ambulatory Assessment (NSAA)</td></tr>
<tr><td>Exploratory Objectives</td><td>Exploratory Endpoints</td></tr>
<tr><td>• To evaluate health-related quality of life impact of viltolarsen treatment on patient's DMD</td><td>• Treatment Satisfaction Questionnaire (TSQM)
• Pediatric Outcome Data Collection Instrument (PODCI)
• Personal Adjustment and Role Skills Scale, 3rd edition (PARS III) Questionnaire</td></tr>
<tr><td>• To evaluate strength of cough in patients with DMD</td><td>• Peak Cough Flow (PCF)</td></tr>
<tr><td>• To evaluate preservation of ambulation of patients with DMD</td><td>• Loss of ambulation</td></tr>
<tr><td>• To evaluate daily activity and sleep-wake patterns to explore impact of viltolarsen treatment on patient's DMD</td><td>• Accelerometry measures of activity and sleep-wake patterns</td></tr>
</table>
</td></tr>
<tr><td>Study Design</td><td>This is a Phase 2, open-label study with DMD boys receiving 80 mg/kg viltolarsen administered IV at weekly doses in ambulant and non-ambulant boys ≥8 years of age with DMD over a 48-week Treatment Period.
<table>
<tr><th>Group</th><th>Number of Patients</th><th>Investigational Product (IP)</th></tr>
<tr><td>1</td><td>20</td><td>Viltolarsen 80 mg/kg/week</td></tr>
</table>
</td></tr>
<tr><td>Study Population</td><td>Inclusion Criteria:
1. Patient (if age 18 years or older) or patient's parent(s) or legal guardian(s) has (have) provided written informed consent and Health Insurance Portability and Accountability Act authorization, where applicable, prior to any study-related procedures; patients younger than age 18 years will be asked</td></tr>
</table>

	to give written or verbal assent according to local requirements; 2. Patient has a confirmed diagnosis of DMD defined as: a. Patient is male with clinical signs compatible with DMD; and b. Patient has a confirmed DMD mutation(s) in the dystrophin gene that is amenable to skipping of exon 53 to restore the dystrophin messenger ribonucleic acid reading frame including determination of unambiguously defined exon boundaries (using techniques such as multiplex ligation-dependent probe amplification, comparative genomic hybridization array, or other techniques with similar capability); 3. Patient is ≥8 years of age at time of first infusion in the study; 4. Patient has a Brooke scale rating of 3 or better OR an upright FVC 30% or greater at Screening; 5. Patient, if sexually active, is willing to abstain from sexual intercourse or employ a barrier or medical method of contraception during and for 3 months following completion of IP administration; 6. Patient and patient's parent(s)/guardian(s) (if patient is <18 years of age) and/or caregiver(s) are willing and able to comply with scheduled visits, IP administration plan, and study procedures; 7. Patient must be on a stable dose of glucocorticoid (GC) or not treated with GC for at least 3 months prior to the first dose of IP and is expected to remain on stable dose of GC treatment or off GC for the duration of the study. **Exclusion Criteria:** 1. Patient has had an acute illness within 4 weeks prior to the first dose of IP; 2. Patient has evidence of symptomatic cardiomyopathy (New York Heart Association Class III or higher); 3. Patient requires ventilation support while awake during the day; 4. Patient has an allergy or hypersensitivity to IP or any of its constituents; 5. Patient has severe behavioral or cognitive problems that preclude participation in the study, in the opinion of the investigator; 6. Patient has a previous or ongoing medical condition, medical history, physical findings, or laboratory abnormalities that could affect patient 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. Patient has had surgery within 3 months prior to the first anticipated administration of IP or has known plans to have surgery during the Treatment Period; 8. Patient has positive test results for hepatitis B antigen, hepatitis C antibody, or human immunodeficiency virus antibody at Screening; 9. Patient has been diagnosed with asthma that requires chronic treatment with a long-acting beta agonist; 10. Patient has relevant history of or current drug or alcohol abuse or use of any tobacco/marijuana products by smoking or vaping within 3 months prior to treatment with IP; 11. Patient is currently taking any other investigational drug or has taken any other investigational drug within 3 months prior to the first dose of IP or within 5 times the half-life of a medication, whichever is longer; 12. Patient has taken any gene therapy; 13. Patient 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 IP; 14. Patient has hydronephrosis, hydroureter, renal or urinary tract calculi, or ureteral stenosis by renal ultrasound; 15. Patient was previously enrolled in an interventional study of viltolarsen. 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 infusions will be supplied as a 5 mL glass vial containing 50 mg/mL of drug substance solution in saline. Patients will receive IV infusions of viltolarsen injection administered once weekly over a 48-week period. Patients will be dosed at 80 mg/kg/week.
Comparator, Dose, and Mode of Administration	None.
Safety Measures	The following assessments will be performed: • Vital signs • Physical examination • Chest X-ray • Renal ultrasound • Echocardiogram

	• Clinical laboratory tests
	  o Hematology and clinical chemistry
	  o Urinalysis
	  o Urine cytology
	• 12-lead ECG
	• Anti-viltolarsen antibodies
	• Anti-dystrophin antibodies
	• TEAEs and SAEs

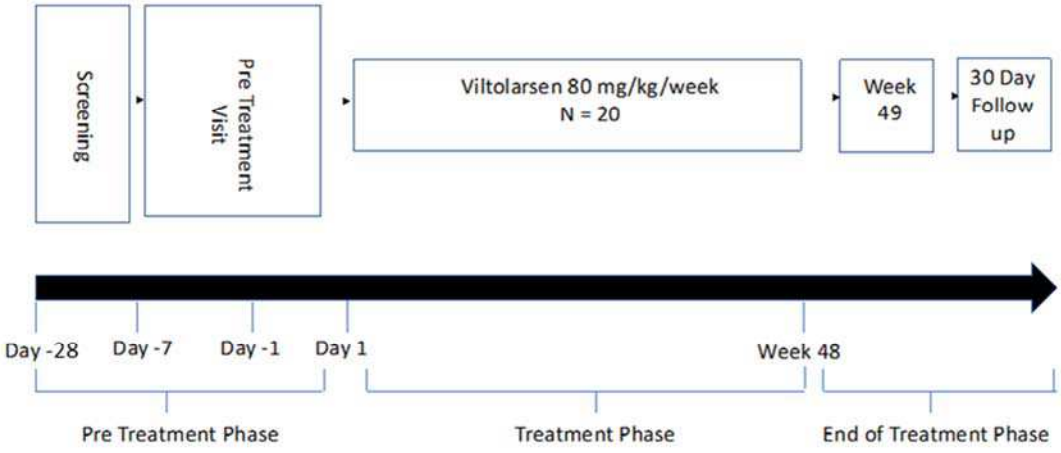
Clinical Efficacy Measures	The following assessments will be performed: • PEF • FVC • FEV1 • PUL • Brooke scale • Vignos scale • Hand-held dynamometer (elbow extension, elbow flexion, knee extension, and knee flexion on the dominant side only) • NSAA
Exploratory Measures	• TSQM • PODCI • PARS III Questionnaire • PCF • Actigraphy • Loss of ambulation
Pharmacokinetic Measures	Viltolarsen levels in plasma will be assessed at time points for each patient in which anti-viltolarsen antibody is detected.
Statistical Methods	**Sample Size:** The target sample size is 20 patients. A minimum of 8 ambulant patients will be enrolled. Assuming a sample size of 20, at least 1 adverse drug reaction with an incidence of 15% may be detected at a probability of ≥95% for the safety profile, which is the primary outcome. Based on this, it was decided that 20 patients should be enrolled to confirm safety. **Analysis Populations:** The Safety Population will consist of all patients who received at least 1 dose of IP. This will be the primary analysis population for the evaluation of safety. The modified Intent-to-Treat Population will consist of all patients who received at least 1 dose of IP and have a baseline assessment and at least 1 post-baseline efficacy assessment. This will be the analysis population for the evaluation of efficacy.

	General Statistical Considerations: All measurements will be analyzed based upon the type of distribution, and descriptive statistics will be presented by time point, as appropriate. **Primary Safety Evaluation:** Safety analyses will be performed using the Safety Population. TEAEs will be summarized by system organ class and preferred term (using the Medical Dictionary for Regulatory Activities), by relationship to IP, and by intensity (Common Terminology Criteria for Adverse Events grade). **Pharmacokinetic Evaluation:** Population pharmacokinetic analyses 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[a]	Pretreatment Phase		Treatment Phase (Day 1 to Week 24)[b]													
	Screening Visit[c,d] 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	X	X														
Confirmed diagnosis of DMD	X															
DMD genetic test[e]	X															
Demographics[f]	X															
Medical history[g]	X	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
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															
Echocardiogram	X															
Laboratory Assessments[o]																
Hematology[p]	X		X		X		X		X		X		X		X	
Chemistry[p]	X		X		X		X		X		X		X		X	
First morning void urinalysis[p,q]	X[r]	X			X		X		X		X		X		X	
Urine cytology[s]		X									X					
Postdose urinalysis[p,t]			X								X					
Antigen and antibody testing[u]	X															
Anti-dystrophin antibody[v]			X								X					
Anti-viltolarsen antibody[v]			X								X					
Pharmacokinetic Assessment																
PK (blood)[o,w]			X								X					

Assessment[a]	Pretreatment Phase		Treatment Phase (Day 1 to Week 24)[b]												
	Screening Visit[c,d] 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												
Other Assessments																
Function and strength[x]	X	X									X					
Patient reported outcomes[y]	X	X									X					
Actigraphy (ActiGraph GT9x)[z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP Administration																
IP administration[aa]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Respiratory Assessment																
PEF	X	X	X								X					
FVC	X	X	X								X					
FEV1	X	X	X								X					
PCF	X	X	X								X					
X-ray																
Chest X-ray[bb]		X														

Abbreviations: DMD = Duchenne muscular dystrophy; ECG = electrocardiogram; eCRF = electronic case report form; FEV1 = forced expiratory volume in 1 second; FVC = Forced Vital Capacity; HEENT = head, ears, eyes, nose, and throat; HIV = human immunodeficiency virus; IP = investigational product; NSAA = North Star Ambulatory Assessment; PARS III = Personal Adjustment and Role Skills Scale, 3rd edition; PCF = Peak Cough Flow; PEF = Peak Expiratory Flow; PK = pharmacokinetic(s); PODCI = Pediatric Outcome Data Collection Instrument; PUL = Performance of Upper Limb.
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. If a patient 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.
b. 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, Inc. reserves the right to require visits to be completed at the site, if needed.
c. The informed consent/assent must be obtained prior to any study-related procedures being conducted.
d. Any parameter/test may be repeated at the investigator's discretion during Screening to determine sustainability and reproducibility. Patients who have failed screening may be retested up to 2 times between Day -28 to Day -8.
e. A DMD genetic test at Screening will be conducted in order to obtain uniform DMD mutation information for the exact intronic boundaries and will be analyzed by a central laboratory.
f. Demographics will include date of birth (if allowed by local regulations), race, ethnicity, and hand dominance. If local regulations do not allow collection of full date of birth, then year of birth should be collected.

g. Medical history will include medical, surgical, concomitant medication, and treatment history.
h. Any updates will be recorded.
i. Ulna length will be measured in all patients. If the patient is able to stand, standing height will also be collected.
j. Weight will be collected with the patient barefoot (without shoes) and wearing light-weight clothes.
k. For each visit that includes an IP administration, vital signs will be performed 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 (modality for determining temperature should be consistent for each patient at all assessment time points throughout the study).
l. Physical and neurological examinations will include an assessment of the following: general appearance, 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 9.10.
m. ECGs will be performed with the patient having rested for at least 5 minutes, and the patient should remain in the supine or semi-recumbent position. A consistent position should be maintained for each individual patient.
n. Renal ultrasound will include imaging of the kidneys, ureters, and bladder.
o. Any blood sampling that occurs during the IP infusion should be collected from the opposite arm. Post-infusion PK blood samples 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 access point in the same arm as the infusion.
p. 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.
q. 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 11.12.1 for details on monitoring of renal function and urine analyses.
r. First morning void urine sample collection and dipstick protein are not required at screening.
s. To be performed on a predose urine sample collected on-site.
t. To be performed on a urine sample collected within 5 hours after completion of infusion.
u. To include hepatitis B antigen, hepatitis C antibody, and HIV antibody.
v. To be collected predose and to be performed on serum blood samples.
w. PK blood samples will be collected predose (within 60 minutes prior to infusion) and 2 hours (±20 minutes) after initiation of infusion on Day 1 and at Week 13.
x. Function and strength tests will include the following: Brooke and Vignos scales, PUL, NSAA, and hand-held dynamometer.
y. PODCI and PARS III Questionnaire.
z. ActiGraph GT9x will be provided at Screening; 10 hour daytime + full nighttime wear for full study period.
aa. IP infusion will be administered every week within a ±3-day window. A minimum of 3 days (72 hours) should elapse between infusions.
bb. The chest X-ray will include images of the heart, lungs, airways, blood vessels, and the bones of the spine and chest.

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

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

Assessment[a]	Treatment Phase (Week 25 to Week 48)[b] ±3 days for each weekly visit														End-of-Treatment Phase		
Week	**25**	**26 to 28**	**29**	**30 to 32**	**33**	**34 to 36**	**37**	**38 to 40**	**41**	**42 to 44**	**45**	**46**	**47**	**48**	**49**	**Follow-up Telephone Call[c] 30 days (±3 days) postdose**	**ET**
Other Assessments																	
Function and strength[s]	X						X								X		X
Patient reported outcomes[t]	X						X							X	X		X
Actigraphy (ActiGraph GT9x)[u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IP Administration																	
IP administration[v]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Respiratory Assessment																	
PEF	X						X								X		X
FVC	X						X								X		X
FEV1	X						X								X		X
PCF	X						X								X		X

Abbreviations: ECG = electrocardiogram; eCRF = electronic case report form; ET = early termination; FEV1 = forced expiratory volume in 1 second; FVC = Forced Vital Capacity; HEENT = head, ears, eyes, nose, and throat; IP = investigational product; NSAA = North Star Ambulatory Assessment; PARS III = Personal Adjustment and Role Skills Scale, 3rd edition; PCF = Peak Cough Flow; PEF = Peak Expiratory Flow; PK = pharmacokinetic(s); PODCI = Pediatric Outcome Data Collection Instrument; PUL = Performance of Upper Limb; TSQM = Treatment Satisfaction Questionnaire.
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. If a patient 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.
b. 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, Inc. reserves the right to require visits to be completed at the site, if needed.
c. Patients will have a telephone call conducted by the site study staff, 30 days (±3 days) following the last IP administration.
d. Medical history will include medical, surgical, concomitant medication, and treatment history. Any updates will be recorded.
e. Ulna length will be measured in all patients. If the patient is able to stand, standing height will also be collected.
f. Weight will be collected with the patient barefoot (without shoes) and wearing light-weight clothes.

g. For each visit that includes an IP administration, vital signs will be performed 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 (modality for determining temperature should be consistent for each patient at all assessment time points throughout the study).
h. Physical and neurological examinations will include an assessment of the following: general appearance, 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 9.10.
i. ECGs will be performed with the patient having rested for at least 5 minutes, and the patient should remain in the supine or semi-recumbent position. A consistent position should be maintained for each individual patient.
j. Renal ultrasound will include imaging of the kidneys, ureters, and bladder. Beginning with the Week 25 Visit, renal ultrasound can occur up to 2 weeks prior to or after the scheduled week, as needed for scheduling purposes.
k. Beginning with the Week 25 Visit, echocardiogram can occur up to 2 weeks prior to or after the scheduled week, as needed for scheduling purposes.
l. Any blood sampling that occurs during the IP infusion should be collected from the opposite arm. Post-infusion PK blood samples 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 access point in the same arm as the infusion.
m. 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.
n. 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 11.12.1 for details on monitoring of renal function and urine analyses.
o. To be performed on a predose urine sample collected on-site.
p. To be performed on a urine sample collected within 5 hours after completion of infusion.
q. To be collected predose and will be performed on serum blood samples.
r. PK blood samples will be collected predose (within 60 minutes prior to infusion) and 2 hours (±20 minutes) after initiation of infusion at Weeks 25, 37, and 48; and 6 hours (± 20 minutes) after initiation of infusion at Week 48.
s. Function and strength tests will include the following: Brooke and Vignos scales, PUL, NSAA, and hand-held dynamometer.
t. TSQM, PODCI, and PARS III Questionnaire. Note: TSQM will be administered only at Week 25 and Week 48. PODCI and PARS III Questionnaire will not be administered at Week 48.
u. ActiGraph GT9x will be provided at Screening; 10 hour daytime + full nighttime wear for full study period.
v. IP infusion will be administered every week within a ±3-day window. A minimum of 3 days (72 hours) should elapse between infusions.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADL	Activities of daily living
AE	Adverse event
AUC	Area under the curve
BMD	Becker muscular dystrophy
BUN	Blood urea nitrogen
CE	Clinical evaluator
CINRG	Cooperative International Neuromuscular Research Group
C_{max}	Maximum plasma concentration
CMO	Contract manufacturing organization
CRO	Clinical research organization
CS	Clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Central venous access
CYP	Cytochrome P450
DMD	Duchenne muscular dystrophy
DNHS	Duchenne muscular dystrophy Natural History Study
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FVC	Forced Vital Capacity
GC	Glucocorticoid
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
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
IL	Interleukin
IP	Investigational product
IPIM	Investigational Product Information Manual
IRB	Institutional Review Board
IV	Intravenous(ly)
K_i	Inhibition constant
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger ribonucleic acid
NCNP	National Center of Neurology and Psychiatry
NOAEL	No observed adverse effect level
NSAA	North Star Ambulatory Assessment

PARS III	Personal Adjustment and Role Skills Scale, 3rd edition
PCF	Peak Cough Flow
PEF	Peak Expiratory Flow
PHI	Protected Health Information
PK	Pharmacokinetic(s)
PMO	Phosphorodiamidate morpholino oligomer
PODCI	Pediatric Outcome Data Collection Instrument
PUL	Performance of Upper Limb
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
TICVAD	Totally implantable central venous access device
TSQM	Treatment Satisfaction Questionnaire
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 patients 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/NCPN-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) was 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) was higher at 80 mg/kg.

   [redacted]
4. Average dystrophin production by group measured by mass spectrometry at 20 to 24 weeks in Study NS-065/NCNP-01-201 was higher at 80 mg/kg (n = 8).
5. Average % of dystrophin positive fiber by group measured by immunofluorescence in Study NS-065/NCNP-01-201 was higher at 80 mg/kg (n = 8).
6. Average exon skipping ratio by group measured by reverse transcriptase polymerase chain reaction (RT-PCR) in both Japan P1/2 (NS065/NCNP01-P1/2) and Study NS-065/NCNP-01-201 was higher at 80 mg/kg.
7. Safety profiles were comparable in both Japan P1/2 (NS065/NCNP01-P1/2) and Study NS-065/NCNP-01-201 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 patients. 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 that required hospitalization for surgery, not-related to drug) was reported in June 2018.

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 the Primary Endpoint and Age Range

The primary endpoint for this study is safety and tolerability. The rationale for using incidence of AEs as the primary endpoint is that AEs seriously affect patient safety and quality of life in daily life.

There is an unmet need for safe and efficacious treatments for Duchenne muscular dystrophy (DMD); to date there is 1 marketed exon 53 skipping agent (Vyondys 53 [Golodirsen], SRP-4053, Sarepta Therapeutics). The ongoing global Phase 3 study (Clinical Study Protocol: NS-065/NCNP-01-301) has an age range of 4 to <8 years. Therefore, this study will investigate safety and tolerability of viltolarsen for patients with DMD who are ≥8 years of age.

2.1.3 Rationale for Study Design and Control Group

For the comparator to assess the secondary endpoint, the natural history group is referred. Although the sponsor understands the complexity in interpreting an open-label study with a natural history, external comparator control group due to the heterogeneity of the disease progression in DMD, an open-label historical control study was designed to account for beneficence, ethics, and the inherent difficulty to enroll a placebo-controlled study after an accelerated approval is granted in the United States (US).

2.1.4 Rationale for Study Duration of 56 Weeks

Individual patient study duration is approximately 56 weeks, which takes into consideration the feasibility of patient enrollment and retention.

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 United Kingdom (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 (Birnkrant et al, [Part 1], 2018; Birnkrant et al, [Part 2], 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 multicenter natural history study to date in DMD, the CINRG DMD Natural History Study (DNHS) (McDonald et al, 2013; Henricson et al, 2013; McDonald et al, 2018). The study included >400 boys and men with DMD, with variable amounts of longitudinal follow-up over the course of a decade (2006 to 2016). The study had annual follow-up visits that included timed function tests, muscle strength, functional assessment questionnaires, 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 muscle 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 09 February 2017, the US Food and Drug Administration (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, weight gain, growth retardation, increased risk for bone fractures, gastritis, cataracts, hypertension, 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). On 31 July 2014, ataluren was granted conditional approval by the European Medicines Agency. 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 et al, 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-Rus 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.

Three oligonucleotides, Eteplirsen (Exondys 51®), Golodirsen (VYONDYS 53®), and Viltolarsen (VILTEPSO™), received accelerated approval from the US FDA based on increased dystrophin expression in treated patients. Viltolarsen also received accelerated approval from the Pharmaceutical and Medical Devices Agency in Japan. They are phosphorodiamidate morpholino oligomers (PMOs) (Mendell et al, 2013; Clemens et al, 2020; Frank et al, 2020).

Eteplirsen (Exondys 51®), approved by FDA on 19 September 2016, targets exon 51 skipping, with dystrophin increase of ~0.4% after 48 weeks of treatment and ~0.9% after 188 weeks of treatment (Charleston et al, 2018). Golodirsen (VYONDYS 53®), approved by FDA on 12 December 2019, targets exon 53 skipping, with dystrophin increase of 0.9% after 48 weeks of treatment. Viltolarsen (VILTEPSO™), approved by FDA on 12 August 2020, also targets exon 53 skipping, with dystrophin increase of 5.3% after 20 to 24 weeks of treatment. These drugs now need to provide supporting data that they slow disease progression as measured by functional outcome measures.

Casimersen (a PMO under development) targets exon 45 skipping, with dystrophin increase of 0.8% after 48 weeks of treatment. A placebo-controlled global Phase 3 study of golodirsen and casimersen is currently ongoing.

A dose-finding safety clinical study is being conducted with SRP-5051, a peptide conjugate PMO targeting exon 51. Although SRP-5051 improves tissue uptake, it is known to be toxic.

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 (IB).

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 Nonclinical 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 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 (C_{max}) occurred at the first sampling time after the injection or at the end of the infusion for mice, rats, and monkeys. 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 the terminal elimination half-life ($t_{1/2}$) were 1.19, 1.19, and 10.5 hours for 6, 20, and 60 mg/kg, respectively. 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 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 7-day collection periods.

Viltolarsen showed weak inhibition to cytochrome P450 (CYP) 3A4 (inhibition constant [K_i] 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, or CYP3A4. Viltolarsen showed weak inhibition to UGT1A1 (K_i 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 half-maximal inhibitory concentration 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- and 13-week rat studies; and ≥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. 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- and 26-week mouse studies, respectively, and 60 mg/kg in 12- and 39-week monkey studies.

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

epdidymides), 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 PND7) (subcutaneous [SC] or IV) at 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 was 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 into SC tissue. Similarly, intramuscular 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-, 13-, 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 and 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 phase and the new liquid phase (LP2, LP2) synthetic process.

Viltolarsen was administered once weekly for 26 weeks at a dose level of 0 (vehicle: physiological saline), 50, 150, and 500 mg/kg (51 mice per group) to male CByB6F1-Tg(HRAS)2Jic mice via IV route 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, but showed no findings in the 500 mg/kg dose group. In subsequent histopathological examinations on these 3 mice, transitional cell carcinoma was 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 infusion of viltolarsen injection in doses of 1.25, 5, 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 AEs (CTCAE) version 4.0-JCOG (Japanese translation, published by the Japan Clinical Oncology Group) 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 1 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 remeasure 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]

[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 (IL) 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 C_{max} and AUC 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 RT-PCR, positive dystrophin fibers by immunofluorescent staining, and dystrophin protein expression by Western blot were detected in 1 patient in Cohort 3, who was the largest patient enrolled in the cohort and hence received the largest absolute dose of viltolarsen injection that was administered in the study.

Phase 2 Studies

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

Study NS065/NCNP01-P1/2

Study NS065/NCNP01-P1/2 was a Phase 1/2 study of viltolarsen injection conducted in Japan. This was a multicenter, parallel-group, open-label, 24-week study. Patients received weekly IV administration of viltolarsen injection 250 mg (40 and 80 mg/kg) over 24 weeks. The primary efficacy endpoint of this study was 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, 1 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. AEs 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 patient, 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 study, 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 was a Phase 2 study conducted in the US and Canada.

This was a multicenter, 24-week dose finding study to assess the safety, tolerability, PK, and pharmacodynamics of viltolarsen in boys with DMD. Patients received weekly IV administration of viltolarsen injection 250 mg (40 and 80 mg/kg) or placebo for the first 4 weeks, followed by weekly IV administration of viltolarsen injection 250 mg (40 and 80 mg/kg) over the remaining 20 weeks. The primary efficacy endpoint of this study was 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 AEs (TEAEs) with 23 TEAEs from patients in the low-dose cohort and 36 TEAEs from patients 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 is the extension study for Study NS-064/NCPN-01-201 and is being conducted in the US and Canada. There are currently 16 DMD patients enrolled. Thus far, there have been no apparent drug-related SAEs reported, no AEs led to study drug discontinuation, and 1 SAE (left tibia/fibula fracture required hospitalization for surgery, not-related to drug) was reported in June 2018.

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 (14 May 2019 to 13 May 2020), and there were no actions taken for safety reasons, or any significant changes in the 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 patient, to reduce the risk of pain.

Function and strength tests will be performed during this study. These include the Brooke and Vignos scales, Performance of Upper Limb (PUL), North Star Ambulatory Assessment (NSAA), and hand-held dynamometer. All tests are associated with muscle soreness, fatigue, and falls.

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

While wearing the ActiGraph GT9x on the wrist, there is a small risk for discomfort or redness at the wear site. Padding will be provided and patients will be instructed to remove the ActiGraph if they experience any discomfort (i.e., redness, irritation, pressure points) and contact the investigator immediately.

3 STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	**Primary Endpoints**

• To evaluate the safety and tolerability of viltolarsen administered IV at weekly doses of 80 mg/kg in ambulant and non-ambulant boys ≥8 years of age with DMD	• Vital signs
	• Physical examination
	• Renal ultrasound
	• Echocardiogram
	• Clinical laboratory tests
	  o Hematology and clinical chemistry
	  o Urinalysis
	  o Urine cytology
	• 12-lead electrocardiogram (ECG)
	• Anti-viltolarsen antibodies
	• Anti-dystrophin antibodies
	• TEAEs and SAEs

Secondary Objective	**Secondary Endpoints**
• To compare the efficacy of viltolarsen administered IV at weekly doses of 80 mg/kg over a 48-week Treatment Period versus natural history controls in ambulant and non-ambulant boys ≥8 years of age with DMD	• Peak Expiratory Flow (PEF) • Forced Vital Capacity (FVC) • Forced expiratory volume in 1 second (FEV1) • PUL • Brooke scale • Vignos scale • Hand-held dynamometer • NSAA
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate health-related quality of life impact of viltolarsen treatment on patient's DMD	• Treatment Satisfaction Questionnaire (TSQM) • Pediatric Outcome Data Collection Instrument (PODCI) • Personal Adjustment and Role Skills Scale, 3rd edition (PARS III) Questionnaire
• To evaluate strength of cough in patients with DMD	• Peak Cough Flow (PCF)
• To evaluate preservation of ambulation of patients with DMD	• Loss of ambulation
• To evaluate daily activity and sleep-wake patterns to explore impact of viltolarsen treatment on patient's DMD	• Accelerometry measures of activity and sleep-wake patterns

4 HYPOTHESIS

Viltolarsen administered at 80 mg/kg/week is safe and well tolerated and ameliorates the clinical course of ambulant and non-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 is a Phase 2, open-label study with DMD boys receiving 80 mg/kg viltolarsen administered IV at weekly doses in ambulant and non-ambulant boys ≥8 years of age with DMD 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 10 study sites in approximately 6 countries, including China, Italy, Russia, Spain, Turkey, and the US.

5.2 Design Implementation

5.2.1 Randomization

Not applicable.

5.2.2 Investigational Product Dosing

The dose per patient (in milligrams) will be calculated based on body weight in kilograms, 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 investigational product (IP) 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 parent/guardian, in consultation with the investigator and consulting surgeon and following adequately informed and voluntary patient/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 patients who experience difficulty with peripheral venous access. Discussions regarding implantable ports for patients will include the study site investigator, medical monitor, and sponsor. Before final decision, NS Pharma, Inc. 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 may be necessary for individual patients. The dose level will be determined jointly by the investigator, study chair, and medical monitor in consultation with the sponsor.

5.2.4 Dose Interruptions

Infusion interruptions may be necessary for individual patients. 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 patient is approximately 56 weeks. The Pretreatment Phase will last approximately 28 days (inclusive of Screening Visit and Pretreatment Visit). The Treatment Phase will last approximately 48 weeks. The follow-up phase is 30 days.

5.3.1 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 patient has completed the study (i.e., last patient 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 patient is assessed or receives an intervention for evaluation in the study (i.e., last patient last visit).

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

5.3.2 End of Treatment

End of treatment is defined as the last assessment for the protocol-specified Treatment Phase of the study for an individual patient.

6 STUDY POPULATION SELECTION

6.1 Study Population

A target sample size of 20 patients (ambulant and non-ambulant boys, ≥8 years of age; a minimum of 8 ambulant patients will be enrolled) with DMD who meet the eligibility criteria below will be enrolled.

6.2 Inclusion Criteria

1. Patient (if age 18 years or older) or patient'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; patients younger than age 18 years will be asked to give written or verbal assent according to local requirements;
2. Patient has a confirmed diagnosis of DMD defined as:
    a. Patient is male with clinical signs compatible with DMD; and
    b. Patient 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, comparative genomic hybridization array, or other techniques with similar capability);
3. Patient is ≥8 years of age at time of first infusion in the study;
4. Patient has a Brooke scale rating of 3 or better OR an upright FVC 30% or greater at Screening;
5. Patient, if sexually active, is willing to abstain from sexual intercourse or employ a barrier or medical method of contraception during and for 3 months following completion of IP administration;
6. Patient and patient's parent(s)/guardian(s) (if patient is <18 years of age) and/or caregiver(s) are willing and able to comply with scheduled visits, IP administration plan, and study procedures;
7. Patient must be on a stable dose of GC or not treated with GC for at least 3 months prior to the first dose of IP and is expected to remain on the stable dose of GC treatment or off GC for the duration of the study.

6.3 Exclusion Criteria

1. Patient has had an acute illness within 4 weeks prior to the first dose of IP;
2. Patient has evidence of symptomatic cardiomyopathy (New York Heart Association Class III or higher);
3. Patient requires ventilation support while awake during the day;
4. Patient has an allergy or hypersensitivity to IP or any of its constituents;
5. Patient has severe behavioral or cognitive problems that preclude participation in the study, in the opinion of the investigator;
6. Patient has a previous or ongoing medical condition, medical history, physical findings, or laboratory abnormalities that could affect patient 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. Patient has had surgery within 3 months prior to the first anticipated administration of IP or has known plans to have surgery during the Treatment Period;
8. Patient has positive test results for hepatitis B antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) antibody at Screening;
9. Patient has been diagnosed with asthma that requires chronic treatment with a long-acting beta agonist;
10. Patient has relevant history of or current drug or alcohol abuse or use of any tobacco/marijuana products by smoking or vaping within 3 months prior to treatment with IP;
11. Patient is currently taking any other investigational drug or has taken any other investigational drug within 3 months prior to the first dose of IP or within 5 times the half-life of a medication, whichever is longer;
12. Patient has taken any gene therapy;
13. Patient 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 IP;
14. Patient has hydronephrosis, hydroureter, renal or urinary tract calculi, or ureteral stenosis by renal ultrasound;

15. Patient was previously enrolled in an interventional study of viltolarsen.

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

Tobacco, vaping, marijuana, and any other drugs of abuse are prohibited during the entire study period.

6.4.3 Activity

Patients are to maintain regular activities.

7 INVESTIGATIONAL PRODUCT

7.1 Description of Viltolarsen

In this study, IP is defined as viltolarsen injection.

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

- Viltolarsen injection 250 mg aqueous infusion: 5 mL glass vial containing 50 mg/mL of drug substance solution in saline

Description:

- Viltolarsen: Colorless clear liquid.
- 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.

IP will be packaged, labeled, and distributed to clinical sites by a contract manufacturing organization (CMO). Additional details for ordering the IP can be found in the IPIM and the Study Reference Manual (SRM).

7.2 Dispensing Investigational Product

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

IP 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 IP (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

Not applicable.

7.5 Treatment Compliance

The patient's compliance with the treatment regimen will be monitored in terms of the patient receiving the IP infusion every week within a ±3-day window. A minimum of 3 days (72 hours)

should elapse between treatments. Weekly IP 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 infusion received should be documented for all infusions.

7.6 Overdose

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

7.7 Packaging and Labeling

IP will be packaged and shipped from the CMO directly to the investigative site as a patient kit. Each patient kit consists of a single carton of 10 vials. Ancillary supplies will be provided by the CMO with each patient kit. The labeling requirements comply with Annex 13 of the European Union Guideline to Good Manufacturing Practice and are in compliance with the requirements of Directive 2003/94/EC.

7.8 Storage and Accountability

IP Storage: Refrigerate (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 IP.

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

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

8 PRIOR AND CONCOMITANT MEDICATIONS AND TREATMENTS

GC 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 IP will be recorded in source documents and in the electronic case report form (eCRF). The date of first GC 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, and start and stop dates.

Any non-pharmacological treatment the patient has received within 3 months prior to the first dose of IP 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.

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 the first dose of IP 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 IP through the duration of the study. Adjustments based on changes in body habitus are permitted. Any other experimental/IPs are prohibited from 3 months prior to the first dose of IP or within 5 times the half-life of a medication, whichever is longer. Any other exon skipping agents and any gene therapies are prohibited. Patients who begin another IP 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, patients should receive full medical care during the study, including transfusions of blood and blood products, treatments with antibiotics, antiemetics, antidiarrheals, analgesics, topical or inhaled steroids, and other care as deemed appropriate, and in accordance with their institutional guidelines. All concomitant blood

products, medications, and supplements will be recorded in source documents and in the relevant eCRF. For a stable dose of GC, a stable dose permits weight-based adjustments (stable mg/kg).

9 STUDY PROCEDURES

9.1 Time and Events Schedule

The Schedules of Study Assessments are described in Table 1 and Table 2; however, a patient can be seen at any time for reasons of safety. Study events are divided into the following phases:

- Pretreatment Phase:
  - From execution of informed consent/HIPAA authorization/assent until Day -1
- Treatment Phase:
  - From Day 1 (first infusion) until Week 48 (last infusion)
- End-of-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, concomitant medications, and actigraphy for all patients

9.1.1 Home Infusion Option

Home infusion is not required for participation in this study. The option of home infusion should be considered if the investigator believes that it will help the patient to derive safety, benefit, and convenience from participation in the study. The option of home infusion would alleviate the need for the patient to visit the primary study site for study treatment. The routine study visits that are eligible to be conducted in the home are limited to those whose study procedures do not extend beyond the following list: IP administration; vital signs collection; review of medical, surgical, concomitant medication, and treatment history; laboratory procedures; actigraphy; and AE review. If necessary, an unscheduled visit may also be conducted by home-health. See the Schedules of Study Assessments (Table 1 and Table 2) for additional details.

Participation in optional home infusion requires written approval from the study sponsor, medical monitor, and investigator. The investigator will submit the request for approval of home infusion to the medical monitor and sponsor, both of whom must provide approval for the home infusion.

As advised by the medical monitor and investigator, infusions taking place outside of the primary study site (e.g., home infusion) would only be considered starting at the Week 6 study visit or after, and only if the patient had not experienced any significant AEs related to infusion

of the IP. Patients must also reside in a municipality or region with access to emergency medical services (such as 911) to be eligible to participate in home infusions. The safety monitoring by the investigator, sponsor, and medical monitor will continue throughout the Treatment Phase for all study visits, regardless of whether the infusion occurs at the study site or the home. Furthermore, the investigator will be responsible for immediate contact with the medical monitor for any safety concern, regardless of whether the infusion occurs at the study site or the home.

Home infusions will only be considered starting at the Week 6 study visit or after. Visits with additional assessments (Weeks 9, 13, 17, 21, 25, 37, 48, and 49 [or early termination]) should be conducted at the primary study site.

9.2 Informed Consent

Each patient and/or patient'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 patient. Consent must be obtained in accordance with the principles outlined in the current version of the Declaration of Helsinki. The patient or patient's parent or guardian (if patient is a minor) 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 patient and patient's parent or guardian (if patient is a minor) will confirm that s/he understands that the patient 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 patient and/or patient's parent or guardian and each patient and/or patient'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 (IRB)/Independent Ethics Committee (IEC) at each site, from the patient or patient's parent or guardian (if the patient is a minor) prior to any study-related procedures, including agreement for discontinuation of any prohibited medications, prior to the start of the study. The written assent of minor patients will be obtained per individual site guidelines.

The ICF must be dated and signed by the investigator or designee and the patient or the patient's legal representative (if the patient is a minor) and the original signed consent form must be kept

by the investigator in the study patient's file. "Legal representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective study patient to the patient's participation in the procedure(s) involved in the research. The study patient'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 patients and repeat the consent process with the amended ICF for any ongoing patients.

9.3 Assignment of Patient Identification Number

Study NS-065/NCNP-01-211 participation begins once written informed consent/assent is obtained from the patient or the parent/legal guardian for a patient (if the patient is a minor) before any study-specific procedures are performed.

Following the signing of the written ICF/Assent Form, patients will be assigned a unique, site-specific, 6-digit patient identification number in sequential order of screening into the study. The patient 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 patient 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 patient identification number. The assigned patient identification number will be retained through enrollment and throughout participation in the study. Patient identification numbers assigned to patients who fail screening may not be used again.

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

9.3.1 Screen Failures

Patients who fail to meet inclusion criteria are considered to be screen failures and are not required to return for additional visits (although a patient can be seen by the investigator at any time for safety reasons). Patients who have failed screening may be retested up to 2 times

between Day -28 to Day -8. Once the patient has failed the retest 2 times, the patient should repeat all Screening procedures. This full rescreening may be performed up to 2 times, after which the patient 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, patients should be reconsented 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 patient's DMD diagnosis and presence of a mutation that is eligible for skipping of exon 53. The date of diagnosis, method of diagnosis, and diagnosis results will be documented in source documents and captured in the relevant eCRF.

A DMD genetic test at Screening 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 and documented in source documents and captured in the relevant eCRF: date of birth (if allowed by local regulations), race, ethnicity, and hand dominance. 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 the Schedules of Study Assessments (Table 1 and Table 2). See Section 8 for additional details.

9.8 Weight and Height

Ulna length will be measured in all patients at the visits specified in the Schedules of Study Assessments (Table 1 and Table 2). If the patient is able to stand, standing height will also be collected with the patient barefoot (without shoes). The patient's legs should be kept as close as

possible, and the patient's heels should be placed back as close to the wall as possible. Weight will be collected with the patient barefoot (without shoes) and wearing light-weight clothes. These measurements are routinely performed during standard clinical examinations of patients with DMD. Weight in kilograms and height in centimeters will be documented in source documents and captured in the relevant eCRF.

9.9 Vital Signs

Vital signs will be performed at the visits specified in the Schedules of Study Assessments (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 patient. 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 patient 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, patients 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.

For each visit that includes IP administration, vital signs will be performed 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 (CS) 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 (modality for determining temperature should be consistent for each patient at all assessment time points throughout the study)

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

For each patient who is eligible and has elected to receive home infusions, the investigator and home infusion nurse will discuss vital sign guidelines for home infusion for each patient. The investigator will take into consideration the range of clinically safe vital signs that have been observed for the patient during past study site infusions. The home infusion nurse will consult with the investigator for any confirmed vital signs outside of these guidelines (low or high). See Section 9.1.1 for additional details on home infusion.

9.10 Physical and Neurological Examination

The physical and neurological examinations will be performed at the visits specified in the Schedules 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
- 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.

9.11 Adverse Events and Serious Adverse Events

Investigators will assess the occurrence of AEs and SAEs at each study visit, or patient contact during the study. AEs and SAEs may be reported by the patient/parent, discovered upon questioning, or detected during examinations or review of test and laboratory 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.

9.12 12-Lead Electrocardiograms

A standard 12-lead ECG will be performed at the visits specified in the Schedules of Study Assessments (Table 1 and Table 2).

ECGs will be performed with the patient having rested for at least 5 minutes, and the patient should remain in the supine or semi-recumbent position. A consistent position should be maintained for each individual patient. 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.

9.13 Echocardiogram

An echocardiogram will be performed at the visits specified in the Schedules of Study Assessments (Table 1 and Table 2) according to the instructions provided in the imaging acquisition manual. Beginning with the Week 25 Visit, echocardiogram can occur up to 2 weeks prior to or after the scheduled week, as needed for scheduling purposes.

Each echocardiogram will be recorded and reviewed locally by the clinical site, and the clinical significance of the echocardiogram findings will be assessed by the investigator. Each echocardiogram will also be sent to an independent central laboratory repository that will conduct a separate centralized review.

9.14 Renal Ultrasound

Renal ultrasound will include imaging of the kidneys, ureters, and bladder and will be performed at visits specified in the Schedules of Study Assessments (Table 1 and Table 2). Beginning with the Week 25 Visit, 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 trained medical professionals.

9.15 Clinical Laboratory Tests

Clinical laboratory assessments will be performed at visits specified in the Schedules of Study Assessments (Table 1 and Table 2). Any blood sampling that occurs during the IP infusion should be collected from the opposite arm. Post-infusion PK blood samples 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 access point in the same arm as the infusion.

9.15.1 Sample Collection, Storage, and Shipping

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

Blood draw volumes for patients will be 8.5 to 16 mL per day at Screening, Day 1, Weeks 3, 5, 9, 13, 17, 21, 25, 37, 48, and end of treatment, totaling up to approximately 135.5 mL over the course of the study. No more than 31.0 mL of blood 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 Schedules 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 11.12.1 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 11.12.1 for additional details on monitoring of renal function and urine analyses.

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, and Urine Cytology – Safety Labs

• Hematology
  ○ Red blood cell count
  ○ Hemoglobin
  ○ Hematocrit
  ○ Reticulocyte count
  ○ Mean corpuscular volume
  ○ Mean corpuscular hemoglobin
  ○ Mean corpuscular hemoglobin concentration
  ○ WBC
  ○ White blood cell differential
  ○ Platelet count
  ○ Fibrinogen
  ○ Activated partial thromboplastin time

- Prothrombin international normalization ratio

- Blood Chemistry
  - Sodium
  - Potassium
  - Chloride
  - Calcium
  - Inorganic phosphorus
  - BUN
  - 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, epithelium, crystals)
  - Protein (benzethonium chloride method)
  - Microalbumin
  - N-acetyl-beta-D-glucosaminidase
  - α1-microglobulin
  - β2-microglobulin
  - Creatinine
  - Protein to creatinine ratio
  - Protein 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

BUN = blood urea nitrogen; WBC = white blood cell count.

9.15.2 Anti-Dystrophin Antibody

Anti-dystrophin antibody testing will be performed on serum blood samples collected predose during the visits specified in the Schedules of Study Assessments (Table 1 and Table 2).

9.15.3 Anti-Viltolarsen Antibody

Anti-viltolarsen antibody testing will be performed on serum blood samples collected predose during the visits specified in the Schedules of Study Assessments (Table 1 and Table 2).

9.15.4 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.

9.16 Pharmacodynamics and Efficacy Assessments

9.16.1 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 patient 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 and will be compiled and stored confidentially in the video review portal in compliance with all International Organization for Standardization 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.

9.16.1.1 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. The force generated for each

muscle strength measure will be documented in source documents and captured in the relevant eCRF.

9.16.1.2 Brooke Scale

The Brooke scale for upper limb has grades ranging from 1 to 6. Grade 1 is given to the patient who can keep both his arms by his sides in the starting position and is then able to abduct the arms fully so that both the arms are touching over the head. Grade 6 is given when the patient is unable to raise his hands to his mouth, and the hands show no functional usefulness.

9.16.1.3 Vignos Scale

The Vignos scale for lower limb has grades ranging from 1 to 10; 1 means that the patient is able to walk and climb stairs without assistance, while 10 means that the patient is bed-bound. Ambulant patients score 1 to 6 and non-ambulant patients score 7 to 10 on the Vignos scale.

9.16.1.4 Performance of Upper Limb

The PUL 2.0 was specifically developed for the assessment of upper limb function in DMD. The PUL 2.0 provides both a total score and sub-scores for the 3 domains (shoulder, middle, and distal) that in DMD are progressively involved with a proximal to distal gradient. The PUL 2.0 includes 22 items with an entry item to define the starting functional level. The 22 items are subdivided into the high level shoulder dimension (6 items), middle level elbow dimension (9 items), and distal wrist and hand dimension (7 items). For weaker patients, a low score on the entry item (0-2) means high level items do not need to be performed. Scoring options vary across the scale between 0-1 and 0-2 according to performance. Each dimension can be scored separately with a maximum score of 12 for the high level shoulder dimension, 17 for the middle level elbow dimension, and 13 for the distal wrist and hand dimension. A total score can be achieved by adding the 3 level scores (for maximum total score of 42).

9.16.1.5 North Star Ambulatory Assessment

NSAA will be performed by a CE at visits specified in the Schedules 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, and 0 = unable to perform the test. Thus, total score can range from 0 (completely non-ambulant) to 34 (no impairment) on these assessments. The NSAA will include an assessment of both grade and time for the Time to Run/Walk 10 Meters Test and the Time to Stand Test. 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.

9.16.1.6 Loss of Ambulation

Time to run/walk 10 meters will be assessed as part of the NSAA for patients performing the NSAA. Loss of ambulation will be defined as the inability to perform the Time to Run/Walk 10 Meters Test in ≤30 seconds at any post-baseline visit and for all remaining assessments.

9.17 Pharmacokinetic Assessments

9.17.1 Collection and Assessment of Pharmacokinetic Samples

PK assessments will be performed at visits specified in the Schedules 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. Viltolarsen levels in plasma will be assessed at time points for each patient in which anti-viltolarsen antibody is detected. Blood will be drawn from patients for PK analysis at the following sampling times:

- Day 1 (first dose):
    - Predose (within 60 minutes prior to infusion)
    - 2 hours (±20 minutes) after initiation of infusion
- Week 13:
    - Predose (within 60 minutes prior to infusion)
    - 2 hours (±20 minutes) after initiation of infusion
- Week 25:
    - Predose (within 60 minutes prior to infusion)
    - 2 hours (±20 minutes) after initiation of infusion

- Week 37:
    - Predose (within 60 minutes prior to infusion)
    - 2 hours (±20 minutes) after initiation of infusion
- Week 48:
    - Predose (within 60 minutes prior to infusion)
    - 2 hours (±20 minutes) after initiation of infusion
    - 6 hours (±20 minutes) after initiation of infusion

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 for analysis. Procedures for the collection, handling, and shipping of laboratory samples will be specified in the Laboratory Manual.

9.17.2 Shipment of Pharmacokinetic Samples

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

9.18 Patient Reported Outcomes

9.18.1 Treatment Satisfaction Questionnaire

The TSQM is a self-administered questionnaire that will be used at Week 25 and Week 48. It is a 14-item instrument, yielding 4 subscale scores: global satisfaction, effectiveness, AEs, and convenience.

9.18.2 Pediatric Outcome Data Collection Instrument

The questionnaire to document health related quality of life is the PODCI. The Pediatric Outcomes Questionnaire is designed to be completed by the parent/guardian of the children aged 10 years old or younger. The Adolescent (parent-reported) Outcomes Questionnaire is designed to be completed by the parent/guardian for adolescents aged 11 to 18 years old, and the Adolescent (self-reported) Outcomes Questionnaire is designed to be completed by adolescents aged 11 to 18 years old. Patients should not switch questionnaires during the study based upon an age change. Please refer to the SRM for further details on how to administer the PODCI questionnaire.

9.18.3 Personal Adjustment and Role Skills Scale, 3rd Edition Questionnaire

PARS III is a questionnaire designed for DMD young men that asks parents/guardians about their child's well-being and psychosocial adjustment (Hendriksen et al, 2009). Please refer to the SRM for further details on how to administer the PARS III Questionnaire.

9.18.4 Other Assessments

9.18.4.1 Actigraphy (ActiGraph GT9x)

During the Screening process and prior to baseline assessments, patients will be provided with an ActiGraph GT9x, specific information regarding the device, and the wear protocol. Patients will wear the ActiGraph on their non-dominant wrist throughout the study period (10 hour daytime + full nighttime wear). Daily bouts of activity (energy expenditure) and percent sleep efficiency, nighttime awakenings, and duration of nighttime awakenings will be explored through the ActiLife data analyses software platform. Sleep-wake activity analyses will be performed using R*Studio and nparACT software to compute several non-parametric measures from raw actigraphy data. Specifically, the interdaily stability, intradaily variability, and relative amplitude of activity will be computed to explore sleep-wake activity rhythms (circadian rhythmicity) in study patients.

9.18.5 Respiratory Assessments

9.18.5.1 Peak Expiratory Flow

PEF is a measure of the maximal flow rate that can be achieved during forceful expiration following full inspiration.

PEF rate will be calculated based on the patient's age, height, and race/ethnicity.

9.18.5.2 Forced Vital Capacity

FVC is the maximum amount of air exhaled by a patient after a maximal inhalation.

9.18.5.3 Forced Expiratory Volume in 1 Second

FEV1 is the amount of air forcefully exhaled by the patient in the first second after full inspiration.

9.18.5.4 Peak Cough Flow

PCF will be measured using a peak flow meter. The test will be performed by asking the patient to inspire completely until total lung capacity and subsequently cough forcefully. During the test, patients breathe through a mouthpiece while wearing noseclips or a face mask linked to a peak flow meter or to a pneumotachograph.

9.18.6 Chest X-ray

The chest X-ray will include images of the heart, lungs, airways, blood vessels, and the bones of the spine and chest.

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 patient's eligibility and a Pre-Infusion Visit. The SRM provides details on order of testing and data collection information.

10.1.1 Screening Visit (-28 to -8 Days)

The ICF/Assent Form 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
- DMD genetic test
- Demographics
- Medical history
- Height and weight
- Vital signs
- Physical and neurological examination
- 12-lead ECG
- Renal ultrasound
- Echocardiogram
- Antigen and antibody testing: hepatitis B antigen, hepatitis C virus antibody, and HIV antibody
- Hematology
- Chemistry
- Urinalysis (random urine)

- Respiratory assessments
  - FVC
  - FEV1
  - PEF
  - PCF
- Function and strength
  - NSAA
  - Vignos scale
  - Hand-held dynamometer
  - Brooke scale
  - PUL
- Patient reported outcomes
  - PODCI
  - PARS III Questionnaire
- AE review
- Provision of the ActiGraph GT9x and wear protocol

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

The following assessments will occur:

- Review of inclusion/exclusion criteria
- Medical history (any updates will be recorded)
- 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)

- Respiratory assessments
    - FVC
    - FEV1
    - PEF
    - PCF
- Function and strength
    - NSAA
    - Vignos scale
    - Hand-held dynamometer
    - Brooke scale
    - PUL
- Patient reported outcomes
    - PODCI
    - PARS III Questionnaire
- Chest X-ray
- AE review
- Ensure wearing of the ActiGraph GT9x

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, Inc. reserves the right to require visits to be completed at the site, if needed.

10.2.1 Day 1 Dosing Visit (First Infusion)

The following assessments will occur:

- Medical history (any updates will be recorded)
- Height and weight
- Vital signs (predose, 1 hour [up to 20 minutes following completion of the infusion] and 2 hours [±20 minutes] after initiation of infusion)
- Physical and neurological examination
- 12-lead ECG

- 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 (predose [within 60 minutes prior to infusion] and 2 hours [±20 minutes] after initiation of infusion)
- IP administration
- Respiratory assessments
    - FVC
    - FEV1
    - PEF
    - PCF
- AE review
- Data upload from ActiGraph GT9x

10.2.2 Week 2

The following assessments will occur:

- Medical history (any updates will be recorded)
- Vital signs (predose, 1 hour [up to 20 minutes following completion of the infusion] and 2 hours [±20 minutes] after initiation of infusion)
- IP administration
- AE review
- Data upload from ActiGraph GT9x

10.2.3 Week 3

The following assessments will occur:

- Medical history (any updates will be recorded)

- Vital signs (predose, 1 hour [up to 20 minutes following completion of the infusion] and 2 hours [±20 minutes] after initiation of infusion)
- 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.
- IP administration
- AE review
- Data upload from ActiGraph GT9x

10.2.4 Week 4

The following assessments will occur:

- Medical history (any updates will be recorded)
- Vital signs (predose, 1 hour [up to 20 minutes following completion of the infusion] and 2 hours [±20 minutes] after initiation of infusion)
- IP administration
- AE review
- Data upload from ActiGraph GT9x

10.2.5 Week 5

The following assessments will occur:

- Medical history (any updates will be recorded)
- Vital signs (predose, 1 hour [up to 20 minutes following completion of the infusion] and 2 hours [±20 minutes] after initiation of infusion)
- 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.
- IP administration
- AE review
- Data upload from ActiGraph GT9x

10.2.6 Weeks 6 to 8

The following assessments will occur:

- Medical history (any updates will be recorded)
- Vital signs (predose, 1 hour [up to 20 minutes following completion of the infusion] and 2 hours [±20 minutes] after initiation of infusion)
- IP administration
- AE review
- Data upload from ActiGraph GT9x

10.2.7 Week 9

The following assessments will occur:

- Medical history (any updates will be recorded)
- Vital signs (predose, 1 hour [up to 20 minutes following completion of the infusion] and 2 hours [±20 minutes] after initiation of infusion)
- 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.
- IP administration
- AE review
- Data upload from ActiGraph GT9x

10.2.8 Weeks 10 to 12

The following assessments will occur:

- Medical history (any updates will be recorded)
- Vital signs (predose, 1 hour [up to 20 minutes following completion of the infusion] and 2 hours [±20 minutes] after initiation of infusion)
- IP administration
- AE review
- Data upload from ActiGraph GT9x

10.2.9 Week 13

The following assessments will occur:

- Medical history (any updates will be recorded)
- Height and weight
- Vital signs (predose, 1 hour [up to 20 minutes following completion of the infusion] and 2 hours [±20 minutes] after initiation of infusion)
- Physical and neurological examination
- 12-lead ECG
- 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 (predose [within 60 minutes prior to infusion] and 2 hours [±20 minutes] after initiation of infusion)

- Respiratory assessments
    - FVC
    - FEV1
    - PEF
    - PCF
- Function and strength
    - NSAA
    - Vignos scale
    - Hand-held dynamometer
    - Brooke scale
    - PUL
- Patient reported outcomes
    - PODCI
    - PARS III Questionnaire
- IP administration
- AE review
- Data upload from ActiGraph GT9x

10.2.10 Weeks 14 to 16

The following assessments will occur:

- Medical history (any updates will be recorded)
- Vital signs (predose, 1 hour [up to 20 minutes following completion of the infusion] and 2 hours [±20 minutes] after initiation of infusion)
- IP administration
- AE review
- Data upload from ActiGraph GT9x

10.2.11 Week 17

The following assessments will occur:

- Medical history (any updates will be recorded)
- Vital signs (predose, 1 hour [up to 20 minutes following completion of the infusion] and 2 hours [±20 minutes] after initiation of infusion)
- 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.
- IP administration
- AE review
- Data upload from ActiGraph GT9x

10.2.12 Weeks 18 to 20

The following assessments will occur:

- Medical history (any updates will be recorded)
- Vital signs (predose, 1 hour [up to 20 minutes following completion of the infusion] and 2 hours [±20 minutes] after initiation of infusion)
- IP administration
- AE review
- Data upload from ActiGraph GT9x

10.2.13 Week 21

The following assessments will occur:

- Medical history (any updates will be recorded)
- Vital signs (predose, 1 hour [up to 20 minutes following completion of the infusion] and 2 hours [±20 minutes] after initiation of infusion)
- 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.
- IP administration
- AE review
- Data upload from ActiGraph GT9x

10.2.14 Weeks 22 to 24

The following assessments will occur:

- Medical history (any updates will be recorded)
- Vital signs (predose, 1 hour [up to 20 minutes following completion of the infusion] and 2 hours [±20 minutes] after initiation of infusion)
- IP administration
- AE review
- Data upload from ActiGraph GT9x

10.2.15 Week 25

The following assessments will occur:

- Medical history (any updates will be recorded)
- Height and weight
- Vital signs (predose, 1 hour [up to 20 minutes following completion of the infusion] and 2 hours [±20 minutes] after initiation of infusion)
- Physical and neurological examination
- 12-lead ECG
- Renal ultrasound
- Echocardiogram
- 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 (predose [within 60 minutes prior to infusion] and 2 hours [±20 minutes] after initiation of infusion)
- Respiratory assessments
    - FVC
    - FEV1
    - PEF
    - PCF
- Function and strength
    - NSAA
    - Vignos scale
    - Hand-held dynamometer
    - Brooke scale
    - PUL
- Patient reported outcomes
    - TSQM
    - PODCI
    - PARS III Questionnaire
- IP administration
- AE review
- Data upload from ActiGraph GT9x

10.2.16 Weeks 26 to 36

The following assessments will occur:

- Medical history (any updates will be recorded)
- Vital signs (predose, 1 hour [up to 20 minutes following completion of the infusion] and 2 hours [±20 minutes] after initiation of infusion)
- 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.
- IP administration
- AE review
- Data upload from ActiGraph GT9x

10.2.17 Week 37

The following assessments will occur:

- Medical history (any updates will be recorded)
- Height and weight
- Vital signs (predose, 1 hour [up to 20 minutes following completion of the infusion] and 2 hours [±20 minutes] after initiation of infusion)
- Physical and neurological examination
- 12-lead ECG
- 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 (predose [within 60 minutes prior to infusion] and 2 hours [±20 minutes] after initiation of infusion)
- Respiratory assessments
    - FVC
    - FEV1
    - PEF
    - PCF
- Function and strength
    - NSAA
    - Vignos scale
    - Hand-held dynamometer
    - Brooke scale
    - PUL
- Patient reported outcomes
    - PODCI
    - PARS III Questionnaire
- IP administration
- AE review
- Data upload from ActiGraph GT9x

10.2.18 Weeks 38 to 47

The following assessments will occur:

- Medical history (any updates will be recorded)
- Vital signs (predose, 1 hour [up to 20 minutes following completion of the infusion] and 2 hours [±20 minutes] after initiation of infusion)
- 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.
- IP administration

- AE review
- Data upload from ActiGraph GT9x

10.2.19 Week 48

The following assessments will occur:

- Medical history (any updates will be recorded)
- Vital signs (predose, 1 hour [up to 20 minutes following completion of the infusion] and 2 hours [±20 minutes] after initiation of infusion)
- Anti-dystrophin antibody (predose)
- Anti-viltolarsen antibody (predose)
- PK blood sample (predose [within 60 minutes prior to infusion], 2 hours [±20 minutes] after initiation of infusion, and 6 hours [±20 minutes] after initiation of infusion)
- Patient reported outcomes
    - TSQM
- IP administration
- AE review
- Data upload from ActiGraph GT9x

10.3 End-of-Treatment Phase

10.3.1 Week 49

The following assessments will occur:

- Medical history (any updates will be recorded)
- Height and weight
- Vital signs
- Physical and neurological examination
- 12-lead ECG
- Renal ultrasound
- Echocardiogram
- 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)
- Respiratory assessments
  - FVC
  - FEV1
  - PEF
  - PCF
- Function and strength
  - NSAA
  - Vignos scale
  - Hand-held dynamometer
  - Brooke scale
  - PUL
- Patient reported outcomes
  - PODCI
  - PARS III Questionnaire
- AE review
- Data upload from ActiGraph GT9x

10.3.2 Follow-up Phone Call

Patients will have a phone call conducted by a member of the site study staff, 30 days (±3 days) following the last IP infusion, to assess AEs; actigraphy; 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 clinical research organization (CRO) retains the right to request additional information for any patient with ongoing AEs at the end of the study, if judged necessary.

10.3.3 Unscheduled Visit

If a patient 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 patient (or the legal guardian acting on behalf of the patient) 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. The following may be justifiable reasons for removing a patient:

- Withdrawal of consent by the patient/legal guardian
- Failure to comply with the protocol
- Lost-to-follow-up
- Illness, condition, or procedural complication (including AEs) affecting the patient's ability to participate or requiring prohibited medication
- In the investigator's judgment, it is deemed in the best interest of the patient to discontinue his/her participation in the study
- The investigator, sponsor, Data and Safety Monitoring Board (DSMB), and/or regulatory authority terminates the study
- Any other reason

A Patient Completion/Discontinuation eCRF, describing the reason for discontinuation, must be completed for any discontinued or withdrawn patient regardless of reason. If a patient withdraws from the study or if the study is prematurely terminated, the investigator or designee will contact the patient or the patient'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.

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

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

- Medical history (any updates will be recorded)

- Height and weight
- Vital signs
- Physical and neurological examination
- 12-lead ECG
- Renal ultrasound
- Echocardiogram
- 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)
- Respiratory assessments
  - FVC
  - FEV1
  - PEF
  - PCF
- Function and strength
  - NSAA
  - Vignos scale
  - Hand-held dynamometer
  - Brooke scale
  - PUL
- Patient reported outcomes
  - PODCI
  - PARS III Questionnaire
- AE review
- Data upload from ActiGraph GT9x

If a patient is lost to follow-up, every reasonable effort must be made by the clinical site personnel to contact the patient and determine the reason for discontinuation/withdrawal

(including assessment of any AEs reported by the patient/caregiver). The measures taken to follow-up must be documented in source documents.

10.3.5 Procedures for Early Termination

If a patient withdraws or is removed from the study for any reason, all early termination procedures should be completed per the Schedules of Study Assessments (Table 1 and Table 2). Reason for withdrawal, date of the discontinuation, and date of the last dose of IP should be recorded in source documents and in the appropriate section of the eCRF. IP assigned to the withdrawn patient may not be assigned to another patient.

The medical monitor and study chair should be consulted prior to the withdrawal of the study patient, 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. At the time of discontinuation, a self-addressed stamped shipper will be sent to the patient for returning of the ActiGraph GT9x and all accessories.

10.4 Patient Replacement

Patients will not be replaced.

10.5 Suspension or Termination of Study

If, in the opinion of the study chair and the medical monitor, clinical observations in the study suggest that it may be unwise to continue, the study may be suspended. The study chair will request a DSMB meeting and consult with the sponsor. If the study chair, 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, Inc. 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
- Failure to adhere to the protocol

If any SAEs or non-SAEs 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 Adverse Events and Adverse Drug Reactions

An AE is any untoward medical occurrence in a patient or clinical investigation patient 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 patient 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 IP

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 patient has recovered from the preexisting condition or in the opinion of the investigator, they represent a CS exacerbation in intensity or frequency. If CS 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 IP and through 30 days after completion of study participation.

A suspected adverse reaction is any noxious and unintended response for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug 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 and/or a suspected adverse reaction is considered “unexpected” if it is not listed in the IB or is not listed at the specificity or severity that has been previously observed. As viltolarsen is approved in the US, the US package insert will be referenced for the purposes of expedited

reporting to the FDA and US sites. During the course of the study, the IB will be updated on an ongoing basis with new important safety information.

11.2 Definition of a Serious Adverse Event

An AE is serious when the patient 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 patient and may require medical or surgical intervention to prevent one of the outcomes listed above

Life-threatening experience: Any AE that places the patient, 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 1 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 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 patient’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 patient's body function/structure, physical activities, and/or quality of life.

Important medical events that may jeopardize the patient 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 patient 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 version 4.03 guidelines for severity assessments will be used to grade AEs for this study (available at evs.nci.nih.gov/ftp1/CTCAE/About.html). The CTCAE version 4.03 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 IP and the AE. The degree of "relatedness" of the AE to the IP 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 IP cannot be excluded.
  - **Probable:** Temporal association, other etiologies are possible but unlikely. The event may respond if the IP is discontinued.
  - **Definite:** Established temporal association with administration of the IP with no other more probable cause. The event should resolve when the IP is discontinued and recur on re-challenge.

11.5 Adverse Events of Special Interest

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

- Access device complication (for patients 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 nephrologist described in Section 11.12.1)
- Any confirmed instances of hematuria or other potentially CS abnormalities on urinalysis

11.6 Disease-Related Signs and Symptoms

Reporting of disease-related or DMD-related signs and symptoms as AEs is based on the investigator's clinical judgment. However, progression of symptoms and signs associated with DMD that is inconsistent with 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 IP. 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
- Investigator's assessment of relationship to IP

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 patient 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 IP administration should be determined by the investigator or study physician after thorough consideration of all facts that are available.

CS changes from time of ICF will be documented as AEs on the AE eCRF. CS 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

AEs 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 patients.

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 IP, must be reported to the designated CRO 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 IP 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

The sponsor must report any suspected adverse reaction to the IP, that is both serious and unexpected, to the US FDA, 21 Code of Federal Regulations 312.32(c)(1)(i), and other national and local health authorities.

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

The NS Pharma, Inc.-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.

11.10 Monitoring and Follow-up of Adverse Events

Patients 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 patient's source documentation. Follow-up laboratory results should be filed with the patient's source documentation.

For all AEs that require the patient 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 patient'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 CRO retains the right to request additional information for any patient with ongoing AEs at the end of the study, if judged necessary.

11.11 Pregnancy Reporting

The NS Pharma, Inc.-designated CRO should be notified in the event that a female partner of a patient becomes pregnant at any time after the patient's first dose of IP. Any such pregnancy occurring on-study or within 3 months of the last administration of IP must be reported on a Pregnancy Notification Form. This must be done whether or not an AE has occurred and within 24 hours of awareness of the pregnancy. The information submitted should also include the anticipated date of birth or pregnancy termination.

Written consent is required prior to collecting and reporting any information on a female partner of a patient.

If possible, the investigator should follow the pregnant female partner of the patient until completion of the pregnancy and notify the medical monitor of the outcome within 5 days or as

specified below. The investigator will provide this information as a follow-up to the initial Pregnancy Notification Form.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including in an aborted fetus]), the investigator should follow the procedures for reporting SAEs (see Section 11.7.3).

11.12 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 CS change from baseline for the individual patient. 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 CS change from baseline for the patient, the investigator should determine if it qualifies as an AE, and if so, an appropriate eCRF will be completed. All CS 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.

11.12.1 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 nephrologist.

In addition, any instances of hematuria or other potentially CS abnormalities on urinalysis will be confirmed at the following week's visit, or sooner at discretion of the investigator. Confirmed CS 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 IP 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 nephrologist.

11.13 Monitoring and Management of Abnormal Electrocardiograms

If a CS ECG abnormality occurs that was not present at baseline (Screening) and the investigator determines that the abnormality is related to IP, 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 CS change from baseline should be reported as an AE regardless of causality.

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

11.14 Intravenous Access Considerations

IP 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 IP 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 patients who have difficulty with peripheral venous access. A TICVAD port 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 patient in this study. Before final decision, NS Pharma, Inc. 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 documented contraindication to the placement of a TICVAD.

11.15 Data and Safety Monitoring Board

It is the responsibility of the DSMB to review data quality, relevant safety data, and AEs for all patients enrolled in the study and to make recommendations to the study chair, 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 2 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. The data will be hosted and processed by Medpace, Inc. Statistical analyses will be performed using SAS® 9.4 or higher and R 4.05 or higher.

All measurements will be analyzed based upon the type of distribution, and descriptive statistics will be presented by time point, as appropriate.

12.2 Determination of Sample Size

Assuming a sample size of 20, at least 1 adverse drug reaction with an incidence of 15% may be detected at a probability of ≥95% for the safety profile, which is the primary outcome. Based on this, it was decided that 20 patients should be enrolled to confirm safety. A minimum of 8 ambulant patients will be enrolled.

12.3 Analysis Populations

The Safety Population will consist of all patients who received at least 1 dose of IP. This will be the primary analysis population for the evaluation of safety.

The modified Intent-to-Treat Population will consist of all patients who received at least 1 dose of IP and have a baseline assessment and at least 1 post-baseline efficacy assessment. This will be the analysis population for the evaluation of efficacy.

12.4 Demographics and Baseline Characteristics

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

12.5 Primary Safety Endpoints

12.5.1 Primary Objective

Safety analyses will be performed using the Safety Population. TEAEs will be summarized by system organ class and preferred term (using the Medical Dictionary for Regulatory Activities [MedDRA]), by relationship to IP, and by intensity (CTCAE grade).

12.5.2 Anthropometrics, Vital Signs, Laboratory Assessments, Electrocardiogram, and Echocardiogram

Anthropometrics, vital signs, hematology, chemistry, urinalysis, ECG, and echocardiogram results will be summarized 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.

12.5.3 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. Coding will be done by system organ class and preferred term (using MedDRA). Level of severity will be assessed using the CTCAE grading system.

Summaries will include:

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

Listing tables will be provided for all AEs.

12.5.4 Concomitant Medications and/or Other Treatments

GCs will be summarized by type of GC (prednisone versus deflazacort), by schedule (daily versus any other), and by treatment. Patients are required not to change the GC dose while on study, if possible. Any changes in doses or schedule will be listed.

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

12.6 Efficacy Assessments

12.6.1 Secondary Objective

The secondary objective is to compare the efficacy of viltolarsen administered IV at weekly doses of 80 mg/kg over a 48-week Treatment Period versus natural history controls in ambulant and non-ambulant boys ≥8 years of age with DMD for the following endpoints: absolute and percent predicted PEF, FVC, and FEV1, Brooke and Vignos functional scales, and the NSAA. The PUL and hand-held dynamometry will be described and the change over time estimated for the viltolarsen-treated group only.

In addition to the comparison methods described below, all outcomes for both the viltolarsen-treated and historical control groups will be summarized and tabulated at each time point assessed. Time points in the historical control will match those of the viltolarsen-treated group within pre-defined tolerances. Outcomes at baseline will be compared between viltolarsen and control groups using methods appropriate for the distribution of each outcome.

12.6.1.1 Peak Expiratory Flow

The change in both absolute and percent predicted PEF rate over the length of the study will be compared between patients receiving viltolarsen and the historical control group using mixed models with repeated measures. These models allow the use of all available assessments per patient, will include a random term per individual, and will assess the additional predictive value of a random slope term. Covariates of age and baseline value will be included. Steroid exposure

will be evaluated and included as an additional covariate if necessary. The pulmonary outcome will be the dependent variable, time and treatment group will be the independent variables, and a time by treatment group interaction will be included if appropriate. Percent predicted values will be calculated from absolute values using equations based on age, height, and ethnicity (see SRM for details).

12.6.1.2 Forced Vital Capacity

The change in absolute and percent predicted FVC will use the same methods described above for percent predicted PEF rate.

12.6.1.3 Forced Expiratory Volume in 1 Second

The change in absolute and percent predicted FEV1 will use the same methods described above for percent predicted PEF rate.

12.6.1.4 Brooke and Vignos Scales

Brooke scale: The change in the Brooke function scale over the length of the study will be compared between patients receiving viltolarsen and the historical control group using mixed models with repeated measures. These models allow the use of all available assessments per patient, will include a random term per individual, and will assess the additional predictive value of a random slope term. These models also have the flexibility to adequately model the quasi-continuous nature of the Brooke functional scale. The pulmonary outcome will be the dependent variable, time and treatment group will be the independent variables, and a time by treatment group interaction will be included if appropriate. Covariates of age and baseline value will be included and steroid exposure will be evaluated and included as an additional covariate if necessary.

Vignos scale: The change in the Vignos functional scale will use the same methods described above for the Brooke functional scale.

12.6.1.5 Muscle Strength Outcomes (Hand-held Dynamometry)

The change over time in hand-held dynamometry values will be estimated in patients receiving viltolarsen using a mixed model with repeated measures. As the historical control group does not contain hand-held dynamometry assessments, no comparisons between viltolarsen and

control will be performed. Here a separate model will be performed for each muscle. Hand-held dynamometry values will act as the dependent variable, time will be the independent variable, and a random term for individual will be included. Covariates of age and baseline value will be included and steroid exposure will be evaluated and included as an additional covariate if necessary.

12.6.1.6 Performance of Upper Limb

The change over time in the PUL will be estimated in patients receiving viltolarsen using a mixed model with repeated measures. As the historical control group does not contain PUL assessments, no comparisons between viltolarsen and control will be performed. PUL values will act as the dependent variable, time will be the independent variable, and a random term for individual will be included. Covariates of age and baseline value will be included and steroid exposure will be evaluated and included as an additional covariate if necessary.

12.6.1.7 North Star Ambulatory Assessment

NSAA will be compared between patients receiving viltolarsen and the historical control group using mixed models with repeated measures. Covariates of age and baseline value will be included. Steroid exposure will be evaluated and included as an additional covariate if necessary.

12.6.1.8 Analyses Comparing NS-065/NCNP-01 Patients to Historical Controls

A matched data set from the CINRG DNHS data will be created. The purpose of the matching is to create a group data set that corresponds in characteristics to the patients in this study. The CINRG DNHS data set includes patients from 2 years old to over 30 years old, some of whom have been followed for close to a decade. Therefore, it is important to create a comparator group which will allow valid group comparisons. No patient-to-patient matched analysis is proposed. The sole purpose of the matching is to create a historical control group which is comparable in its basic characteristics to the study patient group. The final CINRG DNHS data set is expected to have between 16 and 32 patients included with time intervals of evaluations between 6 and 15 months.

12.6.2 Exploratory Objectives

12.6.2.1 Treatment Satisfaction Questionnaire

Descriptive statistics of the TSQM will be generated at each time point the questionnaire is administered for each of the 4 sub-scores: effectiveness, side effects, convenience, and global satisfaction. The change over time in scores will be estimated in patients receiving viltolarsen using a mixed model with repeated measures. Here a separate model will be performed for each sub-score. Sub-score values will act as the dependent variable, time will be the independent variable, and a random term for individual will be included. This will allow exploration of the change, if any, in sub-scores in response to viltolarsen treatment.

12.6.2.2 Pediatric Outcome Data Collection Instrument

Descriptive statistics of the PODCI will be generated at each time point the questionnaire is administered for global function and each of the sub-scores: upper extremity functioning, transfers and basic mobility, sports and physical function, comfort/pain, and happiness with physical condition. The change over time in scores will be estimated in patients receiving viltolarsen using a mixed model with repeated measures. Here a separate model will be performed for each score or sub-score. Score values will act as the dependent variable, time will be the independent variable, and a random term for individual will be included. This will allow exploration of the change, if any, in sub-scores in response to viltolarsen treatment.

12.6.2.3 Personal Adjustment and Role Skills Scale, 3rd Edition Questionnaire

Descriptive statistics of the PARS III Questionnaire will be generated at each time point the questionnaire is administered for total score and each of the 6 sub-scales: peer relations, dependency, hostility, productivity, anxiety/depression, and withdrawal. The change over time in scores will be estimated in patients receiving viltolarsen using a mixed model with repeated measures. Here a separate model will be performed for each score or sub-score. Score values will act as the dependent variable, time will be the independent variable, and a random term for individual will be included. This will allow exploration of the change, if any, in sub-scores in response to viltolarsen treatment.

12.6.2.4 Peak Cough Flow

Descriptive statistics of PCF will be generated at each time point the assessment is performed. The change over time in scores will be estimated in patients receiving viltolarsen using a mixed model with repeated measures. PCF values will act as the dependent variable, time will be the independent variable, and a random term for individual will be included. This will allow exploration of the change, if any, in PCF in response to viltolarsen treatment.

12.6.2.5 ActiGraph GT9x

Validity will be explored through correlation of all clinical strength and function tests and patient reported outcomes with raw data obtained from the AGT9x during clinical testing. Information such as steps, speed, body position/location (using vector magnitude per minute data) will be derived from the raw data; relationships with clinical tests will result from data conversions, descriptive analysis, and correlations with the raw data. Additionally, raw data will be analyzed throughout the study to explore changes in activity and sleep-wake patterns. Throughout the full study, 2-week bouts of continuous data will be analyzed through R*Studio (version 3.5.1, Vienna, Austria) and the nparACT package (version 0.8) to determine sleep-wake rhythms. Sleep-wake rhythms are measured as intradaily variability (quantifies the frequency and extent of transitions between periods of rest and activity on an hourly basis) and relative amplitude (derived from the normalized difference between the most active 10-hour period and least active 5-hour period in an average 24-hour pattern). Raw data will also be analyzed with ActiLife software to identify and score sleep periods defined as nightly percent sleep efficiency (total time in bed/total time asleep), average number of nightly awakenings (mean number of nightly awakenings longer than 3-minute durations), and average duration of nightly awakenings (mean duration of nightly awakenings that are longer than 3 minutes). Effect sizes to determine the magnitude of differences in change over time will be computed.

12.7 Pharmacokinetic Endpoints and Analysis

Population PK analyses will be presented in a separate report.

12.7.1.1 Antibodies and Pharmacokinetics

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

12.8 Interim Analyses

No interim analyses are planned.

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 patient data listing, as they are recorded on the eCRF.

Patients 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 patients with DMD are expected to decline over time, imputing efficacy parameters by last value carried forward mostly biases towards patients 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 2 Open-label Study to Assess the Safety, Tolerability, and Efficacy of Viltolarsen in Ambulant and Non-Ambulant Boys with Duchenne Muscular Dystrophy (DMD) Compared to Natural History Controls
Study Number:	NS-065/NCNP-01-211
Final Date:	21 March 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:

Reviewed by:

Approved by:

Appendix 2 Investigator's Signature

Study Title:	A Phase 2 Open-label Study to Assess the Safety, Tolerability, and Efficacy of Viltolarsen in Ambulant and Non-Ambulant Boys with Duchenne Muscular Dystrophy (DMD) Compared to Natural History Controls
Study Number:	NS-065/NCNP-01-211
Final Date:	21 March 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, Inc. to demonstrate that as an investigator and all study personnel listed on the Food and Drug Administration 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 Food and Drug Administration (FDA)/Health Canada regulatory requirements or International Council for Harmonisation (ICH)/Good Clinical Practice (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 patients, or persons used as controls, that the investigational products (IPs) are being used for investigational purposes and ensure that the requirements relating to obtaining informed consent and Institutional Review Board (IRB)/Independent Ethics Committee (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 (IB), including the potential risks and side effects of the IP;
- 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 patients or others;
- Agree to not make changes in the research without IRB/IEC approval, except where necessary to eliminate apparent hazards to patients; and
- Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements.

Refer also to:

- FDA Regulations Related to 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, and Confidentiality

Informed Consent

The informed consent form (ICF), Assent Form, and consent process must comply with United States (US) 21 Code of Federal Regulations (CFR) Part 50 and local laws. The ICF/Assent Form will document the study-specific information provided to the patient by the investigator or designee and the patient'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 patient, 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 patient must provide a signed and dated ICF before any study-related procedures are performed. In the case of a patient who is incapable of providing informed consent, the investigator or designee must obtain a signed and dated ICF from the patient'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 patients 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 patients 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 patients will be kept in strict confidence and will not appear on electronic case report forms (eCRFs) or other records provided to or retained by the sponsor or the sponsor's authorized representative. Patient 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 patients can be protected by de-identifying (i.e., "blacking-out") the patient's name and replacing the name with the patient's study identification number. The ICF must include appropriate statements explaining these requirements.

Protected Health Information

Information on maintaining patient confidentiality in accordance with US and local patient privacy regulations must be provided to each patient/legal guardian as part of the informed consent process, either as part of the ICF or as a separate signed Health Insurance Portability and Accountability Act (HIPAA) consent. The investigator or designee must explain to each patient that for the evaluation of study results, the patient's Protected Health Information (PHI) obtained during the study may be shared with NS Pharma, Inc. and its designees, regulatory agencies, and IRBs/IECs. As the study sponsor, NS Pharma, Inc. will not use the patient's PHI or disclose it to a third party without applicable patient authorization. It is the investigator's responsibility to obtain written permission to use PHI from each patient/legal guardian. If a patient or patient'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 are collected on the patient. Any data collected up to the point of HIPAA consent withdrawal may be used in analysis of the study results.

Institutional Review Board/Independent Ethics Committee Approval

Before initiation of the study, the investigator must obtain approval or favorable opinion of the research protocol, ICF, and any material related to patient 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.

IRBs and IECs must be constituted according to the applicable laws. It is the responsibility of each clinical site to submit the protocol, IB, patient informed consent, patient 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, Inc.

The documentation should clearly mention the approval/favorable opinion of the protocol, the patient ICF, and patient 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, Inc. (or its authorized clinical research organization [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 patient informed consent, recruitment materials intended for viewing by patients, Investigational New Drug 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 serious adverse events or other safety information reported from the patient or NS Pharma, Inc. or its authorized CRO.

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 ICFs.

The investigator agrees to allow monitoring and auditing of all essential clinical study documents by NS Pharma, Inc. or its authorized representatives and inspection by the FDA or other appropriate regulatory authorities. Monitoring and auditing visits by NS Pharma, Inc. 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 patients. The investigator must sign and return to NS Pharma, Inc. (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, Inc. or its authorized representatives and inspection by the appropriate regulatory authorities.

NS Pharma, Inc. (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 patients are protected, and verify the reported clinical study data are accurate, complete, and verifiable from source documents. This includes review of ICFs, results of tests performed as a requirement for participation in this study, and any other medical records (e.g., laboratory reports, clinic notes, IP disbursement log, pharmacy records, patient sign-in sheets, patient-completed questionnaires, telephone logs, and electrocardiograms [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, IP disposition records, patient ICFs, 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, Inc. 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. Patient 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, Inc. 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, Inc. (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 patients 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 patient who receives IP, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and patient number. Any personal information, including patient 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, Inc.

It is essential that all dates appearing on NS Pharma, Inc. patient 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 patient's participation with the IP under investigation are to be reported to NS Pharma, Inc. The data are to be recorded on the eCRFs and/or other media provided or approved by NS Pharma, Inc.

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

Source Documents

Source documentation is defined as any handwritten 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, IP disbursement log, pharmacy records, patient sign-in sheets, patient 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 patients 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 patient, 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 patient ICFs, adverse event reports, and other regulatory documents) as required by the applicable regulations, must be maintained for 2 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, Inc. 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, Inc. (or designee) and therefore, may be disclosed by NS Pharma, Inc. (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, Inc.

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

NS Pharma, Inc. shall have the right to publish data from the study without approval from the investigator. All publications (e.g., manuscripts, abstracts, oral/slide presentations, and book chapters) may only be prepared through cooperation between NS Pharma, Inc. (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, Inc. for review in accordance with the provisions of such investigator's written agreement with NS Pharma, Inc. (or designee) before submission for publication or presentation. If requested by NS Pharma, Inc. 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 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, multicenter 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.

Disclosure of Data

Patient medical records may be disclosed to and used by NS Pharma, Inc., the Medpace, Inc. group of companies, representatives and contractors of the NS Pharma, Inc. or Medpace, Inc., the FDA, the European Medicines Agency, any authority that has the right to review scientific research and medical records, IRB or Ethics Committees, and regulatory authorities evaluating the effects of the study drug for scientific research, on public health, and for a possible marketing authorization application. Patients' data will be used and disclosed only in accordance with the law and all applicable regulations. Anyone who has access to this data will be bound to keep the information secure and confidential. Collected data are dissociated and there is no way to know the identity of the patients. Only the Principal Investigator/site staff will know the identities of the patients.