A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of NIDO-361 in Patients with Spinal and Bulbar Muscular Atrophy (SBMA)

Short Title: A Randomized, Double-Blind, Placebo-Controlled Study of NIDO-361 in Patients with SBMA

Investigational Product(s)	NIDO-361
Protocol Number	NIDO-361-002
Version Number	11.0 (EMA)
Version Date	24-March-2025
EU CT Number	2023-507128-22-00
Sponsor	Nido Biosciences, Inc. 59 West Dedham Street Unit 180430 Boston, Massachusetts 02118 United States of America

[redacted]

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practices (GCP) as outlined by International Conference on Harmonisation E6(R2), Declaration of Helsinki Regulation (EU) No.536/2014 as applicable, and all applicable local and national regulatory requirements. Enrollment at any clinical study site may not begin prior to that site receiving approval from the ethics committee of record for the protocol and all materials provided to potential participants.

Any amendments to the protocol or changes to the consent document will be approved before implementation of that amendment. Reconsent of previously enrolled participants may be necessary depending on the nature of the amendment.

The Investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the Sponsor and documented approval from the ethics committee of record, unless such a change is necessary to eliminate an immediate hazard to the study participants.

All personnel involved in the conduct of this study have completed Human Subjects Protection and/or GCP Training as outlined by their governing institution.

SPONSOR'S APPROVAL

Title	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Study of NIDO-361 in Patients with Spinal and Bulbar Muscular Atrophy (SBMA)
Protocol Number	NIDO-361-002
Version Number	11.0 (EMA)
Version Date	24-March-2025

The design of this study as outlined by this protocol has been reviewed and approved by the Sponsor's responsible personnel as indicated in the signature table below.

Medical Representative			
Name:	**Title:**	**Signature:**	**Date:**
[redacted]	[redacted]		

INVESTIGATOR'S AGREEMENT

I have read the protocol and accessory materials related to Study NIDO-361-002 and agree to the following:

- To conduct this study as described by the protocol and any accessory materials.
- To protect the rights, safety, and welfare of the participants under my care.
- To provide oversight to all personnel to whom study activities have been delegated.
- To control all investigational products provided by the Sponsor and maintain records of the disposition of those products.
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and Good Clinical Practices as outlined by International Conference on Harmonisation (ICH) E6(R2).
- To obtain approval for the protocol and all written materials provided to participants prior to initiating the study at my site.
- To obtain informed consent – and updated consent in the event of new information or amendments – from all participants enrolled at my study site prior to initiating any study-specific procedures or administering investigational products to those participants.
- To maintain records of each participant's participation and all data required by the protocol.

Name:	**Title:**	**Institution:**
Signature:		**Date:**

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LIST OF ABBREVIATIONS

Abbreviation	Definition
2MWT	Two-minute walk test
6MWT	Six-minute walk test
ADL	Activity of daily living
AE	Adverse event
AF2	Activation function-2
AR	Androgen receptor
AR113Q	Androgen receptor with 113 cytosine-adenine-guanine repeats
AR121Q	Androgen receptor with 121 cytosine-adenine-guanine repeats
ARE	Androgen response element
AUC	Area under the plasma concentration-time curve
$AUC_{(0-24)}$	Area under the time-concentration curve from time zero to 24 hours
BCRP	Breast Cancer Resistance Protein
BF3	Binding function 3
BMI	Body mass index
CAG	Cytosine-adenine-guanine
CL/F	Oral clearance
C_{max}	Maximum observed plasma concentration
$C_{max[unbound]}$	Maximum unbound concentration
C_{min}	Minimum observed plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Drug concentration reached immediately before the next dose
$C_{trough,ss}$	Concentration of drug at steady state immediately before the next dose is administered
CYP	Cytochrome P450
CYP3A	Cytochrome P450 Family 3 Subfamily A
DSMB	Data Safety Monitoring Board
EC	Ethics committee
EC_{50}	Effective concentration at 50% activity
ECG	Electrocardiogram
eCRF	Electronic case report form
EEG	Electroencephalogram
eGFP	Enhanced green fluorescent protein
EOS	End of Study
ET	Early Termination
GCP	Good Clinical Practice

GI	Gastrointestinal
GLP	Good Laboratory Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C virus
HDPE	High-density polyethylene
HED	Human equivalent dose
hERG	Human ether-à-go-go-related gene
HHD	Handheld dynamometer
HIV	Human immunodeficiency virus
IB	Investigator's brochure
IC_{50}	Half-maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonisation
IIEF	International Index for Erectile Function
IRB	Institutional Review Board
IRT	Interactive response technology
LHRH	Luteinizing hormone-releasing hormone
LMV	Lean muscle volume
LNCaP	Lymph node carcinoma of the prostate
LOAEL	Lowest-observed-adverse-effect-level
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MEPB	1-[2-(4-methylphenoxy)ethyl]-2-[(2-phenoxyethyl)sulfanyl]-1H- benzimidazole
MFF	Muscle fat fraction
MFI	Muscle fat infiltration
MRI	Magnetic resonance imaging
m-SBMAFRS	Modified-spinal and bulbar muscular atrophy functional rating scale
MTD	Maximum tolerated dose
nhr	Nuclear hormone receptor
NOAEL	No-observed-adverse-effect level
PD	Pharmacodynamic(s)
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
polyQ	Polyglutamine
PRa	Progesterone receptor alpha
QD	Daily

QTc	Heart rate-corrected QT
RP2D	Recommended phase 2 dose
SAD	Single ascending dose
SAE	Serious adverse event
SARM	Selective androgen receptor modifiers
SBMA	Spinal and bulbar muscular atrophy
SBMAFRS	Spinal and bulbar muscular atrophy functional rating scale
SF-36	36-item short form
SOP	Standard operating procedure
$t_{1/2}$	Half-life
T_{max}	Time to maximum drug concentration
TE	Target engagement
TEAE	Treatment-emergent adverse event
THRb	Thyroid hormone receptor beta
TUG	Timed up and go
UGT	Uridine 5'-diphospho-glucuronosyltransferase
Vz/F	Apparent volume of distribution
wtAR	Wild type androgen receptor

1 SYNOPSIS

Title	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of NIDO-361 in Patients with Spinal and Bulbar Muscular Atrophy (SBMA)
Short Title	A Randomized, Double-Blind, Placebo-Controlled Study of NIDO-361 in Patients with SBMA
Phase	2
Study Design	**Methodology**: This is a randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and efficacy of NIDO-361 in adult patients with SBMA. Patients will be randomly assigned to receive placebo or NIDO-361 at the initial Phase 2 dose of 100 mg once daily for at least 2 months and the recommended Phase 2 dose (RP2D) of 200 mg for the remainder of the study. Patients will receive daily oral doses of NIDO-361 or placebo for a total 12 months.
Study Rationale	The clinical study is designed to evaluate the safety, tolerability, and efficacy of NIDO-361 compared with placebo in participants with SBMA. NIDO-361 is a small molecule modulator of the activity of the androgen receptor (AR). It binds to a novel allosteric pocket, the binding function 3 (BF3) domain, is administered orally, and crosses the blood brain barrier. NIDO-361 is being developed to treat SBMA by correcting mutant AR transcriptional dysregulation thought to drive the molecular mechanisms of the disease.
Target Population	**Inclusion Criteria** To be included in this study, each participant must satisfy all the following criteria: 1. Ability to understand the written study informed consent form(s) (ICF(s)) and provide signed written informed consent prior to any study procedures 2. Ambulatory male 3. Age ≥18 to ≤70 years old 4. Body mass index (BMI) ≥18 kg/m^2 to ≤32 kg/m^2 5. Documented SBMA diagnosis confirmed by DNA genetic testing 6. Able to complete six-minute walk test (6MWT) 7. Spinal and Bulbar Muscular Atrophy Functional Rating Scale (SBMAFRS) scores ≥25 and ≤45 8. On initial whole-body magnetic resonance imaging (MRI), patient has evidence of muscle fat replacement such that the total volume of disease affected muscle (i.e., muscle with at least 10% muscle fat infiltration (MFI) and no more than 50% muscle fat fraction (MFF)) is at least: • 500 cm^3 if only 1 muscle is eligible, or • 250 cm^3 if more than one muscle meets the criteria 9. If using supplements or vitamins, dosing must be stable for at least eight weeks prior to Screening Visit 10. A participant, who is non-sterilized and sexually active with a female partner of childbearing potential, agrees to use adequate contraception from the signing of the informed consent throughout the duration of the study and 90 days from the last dose. Adequate methods of contraception are described in Section 5.3. In addition, participants must be willing to forgo sperm donation for the duration

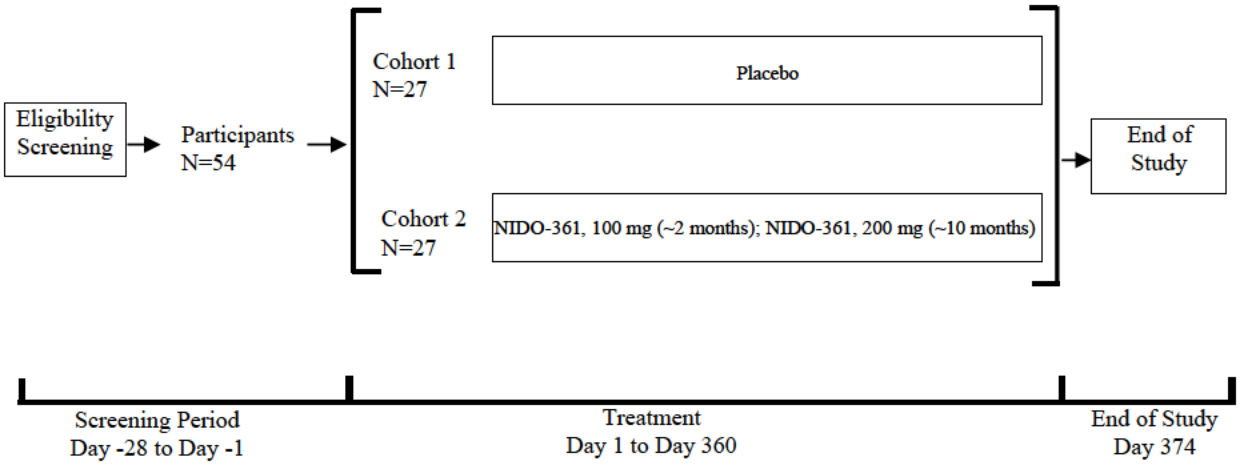
	of the study and 3 months after last dose of study drug. **Exclusion Criteria** If a participant meets any of the following criteria, he is ineligible for this study. 1. Use of other investigational drugs within 30 days or 5 half-lives prior to the planned first drug administration, whichever is longer 2. History of a prior treatment with androgen reducing agents including luteinizing hormone-releasing hormone (LHRH) agonists or antagonists, androgen receptor antagonists, and selective androgen receptor modifiers (SARMs) within the past 3 months or 5 half-lives of the treatment, whichever is longer 3. History of use of medicines that are known to increase the risk of seizures within 90 days prior to Day 1 and until 90 days after the last study dose 4. Clinically significant cardiovascular, endocrine, hepatic, renal, pulmonary, gastrointestinal, neurologic, immunologic, malignant, metabolic, psychiatric, or other condition that, in the opinion of the Investigator, precludes the participant's safe participation in the study or would interfere with the study assessments 5. Clinically significant abnormality at Screening electrocardiogram (ECG), including but not necessarily limited to a confirmed QT interval corrected for heartrate (QTc) ≥450 msec for males 6. Clinically significant laboratory abnormality at Screening Visit 7. History of substance abuse disorder, (except nicotine) within 6 months prior to the Screening Visit 8. History of epilepsy or previous seizure within 10 years prior to the Screening Visit 9. Positive for opioids (unprescribed), cocaine, amphetamines, methadone, barbiturates, methamphetamine, or phencyclidine at the Screening Visit 10. History of malignancy or has received treatment for malignancy, other than treatment for basal cell or squamous cell carcinoma of the skin, within the previous 5 years 11. Positive for Hepatis B virus (HBV) or Hepatis C virus (HCV) 12. Known to be positive for human immunodeficiency virus (HIV) 13. Inability to undergo MRI (mild sedation may be allowed) 14. Involved directly or indirectly in the conduct and administration of this study as an Investigator, sub-investigator, study coordinator, or other study staff member, or the patient is a first-degree family member, significant other, or relative residing with one of the above persons involved directly or indirectly in the study 15. History of hypersensitivity to the excipients of NIDO-361
Number of Participants	Approximately 54 patients
Active Treatment	NIDO-361 100 mg for at least 2 months and 200 mg for the remainder of the study or placebo administered orally once daily for 12 months.
Primary Objectives and Endpoints	**Objectives:** To determine the efficacy of NIDO-361 in restoring muscle volume. To determine the safety and tolerability of NIDO-361 when administered as once daily oral doses in patients with SBMA. **Endpoints:** • Change from baseline in thigh and total lean muscle volume (LMV) as

	assessed by whole-body MRI. • Number of patients with adverse events (AEs) or serious adverse events (SAEs). • Number of patients discontinuing study and number of deaths. • Number of mild, moderate, and severe AEs.
Secondary Objectives and Endpoints	**Objective:** To determine the efficacy of NIDO-361 in restoring muscle strength and muscle endurance. **Endpoints:** • Change from baseline in modified-SBMAFRS (m-SBMAFRS) • Change from baseline in 6MWT • Change from baseline in actigraphy-derived physical activity • Change from baseline in timed up and go (TUG) test • Change from baseline in grip strength as measured by handheld dynamometer (HHD) • Change from baseline in two-minute walk test (2MWT)
Exploratory Objectives and Endpoints	**Objective**: To assess the pharmacokinetics (PK) and pharmacodynamics (PD) of NIDO-361. To assess quality of life and activity of daily living (ADL). **Endpoints**: • Plasma concentrations and derived PK parameters of NIDO-361 including, $AUC_{(0\text{-}24h)}$, C_{max}, T_{max}, C_{min} and/or other parameters deemed appropriate • Change from baseline in 36-Item Short Form (SF-36) Survey • Change from baseline in International Index for Erectile Function (IIEF) questionnaire • Change from baseline in plasma proteomics profile
Number of Sites	Approximately 5 globally
Study Duration	**On Study (Screening to End of Study Follow-up Visit)** Approximately 13.5 months

1.1 Study Schematic

The study schematic for the study is presented in Figure 1.

Figure 1 Flow Diagram of Study NIDO-361-002



1.2 Schedule of Assessments

The Schedule of Assessments for the study is presented in Table 1 and Table 2.

Table 1 Schedule of Assessments

Activity	Screening	Treatment									EOS/ET
Visit	**1**	**2**	**3**	**4**	**5, 6**	**7**	**8, 9**	**10**	**11, 12, 13, 14, 15**	**16**	**17**
Study Day	**D –28 to D –1**	**D1**	**D2**	**D3**	**D30, D60 (±5)**	**D90 (±5)**	**D120 D150 (±5)**	**D180 (±5)**	**D210, D240, D270, D300, D330, (±5)**	**D360 (±5)**	**D374 (±5)**
Informed consent	X										
Eligibility criteria review	X	X									
Demographics	X										
Medical history	X										
Randomization		X									
Physical examination[a]	X	X			X	X	X	X	X	X	X
Vital signs[b,c]	X	X			X	X	X	X	X	X	X
Weight	X	X			X	X	X	X	X	X	X
Height	X										
Prior & concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Hepatitis (HBsAG, HCV)	X										
Clinical laboratory safety tests[c,d]	X	X		X[g]	X	X	X	X	X	X	X
Endocrinology tests[c,e]		X						X			X
Urine drug screen	X										
12-Lead ECG[c,f]	X							X			X
Electroencephalogram (EEG)	X						X[j(D120)]				X
2MWT	X							X		X	X[l(ET)]
6MWT	X	X						X		X	X[l(ET)]
C-SSRS “Baseline/Screening”[i]	X										
C-SSRS “Since Last Visit”[i]								X			X

Activity	Screening	Treatment									EOS/ET
Visit	**1**	**2**	**3**	**4**	**5, 6**	**7**	**8, 9**	**10**	**11, 12, 13, 14, 15**	**16**	**17**
Study Day	**D –28 to D –1**	**D1**	**D2**	**D3**	**D30, D60 (±5)**	**D90 (±5)**	**D120 D150 (±5)**	**D180 (±5)**	**D210, D240, D270, D300, D330, (±5)**	**D360 (±5)**	**D374 (±5)**
SBMAFRS	X							X		X	X [l(ET)]
SF-36		X						X		X	X [l(ET)]
IIEF		X						X		X	X [l(ET)]
Wearable accelerometer device[h]	X							X		X	X [l(ET)]
Whole-body Muscle MRI	X							X		X	X [l(ET)]
TUG		X						X		X	X [l(ET)]
Handheld dynamometer		X						X		X	X [l(ET)]
Pulse oximetry[c]		X			X	X	X	X	X	X	X
PK blood collection[c]		X	X		X[k(D30)]					X	X[l(ET)]
TE blood collection[c]		X						X		X	X[l(ET)]
Dispense study medication		X			X	X	X	X	X		
AE monitoring	X	X	X	X	X	X	X	X	X	X	X

2MWT=two-minute walk test; 6MWT=six-minute walk test; AE=adverse event; C-SSRS=columbia suicide severity rating scale; D=day; ECG=electrocardiogram; EOS=end of study; ET=early termination; HBsAG=hepatitis B surface antigen; HCV=hepatitis C virus; HEENT=head, eyes, ears,nose, and throat; MRI=magnetic resonance imaging; PK=pharmacokinetic; SBMAFRS=spinal and bulbar muscular atrophy functional rating scale; SF-36=36-item short form; TE=target engagement; TUG=timed up and go.

[a] Physical examination includes (at a minimum) general appearance; HEENT, neck (including thyroid and nodes); cardiovascular, respiratory, gastrointestinal, renal, neurological, and musculoskeletal systems; and skin. In addition, the physical examination will include special attention to the motor system, upper and lower extremity measures of strength, tone, and reflexes, as well as ambulation.

[b] Vital signs (oral, tympanic/aural, or axillary temperature, respiration rate, heart rate, and blood pressure) will be obtained. Blood pressure (systolic and diastolic) and heart rate will be measured after participant has rested quietly, sitting or supine for ≥3 minutes.

[c] Detailed assessment timepoints for Days 1–374 are provided in Table 2.

[d] Parameters to be assessed are detailed in Table 3. Samples to be collected non-fasting.

[e] Parameters to be assessed are detailed in Table 4. Endocrinology testing should be performed non-fasting between 7-10 am (±30 minutes).

[f] ECG recordings will be obtained in triplicate in supine position after the participant has rested comfortably for ≥5 minutes. At timepoints when plasma PK is also being collected, the ECG should be performed first, followed by vitals and PK blood collection.

[g] On Day 3, liver function tests only.

[h] Patients will be asked to wear their devices at home from the first day of screening to the end of the study per instructions in the participant guide.
[i] The C-SSRS should be completed prior to any other assessments that day, except informed consent.
[j] EEG to be performed only on D120.
[k] PK blood collection to be performed only on D30 for first 12 patients.
[l] 2/6MWT, SBMAFRS, SF-36, IIEF, wearable accelerometer device, whole-body muscle MRI, TUG, handheld dynamometer, and PK and TE blood collection to be performed only at ET visit.

Table 2 Detailed Schedule of Assessment Timepoints

Visit	**2**					**3**	**4**	**5**					**6, 7, 8, 9**	**10**		**11, 12, 13, 14, 15**	**16**					**17**
Study Day	**D1**					**D2**	**D3**	**D30**					**D60, D90, D120, D150**	**D180**		**D210, D240, D270, D300, D330**	**D360**					**D374 / ET**
	Pre-dose	**1 hr**	**2 hr**	**4 hr**	**6 hr**	**24 hr post dose**	**Pre-dose**	**Pre-dose**	**1 hr**	**2 hr**	**4 hr**	**6 hr**	**Pre-dose**	**Pre-dose**	**4 hr**	**Pre-dose**	**Pre-dose**	**1 hr**	**2 hr**	**4 hr**	**6 hr**	
Window (±)	-4 hr	15 min	15 min	30 min	30 min	1 hr	-4 hr	-4 hr	15 min	15 min	30 min	30 min	-4 hr	-4 hr	30 min	-4 hr	-4 hr	15 min	15 min	30 min	30 min	5 days
Event/Assessment																						
PK blood collection		X	X	X	X	X		X[d]	X[d]	X[d]	X[d]	X[d]					X	X	X	X	X	X[e]
TE blood collection	X														X					X		X[e]
12-lead ECG														X								X
Clinical laboratory tests[a]	X						X[c]	X					X	X		X	X					X
Endocrinology tests[b]	X													X								X
Vital signs	X							X					X	X		X	X					X
Pulse oximetry	X				X			X					X	X		X	X					X

ECG=electrocardiogram; EOS=End of study; ET=early termination; HR=hour; MIN=minutes; PK=pharmacokinetic; TE=target engagement.

[a] Parameters to be assessed are detailed in Table 3. Samples to be collected non-fasting.

[b] Parameters to be assessed are detailed in Table 4. Endocrinology testing should be performed non-fasting between 7-10 am (±30 minutes).

[c] On Day 3, liver function tests only.

[d] PK to be performed only on the first 12 patients.

[e] PK and TE blood collection to be performed only at ET visit.

2 INTRODUCTION

2.1 Background

2.1.1 Target Indication and Population

Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy's disease, is an X-linked recessive inherited neuromuscular disorder. The main symptoms are weakness and atrophy of bulbar and extremity muscles due to lower motor neuron degeneration in the brainstem and spinal cord, concomitant with muscle-autonomous dysfunction. At onset, patients often manifest limb weakness, cramps, tremor, and contraction fasciculations, especially noticeable in face and tongue. Dysarthria is also common, with hypernasality, laryngospasm, and swallowing dysfunction which frequently results in aspiration pneumonia as the disease progresses. More than half of patients die from respiratory infectious diseases (Atsuta et al 2006).

SBMA results from a cytosine-adenine-guanine (CAG) repeat expansion in exon 1 of the AR gene located on the X-chromosome (Kennedy et al 1968, Sobue et al 1989, La Spada et al 1991). Healthy individuals have between 9 and 36 CAG repeats; patients with SBMA typically have a median of 45 repeats (range, 38–68 repeats) with the disease becoming fully penetrant when 38 CAG repeats are present (La Spada et al 1991, Grunseich et al 2014). The disease only manifests in adult males, usually in the 3rd to 5th decade of life, and the prevalence is estimated to be 1 to 2 per 100000 (Breza and Koutsis 2019), although this is thought to be an underestimation as some patients are misdiagnosed with other neuromuscular diseases, such as amyotrophic lateral sclerosis among others (Katsuno et al 2012). The age at onset of disease is thought to be inversely correlated to the size of the CAG-repeat expansions (Andrew et al 1993, Sasaki et al 1996, Rosenblatt et al 2003) whereas disease progression does not seem to be associated with CAG repeat length.

The canonical function of the AR is to regulate gene expression upon androgen binding. The expanded CAG repeat length causes an androgen-dependent toxic gain of function of the AR that affects both neurons and muscle (Jordan and Lieberman 2008). Although the molecular mechanisms of neuronal and muscular dysfunction in SBMA are not fully understood, studies have suggested that they are linked to transcriptional dysregulation (McCampbell et al 2000, Minamiyama et al 2004). Some pathological hallmarks of SBMA are the presence of widespread intranuclear and cytoplasmic inclusions of the pathogenic AR protein, muscle fiber-type switching (reduction of Type II in favor of Type I fibers) and atrophy, and accumulation of fat infiltrates particularly in limb and bulbar muscles and in the liver, all potentially contributing to the pathogenesis and progression of the disease.

In addition to the toxic gain of function, there is loss of normal receptor function, which results in endocrine and metabolic symptoms, such as reduced androgen sensitivity, development of gynecomastia, testicular atrophy, infertility, and erectile dysfunction (Dejager et al 2002, Rosenbohm et al 2018).

Blood testing shows elevated serum levels of creatine kinase and liver enzymes and decreased serum creatinine and glucose intolerance even before the neurological onset. The disease is

invariably progressive leading to profound morbidities and substantial decline in quality of life, and despite this, there are no curative treatments for SBMA. The only approved drug in Japan, leuprolide, a gonadotropin releasing hormone agonist, failed its primary endpoint in a large Phase 3 study (Katsuno et al 2002). However, long-term treatment with leuprolide appeared to delay decline in muscle function and reduce incidence of pneumonia in SBMA patients (Hashizume et al 2017).

The lack of disease-modifying treatments for patients with SBMA together with past clinical trial experience have underlined a great need to solve the multifaceted features of the disease with novel approaches addressing both, the gain of function and the loss of function caused by the mutated AR.

2.1.2 Description of NIDO-361

NIDO-361 is a novel Lipinski rule compliant non-steroidal small molecule allosteric modulator of the activity of AR (allosteric SARM). It can be administered orally, crosses the blood brain barrier in nonclinical species, and binds to a novel allosteric pocket, the BF3 domain (Lack et al 2011). NIDO-361 is being developed to treat patients with SBMA by correcting mutant AR transcriptional dysregulation thought to drive the molecular mechanisms of the disease.

Approaches to treat SBMA have mainly focused on AR antagonism, and attempts have been made to completely or partially shut down androgen biosynthesis, which inevitably resulted in exacerbation of loss-of-function symptoms such as testicular atrophy and feminization (Orr et al 2010). In contrast to pure antagonism approaches and previous SARMs that exhibited weak agonism activity in reproductive organs, NIDO-361 has the potential to be a partial agonist or antagonist depending on tissue context.

Results from a study using a Drosophila model of SBMA suggested that the SBMA degenerative phenotype is a result of a change in polyglutamine (polyQ)-expanded AR-mediated transcriptional activity (Nedelsky et al 2010), which in turn is modified by the binding of various co-regulatory proteins to the activation function 2 (AF2) domain of AR (Smith and O'Malley 2004). This fundamental mechanistic work led to the discovery of 1-[2-(4-methylphenoxy)ethyl]-2-[(2-phenoxyethyl)sulfanyl]-1H-benzimidazole (MEPB), a small molecule AR modulator that rescues SBMA degenerative phenotypes in Drosophila and mouse models (Badders et al 2018). MEPB is a crystallographically characterized small molecule that binds the BF3 pocket (Lack et al 2011). Subsequently, MEPB was shown to modulate co-regulatory protein recruitment at the AF2 domain of AR, and consequently AR-mediated gene expression, through an allosteric conformational reinforcement mechanism (Badders et al 2018). NIDO-361 was developed starting from MEPB and shares most of its properties.

NIDO-361 is of a novel class of molecules that are allosteric SARM. NIDO-361 is being developed based on the now-known mechanism of action of MEPB, from which it was derived through computational design, iterative optimization, and structural activity relationship studies. Similar to MEPB, and unlike AR antagonists, NIDO-361 modulates coregulatory proteins binding to AR. The therapeutic hypothesis is that binding of NIDO-361 to the allosteric AR BF3 pocket alters binding of co-regulators to the AF2 site (Badders et al 2018), thus correcting mutant AR transcriptional dysregulation thought to drive the molecular mechanisms of the disease. Due to this distinct mechanism of action, and unlike AR antagonists, NIDO-361 has the potential to

restore normal AR function, addressing both the toxic gain-of-function and the loss-of-function mechanisms contributing to the disease pathophysiology and clinical manifestations of SBMA.

The NIDO-361 drug product is formulated as a tablet containing 100 mg of NIDO-361 intended for oral administration.

2.1.2.1 Administration Regimen

Eligible patients will be randomly allocated to NIDO-361 100 mg for at least 2 months and 200 mg for the remainder of the study or placebo once daily for 12 months.

2.1.2.2 Justification for Dosing Strategy

A dose escalation regimen will be implemented in this study where patients assigned to active treatment will be receiving 100 mg QD dose for at least 2 months and 200 mg QD dose for the remainder of the study. The dose and dosing regimen selection for this Phase 2 study in SBMA patients are based primarily on evaluation of the nonclinical toxicology and safety pharmacology data to date, on safety results from the multiple ascending dose (MAD) cohort of the completed Phase 1 study in healthy subjects where no significant adverse events after 7 days of once daily dosing of 200 mg of NIDO-361 were observed, i.e., 200 mg QD is the MTD, and on the available blinded safety and plasma PK data from this ongoing study.

The potential to demonstrate the efficacy of NIDO-361 for treating SBMA patients was also considered when selecting a dose for this Phase 2 study. The proposed Phase 2 initial dose of 100 mg QD exceeds the minimum anticipated pharmacologically active dose in human by a factor of approximately two. Dose escalation to 200 mg QD will be implemented upon Data Safety Monitoring Board (DSMB) review of all unblinded available safety data and steady state exposure data at Day 1 and Day 30 of 100 mg of NIDO-361 administered daily in the first 12 patients enrolled in the study (~6 expected to receive 100 mg QD NIDO-361). This would potentially provide added clinical benefit to SBMA patients since the anticipated minimum pharmacologically active dose of 60 mg QD would be exceeded by a factor of approximately three. Please refer to the Investigator's Brochure (IB) for more details.

2.1.3 Supportive Nonclinical Data

The following data is a summary of the information provided in the IB.

The pharmacology, PK, and toxicology programs described in the following sections were designed to characterize the nonclinical efficacy, disposition, and safety of NIDO-361 and to enable selection of an appropriate starting dose for patients with SBMA in this Phase 2 clinical study. All nonclinical studies were conducted in male animals, as SBMA is a disease that only affects men.

2.1.3.1 Pharmacology

Based on the *in vitro* potency and *in vivo* pharmacology data, specifically the free unbound exposures in plasma and target organs, NIDO-361 is expected to reach adequate exposure for target engagement (TE). The projected lowest efficacious dose was determined to be 10 mg/kg/day in mouse.

The safety pharmacology evaluation of NIDO-361 included stand-alone safety pharmacology studies conducted to document the effects of NIDO-361 on organ systems (cardiovascular and

respiratory). In addition, safety pharmacology assessments of the cardiovascular and central nervous system were included in the study designs of the Good Laboratory Practice (GLP) 4-week repeat-dose studies in monkeys and rats, respectively.

2.1.3.1.1 Primary Pharmacodynamics

2.1.3.1.1.1 Primary *In Vitro*

In vitro potency of NIDO-361 was determined based on antagonism in an AR transcriptional reporter structure-activity relationship assay. This transcriptional reporter assay uses androgen-sensitive human prostate adenocarcinoma cells (LNCaP), transfected with an enhanced green fluorescent protein (eGFP) reporter under the regulation of an androgen response element (ARE) promoter. NIDO-361 was a very potent antagonist in the assay with a half-maximal inhibitory concentration (IC_{50}) of 34 nM.

The potency of NIDO-361 was also tested against two different constructs containing varying lengths of polyQ in a transcriptional reporter assay (CV1 cells dual transfected with mutant AR and a reporter luciferase under the control of an ARE promoter). A short repeat AR with 20 CAG repeats (20Q, wild type AR [wtAR]) and one with a longer repeat, 121 CAG repeats (AR121Q) were used. *In vitro* potency assessments against wtAR and polyQ (AR121Q) were respectively 100 nM and 180 nM in the CV1 in antagonism mode, when the assay is run in the presence of saturating levels of an androgen. Weak agonism activity, which is assessed in the absence of androgen, was also noted against wtAR. In LNCaP cells, the agonism was modest with the effective concentration at 50% activity (EC_{50})=5300 nM. The IC_{50} of NIDO-361 was comparable between wtAR and AR121Q, suggesting that its efficacy is not significantly impacted by AR polyQ length and the entire SBMA patient population could potentially benefit from this treatment.

2.1.3.1.1.2 Primary *In Vivo*

Efficacy

Most nonclinical efficacy studies were conducted in the androgen receptor with 113 cytosine-adenine-guanine repeats (AR113Q) knock-in mouse model. This model was selected because it resembles the genetic underpinnings of human SBMA, as well as the slowly progressive nature and pathological hallmarks of the disorder, including transcriptional dysregulation, fiber-type switching in skeletal muscle, polyQ AR aggregation, and motor-driven phenotype (Giorgetti et al 2016; Yu et al 2006).

Dysregulated transcriptional pathways in the AR113Q muscle that were restored after NIDO-361 treatment were particularly relevant to SBMA pathophysiology, including those involved in transcription, cellular homeostasis, and several other pathways related to mitochondria and oxidative phosphorylation which contribute to the metabolic features of SBMA.

AR113Q mice also demonstrated histopathological atrophy of muscle fibers, fiber-type switching, and polyQ AR accumulation. NIDO-361 was able to correct these deficits by restoring muscle fiber health and by reducing polyQ aggregates, at various ages and doses of 10, 30, or 50 mg/kg/day.

NIDO-361 significantly increased rates of survival in the AR113Q mouse model of SBMA in a

dose-dependent fashion; 50% of untreated AR113Q mice die at 30 weeks of age whereas NIDO-361 at 10 and 30 mg/kg/day increased rates of survival in AR113Q mice, with all deaths being prevented by 30 mg/kg. Based on multiple parameters, the 10 mg/kg/day dose of NIDO-361 (corresponding to a drug concentration reached immediately before next dose (C_{trough}) =170 ng/mL) has been established as the lowest efficacious dose in the AR113Q mouse model. This dose in mice corresponds to a minimum human efficacious dose of 60 mg/day based on human PK data from the healthy volunteer Phase 1 study.

In summary, NIDO-361 exhibited specific and dose-dependent activity on the mutated AR, restored dysregulated transcription, corrected histopathological features of the disease in muscle, and provided a significant rescue on survivability. Given these results, NIDO-361 has the potential to become a disease-modifying treatment for SBMA.

2.1.3.1.2 Secondary Pharmacodynamics

NIDO-361 was profiled across 78 kinase, G-protein-coupled receptors, and ion channel secondary pharmacology assays. NIDO-361 did not significantly inhibit any of the targets (>50% at 10 µM). These results suggest that NIDO-361 is highly selective and does not significantly bind or affect the activity of a broad range of targets.

NIDO-361 was profiled using KINOME scan against a panel of 468 kinases and disease relevant mutant variants to assess its potential off-target activities via a competitive binding assay. One kinase, PIM2, showed 93% inhibition under serum free conditions upon incubation of 10 µM NIDO-361 with no significant inhibition noted against any of the other kinases. Inhibition of all PIM sub-families is required to elicit a biological effect (Garcia et al 2014).

NIDO-361 was profiled against 38 nuclear hormone receptors (nhrs) using the DiscoveRx nhrMAX Biosensor Panel. Two nhrs were identified for further evaluation: progesterone receptor alpha (PRa) and thyroid hormone receptor beta (THRb).

NIDO-361 EC_{50} and IC_{50} values were determined for these 2 nhr. The EC_{50} is 0.13 µM against PRa in the agonist mode, and the EC_{50} is 8 µM for THRb in the agonist mode. All other IC_{50} or EC_{50} values were greater than 10 µM, which is approximately 140-fold higher than the observed maximum unbound concentration from the blinded Day 30 plasma PK assessment of this ongoing study ($C_{max,[unbound]}$ = 0.0702 µM) at 100 mg/day, and approximately 70-fold higher than the predicted maximum unbound concentration ($C_{max,[unbound]}$ = 0.140 µM) at 200 mg/day following escalation.

As SBMA is a male disease and PRa does not play a prominent role in males, this off-target modulation may not be as relevant. Additionally, NIDO-361 is >100-fold more potent on AR than THRb; thus, the modulation of this off-target is less likely at the projected human efficacious doses.

2.1.3.1.3 Safety Pharmacology

Cardiac safety was evaluated in a GLP *in vitro* assay for human ether-à-go-go-related gene (hERG) activity, in a GLP *in vivo* study in conscious telemetry-instrumented monkeys, and in a GLP 4-week repeat-dose toxicity study with ECG monitoring in monkeys.

The IC_{50} for the inhibitory effect of NIDO-361 on human hERG potassium current was estimated to be greater than 30 µM which is approximately 430-fold higher than the observed $C_{max,[unbound]}$ (0.0702 µM) from the blinded Day 30 plasma PK assessment of this ongoing study at 100

mg/day, and approximately 210-fold higher than the predicted ($C_{max,[unbound]}$ = 0.140 µM) at 200 mg/day following escalation.

Findings in a cardiovascular study in telemetry-instrumented male cynomolgus monkeys included lower heart rate (-13 and -14 bpm at 100 and 200 mg/kg, respectively), corresponding to longer QT interval (+15 and +18 msec at 100 and 200 mg/kg, respectively), minor alterations in body temperature, and lower activity. The corresponding maximum observed plasma concentration (C_{max}) and area under the time-concentration curve from time zero to 24 hours ($AUC_{(0-24)}$) values after a single administration of 100 mg/kg NIDO-361 were 9390 ng/mL and 179000 h×ng/mL, respectively, which is approximately 11-fold and 12-fold above the observed C_{max} (647 ng/mL) and area under the plasma concentration-time curve (AUC) (11000 h×ng/mL) from the blinded Day 30 plasma PK assessment of this ongoing study, respectively, at 100 mg/day (correcting for free fraction in monkey (0.027) and human (0.035) plasma). Similarly, the predicted exposure multiples are approximately 5-fold and 6-fold based on C_{max} and AUC, respectively, upon dose escalation to 200 mg/day (correcting for free fraction in monkey (0.027) and human (0.035) plasma). No NIDO-361-related qualitative ECG abnormalities or quantitative changes in PR interval, QRS duration, corrected QT interval, or arterial pressure were noted following administration of doses ≤200 mg/kg.

In the GLP 4-week repeat-dose study, there were no NIDO-361-related changes in quantitative ECGs noted on Day 1 of the dosing phase in animals administered up to 600 mg/kg/day and on Day 22 of the dosing phase in animals administered up to 200/100 mg/kg/day; or on Day 22 of the recovery phase in animals administered up to 200/100 mg/kg/day. No NIDO-361-related arrhythmias or abnormal waveforms were observed during the qualitative assessment of the ECGs.

There were no NIDO-361 neurobehavioral and locomotor activity effects noted in rats as part of the GLP 4-week study at doses up to 250/150 mg/kg/day. Additionally, no microscopic abnormalities in neuronal tissues were found in the rat study. In the 4-week study in cynomolgus monkeys, adverse neurobehavioral clinical observations were noted (see description in Section 2.1.3.3).

In a safety pharmacology study evaluating respiratory function in male rats, NIDO-361 dose-dependently decreased respiration rate and minute volume in animals administered >25mg/kg but had no effect on tidal volume.

2.1.3.2 PK

The absorption characteristics of NIDO-361, its moderate-to-high oral bioavailability in nonclinical species and brain-to-plasma ratios observed in mouse and rat suggest that NIDO-361 is orally bioavailable and can penetrate the blood-brain barrier in nonclinical species. Significant oral exposure was observed across all dose cohorts in the Phase 1 study in healthy volunteers, which was consistent with PK predictions based on nonclinical species. Single dose administration of NIDO-361 to healthy human subjects resulted in moderate absorption as evidenced by median time to maximum drug concentration (T_{max}) values between 2 (75 – 225 mg) and 3 h (350 and 500 mg) post-dose. NIDO-361 mean oral clearance (CL/F) in humans was generally low and ranged between 2.77 and 6.48 mL/min/kg, and the apparent volume of distribution during the terminal phase (Vz/F) was generally high and ranged between 7.6 and 12 L/kg. The mean terminal oral half-life ($t_{½}$) was between 21 and 31 hours.

Multiple dosing of NIDO-361 for up to seven days to healthy human subjects resulted in steady state being achieved as evidenced by pre-dose plasma concentrations on Day 7 that are approximately equal to 24 hours plasma concentrations. Accumulation of NIDO-361 in human plasma was observed after multiple dosing with mean accumulation ratios of approximately 2-fold (150 and 200 mg QD) and 3-fold (350 mg QD) based on C_{max}, and approximately 3-fold (150 and 200 mg QD) and 4-fold (350 mg QD) based on $AUC_{(0\text{-}24h)}$.

In summary, the PK profile of NIDO-361 observed in healthy human subjects enables its clinical development as a chronic oral therapy for SBMA in patients.

The *in vitro* metabolism of NIDO-361 was investigated using mouse, rat, dog, monkey, and human cryopreserved hepatocytes. NIDO-361 exhibited low turnover in rat and moderate turnover in mouse, dog, monkey, and human hepatocytes, generating metabolites resulting from oxidation, glucuronidation, and sulfation. All metabolites identified in human hepatocytes were also detected in monkey hepatocytes, thus demonstrating that monkey is an appropriate non-rodent species for assessing toxicology. Most NIDO-361 human metabolites were also observed in mouse, rat and/or dog hepatocytes.

An evaluation of the CYP450 enzymes involved in the *in vitro* metabolism of NIDO-361 was conducted which indicated that CYP1A2 is the main CYP enzyme involved in the *in vitro* metabolism of NIDO-361. As such, patients should not be administered any strong inhibitors of CYP1A2 while on study (see Section 6.2.4.1 for more details). The metabolic stability of NIDO-361 was studied in recombinant human uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes and none were found to substantially metabolize NIDO-361 under the test conditions.

The potential for cytochrome P450 (CYP) and UGT drug-drug interactions with NIDO-361 is generally low. There is a trend toward reversible inhibition of UGT1A9 and UGT2B17, and time-dependent inhibition with cytochrome P450 family 3 subfamily A (CYP3A). Similarly, the potential for transporter inhibition is generally low, but there is a trend toward inhibition of P-glycoprotein (P-gp) & breast cancer resistance protein (BCRP) in the gut. These observed trends should not be an issue for this study given the exclusion criteria in Section 5.2 and lifestyle restrictions in Section 5.3. Nonetheless, caution should be exercised should substrates of these CYP450s, UGTs and transporters need to be administered to patients in this study.

2.1.3.3 Toxicology

The toxicological profile of NIDO-361 was evaluated with a series of GLP repeat-dose studies in male Sprague Dawley rat and male cynomolgus monkey to support daily oral dose administration of NIDO-361 to SBMA patients in the clinic. Toxicology testing also included genotoxicity and phototoxicity studies.

Noteworthy findings in the 4-week toxicology study in monkeys included unscheduled sacrifices due to adverse neurologic observations in some animals administered 200 mg/kg/day or higher. After dose reduction to 100 mg/kg/day, NIDO-361 was well tolerated for the remainder of the dosing phase with no adverse findings. Although 100 mg/kg/day was well tolerated after the dose reduction, the no-observed-adverse-effect-level (NOAEL) for the full 4 weeks of the study was 45 mg/kg/day.

Clinical observations and findings from the 4-week toxicity study in rats included decreased body weights, body weight gain, and food consumption, along with minor, reversible non-adverse NIDO-361-related clinical pathology effects at doses equivalent to or below the

NOAEL of 100 mg/kg/day. NIDO-361-related microscopic findings included minimal testicular tubular degeneration that was accompanied by minimal to slight cell debris in the epididymis of animals administered ≥100 mg/kg/day. All microscopic findings were reversible during the recovery.

Observations and safety findings from the 26-week toxicity study in monkeys were largely consistent to what was observed in the 4-week study, but there was a higher prevalence of abnormal feces, necessitating a dose reduction from 45 to 30 mg/kg/day. Following the dose reduction, 30 mg/kg/day was well tolerated for up to 10 weeks of daily dosing until the end of the dosing phase of the study.

The tolerability of 30 mg/kg/day NIDO-361 for a full 26 weeks of once-daily dosing was established in a second 26-week repeat-dose study in male cynomolgus monkeys. All clinical and veterinary observations were comparable between treated and untreated groups, and as such were not considered to be related to NIDO-361. Clinical pathology evaluations were also comparable between treated and untreated groups, and anatomical pathology revealed no organ weight alterations, gross observations, or microscopic findings. Therefore, 30 mg/kg/day was a tolerated dose and was the NOAEL for a full 26-weeks of once daily dosing to monkeys.

NIDO-361-related observations and safety findings in the 26-week repeat dose study in male Sprague Dawley rats included convulsions, which started on Day 97. Although convulsions are generally considered adverse, none of the rats required veterinary intervention and convulsions resolved on their own with no post-ictal observations. Spontaneous convulsions in rats are frequently observed in long-term toxicity studies, with strain, sex, and age of rats being determining factors. Reproductive tissue findings were also noted, which included the testis (tubular degeneration and/or Leydig cell hypertrophy), epididymis (reduced sperm, cellular debris, and/or decreased weight), and prostate (decreased weight) at doses ≥100 mg/kg/day. Effects in the male reproductive system are anticipated based on the mechanism-of-action of NIDO-361 as a therapeutic agent for AR modulation, and as such are likely to be present at any dose producing a pharmacological effect. These findings were mild, sporadic and reversible or trended to reversibility during the recovery period as would be anticipated with any compound targeting AR. At 100 mg/kg/day, the effects were generally modest, low-grade effects with limited degenerative changes present and were considered adverse to the reproduction based on the continuum with observations (tubular degeneration and decreased sperm) at the highest dose of 175 mg/kg/day. No NIDO-361-related clinical pathology effects were identified and there was no NIDO-361-related mortality through the end of the dosing and recovery phases. The NOAEL for the study was 100 mg/kg/day.

According to calculations outlined in regulatory guidance documents ("Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products" – EMA 2017 and "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" - FDA 2005), a human equivalent dose (HED) was calculated based on the results of the 26-week toxicology studies in rat and monkey to determine the most sensitive toxicological species. Based on the calculations outlined in the guidance, the monkey was deemed the most sensitive species since it generated the lowest HED (9.7 mg/kg versus 16 mg/kg if using rat NOAEL). The HED in monkeys corresponds to approximately 630 mg in human (assuming 65 kg body weight).

Steady-state C_{max} and AUC in human are predicted to be 512 ± 72 ng/mL and 8480 ± 1220 ng×h/mL with 100 mg once daily dosing, respectively. The measured steady-state (Day 30

blinded analysis) C_{max} and AUC in the first 6 SBMA patients on active treatment participating in this ongoing study were 647 ± 168 ng/mL and 11000 ± 3660 ng×h/mL, respectively, which are in good agreement with predicted values. These are approximately 11- and 9-fold (C_{max} and AUC, respectively) lower than the mean steady-state exposure in monkey (C_{max} and AUC) at the NOAEL of 30 mg/kg/day. Upon dose escalation to 200 mg QD, therapeutic indices are expected to be approximately 4 to 5-fold lower than the mean steady-state exposure in monkey at the NOAEL of 30 mg/kg/day.

NIDO-361 was found not to be genotoxic in a definitive *in vivo* micronucleus/comet assay in rat and was not phototoxic in the definitive GLP *in vivo* evaluation of phototoxicity in pigmented male rats.

Based on the results of the nonclinical studies, further investigation of NIDO-361 as a disease modifying agent for treatment of patients with SBMA is acceptable.

2.1.4 Benefit-Risk Assessment

SBMA is a recessive X-linked inherited, progressive and debilitating neuromuscular disorder (Kennedy et al 1968, Sobue et al 1989). Although patients may be able to live independently early in the course of the disease, assistance and full-time care is necessary at later stages of the disease, and life expectancy may be reduced by approximately 12 years (Atsuta et al 2006). The most common cause of death in patients with SBMA is related to complications of respiratory diseases and aspiration pneumonia.

Despite the significant and progressive disability in multiple systems associated with SBMA, no treatments exist that can cure, slow, or reverse the course of SBMA; thus, there is a significant unmet need for a pharmacological treatment with the potential to affect the underlying pathophysiology of the disease and modify its clinical course. NIDO-361 has the potential to be a disease-modifying treatment to address the significant unmet need experienced by patients with SBMA.

The nonclinical toxicology program consisted of non-GLP and GLP repeat-dose toxicology studies of up to 26-weeks in rats and monkeys, standalone safety pharmacology studies and *in vivo* genotoxicity and phototoxicity assessments, and yielded no toxicologically meaningful findings that would prevent initiation of clinical studies at the proposed NIDO-361 dose. The proposed NIDO-361 dose and dosing regimen for the Phase 2 clinical study was selected to adequately balance risk and benefit for patients. The initial 100 mg dose administered QD was chosen based on the results of a single ascending dose (SAD) and multiple ascending dose (MAD) Phase 1 study in healthy volunteers together with the data from nonclinical toxicology studies in rats and monkeys. This dose is expected to provide adequate coverage of the minimum anticipated exposure for pharmacological activity while minimizing the occurrence of AEs.

Results from the 26-week repeat-dose GLP study in male cynomolgus monkeys showed high prevalence of abnormal feces that necessitated a dose reduction from 45 to 30 mg/kg/day on Day 109 of dosing. Following the dose reduction, 30 mg/kg/day was well tolerated for up to 10 weeks of daily dosing until the end of the dosing phase of the study. The tolerability of 30 mg/kg/day NIDO-361 in male cynomolgus monkeys was subsequently established for a full 26 weeks of repeated daily dosing in a second study. No microscopic findings were observed at any dose in either study.

The AEs observed in the monkeys were mainly related to the GI system and are thus easily

monitorable in humans. Provisions will be placed in the Phase 2 study in order to ascertain the patients' well-being, such as physical examinations, vitals, and appropriate laboratory assessments, including electrolytes and liver enzymes.

NIDO-361-related observations and safety findings in the 26-week repeat dose study in male Sprague Dawley rats included convulsions, which started on Day 97. Although convulsions are generally considered adverse, none of the rats required treatment, and all convulsions resolved spontaneously and without post-ictal observations. Spontaneous convulsions in rats are frequently observed in long term toxicity studies, with strain, sex and age of rats being determining factors. For example, spontaneous convulsions have been noted more frequently in the Hsd: Sprague Dawley strain (same strain as was used in the 26-week study), and in male rats primarily after 25 weeks of age (Satomoto et al 2012; Streit 2022). The vast majority of observed convulsions in the 26-week rat study were observed after Day 126, which is when the rats were approximately 25 weeks of age, further suggesting that the observed convulsions were most likely due to the propensity of rats to spontaneously convulse, their sex and age, rather than a drug-related effect. Out of an abundance of caution, the sponsor has chosen to treat the convulsions observed in rats at the highest tested dose of 175 mg/kg/day as being exacerbated by NIDO-361, even though they appear not to be drug-related. As such preventative measures have been implemented for this study and patients will be monitored by electroencephalogram (EEG), participants with history of seizure will be excluded from study and medications known to increase the risk of convulsions will be prohibited.

A spectrum of findings was observed in the reproductive tissues in the 26-week rat toxicology study at doses ≥100 mg/kg/day. These findings were modest, sporadic and reversible or trended to reversibility during the recovery period as would be anticipated with any compound targeting AR. Patients will be assessed using an endocrinology panel and the IIEF questionnaire to monitor potential reproductive adversity.

In addition to nonclinical toxicology studies, the Sponsor has conducted a Phase 1 first-in-human study including both safety and PK measures to enable selection of well tolerated and pharmacologically active doses for further development in humans. Safety data from the Phase 1 study conducted in healthy human volunteers established an acceptable safety profile for NIDO-361 and did not identify safety risks that would prevent its investigation in patients with SBMA. A wide range of doses between 75 mg and 500 mg were assessed in healthy volunteers; no SAEs were reported in any cohort, and most AEs reported were mild in intensity, were transient, and resolved without sequelae. In the SAD cohorts, no clinically meaningful observation and no abnormal trends in hematology or clinical chemistry were reported following dosing. No discontinuations due to AEs or stopping criteria events were observed, and all participants completed the study. In the MAD cohorts, where participants received daily doses of NIDO-361 for seven days, elevated liver enzymes were observed in 6 participants in the 350 mg cohort only. Two of the six participants on active treatment had moderately elevated liver enzymes, which resulted in study drug discontinuation on the last day of dosing (Day 7) for these two participants, while all the others completed study except for 1 participant who withdrew from study after Day 2 due to consent withdrawal. Following study completion, all participants' elevated liver enzymes returned to baseline.

AEs that were assessed as related to study drug were mostly mild and consisted mainly of mild, transient headaches; in the MAD 350 mg cohort, these AEs also included GI events such as abdominal pain/discomfort and gastroesophageal reflux, also of mild severity. All AEs resolved without sequelae. In the Phase 1 study, 200 mg was the MTD hence a dose escalation strategy

will be implemented in the Phase 2 study where patients will receive the initial 100 mg daily dose of NIDO-361 for at least 2 months and will dose escalate to 200 mg daily dose for the remainder of the study upon DSMB review of all unblinded available safety and exposure data at steady state in the first 6 patients on active treatment. Dose escalation to 200 mg would potentially provide added clinical benefit to SBMA patients.

Careful patient monitoring will be implemented in Protocol NIDO-361-002, including frequent blood tests for liver enzymes together with in-clinic assessments of GI functions. Safety monitoring assessments will be implemented, including laboratory assessments, physical examinations, vital signs, ECGs, EEGs, assessments of AEs, and evaluation of potential cumulative toxicities, both during and after completion of dosing with NIDO-361.

The mild and transient nature of the clinical AEs related to the study drug identified in the Phase 1 study and the ability to easily monitor these events during clinic visits reduces any potential safety risk for patients throughout the conduct of the Phase 2 study.

In summary, NIDO-361 has the potential to be an effective disease-modifying agent for the treatment of patients with SBMA. Based on the totality of data from the nonclinical and clinical studies conducted thus far, together with the ability to easily monitor for potential adverse effects in humans, further investigation of NIDO-361 as a potential treatment for SBMA is considered warranted.

2.2 Study Rationale

This clinical study is designed to evaluate the safety, tolerability, and efficacy of NIDO-361 compared with placebo in participants with SBMA.

3 OBJECTIVES AND ENDPOINTS

Tier	Objectives	Endpoints
Primary	To determine the efficacy of NIDO-361 in restoring muscle volume. To determine the safety and tolerability of NIDO-361 when administered as once daily oral doses in patients with SBMA.	• Change from baseline in thigh and total LMV as assessed by whole-body MRI • Number of patients with AEs or SAEs • Number of patients discontinuing study and number of deaths • Number of mild, moderate, and severe AEs
Secondary	To determine the efficacy of NIDO-361 in restoring muscle strength and muscle endurance.	• Change from baseline in m-SBMAFRS • Change from baseline in 6MWT • Change from baseline in actigraphy-derived physical activity • Change from baseline in TUG test • Change from baseline in grip strength as measured by HHD • Change from baseline in 2MWT
Exploratory	To assess the PK and PD of NIDO-361. To assess quality of life and ADL.	• Plasma concentrations and derived PK parameters of NIDO-361 including, $AUC_{(0\text{-}24h)}$, C_{max}, T_{max}, C_{min} and/or other parameters deemed appropriate • Change from baseline in SF-36 • Change from baseline in IIEF • Change from baseline in plasma proteomics profile

4 STUDY PLAN

Please refer to Figure 1 for the Study Schematic.

4.1 Study Design

This randomized, double-blind, placebo-controlled, Phase 2 study in patients with SBMA is designed to assess the safety, tolerability, and efficacy of NIDO-361. Approximately 54 male patients will be enrolled. Female participants will not be included in the study as NIDO-361 is intended for a disease that only affects males. As such, the nonclinical toxicology data only supports clinical investigation in males.

Patients will receive oral doses of NIDO-361 or placebo for 12 months. Patients will be randomly assigned to receive placebo or NIDO-361 at the initial dose of 100 mg. The Data Safety Monitoring Board (DSMB) is responsible for reviewing unblinded available safety and steady state exposure data after 24 hours and 30 days of treatment to inform dose escalation to RP2D of 200 mg. The DSMB will continue to review all the data periodically and on an ad hoc basis throughout the study and may recommend to reduce or increase NIDO-361 dose level or dosing frequency based upon their review.

An amendment may be made to this protocol to specify that this trial will integrate into a Phase 3 trial. The Phase 2/3 trial will evaluate the same patient population but with a functional endpoint, larger sample size, and longer follow-up to generate evidence of functional benefits. The clinical trial assessments will remain unchanged together with the randomization scheme; clear rules for interim/futility analyses will be pre-specified in the protocol amendment. The decision to amend this protocol will be made prior to the unblinding of the Phase 2 trial database, and the data generated from the Phase 2 trial will remain blinded until the completion of the Phase 3 trial.

4.2 Stopping Criteria

The Sponsor may terminate this study at any time, after informing Investigators. The Sponsor (or designee) will notify Investigators when the study is to be placed on hold, completed, or terminated.

Dosing may be terminated by the Sponsor at the recommendation of the DSMB, based exclusively on safety and tolerability data, or at the discretion of the Sponsor; therefore, there are no study-specific stopping rules defined in this protocol.

4.2.1 Individual Stopping Criteria

Dosing will be stopped for an individual participant at any time in the study if:

- A participant experiences a serious or intolerable AE that, in the Investigator's opinion, requires study drug discontinuation.
- A participant experiences the same related treatment emergent adverse event (TEAE) ≥ Grade 3 twice.

The participant will be followed up for safety per protocol. Per the Investigator's judgement, the participant may be allowed to resume participation in the study if or when the event has resolved.

Dose suspension due to individual stopping criteria may not meet criteria for a temporary study

halt and restart.

4.2.2 Communication of Emergent Safety Concerns

Enrollment in the study will be closely monitored by the Sponsor. If the stopping criteria are met at any point in the study, enrollment and dosing will be suspended until the data are reviewed by the DSMB. Notification of dose suspension will be made in accordance with applicable regulations. If a determination is made to resume the study, information will be submitted to the regulatory authorities in accordance with local regulations prior to restarting treatment. The Sponsor and/or contract research organization will inform all sites in writing if enrollment and/or dosing is suspended. In addition, if enrollment is suspended, the interactive response technology (IRT) system will be adjusted such that no patients can be randomized to treatment until the safety review has been completed and a decision has been made to resume enrollment/dosing.

4.3 Design Rationale

The clinical study with NIDO-361 was designed to evaluate the safety, tolerability, and efficacy of the study drug.

As the primary objective of the study is the assessment of safety, tolerability, and efficacy of NIDO-361 in patients with SBMA, placebo is the most appropriate comparator for this study.

4.3.1 Rationale for Dose Selection

A dose escalation regimen is being proposed for this Phase 2 study where patients with SBMA assigned to active treatment will be receiving 100 mg QD dose for at least 2 months and 200 mg QD dose for the remainder of the study. This is based primarily on safety results from the MAD cohort of the Phase 1 study in healthy subjects where no significant AEs after seven days of once daily dosing up to 200 mg NIDO-361 were observed, *i.e.*, 200 mg QD is the maximum tolerated dose (MTD), and on evaluation of the nonclinical toxicology and safety pharmacology data to date.

The potential to demonstrate the efficacy of NIDO-361 for treating SBMA patients was also considered when selecting a dose for the Phase 2 study. The minimum efficacious dose of 10 mg/kg was established in AR113Q mice based on multiple parameters including rescue of skeletal muscle histopathology and survival benefit. Coverage of the concentration of drug at steady state immediately before the next dose is administered ($C_{trough,ss}$), for 24 hours is required to achieve efficacy in AR113Q mice, which translates to $C_{trough,ss}$ = 170 ng/mL in human, The clinical dose expected to achieve 24 hour coverage of $C_{trough,ss}$ = 170 ng/mL in human was determined based on the plasma exposure data from the Phase 1 study in healthy subjects. This corresponds to 60 mg when NIDO-361 is administered orally once daily for at least 7 days. The proposed Phase 2 doses of 100 mg and 200 mg exceed the minimum anticipated pharmacologically active dose in human by a factor of approximately 2 and more than 3, respectively.

Based on regulatory guidance ("Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products" – EMA 2017 and "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" - FDA 2005, HED were calculated from the results of the 26-week

toxicology studies in rat and monkey to determine the most sensitive toxicological species. Based on the calculations outlined in the guidance, the monkey was deemed the most sensitive species since it generated the lowest HED (9.7 mg/kg versus 16 mg/kg if using rat NOAEL). The HED in monkeys corresponds to approximately 630 mg in human (assuming 65 kg body weight).

Steady-state C_{max} and AUC in human are predicted to be 512 ± 72 ng/mL and 8480 ± 1220 ng×h/mL with 100 mg once daily dosing, respectively. The measured steady-state (Day 30 blinded analysis) C_{max} and AUC in the first 6 SBMA patients on active treatment participating in the currently ongoing study were 647 ± 168 ng/mL and 11000 ± 3660 ng×h/mL, respectively, which are in good agreement with predicted values. These are approximately 11- and 9-fold (C_{max} and AUC, respectively) lower than the mean steady-state exposure in monkey (C_{max} and AUC) at the NOAEL of 30 mg/kg/day. Upon dose escalation to 200 mg QD, therapeutic indices are expected to be approximately 4 to 5-fold lower than the mean steady-state exposure in monkey at the NOAEL of 30 mg/kg/day.

A spectrum of findings was observed in the reproductive tissues in the 26-week rat toxicology study, which included the testis (tubular degeneration and/or Leydig cell hypertrophy), epididymis (reduced sperm, cellular debris, and/or decreased weight), and prostate (decreased weight) at doses ≥100 mg/kg/day. Effects in the male reproductive system are anticipated based on the mechanism-of-action of NIDO-361 as a therapeutic agent for AR modulation, and as such are likely to be present at any dose producing a pharmacological effect. These findings were reversible or trended to reversibility during the recovery period as would be anticipated with any compound targeting AR. At 100 mg/kg/day, the effects were generally modest, low-grade effects with limited degenerative changes present and were considered adverse to the reproduction based on the continuum with observations (tubular degeneration and decreased sperm) at the highest dose of 175 mg/kg/day.

Patients participating in the proposed Phase 2 study will be advised of the nature of systemic and reproductive adverse and non-adverse events from nonclinical toxicity studies through the ICF, and provisions to mitigate potential adverse events in humans will be implemented. For example, GI AEs and patients' well-being are easily monitorable in humans and patients will be specifically asked to report any GI AEs during clinic visits, and appropriate laboratory assessments. An endocrinology hormonal panel will be run in patients to monitor potential reproductive adversity. In addition, although convulsions observed in the rat 26-week toxicology study were likely not drug-related, out of an abundance of caution, patients will be monitored by EEG, participants with history of seizure will be excluded from study and medications known to increase the risk of convulsions will be prohibited.

In summary, a daily dose of 200 mg, orally administered NIDO-361 has the potential to provide benefit to SBMA patients in light of the predicted minimally pharmacologically active dose of 60 mg once daily. This dose also is expected to be well tolerated by SBMA patients given the safety results from the Phase 1 study (where the MTD was 200 mg/day) and the calculated therapeutic indices based on the 26-week toxicology studies in rat and monkey. A dose escalation regimen will also ensure that the optimal dose of 200 mg is reached while minimizing the potential occurrences of AEs.

5 STUDY POPULATION

Approximately 54 adult male patients with SBMA will be enrolled.

Participants officially enter the screening period following provision of informed consent.

A screen failure is a consented participant who has been deemed ineligible on the basis of one or more eligibility criteria or who has withdrawn consent prior to treatment assignment. Rescreening for participants who previously failed screening, will only be permitted with approval from Sponsor.

5.1 Inclusion Criteria

To be included in this study, each participant must satisfy all the following criteria:

1. Ability to understand the written study ICF(s) and provide signed written informed consent prior to any study procedures
2. Ambulatory male
3. Age ≥18 to ≤70 years old
4. BMI ≥18 kg/m^2 to ≤32 kg/m^2
5. Documented SBMA diagnosis confirmed by DNA genetic testing
6. Able to complete 6MWT
7. SBMAFRS scores ≥25 and ≤45
8. On initial whole-body MRI, patient has evidence of muscle fat replacement such that the total volume of disease affected muscle (i.e., muscle with at least 10% MFI and no more than 50% MFF) is at least:
    - 500 cm^3 if only 1 muscle is eligible, or
    - 250 cm^3 if more than one muscle meets the criteria
9. If using supplements or vitamins, dosing must be stable for at least eight weeks prior to Screening Visit
10. A participant who is non-sterilized and sexually active with a female partner of childbearing potential agrees to use adequate contraception from the signing of the informed consent throughout the duration of the study and 90 days from the last dose. Adequate methods of contraception are described in Section 5.3 In addition, participants must be willing to forgo sperm donation for the duration of the study and 3 months after last dose of study drug.

5.2 Exclusion Criteria

If a participant meets any of the following criteria, he is ineligible for this study:

1. Use of other investigational drugs within 30 days or 5 half-lives prior to the planned first drug administration, whichever is longer
2. History of a prior treatment with androgen reducing agents including LHRH agonists or antagonists, androgen receptor antagonists, and SARMs within the past 3 months or 5 half-lives of the treatment, whichever is longer
3. History of use of medicines that are known to increase the risk of seizures within 90 days prior to Day 1 and until 90 days after the last study dose.
4. Clinically significant cardiovascular, endocrine, hepatic, renal, pulmonary, gastrointestinal, neurologic, immunologic, malignant, metabolic, psychiatric, or other condition that, in the opinion of the Investigator, precludes the participant's safe participation in the study or would interfere with the study assessments

5. Clinically significant abnormality at Screening ECG, including but not necessarily limited to a confirmed QT interval corrected for heartrate (QTc) ≥450 msec for males
6. Clinically significant laboratory abnormality at Screening Visit
7. History of substance abuse disorder, (except nicotine) within 6 months prior to the Screening Visit
8. History of epilepsy or previous seizure within 10 years prior to Screening Visit.
9. Positive for opioids (unprescribed), cocaine, amphetamines, methadone, barbiturates, methamphetamine, or phencyclidine at the Screening Visit
10. History of malignancy or has received treatment for malignancy, other than treatment for basal cell or squamous cell carcinoma of the skin, within the previous 5 years
11. Positive for Hepatis B virus (HBV) or Hepatis C virus (HCV)
12. Known to be positive for human immunodeficiency virus (HIV)
13. Inability to undergo MRI (mild sedation may be allowed)
14. Involved directly or indirectly in the conduct and administration of this study as an Investigator, sub-investigator, study coordinator, or other study staff member, or the patient is a first-degree family member, significant other, or relative residing with one of the above persons involved directly or indirectly in the study
15. History of hypersensitivity to any of the excipients of NIDO-361

5.3 Lifestyle Restrictions

As noted in the inclusion criteria, participants and their partners of childbearing potential must practice true abstinence or use adequate methods of contraception. True abstinence is defined as refraining from heterosexual intercourse for the duration of the study. Female partner of childbearing potential, fertile male, and highly effective methods of contraception are defined below.

5.3.1 Female Partner of Childbearing Potential

A female partner is considered of childbearing potential (i.e., fertile) following the menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause.

5.3.2 Fertile Male

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

5.3.3 Highly Effective Methods of Contraception

Contraception methods that can achieve a failure rate of <1% per year when used consistently and correctly are considered highly effective birth control methods. Such methods are defined as one of the following:

- True abstinence, defined as refraining from heterosexual intercourse for the duration of the study, when in line with the preferred and usual lifestyle of the patient
- Biologically sterile or surgically sterile (i.e., the male participant has undergone effective surgical sterilization such as vasectomy) before entering the clinical trial and has obtained documentation of absence of sperm in his ejaculate

- Use of a combination of a condom in addition to having a female partner of childbearing potential use one of the following effective methods of contraception:
    - Oral and intravaginal combined (estrogen and progestogen containing) hormonal contraceptives
    - Oral, injectable, or implantable progesterone-only hormonal contraceptives associated with inhibition of ovulation
    - Intrauterine device or intrauterine hormone-releasing system
    - Bilateral tubal ligation/occlusion

5.4 Rationale for Exclusion of Specific Groups

Female participants will not be included in the study as NIDO-361 is intended for a disease that only affects males.

6 STUDY CONDUCT

6.1 Study Procedures

The Schedule of Assessments for the study is presented in Table 1 and Table 2.

6.1.1 Screening Period (Day -28 to Day -1)

During the Screening Period, patients will be assessed for study eligibility and prohibited medications will be discontinued if medically appropriate. Rescreening for participants who previously failed screening will only be permitted with approval from Sponsor. For all procedures and assessments to be performed at the Screening Visit, see Table 1 and Table 2.

The recording of AEs/concomitant medication will begin following consent and will continue through the Follow-up visit.

6.1.2 Treatment Period (Day 1 – Day 360)

On Day 1, patients will be randomized to receive a single oral dose of placebo (N=27) or NIDO-361 100 mg followed by 200 mg (N=27).

Patients will undergo procedures and assessments on the days and at the timepoints indicated in Table 1 and Table 2. For details on assessments and blood sample collection, see Section 6.2.

6.1.3 EOS (Day 374)

Patients will return to the clinic on Day 374 for follow-up assessments at the timepoints indicatedin Table 1 and Table 2.

6.2 Study Assessments

Sites should try to maintain the same sequence of assessments across visits for each patient and the same raters should be used across the visits for each patient to decrease variability as much as possible.

6.2.1 Medical History and Demographics

A general medical history will be obtained at the Screening Visit. The Investigator will assess information regarding any significant medical, surgical, psychiatric, and/or neurological conditions and treatments.

Demographic data will be collected and summarized.

6.2.2 Physical Examination

A complete physical examination will be performed at the timepoints described in the Schedule of Assessments. The physical examination will include (but is not limited to) an examination of general appearance; head, eyes, ears, nose, and throat; neck (including thyroid and nodes); cardiovascular, respiratory, gastrointestinal, renal, neurological, and musculoskeletal systems; and skin. In addition, the physical examination will include special attention to the motor system, upper and lower extremity measures of strength, tone, and reflexes, as well as ambulation.

6.2.3 Height, Weight, and BMI

The participant's height and weight will be measured at the timepoints described in the Schedule of Assessments. BMI will be calculated based on height and weight measurements.

6.2.4 Prior and Concomitant Medications

Prior medications are any ongoing medications at the Screening Visit with a start date before the first dose of study drug. Concomitant medications are any medications given in addition to the study drug. At each study visit, participants will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through end of the study), and all medications including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the electronic case report form (eCRF). Documentation must include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

Prior and concomitant medications in this study will be coded using version March 2022 or higher of WHODrug Global.

6.2.4.1 Excluded Medications

Use of prescription drugs, over-the counter drugs, and herbal supplements that are strong inhibitors of CYP1A2 within 1 week or 5-half-lives, whichever is more, prior to planned first drug administration and throughout the study is prohibited.

As mentioned in Section 2.1.3.2, the potential for drug-drug interactions with NIDO-361 is generally low, with the exception of CYP3A time dependent inhibition, UGT1A9, UGT2B17, P-gp and BCRP. It is not practical to provide an exhaustive list of all CYP3A, UGT, P-gp and

BCRP substrates. The Sponsor recommends that the label of a concomitant medication is consulted prior to drug administration. It is generally acknowledged that the magnitude of UGT inhibition is lower than what is observed with CYP450s.

Additionally, use of any medicines that are known to increase the risk of seizures are prohibited within 90 days prior to Day 1, throughout the study duration, and for 90 days after last study dose.

6.2.5 Vital Signs

Vital signs will include body temperature (oral, tympanic/aural, or axillary), blood pressure (systolic and diastolic), respiration rate, and heart rate. Vital sign measurements will be taken as per standard site practice, after the participant has rested quietly (either lying flat or sitting) for a period of at least 3 minutes. Vital signs will be collected according to the schedule shown in the Schedule of Assessments. As feasible, the same temperature measurement method (either oral, tympanic/aural, or axillary) should be used for all subsequent temperature measurements during the study for an individual participant. As feasible, the same position (either lying flat or sitting) should be used for all subsequent blood pressure measurements during the study for an individual participant. If the initial reading is high, the measurements will be repeated twice, and the average of the 3 readings will be used.

6.2.6 ECGs

ECG recordings will be obtained in triplicate in the supine position after the participant has rested comfortably for ≥5 minutes. At timepoints when plasma PK is also being collected, the ECG should be performed first, followed by vitals and PK blood collection.

6.2.7 EEGs

EEG recordings will be obtained in a sitting position and will normally last 20-40 minutes. EEGs will be performed at the timepoints noted in the Schedule of Assessments.

6.2.8 Urine Drug Screen

A urine drug screen for opioids, cocaine, amphetamines, methadone, barbiturates, methamphetamine, and phencyclidine will be performed at Screening Visit. Drug screen tests will be evaluated by a central laboratory.

6.2.9 Hepatitis (Hepatitis B Surface Antigen, HCV)

A hepatitis panel, including hepatitis B surface antigen and anti-HCV test will be performed at Screening Visit and analyzed by a central laboratory.

6.2.10 Pulse Oximetry

Pulse oximetry will be performed at the timepoints noted in the Schedule of Assessments.

6.2.11 Whole-body MRI

Whole-body MRI will be collected at the timepoints noted in the Schedule of Assessments. Whole-body MRI will be performed using integrated matrix coils (phased array) and non-contrast axial fat-water separated images will be obtained using 2-point Dixon sequences (T1-Dixon). Liver imaging for the MRI-PDFF assessment will also be performed during the same MRI session.

During the whole-body MRI, legs will be scanned at multiple axial stations to cover from iliac crest to ankles. The patient and coils will be repositioned for scanning of the torso and neck as well as the liver, after which the patient will again be repositioned for scanning each of the arms. The duration of the examination will be approximately 45 minutes.

The configuration of the sequences may differ between different scanner manufacturers and models, and the exact setting will be provided in the MRI scanning guide.

Water, fat, in-phase, and out-of-phase images will be reconstructed using a 3T scanners built in phase-sensitive reconstruction. The images will then be analyzed by AMRA® Researcher (AMRA Medical, Linköping Sweden).

Please refer to Study Operations Manual for more information.

6.2.12 2MWT and 6MWT

The 2MWT and 6MWT have been used as markers of disease progression. The walk test measures the distance a person can walk within 2 minutes or 6 minutes and is regarded as a proxy of neuromuscular abilities.

The 6MWT is relatively simple and cost-effective and it has been widely adopted as an outcome measure in several neuromuscular conditions. The 6MWT is traditionally considered a reliable marker of motor impairment and it has been used as a primary outcome measure in SBMA clinical trials and it reliably captures decline over time. The 2MWT is reliable and appears to correlate with the 6MWT. From a standing start, the participant is asked to walk for 2 minutes or 6 minutes as quickly as possible. Assistive devices, orthoses, and ankle branches are allowed. The distance traveled in 2 minutes or 6 minutes is recorded.

6.2.13 SBMAFRS

SBMAFRS is a validated functional rating scale developed from the Amyotrophic Lateral Sclerosis Functional Rating Scale to specifically address the disability profile of patients with SBMA (Hashizume et al 2015). It is a questionnaire-based scale that measures physical function in ADL and consists of five main domains measuring bulbar, upper-limb, lower-limb, truncal, and respiratory function. Each item has five responses options scoring 0 (worst) to 4 (normal). A higher score indicates better functioning.

6.2.14 Suicidality Assessment (Columbia-Suicide Severity Rating Scale)

The Columbia-Suicide Severity Rating Scale (C-SSRS) is an assessment tool used to assess the lifetime suicidality of a patient (C-SSRS at baseline) as well as any new instances of suicidality (C-SSRS since last visit). The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual/potential lethality. The C-SSRS consists of 2 forms: a form measuring symptoms at Screening (baseline/screening version) that includes a lifetime history and a form measuring symptoms since the last study visit ("since last visit" version). The baseline/screening form will be performed at the Screening Visit, and the "since last visit" form will be performed at all later time points, as described in the Schedule of Assessments (Posner et al 2011).

6.2.15 Handheld Dynamometer

A HHD will be used to provide an objective quantitative measurement of strength, which is a key hallmark of disease progression in patients with SBMA. For the HHD assessment, patients should be sitting in a hard-backed chair with armrests. Muscle strength will be tested using the HHD device. Standard positions for muscle and HHD placement will be specified in the Study Operations Manual. Measurements will be recorded in pounds. A value of 0 will be assigned to a given muscle if a patient cannot assume the testing position due to weakness.

Please refer to Study Operations Manual for more information.

6.2.16 Actigraphy-derived physical activity

Physical activity will be measured with a wrist-worn device made by ActiGraph throughout the study using standardized instructions.

The ActiGraph device is a small, lightweight, and non-invasive research-grade accelerometer-based wearable device that will be used to objectively assess free-living physical activity. The data from these devices will be used to assess and detect changes in physical activity intensity, upper arm movements and walking patterns.

Please refer to Study Operations Manual for more information.

6.2.17 TUG

The TUG will be used to assess mobility and to provide estimate on balance and risk of falling. Patients are asked to rise from a chair, walk 3 meters, turn around, return to the chair, and sit. The time that it takes to complete the task is recorded. Assistive devices, orthoses, and ankle braces are allowed. Interpretation: ≤ 10 seconds = normal, ≤ 20 seconds = good mobility, can go out alone, mobile without gait aid ≤ 30 seconds = problems, cannot go outside alone, requires gait aid. A score of ≥ 14 seconds has been shown to indicate high risk of falls (Podsiadlo 1991).

6.2.18 SF-36

The SF-36 questionnaire is a tool used to survey health status. The scale assesses eight health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions.

6.2.19 IIEF

The IIEF survey addresses the relevant domains of male sexual function (that is, erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction), is psychometrically sound, and has been linguistically validated in 10 languages. This questionnaire is often used in research or clinical settings and has demonstrated sensitivity and specificity for detecting treatment-related changes in patients with erectile dysfunction. The survey consists of 15 questions.

6.2.20 Clinical Laboratory Tests

Clinical laboratory safety testing and endocrinology tests will be collected at the timepoints described in the Schedule of Assessments. Samples will be collected non-fasting and analyzed at a central laboratory. The parameters to be assessed are presented in Table 3 and Table 4.

Table 3 Clinical Laboratory Safety Tests

Hematology	Chemistry	Urinalysis*
Complete blood count, including: • White blood cell count (with differential) • Red blood cell count • Hemoglobin • Hematocrit • Platelet count • Reticulocyte count • Mean cell volume (MCV) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean Platelet Volume • Red Cell DistributionWidth	• Sodium • Potassium • Phosphorus • Chloride • Bicarbonate • Blood urea nitrogen • Creatinine • Creatine phosphokinase • eGFR • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Alkaline phosphatase • Bilirubin (total and direct) • Total Protein • Globulin • Glucose • Calcium • Calcium (Adjusted) • Lactate Dehydrogenase (LD) • Gamma-glutamyl transferase (GGT) • Albumin • Anion Gap • Total Cholesterol • Low-density lipoprotein (LDL) Cholesterol • High-density lipoprotein (HDL) Cholesterol • Non-HDL Cholesterol • Triglycerides	• pH • Specific gravity • Protein • Glucose • Blood • Nitrite • Leukocyte esterase • Ketones • Bilirubin • Urobilinogen

*If a positive result for a urinalysis dipstick, sample should be sent for microscopy.

Table 4 Endocrinology Panel

Endocrinology Panel
• Luteinizing hormone • Follicle stimulating hormone (FSH) • Insulin-like Growth Factor (IGF1) • Dehydroepiandrosterone (DHEA) • Estradiol • Myoglobin (serum) • Total testosterone • Free testosterone • Sex hormone binding globulin • Prostate-specific antigen

6.2.21 PK/TE Assessments

6.2.21.1 PK Assessments

Plasma samples for analysis of exposure to NIDO-361 will be collected at the timepoints specified in the Schedule of Assessments. The date and time of the sample collection will be recorded. In order to better define the PK profile, the timing of the PK and TE sample collections may be altered based on emergent data.

Samples will be analyzed by a bioanalytical laboratory to determine concentrations of NIDO-361 using a validated method. Detailed instructions for sample collection, storage, processing, and shipping will be provided in the Laboratory Manual.

See Section 10.6 regarding the potential use of residual samples.

6.2.21.2 TE Assessments

Plasma samples will be collected at the timepoints noted in the Schedule of Assessments to assess changes from baseline in plasma proteins. Detailed instructions for sample collection, storage, processing, and shipping will be provided in the Laboratory Manual.

See Section 10.6 regarding the potential use of residual samples.

6.3 Discontinuation or Withdrawal

Participants are free to withdraw from the study or discontinue treatment with study drug at any time upon request without prejudice to their future medical care by the Investigator or at the study site. Participant participation in the study may also be stopped at any time at the discretion of the Investigator or at the request of the Sponsor, as described in Section 6.3.1.2. Participants who withdraw or discontinue from the study will no longer receive study drug.

6.3.1 Individual Participants

6.3.1.1 Discontinuation of Treatment

A participant must permanently discontinue treatment with the study drug for any of the following reasons:

- The participant is withdrawn from the study.
- The participant experiences a serious or intolerable AE (as defined in Section 8.1) that, in the Investigator's opinion, requires treatment discontinuation.
- A change in the participant's medical condition not consistent with the protocol requirements or justifies withdrawal from the study or study drug.

If a participant discontinues treatment, they will be encouraged to remain in the study to be monitored and to complete all study-related procedures, unless consent is withdrawn. Participants who discontinue treatment due to an AE may require longer follow-up per Investigator and/or Medical Monitor discretion.

6.3.1.2 Withdrawal From Study

Participants must be withdrawn from the study for any of the following:

- Participant's withdrawal of consent
- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation
- Termination of the study by the Sponsor

Any participant for whom consent to participate in the study is withdrawn will be removed from further treatment and study observation immediately upon the date of request. These participants should be encouraged to complete the Early Termination (ET) study procedures and observations prior to the time of withdrawal.

6.3.1.3 Replacement of Participants

Participants will not be replaced.

6.3.1.4 Participants Lost to Follow-up

Participants who fail to return for final assessment will be contacted by the site in an attempt to have them comply with the protocol. A minimum of three documented contact efforts should be made on different days over the course of two weeks. If the participant is unreachable by telephone, a registered letter will be sent to the participant, requesting him to contact the study site. If contact with the participant is not established after all above attempts, this participant will be considered lost to follow-up.

7 INVESTIGATIONAL PRODUCT

7.1 Dose and Investigational Drug/Placebo Administration

7.1.1 Identity of Investigational Drug

7.1.1.1 Active Treatment – NIDO-361

The drug products are tablets containing 100 mg of NIDO-361. NIDO-361 tablet is an immediate release, white to off-white, oval shaped tablet with no markings for oral administration. Please refer to the IB for further details on the excipients.

7.1.1.2 Placebo

The NIDO-361 placebo tablets are white to off-white, oval shaped tablets with no markings for oral administration. Excipients commonly used for oral pharmaceutical formulations were chosen for use in the placebo. Please refer to the IB for further details on the excipients.

7.1.2 Administration of Investigational Drug

Investigational drug will be administered orally once a day at flat-fixed doses (not by body weight or body surface area). Details on dose preparation are detailed in the Pharmacy Manual.

Participants should take their dose at approximately the same time (24 ±4 hours interval on each dayof dosing) with a glass of water (approximately 240 mL or 8 ounces). Study treatment should be taken in the morning. Tablets should be ingested whole and should not be chewed or crushed. Patients should take the investigational drug on an empty stomach at least 1 hour before or 2 hours after a meal. Water is allowed during this period.

Participants will be required to record all missed doses in their participant handbook and return unused medication and bottles to the study team for compliance checks.

7.2 Management of Clinical Supplies

7.2.1 Investigational Drug Packaging and Storage

NIDO-361 and placebo tablets are supplied in high-density polyethylene (HDPE) bottles containing 1g HDPE desiccant canister and closed via induction sealing with a child-resistant polypropylene cap.

Each bottle of NIDO-361 or placebo will contain 30 tablets. A booklet-panel label that includes pertinent drug and study information will be affixed to each bottle of NIDO-361 or placebo.

All study drugs will be transported, received, stored, and handled in accordance with the container and product label, the instructions supplied to the pharmacy manual, relevant institution's standard operating procedures (SOPs), and applicable regulations. Study drugs will be stored at 15-25°C in a locked area accessible only to the pharmacy personnel.

Further details on drug packaging, labeling, and storage are provided in the Pharmacy Manual.

7.2.2 Study Drug Accountability

Drug supplies will be counted and reconciled at the site before being destroyed at site's pharmacy.

The Investigator or designee must ensure that the Sponsor-supplied drug is used in accordance with the protocol and is dispensed only to the participants enrolled in the study. To document appropriate use of Sponsor-supplied drug, the Investigator or designee must maintain records for all Sponsor-supplied drug delivery to the site, site inventory, dispensation, and use by each participant and destruction.

Upon receipt of the Sponsor-supplied drug, the Investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, the Investigator or designee should acknowledge the receipt of the shipment. If there are any discrepancies between the packing list versus the actual product received, the Sponsor must be contacted to resolve the issue. The packing list should be filed in the Investigator's essential document file.

The Investigator or designee must maintain 100% accountability for all Sponsor-supplied drugs received and dispensed during his or her entire participation in the study. The Investigator or designee must record the current inventory of all Sponsor-supplied drugs on a Sponsor-approved drug accountability log. The Investigator or designee will be responsible for maintaining accurate records of the receipt of drug supplies, including dates of receipt. In addition, accurate records will be kept regarding when each treatment is administered, which participants received treatment, and the name of the personnel administering the treatment. Reasons for departure from the expected treatment regimen must also be recorded. Only trained site staff are permitted to treat study participants.

Prior to site closure or at appropriate intervals, a representative from the Sponsor or its designee will perform Sponsor-supplied drug accountability and reconciliation before Sponsor-supplied drugs are destroyed by the site's pharmacy or returned to depot. A study monitor will review the accountability records.

7.3 Treatment Assignment and Bias Minimization

7.3.1 Method of Assigning Patients to Investigational Drug or Placebo

Patients who qualify according to all the inclusion and exclusion criteria, will be randomized into the study. Treatment will be assigned through randomization performed using a centralized IRT system.

7.3.2 Randomization Strategy and Procedure

Subjects will be registered at the Screening Visit and randomized only after all baseline

assessments have been completed and the Investigator has verified that the subjects are eligible per criteria in Section 5. No subject may begin treatment prior to assignment of a unique identification number (registration) and randomization. Any subject identification numbers or randomization schedule assignments that are assigned will not be reused even if the subject does not receive treatment. Rescreened subjects will be assigned a new number.

Subjects will be randomized to receive NIDO-361 or placebo in a 1:1 ratio using a static permuted block randomization schedule. No criteria will be used to stratify the randomization. Subjects who withdraw from the study may not be replaced.

7.3.3 Blinding

This is a randomized, double-blind, placebo-controlled study. All study staff and health care professionals performing study assessments and procedures should remain blinded to a patient's treatment assignment and only have access to information necessary to carry out their responsibilities.

To maintain the study blind, it is imperative that subject treatment assignments are not shared with the subjects, their families, or any member of the blinded study team, either at the study site or at Sponsor or its representatives, except the unblinded [redacted] safety staff and designated unblinded statistician for duration of the study until database lock.

7.3.4 Unblinding Procedures

7.3.4.1 Unblinding for Medical Emergency

A participant's treatment assignment should remain blinded until the end of study. However, in the event of a medical emergency when the medical treatment of the participant depends on knowing the study treatment the participant received, the treatment blind may be broken immediately and without restrictions by the Investigator. Access for emergency unblinding will be provided through the IRT. The Investigator must document the reasons for unblinding in the participant's source documents. The Investigator is strongly advised not to divulge the participant's treatment assignment to any individual not directly involved in managing the medical emergency nor to personnel involved with the analysis and conduct of the study.

7.3.4.2 Recording the Unblinding

If an unblinding occurs, the date on which the code was broken, together with the identity of the person responsible for breaking the blind, must be documented in the participant's source documents. The unblinded treatment information will not be disclosed to the Sponsor. In consultation with the Medical Monitor and the Sponsor, the participant may be withdrawn from the study, if the blind is broken.

The documentation should include, but is not limited to, the following information:

- Participant information
- Reason for unblinding
- Date and time of unblinding
- Name of the person requesting/responsible for the unblinding

8 SAFETY MONITORING

8.1 Definitions of Adverse Events

- **AE** – An AE is any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
- **Intolerable AE**: - An AE of any severity or causality that in the Investigator's opinion requires permanent treatment discontinuation.
- **TEAE** – an event not present before exposure to study treatment or any event already present that worsens in either intensity or frequency after exposure to study treatment.
- **SAE** – An event is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:
  - Death
  - A life-threatening AE (An event is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient or participant at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.)
  - Inpatient hospitalization or prolongation of existing hospitalization
  - A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
  - A congenital anomaly/birth defect
  - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- **Causality or relatedness** – The causality of each AE should be assessed and classified by the Investigator as "unrelated," "unlikely," "possible," "probable," or "definite." An event is considered related if there is a reasonable possibility that the event may have been caused by the product under investigation (i.e., there are facts, evidence, or arguments to suggest possible causation).
- **Adverse reaction** – An adverse reaction is any AE caused by a drug.
- **Suspected adverse reaction** – A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.
- **Unexpected** – An event is considered unexpected if it is not listed in the Reference Safety Information section of the IB, is not listed at the specificity or severity that has been observed, or, if an IB is not required or available, is not consistent with the risk information described in the General Investigational Plan. Unexpected also refers to

events that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

- **Severity or intensity** – The severity of each AE will be assessed as described below and reported in detail as indicated on the eCRF:
  - Mild: awareness of sign or symptom but easily tolerated, causing minimal discomfort, and not interfering with normal everyday activities
  - Moderate: sufficiently discomforting to interfere with normal everyday activities
  - Severe: incapacitating and/or preventing normal everyday activities
  - Life-Threatening: life-threatening consequences; urgent intervention indicated
  - Death

8.2 Documenting Adverse Events

All AEs reported or observed during the study from the point of informed consent, including AEs resulting from concurrent illnesses or reactions to concurrent medications will be recorded on the AE page in the eCRF and in the participant's source documents. The eCRFs used to document AEs are designed to help ensure this information is collected in a standard way. Information to be collected includes event term, date and time of onset, date and time of resolution, Investigator-specified assessment of severity and relationship to study drug, action taken with respect to study drug, seriousness, any required treatment or evaluations, and outcome. All AEs will be followed until the ET or End of Study (EOS) visit, at a minimum.

The site will be provided with completion guidelines for the eCRF, which will further guide them on how to record the data, including AEs. The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be used to grade all AEs.

Any medical condition that is present at the time that the participant signs informed consent but does not worsen should not be reported as an AE. However, if it worsens at any time during the study, it should be recorded as an AE.

In addition to the observations of the participant, AEs identified from any study data (e.g., laboratory values, physical examination findings, or ECG changes) or identified from review of other documents that are considered clinically significant will be documented on the AE page in the eCRF.

AEs will be assessed at each visit by direct questioning as well as elicited from physical examination by site staff. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

8.2.1 Timeframe for Collection

AEs will be recorded from the time informed consent is obtained through the study follow-up. If an AE is ongoing at the ET or EOS visit, every reasonable attempt should be made to follow and appropriately treat the participant until the AE resolves or until the Investigator deems the AE to be chronic or stable.

In the event that a participant discontinues from the study and has an ongoing AE at the time of discontinuation or is withdrawn from the study because of an AE, the participant should be followed and appropriately treated until the AE resolves or until the Investigator deems the AE to be chronic or stable.

8.2.2 Classification of Events

AEs will be classified according to System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA)Version 25.0 or later.

8.3 Reporting SAEs

Any AE that meets SAE criteria (Section 8.1) must be reported to the Sponsor and/or its designee immediately (within 24 hours) after the site personnel first learn about the event using the SAE Report Form provided for the study. Regardless of causality, all SAEs that occur during the study (from the time the participant signs the ICF to the ET/EOS visit) must be reported to the Sponsor and recorded on the AE page of the participant's source document/medical file.

The initial report should include at least the following information:

- Study number
- Participant's identification number
- Description of the event
- Date and time of onset of the event
- Seriousness criteria
- Causality assessment to study drug

If follow-up is obtained or requested by the Sponsor and/or designee, the additional information should be emailed on an SAE Report Form to the Sponsor in a timely manner according to the procedures outlined above. Copies of the discharge summaries, consultant reports, autopsy reports, and any other relevant documents may also be requested.

The Investigator will be responsible for reporting all applicable SAEs to the Ethics Committee (EC) / Institutional Review Board (IRB) as per local requirements. The Sponsor will be responsible for reporting to the regulatory authorities and Central EC/IRB, as per local requirements. All suspected unexpected serious adverse reactions (SUSARs) will be reported unblinded through to the EudraVigilance system.

8.3.1 SAE Contact Information

Serious adverse event contact information is provided below.

[redacted]

8.4 Overdose or Misuse

The study drugs may only be dispensed by trained study staff. Administration will be performed in accordance with the IB and instructions in a study-specific manual. Any incidence of overdose should be recorded as an SAE.

No clinical data are available regarding overdose with NIDO-361. As with any agent, if overdose

occurs, general supportive measures and close observations should be instituted.

8.5 Pregnancies

Subjects should not impregnate their partners during the study and for 12 weeks after their last dose of study drug. If the female partner of a study subject becomes pregnant, the study subject should inform the Investigator within 24 hours.

All pregnancies of female partners, who provide specific informed consent, will be followed through the outcome and the infant will be followed for 1 year after birth. The Investigator or study site staff must report the outcome of the pregnancy to [redacted] Clinical Safety (Section 8.3.1). Congenital abnormalities and birth defects in the offspring of study subjects should be reported as an SAE if conception occurred during the study treatment period.

9 STATISTICAL METHODS

The objectives of the study and the endpoints to be analyzed are listed in Section 3.

9.1 Demography and Baseline Disease Characteristics

Demographics and baseline data will be summarized by treatment group with summary statistics (mean, standard deviation, median, and range) or with frequency distributions.

9.2 Efficacy and Pharmacodynamics

9.2.1 Analysis Population

The modified intent-to-treat population, defined as all participants who were randomized and received at least 1 dose of study treatment (NIDO-361 or placebo), will be used for the efficacy analyses. For each endpoint, additional conditions may apply to the definition of the population for the analysis. Participants will be analyzed in the groups to which they were randomized.

9.2.2 Methods of Analysis

Summary statistics will be presented. For continuous endpoints, summary statistics will generally include: number of participants with data, mean, standard deviation, median, and range. For categorical endpoints, this will generally include: number of participants randomized or dosed, number with data, and the percent of those with data in each category. Statistical testing for efficacy endpoints will be made between NIDO-361 regimen and placebo. All statistical tests will be 2-sided.

9.2.2.1 Analysis of Clinical Effects Endpoints

The trajectory from baseline of the clinical effects endpoints will be compared between randomization groups using generalized linear mixed-effects models. The models will include a random intercept for patient and the following fixed effects: factor variables for time, randomization group, and the interaction between time and randomization group. For each endpoint, the null hypothesis that there is no interaction between time and randomization group will be tested using a two-sided type III test of fixed effects at the 0.05 level. Model-estimated means and contrasts to placebo will be provided with 95% confidence intervals for each combination of time and randomization group.

9.3 Pharmacokinetics

The population for PK analysis is defined as all participants who were randomized, were dosed with study treatment, and had at least 1 measurable NIDO-361 concentration in plasma.

The population PK characteristics of NIDO-361 will be determined by a nonlinear mixed effects approach. Covariates that might influence the disposition of NIDO-361 (e.g., body weight, age) will be evaluated and the potential exposure-response relationships will be explored.

9.4 Safety Analysis

9.4.1 Analysis Population

The safety population is defined as all participants who received at least 1 dose of study treatment (including placebo and NIDO-361).

9.4.1.1 Adverse Events

Only TEAEs will be presented in the summary tables. Treatment emergent is defined as having an onset date that is on or after the start of study treatment, or as worsening after the start of study treatment. Incidence of TEAEs will be summarized by treatment groups, overall, by severity, and by relationship to study treatment for the 12 months of study. The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class. AEs will be coded using the MedDRA.

9.4.1.2 Clinical Laboratory Results

Laboratory data will be summarized using shift tables. Shifts from baseline to high/low status for hematology and blood chemistry parameters, and shifts from baseline to high/positive status for urinalysis will be presented. In addition, the shift from baseline to the maximum post-baseline value and the shift from baseline to the minimum post-baseline status will be presented for each laboratory test by treatment group. Also, summaries of laboratory values categorized based on common toxicity criteria grade will be created. Summary statistics for actual values and change from baseline will also be presented for quantitative laboratory data.

9.4.1.3 Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities.

9.4.1.4 ECG

The number and percentage of participants with shifts to categorical values (abnormal not AE, or abnormal AE) will be summarized by treatment group.

9.5 Sample Size Considerations

The study's sample size is based, in part, on results from an observational study (Study NDO-000-001) as well as published literature.

Under the primary analysis linear mixed model, a sample size of 27 participants per treatment group will have approximately 80% power to detect a 50% slowing (in the treatment group relative to control) of decline in total LMV over 48 weeks. This power calculation is based on a two-sided test with a final significance level of 0.05. The *longpower* R package is used to estimate the sample size using a mixed-effect model with parameters estimated from 26 participants with LMV measurements (18 of whom had a 26-week visit, 6 had a 52-week visit, and 1 had a 78-week visit). The estimated slope used in the calculation is -0.041 with standard error of 0.008.

10 ETHICAL CONSIDERATIONS

10.1 GCP

The study will be conducted according to the study protocol and SOPs that meet the guidelines provided by the ICH for GCP in clinical studies and any other applicable local regulatory requirements.

10.2 IRBs/ECs

Federal regulations and ICH guidelines require that approval be obtained from an IRB/ EC before participation of human participants in research studies. Before study onset, the protocol, ICF, and advertisements to be used for the recruitment of study participants and any other written information regarding this study to be provided to the participant must be approved by the IRB/EC. The documentation of all IRB/EC approvals and of the IRB/EC compliance with ICH guideline E6(R2): GCP will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB/EC approvals should be signed by the chairman or designee and should identify the IRB/EC name and address, the clinical protocol by title or protocol number or both, and the date of approval or when the favorable opinion was granted. The study protocol, appendices, and ICFs must be approved by the IRB/EC.

The Investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding one year or as otherwise specified by the IRB/EC, and where applicable, the institution with written reports on any changes significantly affecting the conduct of the study or increasing the risk to participants.

10.3 ICFs

Signed ICFs in compliance with the Declaration of Helsinki, current ICH and GCP guidelines, US Title 21 Code of Federal Regulations Part 50, and applicable local regulations will be obtained from each participant before enrolling the participant in the study or performing any unusual or nonroutine procedure that involves risk to the participant.

ICF templates will be provided by the Sponsor or designee. If any institution-specific modifications to study-related procedures are proposed or made by the site, the ICF(s) must be reviewed by the Sponsor or its designee or both before IRB/EC submission. Once reviewed, the ICF(s) will be submitted by the Investigator to his or her IRB/EC for review and approval before the start of the study. If the ICF(s) is revised during the course of the study, all actively participating participants must sign the revised form.

Before Screening, each prospective participant will be given a full explanation of the study and be allowed to read the approved ICF. Once the Investigator is assured that the participant understands the implications of participating in the study, the participant will be asked to give consent to participate in the study by signing the appropriate ICF.

The Investigator will retain the signed original ICF(s) and give a copy of the signed original ICF(s) to the participant.

10.4 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as required by law or as necessary for monitoring and auditing by the Sponsor, its designee, applicable regulatory agencies, or the IRB/EC.

The Investigator and all site staff involved with this study may not disclose or use for any purpose other than the performance of the study any data, record, or other unpublished confidential information disclosed to those individuals for the purpose of the study.

The conduct of this study and the processing of any personal data collected from each participant (or from a participant's healthcare professional or other relevant third-party sources) by the Sponsor or its designee, the site and the Investigator for use in the study will fully adhere to the requirements set out in applicable data protection and medical privacy laws or regulations, including, without limitation, the General Data Protection Regulation (GDPR) EU 2016/679. The Sponsor or its designee will ensure that at all times it has an appropriate legal basis for processing personal data under applicable data protection law. Site-based organizational and technical arrangements to avoid unauthorized access vary by site but all include access-controlled/access-limited document control and technical solutions including passwords and security control measures to protect study-specific data, both in paper and electronic format.

The Investigators will provide coded data to the Sponsor or its designee, which does not reveal the patient's name, full date of birth, or any other information which can identify the patient. All personal information will be replaced with a Subject Identification Code (SID) before any information leaves the study sites.

The study site will promptly (in no more than three days) report any data breaches that might occur to the Sponsor or its designee. The Sponsor has implemented a Business Practice to address data breaches that complies with the requirements of applicable laws and regulations. The data breach procedures in the Business Practice provide specific responses to actual or potential threats and involve investigation, containment and mitigation. If applicable, the authorities and the data participants will be notified of a data breach, within the required timeframes of the applicable laws and regulations.

10.5 Disclosure

The Sponsor will post results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Sponsor's Policy/Standard, applicable laws, and/or regulations.

10.6 Biological Specimens and Data

Any residual samples remaining after the protocol-defined analysis has been performed may be used only by the Sponsor for additional exploratory analysis. Given the exploratory nature of the work, the analytical method used for those assessments will not be validated. As such, the results from this exploratory analysis will not be included in the clinical study report.

Samples will only be used by the Sponsor and/or a contracted vendor for research related to the development of NIDO-361 and stored for a maximum of ten years. All biological material will be stored and secured in a way that ensures that unauthorized access is prohibited, and the samples

are not lost, deteriorated, or destroyed accidentally or illegally.

11 OVERSIGHT

11.1 Data Safety Monitoring Board

An unblinded, independent DSMB consisting of at least three members will review unblinded, aggregate safety data periodically. The DSMB is responsible for reviewing unblinded available safety data and steady state exposure data after 24 hours and 30 days of treatment to inform dose escalation to the RP2D of 200 mg. Throughout the study, all aggregate safety data will be reviewed periodically and on an ad hoc basis by the DSMB. The DSMB will review any SAEs that occur in order to recommend whether dosing at the current dose level should continue or if a lower dose is recommend. In addition, if TEAEs occur that meet the stopping criteria, the DMSB also will review the safety data and determine whether to recommend proceeding with dosing the current dose level or if a lower or higher dose level is recommended. Further details regarding the DSMB, including committee membership, will be provided in a DSMB Charter.

11.2 Quality Control and Assurance

11.2.1 Monitoring

Monitoring details describing strategy, methods, responsibilities, and requirements are provided in the Monitoring Plan. Monitoring and auditing procedures developed by the Sponsor or designee will be followed in order to comply with ICH GCP guidelines.

During the study, a monitor from the Sponsor or designee will have regular contact with the study site. Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

11.2.2 Audits

The Investigators and study sites involved in the study will provide Sponsor (or its designee) and/or regulatory agencies direct access to all study records for study-related audits.

11.2.3 Protocol Deviations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the IRB/EC. A major protocol deviation is any deviation that impacts the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being.

The Investigator or designee must document and explain any protocol deviation in the participant's source documentation. The Investigator may implement a deviation from the protocol to eliminate the immediate hazard to study participants without prior IRB/EC approval. As soon as possible after such occurrence, the implemented deviation, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/EC for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required. Any deviation from the study protocol that is due to coronavirus disease 2019 considerations should be noted as such.

Protocol deviations will be documented by the clinical monitor in the clinical study management

system and on monitoring reports throughout the course of monitoring visits. Investigators will be notified in writing by the monitor of deviations. As required by local regulatory authorities, the Investigator will notify the IRB/EC of any applicable protocol deviations in a timely manner.

11.2.4 Records

11.2.4.1 Data Capture and Management

Participant data will be captured in an electronic data capture system provided by the Sponsor or designee. Data will be entered directly from the source documents to the eCRFs following the eCRF Completion Guidelines. All source documents should be completed in a neat and legible manner to ensure accurate interpretation of data. The Investigator is responsible for ensuring that the data entered on the eCRFs are accurate and complete and all data are entered in a timely manner.

The final eCRF data and audit trails will be archived in an electronic media.

11.2.4.2 Source Documentation

The Investigator and study site must maintain accurate documentation (source data) that supports the information entered in the eCRF.

11.2.4.3 Records Retention

The Investigator will maintain all essential documents necessary for the conduct of the study per ICH E6(R2) requirements which will be updated by the site throughout the study. The essential documents must be available for review by the monitor, be ready for Sponsor audit as well as for inspection by health authorities during and after the study. If archiving of the study site file is no longer possible at the site, the Investigator must notify the Sponsor.

The Investigator/study site will retain essential documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region for at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. However, these documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. No records may be transferred to another location or party without prior written consent of the Sponsor.

11.2.5 Considerations Due to COVID-19

Due to the COVID-19 endemic, it is possible that modifications to the planned schedules of assessments may be necessary in response to the local mandates, site closures, quarantines, travel limitations, etc. The following guidelines should be followed to ensure compliance in situations where trial conduct may need to be modified in response to the COVID-19 endemic.

Screening Activities: Screening activities may continue as long as local and institutional guidelines permit and if the protocol can be followed using the protocol allowed visit windows. If this cannot be achieved, sites should temporarily halt screening new patients until local and institutional restrictions have been lifted.

Informed Consent Forms: If the ICF cannot be signed in person due to COVID-19 restrictions, or in the case of re-consent due to study changes, the Investigator may review the ICF via video or phone call to the patient, in the presence of an impartial witness. Either a photograph of the signed

ICF or a witness attestation should be filed in the medical record if a signed copy of the form cannot be obtained from the patient. In the event a photograph of the ICF is used, an attestation should be made in the medical record by the person entering the form as to how the photograph was obtained. A certified electronic or paper ICF is preferred and should be collected and archived when possible.

Active Study Patients: Study dosing may continue as long as local and institutional guidelines permit, and safety monitoring is possible. If patients cannot be seen in clinic due to shelter-in place orders or institutional guidance, the Investigator should temporarily discontinue administration of study drug and complete study visits that are amenable to remote or local assessments. For study visits with assessments that can be performed locally, the Investigator should make every attempt to have a local laboratory perform the tests, or assess whether a home health service is available to collect samples at a patient's home by a trained nurse/phlebotomist.

11.3 Study Termination or Study Site Closure

Although the Sponsor has every intention of completing the study, the Sponsor may terminate the study or close an individual study site. Reasons for terminating a study or closing a site may include, but are not limited to, the following:

1. The research can no longer meet its stated scientific purpose, and this assessment has been confirmed by the medical ethical review committee, which has given a positive assessment of the research.
2. Severe noncompliance to this protocol as judged by the Investigator and/or the Sponsor
3. Due to unforeseen circumstances that prevent continuation of the research (e.g., financial issue)

The end of the study is defined as the date on which the last participant completes the last visit.

Upon completion or termination of the study, the study monitor will conduct site closure activities with the Investigator or site staff (as appropriate) in accordance with applicable regulations, ICH GCP, and SOPs.

12 PUBLICATION POLICY

The Sponsor has proprietary rights to all information generated from this study and reserves the right to use it in any manner it deems appropriate, including but not limited to regulatory submissions, annual reports, and other scientific or business affairs of the company.

After completion of the study at all sites, Sponsor will prepare a clinical study report according to ICH Structure and Content of Clinical Study Reports E3 (ICH E3).

All information provided regarding the study, as well as all information collected/documented during the course of the study, is confidential. The Sponsor reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per the Sponsor's publication strategy. Inclusion of the Investigator in the authorship of any multicenter publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting, and/or critically revising any manuscript(s) derived from the study. The Investigator acknowledges that the study is a multicenter study and agrees that any publication by the Investigator of the results of the study conducted at her/his research site shall not be made before the first multicenter publication. In the event there is no multicenter publication within [12/15/18] months after the study has been completed or terminated at all study sites and all data has been received, the Investigator shall have the right to publish the results of the study at their site, subject to the notice requirements described herein and subject to acknowledgement of the Sponsor as appropriate. The Investigator shall provide the Sponsor with 60 days to review a manuscript or any poster presentation, abstract or other written or oral material that describes the results of the study. Sponsor will review for purposes of determining if any confidential or patentable information is disclosed thereby and, if the Sponsor requests, the Investigator will delay any publication or presentation an additional 60 days to permit the Sponsor to seek patent protection. Sponsor may also comment on any proposed publication which comments will be considered by Investigator in good faith but Investigator is under no obligation to incorporate those suggestions.

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