Clinical Study Protocol	
EudraCT No.	2020-006053-22
Investigational Medicinal Product	NLX-112
Sponsor study code	NLX-112-DYS-101
Protocol Version and Date	Final version 3.1; 07MAR2022

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE SAFETY, TOLERABILITY AND PRELIMINARY EFFICACY OF NLX-112 VERSUS PLACEBO IN LEVODOPA-INDUCED DYSKINESIA IN PARKINSON'S DISEASE

Phase	IIa
Indication	Levodopa-induced dyskinesia in Parkinson's disease patients
Test product and dose	NLX-112, 2 mg/day
Unique ingredient identifier (UNII)	RAT9OHA1YH
Sponsor signatory	[redacted]
Coordinating Investigator	[redacted]
Clinical study management	Clinical Trial Consultants AB (CTC AB) Dag Hammarskjölds väg 10B SE-752 37 Uppsala, Sweden

1 STUDY SYNOPSIS

Study title A Randomized, Double-blind, Placebo-controlled Study to Assess the Safety, Tolerability and Preliminary Efficacy of NLX-112 versus Placebo in Levodopa-induced Dyskinesia in Parkinson's Disease	
Study code NLX-112-DYS-101	
Planned study period Q3 2021 to Q4 2022	**Phase of development** IIa
Principal Investigator [redacted] ASC Torsplan, Stockholm, Sweden	
Study design This is a double-blind, randomized, placebo-controlled Phase 2a study evaluating the safety, tolerability, and preliminary efficacy of up to 2 mg/day (1 mg BID) of NLX-112 versus placebo in patients with moderate to severe L-DOPA induced dyskinesia (LID) in Parkinson's disease (PD). NLX-112 will be up-titrated to either 2 mg/day or to the highest well-tolerated dose less than 2 mg/day over 4 weeks, maintained at the well-tolerated dose for an additional 2 weeks, and then down-titrated over 2 weeks.	
Objectives Primary objective To evaluate the safety and tolerability of NLX-112, titrated up to a maximum of 2 mg/day, compared to placebo during 8 weeks of daily treatment in PD patients with LID. Secondary objective To assess the preliminary efficacy of NLX-112 treatment in reducing troublesome LID. Exploratory objectives To assess the preliminary efficacy of NLX-112 treatment in improving selected non-motor symptoms of PD, including pain, bladder function, sleep function, mood and quality of living with PD. To collect blood samples for potential NLX-112 plasma concentration analysis.	
Endpoints Primary endpoints • Frequency, intensity and seriousness of adverse events (AEs) • Clinically significant changes from baseline in electrocardiogram (ECG), vital signs, safety laboratory parameters and physical examinations. • Suicidal ideation/behavior as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS).	

Secondary endpoints

- Change from baseline at the final efficacy clinic visit (Day 42) in the Unified Dyskinesia Rating Scale (UDysRS) total score [Timeframe: Baseline to Day 42]. Patients will be challenged with 150% of their standard L-DOPA dose (maximum L-DOPA dose 250 mg) 30 minutes prior to the first UDysRS assessment.
- Change from baseline in UDysRS total score at Day 28, after a 150% L-DOPA dose challenge.
- Change from baseline in total objective score (Parts III, IV) of the UDysRS at Day 28 and Day 42, after a 150% L-DOPA dose challenge.
- Change from baseline in ON Time Without Troublesome Dyskinesia (ON Without Dyskinesia plus ON With Non-troublesome Dyskinesia) based on a PD Home Dyskinesia Diary.
- Change from baseline in Unified Parkinson's Disease Rating Scale (UPDRS) scores (Part III, motor examination).
- Change from baseline in UPDRS combined scores (Parts I, II, III and IV).
- Clinical Global Impression of Change (CGI-C) in overall PD symptoms
- Change from baseline in dyskinesia scores measured by the Kinesia 360 (Great Lakes Neurotechnologies, Inc) wearable dyskinesia assessment system.

Exploratory endpoints

- Change from baseline in the King's Parkinson's Disease Pain Scale (KPPS) total score and in each of the 7 pain domain sub-scores.
- Change from baseline in the Parkinson's Disease Questionnaire (PDQ39) total score and domain scores.
- Change from baseline in the Hospital Anxiety Depression Scale (HADS)
- Change from baseline in the International Consultation on Incontinence Questionnaire (ICIQ) Overactive Bladder Module (ICIQ-OAB) total score.
- Change from baseline in the Epworth Sleepiness Scale (ESS).
- Plasma concentrations of NLX-112.

The NLX-112 plasma concentration analysis may only be performed if the Sponsor deems it necessary to answer any questions regarding compliance. The outcome of the results may not be reported in the clinical study report (CSR).

Number of patients planned

A total of 24 patients will be randomized in the study. Patients will be recruited at 5 clinical sites, with an average of 4 to 6 patients per site.

To account for potential drop-outs, additional patients may be included in the study. For replacements of patients who discontinue from the study.

Diagnosis and main eligibility criteria

Inclusion criteria:

1. Patient is 30 – 85 years old (inclusive) with a diagnosis of idiopathic PD according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnosis criteria.

2. PD patient is stably and optimally treated with L-DOPA; other anti-PD treatments are allowed if used for at least 4 weeks of previous continuous treatment.

3. Patient agrees to be challenged with 150% of their normal L-DOPA dose (maximum L-DOPA dose 250 mg) 30 minutes prior to efficacy assessments at baseline (Visit 2) and at the 2 efficacy clinic visits (Visits 6 and 7).

4. PD patient exhibits troublesome peak-dose LID, confirmed by a score of at least 1 on part IV, item 33 (disability) of the Unified Parkinson's Disease Rating Scale (UPDRS) at screening (Visit 1) and at Day 1 (baseline, Visit 2).

5. At least 90 minutes in total for each 24-hour period during 2 days are indicated as "ON with troublesome dyskinesia" (according to the PD Home Dyskinesia Diary) prior to Day 1 (baseline, Visit 2).

6. Patient (and/or caregiver) demonstrates ability to accurately complete the PD Home Dyskinesia Diary entries during the screening visit.

7. Patient can read well enough to understand the informed consent document and other subject materials.

8. Female patients of child-bearing potential must have a negative urine pregnancy test at screening (Visit 1) and on Day 1 (Visit 2), must agree to avoid pregnancy during the study, and must practice abstinence (only allowed when this is the preferred and usual lifestyle of the subject) or must agree to use a highly effective method of contraception with a failure rate of < 1% to prevent pregnancy (combined [oestrogen and progestogen containing] hormonal contraception associated with inhibition of ovulation [oral, intravaginal, transdermal], progestogen-only hormonal contraception associated with inhibition of ovulation [oral, injectable, implantable], intrauterine device [IUD] or intrauterine hormone-releasing system [IUS]) starting from 4 weeks prior to administration of the study drug and continuing during the course of the study until 4 weeks after last after IMP administration. Female subjects must agree to refrain from donating eggs from the date of dosing until 3 months after dosing with the IMP. Their male partner must agree to use a condom during the same time frame if he has not undergone vasectomy.

Females of non-childbearing potential are defined as pre-menopausal females who are sterilised (tubal ligation or permanent bilateral occlusion of fallopian tubes); or females who have undergone hysterectomy or bilateral oophorectomy; or post-menopausal defined as 12 months of amenorrhea (in questionable cases a blood sample with detection of follicle stimulating hormone [FSH] 25-140 IE/L is confirmatory).

Male patients must be either vasectomised, consent to use condom or practice sexual abstinence to prevent pregnancy and drug exposure of a partner and refrain from donating sperm from the date of dosing until 3 months after dosing with the IMP. Their female partner of child-bearing potential must use highly effective contraceptive methods with a failure rate of < 1% to prevent pregnancy (see above) during the same period.

Exclusion criteria:

1. Patient has severe PD with a Hoehn and Yahr stage = 5.

2. Patient has unstable medical status, prior brain surgery against tumors or hemorrhage (excluding deep brain stimulation [DBS], i.e., DBS patients will be allowed to be enrolled) or is scheduled to receive surgery during the trial period.

3. Patient has orthostatic hypotension: a decrease in systolic blood pressure (at least 20 mm Hg) or diastolic blood pressure (at least 10 mm Hg) within 3 minutes of the patient standing up, compared to pressures obtained while in a sitting position for at least 5 minutes. At screening and baseline visits (Visit 1 and Visit 2), vital signs to assess orthostatic hypotension will be conducted in triplicate, 15-20 minutes apart, with the average of the 3 assessments used for exclusion.

4. Patient has dementia (MMSE <20).

5. Patient has clinically significant renal or liver disorder.

6. Patient currently exhibits generalized obsessive-compulsive disorder, panic disorder, bipolar disorder, post-traumatic stress syndrome (PTSD), clinically significant parasomnias or any other psychotic disorder as established by structured clinical interview for DSM disorders (SCID). Visual hallucinations are allowed.

7. Any suicidal actions in the past 2 years (per investigator judgement i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior).

8. Any suicidal ideation of type 4 or 5 in the C-SSRS in the past 3 months (i.e. active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent).

9. Patient has taken an anti-convulsant, an anti-psychotic (except quetiapine), pindolol, tertatolol or buspirone within 4 weeks of baseline (Day 1, Visit 2).

10. Patient has taken, within 4 weeks of baseline (Day 1, Visit 2), any medication that inhibits or up-regulates CYP450 3A4.

11. Patient is concurrently participating in another investigational drug trial or has participated in another investigational drug trial within the past 3 months.

12. Patient is at high risk of non-compliance in the Investigator's opinion.

Methodology

Patients will report to the study clinic for a screening visit (Visit 1), followed by a baseline visit on Day 1 (Visit 2) where patients will be randomized and begin treatment. Two remote safety visits over telephone (Days 7 and 49 [Visit 3 and Visit 8]) will be conducted. Once treatment has commenced, there will be 2 in-person safety visits to the clinic (Days 14 and 21 [Visit 4 and Visit 5]), 2 in-person efficacy visits to the clinic (Days 28 and 42 [Visit 6 and Visit 7]) and one follow-up in-person final safety visit (Day 70 [Visit 9]). In total, patients will report to the clinic for 7 in-person visits. Patients entering the study will be randomized in a 2:1 ratio (16:8 patients) to receive either NLX-112 or placebo.

At Visits 2, 6 and 7, efficacy assessments will start 30 minutes after the patient has taken 150% of his or her regular L-DOPA dose, when the patient is ON and experiencing typical dyskinesia.

A PD Home Dyskinesia Diary (electronic) will be completed by the patients and/or caregiver with concordance in ON time with dyskinesia between study staff and patient. Two consecutive 24-hour diaries will be completed prior to randomization (baseline, Visit 2) and prior to the clinic visits on Days 28 and 42 (Visits 6 and 7).

A wearable dyskinesia assessment device will be used to monitor dyskinesias during a 2-day period prior to the baseline visit (Day 1, Visit 2) and a 2-day period prior to the clinic visits on Days 28 and 42 (Visits 6 and 7, respectively).

Blood will be collected for possible NLX-112 plasma concentration measurements on Days 14, 21, 28, 42 and 70 (Visits 4, 5, 6, 7 and 9).

Patients will self-administer NLX-112 or placebo 2 times each day, once in the morning and once in the evening. Tablets should be taken with approximately 240 mL water during a meal. Active tablets will contain 0.25 mg NLX-112. Dose escalation will be as follows:

Up-titration period (4 weeks):

- Days 1-4 (0.25 mg/day): 1 tablet in the morning, none in the evening
- Days 5-8 (0.5 mg/day): 1 tablet in the morning and 1 tablet in the evening
- Days 9-12 (0.75 mg/day): 2 tablets in the morning, 1 tablet in the evening
- Days 13-16 (1.0 mg/day): 2 tablets in the morning, 2 tablets in the evening
- Days 17-20 (1.25 mg/day): 3 tablets in the morning, 2 tablets in the evening
- Days 21-24 (1.5 mg/day): 3 tablets in the morning, 3 tablets in the evening
- Days 25-28 (1.75 mg/day): 4 tablets in the morning, 3 tablets in the evening

Constant dose period (2 weeks):

- Days 29-42 (2 mg/day): 4 tablets in the morning, 4 tablets in the evening

Down-titration period (2 weeks, down-titration by 0.25 mg/day every 2 days):

- Days 43-44 (start of down-titration period [1.75 mg/day])
- Days 45-46 (1.5 mg/day)
- Days 47-48 (1.25 mg/day)
- Days 49-50 (1 mg/day)
- Days 51-52 (0.75 mg/day)
- Days 53-54 (0.5 mg/day)
- Days 55-56 (0.25 mg/day)

Patients in the placebo arm will follow the same dose escalation, constant dose and down-titration schedule, but will be taking the matching placebo tablets. Patients who have intolerable adverse events (AEs) during the 28-day up-titration period will be allowed to return to the previous tolerated dose at the discretion of the Investigator, or they may withdraw from the study if they so choose.

Investigational Medicinal Product (IMP), dosage and mode of administration

NLX-112, also known as F13640 and Befiradol, in tablets of 0.25 mg administered orally. NLX-112 will be up-titrated to 2 mg/day (or to the highest well-tolerated dose less than 2 mg/day) over 4 weeks, maintained at that dose for 2 weeks, then followed by a 2 week down-titration period.

Placebo will be matching tablets (identical weight, shape and color) administered orally using the same dose escalation, constant dose and down-titration schedule.

Duration of treatment

Patients will be treated for a total of 8 weeks (56 days), receiving the IMP twice daily, once in the morning and once in the evening.

Duration of each patient's involvement in the study

The total duration of participation for each patient will be approximately 10 weeks, not including screening.

Safety assessments

Safety/tolerability assessments will include: medical history (screening), physical examination (screening and follow-up), 12-lead ECG (all clinic visits), vital signs (all clinic visits), AEs (from baseline visit through follow up visit), assessment of suicidal ideation/behavior (C-SSRS; all clinic visits), and clinical labs (hematology, blood chemistry, and urinalysis; all clinic visits).

Efficacy assessments

- UDysRS
- PD Home Dyskinesia Diary (ON time without troublesome dyskinesia)
- UPDRS, parts I-IV
- CGI-S, CGI-C
- Wearable dyskinesia assessment device data collection
- KPPS
- PDQ39
- HADS
- ICIQ-OAB

- ESS

Efficacy assessments will be collected on Days 1, 28 and 42 (Visits 2, 6 and 7, respectively).

Diary data will be based on 2 consecutive 24-hour diaries taken prior to the baseline visit (Visit 2) and prior to Days 28 and 42 (Visits 6 and 7, respectively). Similarly, wearable data collection will take place during a 2-day period prior to the baseline visit (Visit 2) and a 2-day period prior to the clinic visits on Days 28 and 42 (Visits 6 and 7, respectively).

Rater and self-assessments

An independent neurologist or the treating physician will rate patients at each clinical site. At each applicable visit (Visits 2, 6 and 7) the same rater (if possible) will conduct efficacy assessments beginning 30 minutes after the patient has taken 150% of his or her regular L-DOPA dose, when the patient is ON and experiencing typical dyskinesia. The UDysRS assessments will be videotaped at Visits 2, 6 and 7.

Patients (and/or caregivers) need to demonstrate the ability to complete the electronic PD Home Dyskinesia Diary, with concordance in ON time with dyskinesia between study staff and patient.

A wearable dyskinesia assessment device will be used to monitor dyskinesias during a 2-day period prior to the baseline visit (Day 1, Visit 2) and a 2-day period prior to the clinic visits on Days 28 and 42 (Visits 6 and 7, respectively).

Plasma concentration assessment

Blood samples, for possible later assessment of NLX-112 plasma concentration, will be collected at clinic visits on days 14, 21, 28, 42 and 70 (Visits 4, 5, 6, 7 and 9, in total 5 samples per patient).

Statistical methods

Analysis Populations

- Safety analysis set: All enrolled patients who receive at least one dose of study medication.
- Full analysis set (FAS): All randomized patients who were dosed and who provided at least one post-baseline assessment of the UDysRS.
- Per protocol set (PPS): All patients included in the FAS population who do not have any major protocol violations assessed to compromise the analysis of study data.

General

Data will be summarized and presented by treatment, and by assessment time as applicable. Individual patient data will be listed by patient number, treatment, and by assessment time.

Safety analysis

The safety analyses will be based on the safety dataset.

An overview of all AEs, including SAEs, intensity, relationship to IMP, and deaths will be presented by treatment group. Incidence of AEs and SAEs will be summarized by system organ class (SOC) and preferred term (PT) by treatment. Separate tables will be provided, if relevant, for serious AEs (SAEs) or events leading to withdrawal from study.

Summary statistics by treatment group and time point will be produced for vital signs, ECG parameters and physical examinations. Laboratory data will also be summarized for baseline and all post-treatment clinic visits.

Efficacy analysis

All efficacy analyses will be performed separately on both the FAS and PP sets if deemed appropriate. To explore statistically significant differences between active treatment and placebo, Wilcoxon signed-rank tests for efficacy endpoints will performed by each assessment timepoint.

Sample size

No formal sample size calculation has been performed. The sample size of 24 patients is considered sufficient to evaluate the primary objective and to allow for a preliminary efficacy evaluation.

Study reporting

After completion of the study, an International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E3 compliant CSR will be prepared.

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or term	Explanation
5-HT	5-hydroxytryptamine, serotonin
ADL	Activities of daily living
AE	Adverse event
ADR	Adverse drug reaction
AIM	Abnormal Involuntary Movements
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the plasma concentration versus time curve
BMI	Body mass index
CA	Competent authority
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CIOMS	Council for International Organizations of Medical Sciences
CPK	Creatine phosphokinase
C_{max}	Maximum plasma concentration
CRP	C-reactive protein
CS	Clinically significant
CSP	Clinical study protocol
CSR	Clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CTC AB	Clinical Trial Consultants AB
CTCAE	Common terminology criteria for adverse events
DA	Dopamine
DBS	Deep brain stimulation
DMP	Data management plan
DNP	Diabetic neuropathy
DSUR	Development safety update report
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
ESS	The Epworth Sleepiness Scale
FAS	Full analysis set
FDA	U.S. Food and Drug Administration

GCP	Good clinical practice
GDPR	General data protection regulation
GMP	Good manufacturing practice
GGT	Gamma glutamyl transpeptidase
HADS	The Hospital Anxiety Depression Scale
Hb	Hemoglobin
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICIQ-OAB	International Consultation on Incontinence Questionnaire Overactive Bladder Module
IEC	Independent ethics committee
IME	Important medical event
IMP	Investigational medicinal product
ISF	Investigator site file
KPPS	King's Parkinson's disease Pain Scale
L-DOPA	Levodopa, L-3,4-dihydroxyphenylalanine
LID	Levodopa-induced dyskinesia
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
mmHg	Millimeter mercury (unit for blood pressure measurements)
MMSE	Mini Mental Status Exam
N	number
NCS	Not clinically significant
NOAEL	No observed adverse effect level
NOEL	No observed effect level
PD	Parkinson's disease
PD-LID	L-DOPA- induced-dyskinesia in Parkinson's disease
PDQ39	The Parkinson's Disease Questionnaire
PII	Personally Identifiable Information
PK	Pharmacokinetic
PK (INR)	Prothrombin complex international normalized ratio
PPS	Per protocol set
PT	Preferred term
PTSD	Post-traumatic stress syndrome
QA	Quality assurance
QC	Quality control

RBC	Red blood cell
RBM	Risk-based monitoring
RSI	Reference safety information
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SCID	Structured clinical interview for DSM disorders
SD	Standard deviation
SDV	Source data verification
SOC	System organ class
SOP	Standard operating procedures
SSRI	Selective serotonin reuptake inhibitor
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Half-life
T_{max}	Time to C_{max}
TEAE	Treatment emergent adverse event
TMF	Trial master file
UDysRS	Unified Dyskinesia Rating Scale
ULN	Upper limit of normal
UPDRS	Unified Parkinson's Disease Rating Scale
WBC	White blood cell
WHO	World Health Organization

4 IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

4.1 Medical emergencies contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes a serious adverse event (SAE) and is to be reported as such. Detailed SAE reporting procedures are described in Section 11.2.1.13.

In the case of a medical emergency, the Investigator may contact Sponsor's medical representative/Medical Monitor (Table 4.1-1).

Table 4.1-1 Medical emergencies contact

Name	Function in the study	Telephone number and e-mail
[redacted]		[redacted]

5 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor
Neurolixis
2 rue Georges Charpak
L'Arobase Le Causse Espace d'Entreprises
FR-81290 Labruguiere
France

Sponsor's Medical Representative
[redacted]

Sponsor's Project Manager
[redacted]

Clinical conduct

Site 1
ASC Torsplan, Stockholm, Sweden

Coordinating Investigator
[redacted]

Site 2
Karolinska University Hospital, Stockholm, Sweden

Principal Investigator
[redacted]

Site 3 CTC Clinical Trial Consultants AB (CTC) Uppsala, Sweden	**Principal Investigator** [redacted]
Site 4 Sahlgrenska Hospital, Gothenburg, Sweden	**Principal Investigator** [redacted]
Site 5 Skåne University Hospital, Lund, Sweden	**Principal Investigator** [redacted]
Study management CTC AB Dag Hammarskjölds väg 10B SE-752 37 Uppsala, Sweden	**Clinical Research Manager** [redacted] **Biostatistician** [redacted] **Medical writer** [redacted] **Medical monitor** [redacted]
Laboratory (Safety)	Local hospital laboratories
Laboratory (Bioanalysis, if performed)	Lablytica Life Science AB Virdings allé 18 SE-754 50 Uppsala, Sweden
Investigational medicinal product (IMP) manufacturing, packaging and labelling	Sharp Clinical 2400 Baglyos Circle Bethlehem, PA 1802, United States
IMP importation, release and destruction	ClinStorage Banvaktsvägen 22 SE-171 48 Solna, Sweden
Pharmacy	Apoteket AB Clinical Trial Unit Dag Hammarskjölds väg 18, Entrance C7 SE-751 85 Uppsala, Sweden
Electronic data capture (EDC) system provider:	Viedoc Technologies AB Stationsgatan 23 SE-753 40 Uppsala, Sweden

Signatures are provided in Section 19.

6 INTRODUCTION

6.1 Background

6.1.1 *Overview of NLX-112*

NLX-112, also known as F13640 and Befiradol, or 4-piperidinemethanamine, 1-(3-chloro-4-fluorobenzoyl)-4-fluoro-N-[(5-methyl-2-pyridinyl)-methyl], (2E)-2-butenedioate, is a structurally novel, centrally acting, high-efficacy selective 5-HT1A receptor agonist with nanomolar affinity for 5-HT1A receptors. It was previously developed for the treatment of neuropathic pain by Pierre Fabre, but was ineffective in the clinic and is being re-purposed by Neurolixis as a treatment for L-DOPA- induced-dyskinesia in Parkinson's disease (PD-LID). The serotonin (5-hydroxytryptamine, 5-HT) system has emerged as a key player in the induction of LID. 5-HT neurons possess the enzymes necessary to convert exogenous L-DOPA to dopamine (DA) and mediate its vesicular storage and ´false neurotransmitter´ release. However, 5-HT neurons lack appropriate control mechanisms to regulate synaptic DA levels (e.g., via presynaptic D2 receptors or DA transporters), resulting in excessive DA release and pulsatile stimulation of post-synaptic DA receptors that generate dyskinesia. Compelling neurophysiological, pharmacological, and clinical evidence supports this model, as well as the hypothesis that a potent, highly selective 5-HT1A agonist such as NLX-112 should be effective in treating LID.

NLX-112 rapidly penetrates the brain from the oral compartment and does not modify L-DOPA pharmacokinetics (PK) upon co-administration. Systemically administered NLX-112 fully occupies rat brain 5-HT1A receptors in brain regions implicated in motor control. NLX-112 occupies 5-HT1A receptors at doses that reduce or eliminate dyskinesia in rat models of LID. NLX-112 efficaciously and completely inhibits the electrical activity of dorsal raphe 5-HT neurons via activation of presynaptic 5-HT1A autoreceptors. Serotonergic activity due to striatal 5-HT release is profoundly reduced by NLX-112 in 6-OH-DA-lesioned rats treated with L-DOPA, confirming the capacity of NLX-112 to inhibit 5-HT neurons responsible for the "false neurotransmitter" surge in DA levels. Abnormal Involuntary Movements (AIM) scores in hemiparkinsonian rats chronically treated with L-DOPA were dose-dependently reduced or eliminated by NLX-112. These anti-AIM effects of NLX-112 were entirely reversed by a selective 5-HT1A antagonist. In addition, the anti-AIM activity of NLX-112 was maintained upon chronic treatment (14 days), consistent with studies of older serotonergic drugs showing that the antidyskinetic effects of 5-HT1A agonists do not show desensitization. In non-human primate experiments, NLX-112 significantly attenuated LID in parkinsonian (i.e. MPTP-treated) marmosets, a robust model of anti-dyskinetic activity with high predictive value for clinical efficacy. Importantly, NLX 112 did not negatively affect the therapeutic-like actions of L-DOPA and even exhibited anti-parkinsonian activity of its own. Neurolixis also tested NLX-112 in a second non-human primate species (MPTP-treated macaques). Once again, NLX-112 significantly attenuated LID and did not negatively affect the therapeutic-like actions of L-DOPA.

6.1.2 *Non-clinical studies: toxicology and pharmacokinetics*

As with other 5-HT1A agonists (e.g., buspirone), acute exposure of rats to NLX-112 causes various, transient in vivo expressions of 5-HT1A receptor activation, including signs of the behavioral 5-HT syndrome, hypothermia, and hyperglycemia. With continuous treatment,

tachyphylaxis develops such that those effects are no longer apparent after a few hours or days.

A battery of safety pharmacology studies has been performed to evaluate the effects of NLX-112 on the central nervous, cardiovascular, and respiratory systems. Concerning the central nervous system and after oral administration in mice, observed effects were hypothermia (from 0.625 mg/kg onward), modification of gait (from 2.5 mg/kg onward), decrease in exploration, traction capacity and reaction to touch, and increase of ataxia (from 10 mg/kg onward). Pro-convulsant effects occurred at 2.5 mg/kg and higher doses.

Concerning the cardiovascular system, oral doses of 0.63 mg/kg and higher decreased blood pressure and heart rate in a telemetry study in rats. In a telemetry study in dogs, NLX-112 from 0.16 mg/kg onward induced a significant decrease in blood pressure and from 0.40 mg/kg onward, an increase in heart rate. In a hemodynamic study in dogs, the PQ was significantly increased only at the highest dose tested (i.e., 160 µg/kg intravenous). In a respiratory study in dogs by the oral route, NLX-112 increased the frequency and decreased the amplitude of respiration at 0.064 mg/kg and higher doses.

The PK of NLX-112 have been evaluated in 2 animal species, rat and dog. After oral administration, NLX-112 is rapidly absorbed (15 min), with a good resorption (75-80%) and bioavailability between 50 and 70%. The plasma concentration and area under the plasma concentration versus time curve (AUC) were linear over the dose range in both species.

After repeated daily dosing in 4- and 13-week toxicology studies, accumulation was observed in rat, but not dog or monkey. A gender effect was observed in rat after 4- and 13-week administration (plasma levels were higher in female as compared to male rats) and in dog after 4-week administration only (plasma levels were higher in male as compared to female dogs). In rat, the distribution into the tissues was generally high and rapid. Maximal tissue concentrations were observed at l h post-administration and tissue levels were below quantifiable limits in male and female rats at 28 days and at 42 days post-administration, respectively. In pigmented rats, measurable levels remained in the choroid layer of the eye and the pigmented fur/skin at 42 days post-administration.

NLX-112 was extensively metabolized in both species. Cytochrome P450 enzymes, especially CYP3A4, were largely involved in the metabolism of NLX-112. At least 5 metabolites were generated. The main in vitro metabolites observed were identical between human and animal microsomes (rat and dog). There are no known human specific metabolites. In vitro, NLX-112 at 3 µM or higher inhibits CYP2C19 activity in human hepatocytes. In human hepatocytes in vitro, CYP450 activities were not induced at 10 µM NLX-112, while CYP1A2 activity was upregulated at 100 µM. Excretion mass balance was complete, mostly during the first 24 hour-period. NLX-112 was excreted via urine and feces almost entirely as metabolites (no parent drug in urine; 1-2% parent in feces).

In an oral single dose toxicity study the LD_{50} was 910 and 866 mg/kg in male and female rats, respectively. Four and 13-week repeat-dose toxicology studies were conducted in rat and dog; 2 separate 13-week studies were conducted in cynomolgus monkey. In rat, at 2, 10, or 45 mg/kg/day transient serotonergic effects (lower lip retraction, flat body posture, hyperactivity) were seen in all treated groups. Salivation was noted in the 45 mg/kg/day group. A slight decrease in mean body weight gain was observed in all treated males during pre-treatment (dose-escalation) and treatment periods, but only in the pre-treatment period in 45 mg/kg/day females. Reversible modifications were observed in some blood and renal

parameters. There were no treatment-related histological lesions (including spermogram and staging) in any dose group. Based on these observations, the no observed adverse effect level (NOAEL) in rat after daily administration of NLX-112 over a 4-week period was considered to be below 2 mg/kg/day, due to adverse serotonergic (pharmacological) effects.

In dogs, at daily doses of 0.06, 0.20, and 0.60 mg/kg/day (after a pre-treatment period with dose escalation) serotonergic effects were noted from 0.20 mg/kg/day onward (salivation, muscular rigidity and trembling) in all animals. There were no significant treatment effects on body weight or biological parameters, except for a moderate and reversible increase in the bilirubin blood level in females at the highest dose (0.60 mg/kg/day). Slight to moderate increases in respiratory frequency were recorded in males at 0.20 mg/kg/day and in both sexes at 0.60 mg/kg/day; these respiratory effects were reversible and were not seen in the post dosing period. No relevant macroscopic and microscopic changes were noted. Thus, in dog after daily oral administration of NLX-112, the no observed effect level (NOEL) was considered to be 0.06 mg/kg/day and the NOAEL was considered to be 0.20 mg/kg/day.

The daily oral repeated administration of NLX-112 to rats for 13 consecutive weeks at 1, 7, and 45 mg/kg/day was well-tolerated, but induced reversible, dose-dependent clinical (pharmacological) signs. A reversible (slight to moderate), dose-dependent reduction of body weight gain was found in males. In males only, there was a reversible, dose-related, slight to moderate decrease in urinary volume, urea, creatinine, and electrolytes excretion outputs. No relevant histological lesion was noted. Due to the occurrence of serotonergic signs from the lowest dose tested onward, the NOEL could not be determined.

A second 13-week general toxicology study (with a 4-week treatment-free period) was conducted in the rat at higher doses of 10, 30, and 90 mg/kg/day (LD, MD, and HD, respectively). Again, NLX-112 was reasonably well-tolerated, but induced reversible clinical signs in all dose groups, as previously seen; no new, unexpected clinical signs were found at the previously unexplored HD of 90 mg/kg/day. Body weight and food/water consumption were modestly reduced, but recovered during the treatment-free period, similar to results from the previous 13-week rat study. Laboratory analyses of hematology, chemistry, and urinalysis did not reveal unexpected, toxicologically relevant changes, or irreversible changes, not previously seen in the prior study. There were no adverse macroscopic or microscopic changes attributable to NLX-112 treatment. The NOAEL was considered to be 30 mg/kg/day for 13 weeks.

The daily oral repeated administration of NLX-112 to dogs at 0.06, 0.20, and 0.60 mg/kg/day during 13 consecutive weeks was well-tolerated but induced reversible clinical signs of serotonergic activity (with a dose related frequency and intensity) at each dose level until the end of the treatment period. A very slight decrease in mean body weight gain, as well as a slight to moderate increase in respiratory frequency during the treatment period, were recorded at each dose in both sexes without any apparent dose relationship. All these changes were reversed after a 4-week treatment-free period. No relevant histological lesion was related to treatment by the oral route with NLX-112. Due to the occurrence of serotonergic signs from the lowest dose tested onward, the NOEL could not be determined.

In the cynomolgus monkey, twice-daily (BID) oral gavage administration of NLX-112 at doses of 4, 14, and 40 mg/kg/day (i.e., 2, 7 and 20 mg/kg BID) for 13 weeks (following a 14-day pre-treatment dose escalation period) produced pharmacological clinical signs of loss of balance, decreased activity, shaking, abnormal movements, and increased sexual behavior. These pharmacological signs were short-lived (generally ≤l hour) and mainly occurred

immediately after dosing during the 14-day dose escalation period. Low and mid-dose males and LD females experienced transient reductions of heart rate on constant dose Day 1 and Day 16; only LD males experienced mild transient bradycardia at the week 13 assessment. LD and some MD animals experienced transient QTc prolongation, which may have been related to the reduction of heart rate. The QT prolongation was generally seen only at l hour post dose. There were no treatment-related changes in body weight. Sporadic reductions in food consumption were not correlated with body weight changes so were not considered toxicologically relevant. There were no toxicologically relevant ophthalmologic, serum chemistry, hematological, or urinary changes. There were no macroscopic or microscopic histologic changes. The NOAEL after 13 weeks of oral administration of NLX-112 was considered to be 40 mg/kg/day.

NLX-112 did not show evidence of mutagenic potential.

Despite maternal toxicity, NLX-112 was free of any embryotoxic and/or teratogenic effects in rat (oral doses of 1, 7, and 45 mg/kg/day) and rabbit (0.25, 1, and 4 mg/kg/day) and testicular staging in rat was negative.

6.1.3 *Clinical experience*

One hundred ninety-nine healthy volunteers have been involved in 9 Phase 1 clinical trials. NLX-112 was administered to 173 volunteers (26 subjects received placebo). Six hundred thirty-four patients have been involved in 5 Phase II clinical studies. NLX-112 was administered to 433 patients (200 subjects received placebo); one subject was enrolled but not dosed.

Absorption of NLX-112 after oral administration is rapid, with T_{max} occurring between 0.5 -1 h with an oral solution, and between 1-3 h after dosing with an oral tablet. C_{max} and AUC increased more rapidly than the dose after single dose, while both parameters increased with an apparent dose proportionality after repeated drug administration. The mean half-life ($T_{1/2}$) ranged between 34 and 41 h.

In young female volunteers, concentration peaks and plasma exposures were slightly higher (21% and 35%, respectively) when compared to those in young male volunteers. The other PK parameters (T_{max} and $T_{1/2}$) and inter-individual variability was not different between males and females.

When comparing PK parameters from healthy elderly (≥65 years) males to those in young males, a higher plasma exposure was observed in elderly men (about 30%); the gender effect observed in young subjects was of the same magnitude in elderly subjects (40% increase in plasma AUC in elderly women vs elderly men). For both elderly men and women, the plasma $T_{1/2}$ remained similar to that in young subjects.

CYP3A4 is the major mediator of NLX-112 biotransformation. A study of the effects of single and repeated oral doses of NLX-112 on CYP3A4 activity used midazolam as a metabolic probe; in accordance with the standard classification, NLX-112 was characterized as a weak CYP3A4 inhibitor. Investigation of the potential impact of repeated oral doses of the potent CYP3A4 inhibitor, ketoconazole (given 400 mg q.d.) confirmed the involvement of CYP3A4 in NLX-112 metabolism and led to a mean increase of 2.5-fold in NLX-112 plasma exposure, with individual values ranging from 1.49 to 3.89-fold.

The most frequent treatment emergent adverse events (TEAEs) observed in Phase 1 studies (observed in more than 20% of volunteers in at least 2 different studies) were: dizziness,

somnolence, malaise, headache, and nausea, consistent with the PK profile of NLX-112. In the Phase 2 study in diabetic neuropathy (DNP) patients, dizziness, headache, nausea, and insomnia were the most common TEAEs. These TEAEs occurred mostly during the up-titration period (when employed) or during the first few days of fixed dose administration and were most frequent at the highest doses. Somnolence was seldom seen in the Phase II studies, perhaps due to the up-titration periods employed in these studies.

Undesirable hemodynamic effects, (i.e., decrease in blood pressure, postural hypotension) were observed in healthy elderly volunteers. Of the twelve elderly subjects, 2 experienced orthostatic hypotension (one episode of moderate intensity in one subject, and 2 episodes of severe orthostatic hypotension with syncope in another subject).

The only SAE noted in the Phase 1 program was one that occurred in a subject that received midazolam as a probe (2 mg oral dose) co-administered with NLX-112 (2.25 mg single oral dose). The SAE, which was interpreted as a 'partial serotonin syndrome' occurred 30 minutes post-dosing and resolved spontaneously within 40 minutes. It should be noted that the subject had previously suffered from nausea, headache, and vomiting on Day -1 (prior to inclusion in the study) and the administration of a benzodiazepine (alprazolam and/or bromazepam) in several subjects exposed to NLX-112 in another Phase 1 study did not induce any serotonergic manifestations.

Two Phase 2 studies provide the bulk of the safety information for NLX-112. A 12-week randomized, placebo-controlled study in 124 DNP patients was well-tolerated and safe at 1 mg BID (i.e. 2 mg/day); the incidence of SAEs was low (3%) and no SAE was related to NLX-112 intake. Only one NLX-112-treated subject withdrew from the study due to a TEAE, a recurrent mild dizziness. Ninety-four percent of TEAEs were mild or moderate. Only dizziness and headache had a greater incidence in the NLX-112 group as compared to placebo (difference > 5%). The most frequently reported TEAEs mainly occurred at the beginning of the treatment and resolved quickly. No clinically significant changes were observed in electrocardiogram (ECG) and laboratory safety tests included glycaemia parameters.

A follow-on Phase 2 study in DNP with 456 patients tested 3 doses of NLX-112 [0.5, 1.0, and 1.5 mg BID (1.0, 2.0, 3.0 mg/day)] vs placebo (Study CP201). Safety and tolerability in this study, which employed an 11-day up-titration period prior to and a 10-day down titration period after the 6-week fixed-dose period, were similar to the previous phase 2 study. Four SAEs occurred but none were related to NLX-112. Dizziness, headache, nausea and insomnia were the most common TEAEs and occurred predominantly during the up-titration period or the first fixed-dose week (Table 6.1-1). Please refer to the NLX-112 Investigators' Brochure for additional details on safety, tolerability and adverse events (AEs) in the NLX-112 phase 2 clinical program.

Table 6.1-1 Most Common Drug-related TEAEs (incidence > 2% of patients) Listed By Number of Patients in Each Dose Group in Study CP201

Preferred Term	PBO (N=112)	NLX-112 Groups		
		1 mg (N=113)	2 mg (N=114)	3 mg (N=117)
Dizziness	1 (0.9%)	8 (7.1%)	15 (13.2%)	15 (12.9%)
Nausea	4 (3.6%)	6 (5.3%)	12 (10.5%)	16 (13.7%)
Headache	3 (2.7%)	3 (2.7%)	6 (5.3%)	9 (7.7%)
Insomnia	-	3 (2.7%)	3 (2.6%)	6 (5.1%)

Preferred Term	PBO (N=112)	NLX-112 Groups		
		1 mg (N=113)	2 mg (N=114)	3 mg (N=117)
Withdrawal syndrome	1 (0.9%)	4 (3.5%)	4 (3.5%)	5 (4.3%)
Paresthesia	1 (0.9%)	3 (2.7%)	4 (3.5%)	2 (1.7%)
Vomiting	-	-	-	5 (4.3%)
Hypotension	-	3 (2.7%)	2 (1.8%)	2 (1.7%)
Accidental overdose	1 (0.9%)	3 (2.7%)	3 (2.6%)	2 (1.7%)
Hypertension	-	1 (0.9%)	1 (0.9%)	3 (2.6%)
Mood Swings	2 (1.8%)	-	2 (1.8%)	3 (2.6%)
ALAT increased	1 (0.9%)	1 (0.9%)	3 (2.6%)	-

Thus, based on Phase 1 and 2 study results, NLX-112 could be safely administered up to the dose of 3.0 mg/day with a progressive up-titration to maximize the tolerability of the drug and a down-titration to prevent withdrawal symptoms.

6.2 Study rationale

L-DOPA (levodopa, L-3,4-dihydroxyphenylalanine) is the gold-standard pharmacotherapy for PD. L-DOPA is converted to DA primarily in dopaminergic neurons and, given that motor symptoms of PD are caused by a lack of DA, L-DOPA decreases the severity of these symptoms. However, after several years of treatment, use of L-DOPA often leads to fluctuations in therapeutic efficacy (ON and OFF periods) and to induction of dyskinesia which can be serious and disabling. Dyskinesias are AIMs that interfere with normal movements and can occur even at rest. Since dyskinesias are induced by L-DOPA, they are often referred to as L-DOPA-induced dyskinesia, or LID [1, 2].

LID is poorly treated, with few options available to the treating neurologist or physician. Some LID patients respond to amantadine, although tolerability and efficacy are limited. Alternatively, physicians lower the daily doses of L-DOPA or reduce administration intervals and L-DOPA doses to avoid peak-dose LID. However, this may increase periods of OFF and increase parkinsonism in PD patients [1, 3, 4]. LID has been shown to reduce the patient's quality of life (QOL), as well as to increase the risk of falls and health care costs. LID has been shown to worsen the activities of daily living (ADL), and patients report that their dyskinesia negatively impacts walking and balance, public and social settings, exciting or emotional settings, doing hobbies and other activities, handwriting, and dressing [5, 6].

Although Parkinson's disease is strongly associated with dysfunction of the dopaminergic system, serotonin (5-hydroxytryptamine, 5-HT) levels are also reduced in the brain of PD patients, as shown in post-mortem analyses. The dyskinesia observed in PD patients receiving L-DOPA is due to the fact that serotonergic neurons can take up L-DOPA and convert it to DA (similarly to dopaminergic neurons), but in a dysregulated manner as a 'false neurotransmitter' [7-9]. Hence, experiments in animal models as well as brain imaging studies in human PD-LID patients show that when serotonergic neurons are inhibited, the dyskinesia induced by L-DOPA is markedly reduced. These results and others indicate that inhibition of

5-HT neurons using drugs such as NLX-112, which is an agonist at inhibitory 5-HT1A somatodendritic autoreceptors, is a promising strategy to treat LID in PD patients [10-13].

NLX-112 (also known as befiradol and F13640) is a novel compound that activates serotonin 5-HT1A receptors. NLX-112 has 2 main advantages over previous serotonergic drugs: (i) NLX-112 is exceptionally selective for 5-HT1A receptors, for which it displays an affinity which is over 1000-fold greater than for other receptors and binding sites (Figure 8.1); (ii) NLX-112 is an extremely efficacious 'full agonist', i.e. it maximally activates 5-HT1A receptors, unlike previous serotonergic drugs that only partially activate the receptors [14, 15].

NLX-112 has been tested by Neurolixis in a recognized rat model of PD, the 6-OHDA lesioned hemiparkinsonian rat. In this animal model, the repeated administration of L-DOPA induces dyskinesia that is completely reversed by systemic administration of NLX-112 without impairing the therapeutic effects of L-DOPA [13, 16]. This distinguishes NLX-112 from older serotonergic compounds that have been previously tested in the same rat model: they only partially reverse LID but also negatively interfere with the therapeutic-like actions of L-DOPA [10, 17]. In more recent non-human primate experiments, NLX-112 significantly attenuated LID in parkinsonian (i.e. MPTP-treated) marmosets, a robust model of anti-dyskinetic activity with high predictive value for clinical efficacy [18]. Importantly, NLX-112 did not negatively affect the therapeutic-like actions of L-DOPA and even exhibited anti-parkinsonian activity of its own. Neurolixis also tested NLX-112 in a second non-human primate species (MPTP-treated macaques). Once again, NLX-112 significantly attenuated LID and did not negatively affect the therapeutic-like actions of L-DOPA [19].

Taken together, these data suggest that NLX-112 is a promising candidate for the treatment of LID in PD patients. Neurolixis currently wishes to carry out a phase 2a clinical trial with NLX-112 to test its safety and tolerability in PD/LID patients, and preliminary clinical efficacy in reducing LID symptoms.

6.3 Risk/benefit assessment

6.3.1 *Potential risks*

In prior clinical studies of NLX-112, the most frequently reported undesirable treatment effects were dizziness, somnolence, headache, nausea, and malaise; these effects are consistent with the pharmacological profile of NLX-112. These effects occurred mostly during the first days of treatment and were most frequent at the highest doses of study drug (i.e., ≥3.0 mg/day).

The study of the tolerability and safety of NLX-112 administered as multiple doses after an adaptive dose titration in healthy subjects showed that progressive up-titration, and adjusting dose escalation based on individual tolerability, allowed some healthy men to tolerate 10 mg/day, when administered as 5 mg BID.

Abrupt discontinuation of NLX-112 after multiple daily dosing of 3.0 mg/day or higher was associated with the sporadic occurrence of withdrawal symptoms (mainly nightmare, anxiety, hallucination, and euphoric mood) which were reduced in severity with progressive down-titration.

Undesirable hemodynamic effects (i.e., decrease in blood pressure and postural hypotension) were observed in some elderly subjects.

Thus, based on prior human experience, NLX-112 can be safely administered up to the dose of 3.0 mg/day (1.5 mg BID), with a progressive up-titration to maximize the tolerability of the drug and a down-titration regimen after the fixed dose period to minimize potential withdrawal symptoms.

In cases of accidental overdose, standard supportive measures should be adopted as required. For further information regarding overdosing, refer to Section 11.2.1.17.

Each patient will be provided with a patient information card with information about the patient's participation in a study, see Section 14.4.

The Principal Investigator at the research clinic will ascertain that adequate facilities and procedures are available to handle emergency situations should they occur during the study.

Besides the risks related to the IMP as described above, there may also be risks related to the medical devices used in the study, e.g., devices used for venipuncture. However, these are devices that are used in routine medical care and the risk associated with their use is considered low and ethically justifiable. Study specific evaluations and sampling procedures, like blood-pressure measurements using a blood pressure cuff and frequent blood-sampling, may cause transient discomfort but the risk is deemed to be low and ethically justifiable.

6.3.2 *Potential benefits*

NLX-112 is an IMP. Therefore, it is not possible to predict whether there will be a direct medical benefit to the study participants.

Patients will not receive monetary benefits to participate in the study.

6.3.3 *Risk-benefit conclusion*

The combined safety data from non-clinical and clinical studies, in which 606 subjects have been exposed to NLX-112, form the basis for the current knowledge about the safety of NLX-112 in humans.

The available non-clinical data of NLX-112 show findings consistent with an exaggerated pharmacological effect, which were reversible after cessation of dosing. There were no clinically relevant ophthalmologic, hematologic, serum chemistry or urinary changes, except a few reversible chemistry and urinalysis changes in the rat. No macroscopic or microscopic histologic changes were seen in any species.

With regard to clinical data, the most frequently reported undesirable treatment effects in human subjects were dizziness, somnolence, headache, nausea and malaise, which are consistent with the pharmacological profile of NLX-112. In order to limit the prevalence and intensity of these potential adverse reactions and to maximize tolerability, a slow up-titration of the dose is applied in the current clinical study where the Investigator has the option to stop or decrease the dose if required.

While keeping the above-mentioned risk factors at a minimum level in order to not expose the patients participating in the study for risks that would not be ethically justifiable, it is concluded that the planned study assessments are considered sufficient to meet the scientific and medical goals for the study. It is further concluded that the potential benefits from the study will outweigh the potential risks for the treated patients.

More detailed information about the known and expected benefits and risks and reasonably expected adverse drug reactions (ADRs) of NLX-112 is found in current version of the Investigator's Brochure (IB).

6.3.4 *Risk assessment with regards to the Covid-19 pandemic:*

Current recommendations from the Public Health Agency of Sweden (Folkhälsomyndigheten) and other authorities will be considered on a day-to-day basis. Assessment sessions with Sponsors, Investigators and CRO/vendor representative members to align on local restrictions, impact assessment, contingency plans and study-specific risk mitigation strategies will be made to safeguard the study conduct and the safety of the patients included in the study. Risks regarding patient safety, study performance and data quality/integrity will be assessed on an ongoing basis during the study. Any identified risks and mitigating actions will be documented in a risk log as part of the Sponsor's trial master file (TMF).

EMAs Guidance on the Management of Clinical Trials during the Covid-19 (Coronavirus) pandemic as well as local guidelines from the Swedish Medical Products Agency will be taken into consideration.

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Primary objective

To evaluate the safety and tolerability of NLX-112, titrated up to a maximum of 2 mg/day, compared to placebo during 8 weeks of daily treatment in PD patients with LID.

7.1.1 *Primary endpoints*

- Frequency, intensity and seriousness of AEs
- Clinically significant changes from baseline in:
  - ECG
  - Vital signs
  - Safety laboratory parameters
  - Physical examinations
- Suicidal ideation/behavior as assessed by the Columbia Suicide Severity Rating Scale (C-SSRS).

7.2 Secondary objective

To assess the preliminary efficacy of NLX-112 treatment in reducing troublesome LID.

7.2.1 *Secondary endpoints*

- Change from baseline at the final efficacy clinic visit (Day 42) in the Unified Dyskinesia Rating Scale (UDysRS) total score [Timeframe: Baseline to Day 42]. Patients will be challenged with 150% of their standard L-DOPA dose (maximum L-DOPA dose 250 mg) 30 minutes prior to the first UDysRS assessment.

- Change from baseline in UDysRS total score at Day 28, after a 150% L-DOPA dose challenge.
- Change from baseline in total objective score (Parts III, IV) of the UDysRS at Day 28 and Day 42, after a 150% L-DOPA dose challenge.
- Change from baseline in ON Time Without Troublesome Dyskinesia (ON Without Dyskinesia plus ON With Non-troublesome Dyskinesia) based on a PD Home Dyskinesia Diary.
- Change from baseline in Unified Parkinson's Disease Rating Scale (UPDRS) scores (Part III, motor examination).
- Change from baseline in UPDRS combined scores (Parts I, II, III and IV).
- Clinical Global Impression of Change (CGI-C) in overall PD symptoms
- Change from baseline in dyskinesia scores measured by the Kinesia 360 (Great Lakes Neurotechnologies, Inc) wearable dyskinesia assessment system.

7.3 Exploratory objectives

- To assess the preliminary efficacy of NLX-112 treatment in improving selected non-motor symptoms of PD, including pain, bladder function, sleep function, mood and quality of living with PD.
- To collect blood samples for potential NLX-112 plasma concentration analysis.

7.3.1 *Exploratory endpoints*

- Change from baseline in the King's Parkinson's Disease Pain Scale (KPPS) total score and in each of the 7 pain domain sub-scores.
- Change from baseline in the Parkinson's Disease Questionnaire (PDQ39) total score and domain scores.
- Change from baseline in the Hospital Anxiety Depression Scale (HADS)
- Change from baseline in the International Consultation on Incontinence Questionnaire (ICIQ) Overactive Bladder Module (ICIQ-OAB) total score.
- Change from baseline in the Epworth Sleepiness Scale (ESS).
- Plasma concentrations of NLX-112.

The NLX-112 plasma concentration analysis may only be performed if the Sponsor deems it necessary to answer any questions regarding compliance. The outcome of the results may not be reported in the clinical study report (CSR).

8 STUDY DESIGN

8.1 Overall study design and schedule of events

This is a two-arm, double-blind, randomized, placebo-controlled Phase 2a study evaluating the safety, tolerability, and preliminary efficacy of up to 2 mg/day of NLX-112 versus placebo in patients with moderate to severe L-DOPA induced dyskinesia (LID) in Parkinson's disease (PD). NLX-112 will be up-titrated to either 2 mg/day (1 mg BID) or to the highest well-tolerated dose less than 2 mg/day over 4 weeks, maintained at the well-tolerated dose for an additional 2 weeks, and then down-titrated over 2 weeks. An overview of the study design is shown in Figure 1.

Patients will report to the study clinic for a screening visit (Visit 1), followed by a baseline visit on Day 1 (Visit 2) where patients will be randomized and begin treatment. Two remote safety visits over telephone (Days 7 and 49 [Visit 3 and Visit 8]) will be conducted. Once treatment has commenced, there will be 2 in-person safety visits to the clinic (Days 14 and 21 [Visit 4 and Visit 5]), 2 in-person efficacy visits to the clinic (Days 28 and 42 [Visit 6 and Visit 7]) and one follow-up in-person final safety visit (Day 70 [Visit 9]). In total, patients will report to the clinic for 7 in-person visits. Patients entering the study will be randomized in a 2:1 ratio (16:8 patients) to receive either NLX-112 or placebo.

At Visits 2, 6 and 7, efficacy assessments will start 30 minutes after the patient has taken 150% of his or her regular L-DOPA dose, when the patient is ON and experiencing typical dyskinesia.

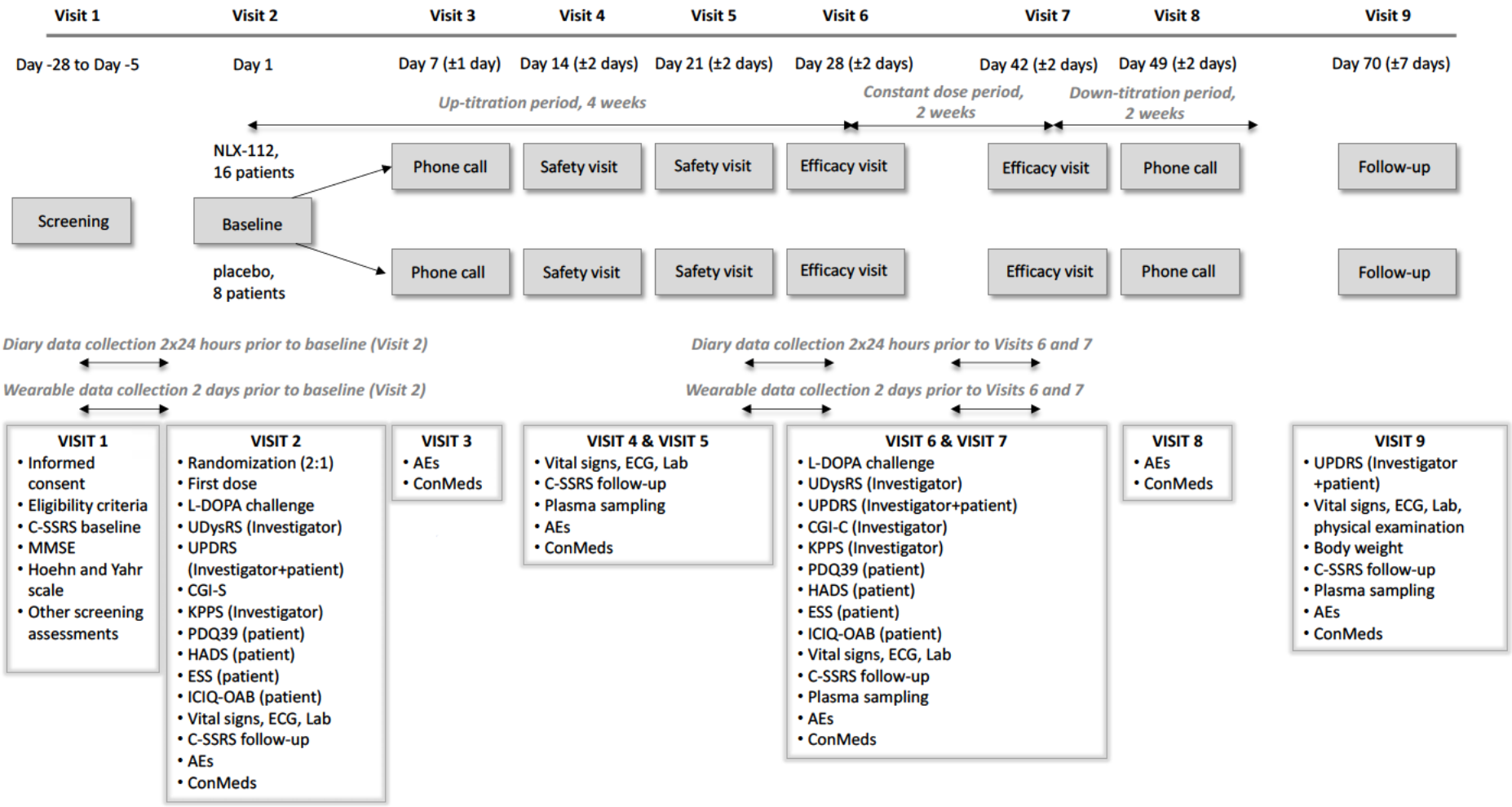
The order of assessments at each visit is specified in Section 8.2.

A PD Home Dyskinesia Diary (electronic) will be completed by the patients and/or caregiver with concordance in ON time with dyskinesia between study staff and patient. Two consecutive 24-hour diaries will be completed prior to randomization (baseline, Visit 2) and prior to the clinic visits on Days 28 and 42 (Visits 6 and 7).

A wearable dyskinesia assessment device will be used to monitor dyskinesias during a 2-day period prior to the baseline visit (Day 1, Visit 2) and a 2-day period prior to the clinic visits on Days 28 and 42 (Visits 6 and 7, respectively).

Blood will be collected for possible NLX-112 plasma concentration measurements on Days 14, 21, 28, 42 and 70 (Visits 4, 5, 6, 7 and 9).

Figure 1 Overview of study design



AEs=adverse events, CGI-C=Clinical Global Impression of Change, ConMeds=Concomitant medications, C-SSRS=Columbia Suicide Severity Rating Scale, ECG=electrocardiogram, ESS=the Epworth Sleepiness Scale, HADS=the Hospital Anxiety Depression Scale, ICIQ-OAB=the International Consultation on Incontinence Questionnaire Overactive Bladder Module, KPPS=the King's Parkinson's disease Pain Scale, MMSE= Mini Mental Status Exam, UPDRS= the Unified Parkinson's Disease Rating Scale, PDQ39=the Parkinson's disease Quality of Life Scale (39-item), UDysRS=the Unified Dyskinesia Rating Scale.

Patients will self-administer NLX-112 or placebo 2 times each day, once in the morning and once in the evening. Tablets should be taken with approximately 240 mL water during a meal. Active tablets will contain 0.25 mg NLX-112. Dose escalation will be as follows:

Up-titration period (4 weeks):

- Days 1-4 (0.25 mg/day): 1 tablet in the morning, none in the evening
- Days 5-8 (0.5 mg/day): 1 tablet in the morning and 1 tablet in the evening
- Days 9-12 (0.75 mg/day): 2 tablets in the morning, 1 tablet in the evening
- Days 13-16 (1.0 mg/day): 2 tablets in the morning, 2 tablets in the evening
- Days 17-20 (1.25 mg/day): 3 tablets in the morning, 2 tablets in the evening
- Days 21-24 (1.5 mg/day): 3 tablets in the morning, 3 tablets in the evening
- Days 25-28 (1.75 mg/day): 4 tablets in the morning, 3 tablets in the evening

Constant dose period (2 weeks):

- Days 29-42 (2 mg/day): 4 tablets in the morning, 4 tablets in the evening

Down-titration period (2 weeks, down-titration by 0.25 mg/day every 2 days):

- Days 43-44 (start of down-titration period [1.75 mg/day])
- Days 45-46 (1.5 mg/day)
- Days 47-48 (1.25 mg/day)
- Days 49-50 (1 mg/day)
- Days 51-52 (0.75 mg/day)
- Days 53-54 (0.5 mg/day)
- Days 55-56 (0.25 mg/day)

Patients in the placebo arm will follow the same dose escalation, constant dose and down-titration schedule, but will be taking the matching placebo tablets. Patients who have intolerable AEs during the 28-day up-titration period will be allowed to return to the previous tolerated dose at the discretion of the Investigator, or they may withdraw from the study if they so choose.

Each patient is expected to participate in the study for approximately 10 weeks, not including screening. Patients will be treated with IMP for a total of 8 weeks (56 days).

The timing of events is summarized in Table 8.1-1. Study assessments are described in Section 11.

Table 8.1-1 Schedule of events

Study visit number		**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**
Study period		**Screening**	**Baseline**	**Phone Safety Visit**	**Clinic Safety Visit**	**Clinic Safety Visit**	**Clinic Efficacy Visit**	**Clinic Efficacy Visits**	**Phone Safety Visit**	**Follow-up Clinic Visit[1]**
Study day	**Protocol Section**	**Day -28 to Day -5**	**Day 1**	**Day 7 ±1 day**	**Day 14 ±2 days**	**Day 21 ±2 days**	**Day 28 ±2 days**	**Day 42 ±2 days**	**Day 49 ±2 days**	**Day 70 ±7 days**
Informed Consent	14.3	X								
Eligibility criteria	9.4 & 9.5	X	X[2]							
Demographics	11.1.3	X								
Vital signs[3]	11.2.3	X	X		X	X	X	X		X
Physical examination	11.2.2	X								X
Body weight and height[4]	11.1.4	X								X
Hoehn and Yahr scale[5]	11.1.8	X	X							
Medical and psychiatric history	11.1.5	X								
Pregnancy test[6]	11.1.7	X	X							X
12-lead ECG	11.2.4	X	X		X	X	X	X		X
Safety laboratory[7]	11.2.6	X	X		X	X	X	X		X
MMSE	11.1.9	X								
C-SSRS[8]	11.2.5	X	X		X	X	X	X		X
UPDRS[9]	11.3.1	X	X				X	X		X
Diary and wearable device training	11.3.3&11.3.6	X	X							
Randomization	9.9		X							
Study drug dispensing	10.5		X				X	X		
Treatment (Day 1 - Day 56)	10.6					X				

Study visit number		**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**
Study period		**Screening**	**Baseline**	**Phone Safety Visit**	**Clinic Safety Visit**	**Clinic Safety Visit**	**Clinic Efficacy Visit**	**Clinic Efficacy Visits**	**Phone Safety Visit**	**Follow-up Clinic Visit[1]**
Study day	**Protocol Section**	**Day -28 to Day -5**	**Day 1**	**Day 7 ±1 day**	**Day 14 ±2 days**	**Day 21 ±2 days**	**Day 28 ±2 days**	**Day 42 ±2 days**	**Day 49 ±2 days**	**Day 70 ±7 days**
Diary data collection[10]	11.3.3		X				X	X		
Wearable device data collection[11]	11.3.6		X				X	X		
L-DOPA challenge	11.3.1		X				X	X		
UDysRS	11.3.2		X				X	X		
Video taping (UDysRS)	11.3.2		X				X	X		
CGI-S/CGI-C[12]	11.3.5		X				X	X		
KPPS	11.4.1		X				X	X		
PDQ39	11.4.2		X				X	X		
HADS	11.4.3		X				X	X		
ICIQ-OAB	11.4.4		X				X	X		
ESS	11.4.5		X				X	X		
NLX-112 plasma concentration sampling	11.4.6				X	X	X	X		X
Drug accountability	10.5						X	X		X
Baseline symptoms	11.1.10	X								
Adverse events[13]	11.2.1		X							
Prior and concomitant medications	11.1.6		X							

CGI-S/CGI-C=Clinical Global Impression of Severity and Clinical Global Impression of Change, C-SSRS=Columbia Suicide Severity Rating Scale, ESS=the Epworth Sleepiness Scale, HADS=the Hospital Anxiety Depression Scale, ICIQ-OAB=the International Consultation on Incontinence Questionnaire Overactive Bladder Module,

KPPS=the King's Parkinson's disease Pain Scale, UPDRS=the Unified Parkinson's Disease Rating Scale, MMSE=Mini Mental Status Exam, PDQ39=the Parkinson's disease Quality of Life Scale (39-item), UDysRS=the Unified Dyskinesia Rating Scale

1. Also early withdrawal follow-up visit
2. Confirmation of eligibility
3. Blood pressure (including orthostatic hypotension assessment), pulse, respiratory rate and temperature. At screening and baseline (Visit 1 and Visit 2), vital signs to assess orthostatic hypotension will be conducted in triplicate, 15-20 minutes apart, with the average of the 3 assessments used for exclusion.
4. Body weight at Visit 1 and Visit 9. Height at Visit 1 only.
5. The Modified Hoehn and Yahr scale will be used to establish the PD stage of the patient.
6. Women of child-bearing potential only.
7. Hematology, coagulation, serum biochemistry and urinalysis.
8. C-SSRS: the baseline scale will be used at the first assessment (screening, Visit 1) and the follow-up scale will be used at all subsequent visits.
9. UPDRS - Screening: part IV only. Other visits: parts I-IV
10. PD Home Dyskinesia Diary: 2 consecutive 24-hour diaries taken prior to the visits indicated above.
11. Wearable data collection will take place during a 2-day period prior to the visits indicated above.
12. CGI-S at baseline (Day 1, Visit 2), CGI-C at other visits.
13. Collection of AEs from the first dose of IMP.

8.2 Order of assessments

Safety assessments should be performed before the L-DOPA challenge at Visit 2, 6 and 7.

The efficacy assessments at Visits 2, 6 and 7 should be performed in the order outlined in Table 8.2-1.

Table 8.2-1 Order of efficacy assessments

Assessment	Assessor	
	Investigator	Patient
UDysRS (Parts III and IV repeated 3 times at approximately 30, 60 and 90 minutes after the 150% L-DOPA challenge)	X	
UPDRS part III in ON (within 30-90 minutes after the 150% L-dopa challenge)	X	
UPDRS parts I, II and IV	X	X[1]
CGI-C	X	
KPPS	X	
UDysRS (Parts I and II)		X
PDQ39		X
HADS		X
ESS		X
ICIQ-OAB		X

CGI-C=Clinical Global Impression of Change, ESS=the Epworth Sleepiness Scale, HADS=the Hospital Anxiety Depression Scale, ICIQ-OAB=the International Consultation on Incontinence Questionnaire Overactive Bladder Module, KPPS=the King's Parkinson's disease Pain Scale, UPDRS=Unified Parkinson's Disease Rating Scale, PDQ39=the Parkinson's disease Quality of Life Scale (39-item), UDysRS=the Unified Dyskinesia Rating Scale

[1]End of Part I and Part II

8.3 Rationale for study design

This is a double-blind, randomized, placebo-controlled Phase 2a study evaluating the safety, tolerability, and preliminary efficacy of up to 2 mg/day of NLX-112 versus placebo in PD patients with moderate to severe LID. NLX-112 will be up-titrated to either 2 mg/day (1 mg BID) or to the highest well-tolerated dose less than 2 mg/day over 4 weeks, maintained at the well-tolerated dose for an additional 2 weeks, and then down-titrated over 2 weeks. The study will provide important safety and preliminary efficacy data to support the design of further studies in PD-LID patients.

Since NLX-112 is being developed as an anti-dyskinetic therapy, its anti-dyskinetic capacity will be addressed in the present study. Since dyskinesias vary over time, the patients will be given 150% of their regular L-DOPA dose as a challenge before the UDysRS assessment(s). The maximum L-DOPA dose to be administered in the study is 250 mg. 150% of the regular L-DOPA dose as a challenge is routinely given when L-DOPA tests are done to evaluate L-DOPA responsivity in standard clinical practice. Should the Investigator consider it

medically warranted to reduce the L-DOPA challenge in a specific patient for safety or tolerability reasons, this should be approved by the Sponsor prior to implementation. It is critical that the same dose is given at all visits with L-DOPA challenges for a given patient.

A placebo control will be used to establish the frequency and magnitude of changes in endpoints that may occur in the absence of active treatment.

Randomization will be used to minimize bias in the assignment of patients to dose groups and to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across treatment groups.

Blinded treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

Blood samples to be possibly used for measurement of plasma NLX-112 concentration will be collected at clinic visits on Days 14, 21, 28, 42 and 70. These plasma levels could serve as a rough measure of compliance with the study medication regimen and Sponsor may choose to determine the NLX-112 plasma concentration if deemed useful to answer any questions regarding compliance.

8.4 Selection of dose

The effective doses of NLX-112 in PD-LID patients were estimated based on PK and pharmacodynamic data from animal studies (Neurolixis Position paper NSR-16-005-02). The methods employed in these studies have previously been used with a number of CNS compounds and have generally predicted outcomes in an appropriate clinical range. The methods include: allometric scaling between rat and human; comparisons of total and free plasma exposure between rat and human; translational biomarker study on corticosterone / cortisol release; translational biomarker study on body temperature decreases; and physiologically-based pharmacokinetic and pharmacodynamic (PKPD) modelling.

Dosing calculations based on biomarker data carry considerable face validity because cortisol release and hypothermia are well-characterized responses to central 5-HT1A receptor agonists and are highly translatable between rodent and human: they predicted doses in the range 0.3 to 1.25 mg. These dose predictions tally with those derived from plasma exposure calculations (0.5 to 1.25 mg) and allometric scaling predictions (0.45 mg). Overall, the results of these analyses suggest that doses in the range from 0.3 to 1.25 mg/day may be efficacious in treating PD-LID. The PKPD modeling study yielded a somewhat higher estimate of 3 mg.

It should be noted that repeated dosing of NLX-112 results in an approximate 2-fold accumulation of drug at steady state, and exposure levels of NLX-112 in elderly males were 30% higher than in young male volunteers (as shown in a Phase 1 study in aged volunteers – Study F13640 GE102). This is relevant to the present study because the majority of PD patients are typically over 65 years old.

Taken together, these data suggest that efficacious doses of NLX-112 for treatment of LID will be in the low milligram or sub-milligram range.

9 STUDY POPULATION

Prospective approval of protocol deviations to eligibility criteria, also known as protocol waivers or exemptions, is not permitted.

9.1 Recruitment

Potential participants in the study will be identified according to the routines of the clinical study sites. Patients will be recruited at 5 clinical sites, with an average of 4 to 6 patients per site.

9.2 Screening and enrolment log

Investigators must keep a record of all screened patients even if they were not subsequently included in the study. This information is necessary to verify that patients were selected without bias. The reason for screen failure should be stated for all patients screened but not included. The reason for withdrawal should be stated for all patients included but not completed.

A screening number will be allocated to each patient in connection to the informed consent process at the Screening visit. The screening number is generated automatically in the electronic case report form (eCRF). The screening number will allow identification of patients irrespective of their possible eligibility for the study.

Patients that are included and randomized will be assigned a randomization number.

If a patient cannot receive the planned dose of IMP within 28 days after screening (*i.e.*, the time interval between signing informed consent until dose administration) the patient should be rescreened before proceeding in the study.

9.3 Number of patients

A total of 24 patients will be randomized in the study.

To account for potential drop-outs, additional patients may be included in the study. For replacements of patients who discontinue from the study, see Section 9.8.

9.4 Inclusion criteria

To be eligible to participate in the study, a patient must meet ALL of the following inclusion criteria:

1. Patient is 30 – 85 years old (inclusive) with a diagnosis of idiopathic PD according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnosis criteria.
2. PD patient is stably and optimally treated with L-DOPA; other anti-PD treatments are allowed if used for at least 4 weeks of previous continuous treatment.
3. Patient agrees to be challenged with 150% of their normal L-DOPA dose (maximum L-DOPA dose 250 mg) 30 minutes prior to efficacy assessments at baseline (Visit 2) and at the 2 efficacy clinic visits (Visits 6 and 7).

4. PD patient exhibits troublesome peak-dose LID, confirmed by a score of at least 1 on part IV, item 33 (disability) of the UPDRS at screening (Visit 1) and at Day 1 (baseline, Visit 2).
5. At least 90 minutes in total for each 24-hour period during 2 days are indicated as "ON with troublesome dyskinesia" (according to the PD Home Dyskinesia Diary) prior to Day 1 (baseline, Visit 2).
6. Patient (and/or caregiver) demonstrates ability to accurately complete the PD Home Dyskinesia Diary entries during the screening visit.
7. Patient can read well enough to understand the informed consent document and other subject materials.
8. Female patients of child-bearing potential must have a negative urine pregnancy test at screening (Visit 1) and on Day 1 (Visit 2), must agree to avoid pregnancy during the study, and must practice abstinence (only allowed when this is the preferred and usual lifestyle of the subject) or must agree to use a highly effective method of contraception with a failure rate of < 1% to prevent pregnancy (combined [oestrogen and progestogen containing] hormonal contraception associated with inhibition of ovulation [oral, intravaginal, transdermal], progestogen-only hormonal contraception associated with inhibition of ovulation [oral, injectable, implantable], intrauterine device [IUD] or intrauterine hormone-releasing system [IUS]) starting from 4 weeks prior to administration of the study drug and continuing during the course of the study until 4 weeks after last after IMP administration. Female subjects must agree to refrain from donating eggs from the date of dosing until 3 months after dosing with the IMP. Their male partner must agree to use a condom during the same time frame if he has not undergone vasectomy.
   Females of non-childbearing potential are defined as pre-menopausal females who are sterilised (tubal ligation or permanent bilateral occlusion of fallopian tubes); or females who have undergone hysterectomy or bilateral oophorectomy; or post-menopausal defined as 12 months of amenorrhea (in questionable cases a blood sample with detection of follicle stimulating hormone [FSH] 25-140 IE/L is confirmatory).

   Male patients must be either vasectomised, consent to use condom or practice sexual abstinence to prevent pregnancy and drug exposure of a partner and refrain from donating sperm from the date of dosing until 3 months after dosing with the IMP. Their female partner of child-bearing potential must use highly effective contraceptive methods with a failure rate of < 1% to prevent pregnancy (see above) during the same period.

9.5 Exclusion criteria

If the patient meets any of the following criteria, the patient MUST NOT be enrolled:

1. Patient has severe PD with a Hoehn and Yahr stage = 5.
2. Patient has unstable medical status, prior brain surgery against tumors or hemorrhage (excluding deep brain stimulation [DBS], i.e., DBS patients will be allowed to be enrolled) or is scheduled to receive surgery during the trial period.

3. Patient has orthostatic hypotension: a decrease in systolic blood pressure (at least 20 mm Hg) or diastolic blood pressure (at least 10 mm Hg) within 3 minutes of the patient standing up, compared to pressures obtained while in a sitting position for at least 5 minutes. At screening and baseline visits (Visit 1 and Visit 2), vital signs to assess orthostatic hypotension will be conducted in triplicate, 15-20 minutes apart, with the average of the 3 assessments used for exclusion.
4. Patient has dementia (MMSE <20).
5. Patient has clinically significant renal or liver disorder.
6. Patient currently exhibits generalized obsessive-compulsive disorder, panic disorder, bipolar disorder, post-traumatic stress syndrome (PTSD), clinically significant parasomnias or any other psychotic disorder as established by structured clinical interview for DSM disorders (SCID). Visual hallucinations are allowed.
7. Any suicidal actions in the past 2 years (per investigator judgement i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior).
8. Any suicidal ideation of type 4 or 5 in the C-SSRS in the past 3 months (i.e. active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent).
9. Patient has taken an anti-convulsant, an anti-psychotic (except quetiapine), pindolol, tertatolol or buspirone within 4 weeks of baseline (Day 1, Visit 2).
10. Patient has taken any medication, within 4 weeks of baseline (Day 1, Visit 2) that inhibits or up-regulates CYP4503A4, see Section 9.6.2.
11. Patient is concurrently participating in another investigational drug trial or has participated in another investigational drug trial within the past 3 months.
12. Patient is at high risk of non-compliance in the Investigator's opinion.

9.6 Restrictions during the study

The patients must be willing to comply to the following restrictions during the entire study duration *i.e.*, from screening to the end-of-study visit.

9.6.1 *General restrictions*

- Contraception Requirements:

  All females of child-bearing potential must use highly effective contraception (defined in inclusion criterion No 8) or practice abstinence during the study and for 4 weeks after IMP administration and refrain from donating eggs from the date of dosing until 3 months after dosing with the IMP. Their male partner is expected to use a condom during the same time frame if he has not undergone vasectomy.
  The male patients must be either vasectomised, consent to use condom or practice sexual abstinence to prevent pregnancy and drug exposure of a partner and refrain from donating sperm from the date of dosing until 3 months after dosing with the IMP. Their fertile female partner is expected to use highly effective contraceptive methods to prevent pregnancy (for details, refer to inclusion criterion No 8) during the same period.

- Meals and Dietary Restrictions: The IMPs should be taken during a meal and swallowed with approximately 240 mL of tap water.
- Products affecting CYP450 3A4 activity: Consumption of grapefruit and/or grapefruit containing products or star fruit is not allowed during the study.
- Blood donation: The patients must not donate blood or plasma during the study until 3 months after the final medical examination at the end-of-study visit.

9.6.2 *Prior and concomitant therapy*

Use of an anti-convulsant, an anti-psychotic (except quetiapine), pindolol, tertatolol or buspirone within 4 weeks of baseline (Day 1, Visit 2) and during the study is prohibited.

In addition, the following drugs which may affect CYP450 3A4 activity are prohibited from 4 weeks prior to baseline (Day 1, Visit 2) and during the study:

Inducers: barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, phenobarbital, phenytoin, rifampin, Saint-John's wort, troglitazone, oxcarbazepine, pioglitazone, rifabutin.

Inhibitors: amiodarone, aprepitant, chloramphenicol,cimetidine, clarithromycin,delaviridine, diethyl-dithiocarbamate, diltiazem, erythromycin, fluconazole, fluvoxamine, gestodene, imatinib, indinavir, itraconazole, ketoconazole, mifepristone, nefazodone, nelfinavir, norfloxacine, norfluoxetine, mibefradil, verapamil, ritonavir, voriconazole.

Prohibited concomitant medications also include those, which in the Investigator's opinion (with Sponsor agreement), may negatively interact with the study medication NLX-112 and lead to untoward side effects or otherwise affect patient safety.

Medications considered necessary for the patient's safety and wellbeing may be given at the discretion of the Investigator. Following consultation with the Sponsor, the Investigator will determine whether or not the patient should continue in the study.

Use of selective serotonin reuptake inhibitors (SSRIs), benzodiazepines and amantadine is allowed as is occasional use of apomorphine as judged by the Investigator. In addition, Covid-19 vaccination is allowed.

9.7 Screen failures

Screen failures are defined as patients who consent to participate in the clinical study by signing the ICF, but do not fulfil all eligibility criteria and are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients. Minimal information includes documentation of signed and dated informed consent form (ICF), age, gender and reason(s) for screening failure.

Rescreening can be performed once if any of the following were reasons for screening failure or non-randomization (as judged by the Investigator):

- Practical reasons.
- Non-significant medical conditions (e.g. influenza, nasopharyngitis).
- Plasma or blood donation or use of prior medications outside allowed time windows.

For patients who are rescreened, a new screening number will be assigned and a new, signed ICF will be collected.

9.8 Patient withdrawal

9.8.1 *General withdrawal criteria*

Patients are free to discontinue their participation in the study at any time and for whatever reason without affecting their right to an appropriate follow-up investigation or their future care. If possible, the reason for withdrawal of consent should be documented.

Patients may be discontinued from the study at any time at the discretion of the Investigator.

Reasons for discontinuation include:

- Patient decision (withdrawal of consent)
- Severe non-compliance to study protocol procedures, as judged by the Investigator and/or Sponsor
- Permanent discontinuation of IMP. Temporarily treatment interruptions of ≥3 days may result in study discontinuation as judged by the Investigator and Sponsor.
- Patient is lost to follow-up. If a patient misses a scheduled visit and is repeatedly unable to be contacted, the patient will be withdrawn from the study.
- Significant AEs posing a risk for the patient, as judged by the Investigator and/or Sponsor
- Withdrawal of informed consent to the use of biological samples
- Pregnancy
- Death - Request an autopsy report
- Use of prohibited medication as judged by the Investigator and/or Sponsor
- The patient exhibits serious suicidality, in the clinical judgement of the investigator or according to criteria below:
    - Any suicidal behavior (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior)
    - Any suicidal ideation of type 4 or 5 in the C-SSRS (i.e. active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent)

9.8.2 *QTc withdrawal criteria*

A patient meeting the criteria below will be withdrawn from the study. The same QT correction formula will be used to determine discontinuation throughout the study.

- QTcF > 500 msec
- Change from baseline: QTc > 60 ms

Withdrawal decisions will be based on an average QTc value of triplicate ECGs. If an ECG demonstrated a prolonged QT interval, 2 more ECGs will be obtained over a brief period and

the averaged QTc values of the 3 ECGs used to determine whether the patient should be discontinued from the study.

9.8.3 *Liver chemistry withdrawal criteria*

Liver chemistry threshold stopping criteria have been designed to assure patient safety and to evaluate liver event etiology. Study treatment will be stopped for the individual patient if any of the following liver chemistry stopping criteria, defined in the U.S. Food and Drug Administration (FDA) Guidance on Drug-Induced Liver Injury [22], is met:

- Alanine aminotransferase (ALT) 3 x upper limit of normal (ULN) and total bilirubin ≥ 2xULN (>35% direct bilirubin); **or** ALT 3xULN and INR > 1.5)

NOTE: plasma bilirubin fractionation will be performed. Bilirubin is also measured via urine dipstick (a measurement of direct bilirubin, which would suggest liver injury).

- ALT 5xULN.
- ALT 3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).

- Patients with ALT 3xULN **and** < 5xULN **and** bilirubin < 2xULN, who do not exhibit hepatitis symptoms or rash, will be allowed to continue study treatment as long as they are monitored weekly for 4 weeks.

9.8.4 *Procedures for discontinuation of a patient from the study*

A patient who prematurely discontinues participation in the study will always be asked about the reason(s) for discontinuation and the presence of any AEs. If a patient withdraws consent, the Investigator must ask the patient if he/she is willing, as soon as possible, to be assessed according to the procedures scheduled for the final follow-up visit (Visit 9). If the patient withdrew consent, was non-compliant, or was lost to follow-up, no further follow-up will take place after the final clinical evaluation. The Sponsor will determine on a case-by-case basis if a patient who withdraws for other reasons requires follow-up after the final clinical evaluation. Any ongoing AEs will be followed as described in Section 11.2.1.15. Pregnancies will be followed as described in 11.2.1.16.

The primary reason for discontinuation/early withdrawal must be specified in the eCRF and final drug accountability must be performed.

9.8.5 *Patient replacement*

Patients who are prematurely withdrawn from the study for any reason except the occurrence of AEs assessed as possibly or probably related to study treatment may be replaced during the course of the study.

9.9 Randomization

On Day 1, patients will be randomized to receive either NLX-112 or placebo. The randomization will be performed per site using SAS with the ratio 2:1 for active treatment to placebo. This will give approximately 16 patients receiving NLX-112 and 8 patients receiving

placebo in total in the study. In addition, approximately the same ratio will be attained within each site. The study will use competitive enrollment between sites.

9.10 Blinding

This is a double-blind study and the allocation of treatments will not be disclosed until clean file has been declared and the database has been locked.

The IMP and the placebo are identical in appearance and taste.

9.11 Emergency unblinding during the study

The treatment code may only be broken by the Principal Investigator or delegate in case of emergency when knowledge of the treatment received is necessary for the proper medical management of the patient. This will either be performed via the EDC system or using sealed individual, treatment code envelopes that are kept at the clinic in a locked and restricted area. The code breaking procedure should be carefully documented.

For unblinding procedures in case of a potential suspected unexpected serious adverse reaction (SUSAR), refer to Section 11.2.1.14.

10 TREATMENTS

10.1 Identity of investigational medicinal products

NLX-112 will be supplied as tablets containing 0.25 mg NLX-112.

Placebo will be matching tablets (identical weight, shape and color) without NLX-112.

10.2 Manufacturing, packaging and labelling

The IMP, including placebo, is manufactured by Sharp Clinical, Bethlehem, United States.

Labels will comply with applicable Good Manufacturing Practice (GMP), with Annex 13 of the European Union GMP regulations and local regulatory requirements [23].

10.3 Importation, release and distribution

The IMP will be imported, released and distributed by ClinStorage, Solna, Sweden.

10.4 Conditions for storage

All study drug must be stored and disposed of according to the Sponsor's instructions. Study drug must be stored at the study site in a limited-access area or in a locked cabinet at ambient room temperature.

Temperature logs will be kept for the area where the IMP is stored. The temperature should be noted on a daily basis (working days only unless automatic temperature readings are available).

IMP that is brought home by the patients should be stored at room temperature.

10.5 Dispensing and accountability

The IMP received at the site must be inventoried and accounted for throughout the study. The Investigator will maintain a Storage and Accountability Log as well as a Drug Dispensing Log detailing the dates and quantities of study medication received, prepared for and used by each patient and study medication returned or destroyed at the end of the study. Patients must be instructed to return all original containers, whether empty or containing drug.

Unused study drug, and study drug returned by the patient, must be available for verification by the study site monitor during on-site monitoring visits. Any discrepancies between prepared and returned study must be explained and documented. Products deliberately and/or accidentally destroyed by the site or the patient must be accounted for.

Study drug must be dispensed under the supervision of the Investigator or qualified designee, or by a hospital/clinic pharmacist.

At Visits 2, 6 and 7 (Day 1, Day 28, and Day 42) patients will be provided with a small bottle of tablets with explicit dosing instructions, including a dosing instruction sheet as well as a worksheet to keep track of daily doses. The bottle will contain sufficient drug supplies to last until the next scheduled clinic visit. Patients will return the previously used bottle at the next clinic visit including any unused IMP.

10.6 Treatment administration

Patients will self-administer NLX-112 or placebo 2 times each day, once in the morning and once in the evening, according to a dosing instruction sheet. Tablets should be taken with approximately 240 mL water during a meal.

10.7 Continuation of treatment with investigational medicinal product

There will be no treatment with NLX-112 after end of study participation.

10.8 Treatment compliance

Patients will self-administer the IMP at home. At each visit to the clinic, patients will be asked to return any unused IMP and all empty/partially used IMP containers.

Treatment compliance may also be addressed by NLX-112 plasma concentration measurements at visits outlined in Table 8.1-1.

10.9 Return and destruction of investigational medicinal products

Following confirmation by the Sponsor, any unused study medication will be returned to ClinStorage AB, Solna, Sweden for destruction or subsequent return to the Sponsor. Empty containers will be destroyed at the study site. The Monitor will perform final IMP accountability reconciliation at the study end to verify that all unused IMP is adequately destroyed/returned and documented.

11 STUDY ASSESSMENTS

The study assessments are described in the sections below and the timing of these assessments are detailed in the schedule of events (Table 8.1-1)

11.1 Recording of data

The Principal Investigator will provide the Sponsor with all data produced during the study from the scheduled study assessments. He/she ensures the accuracy, completeness, legibility, and timeliness of the data reported to Sponsor in the eCRF and in all required reports.

11.1.1 *Informed consent*

Signed informed consent must be obtained before any screening procedures are initiated. The informed consent procedure is further described in Section 14.3.

11.1.2 *Eligibility criteria*

Eligibility criteria should be checked during screening and verified before randomization. The criteria are specified in Sections 9.4 and 9.5.

11.1.3 *Demographic information*

The following demographic data will be recorded: gender, age, ethnicity and race.

11.1.4 *Weight and height*

Weight and height will be measured with the patient wearing light clothes and no shoes. Body mass index (BMI) will be calculated, with one decimal, from the height and weight recorded.

11.1.5 *Medical and psychiatric history*

A complete medical and psychiatric history will include evaluation for past or present cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, endocrine, metabolic, lymphatic, hematologic, immunologic, dermatologic, psychiatric, genitourinary, drug, and surgical history, or any other diseases or disorders (including past diagnosis of HIV or hepatitis B/C).

As part of the medical history at screening, patients will be evaluated using the C-SSRS (Section 11.2.5), which will be scored by the Investigator to confirm the patient's eligibility for the study.

11.1.6 *Prior and concomitant medication*

Medications taken within 4 weeks of the screening visit (Visit 1) will be obtained by patient interview.

Medications are classified as prior if the stop date was before or on the day of the first dose administration (pre-dose) and as concomitant if ongoing on the day of the first dose administration, stopped after the first dose administration or started after the first dose administration. To distinguish between prior and concomitant medications on Day 1 (i.e. the

first dosing day), the start time of any newly introduced medication or the stop time of any previously ongoing medication must be recorded in the eCRF.

Any use of prior or concomitant medication from screening until the last end-of-study visit must be documented appropriately in the patient's eCRF. Relevant information (*i.e.* name of medication, dose, dose form, unit, route, frequency, start and stop dates, reason for use) must be recorded. All changes in medication should be noted in the eCRF.

11.1.7 *Pregnancy test*

All women of child-bearing potential will do a urine pregnancy test at screening (Visit 1) and at baseline (Visit 2).

11.1.8 *Hoehn and Yahr scale*

The Modified Hoehn and Yahr scale will be used to establish the PD stage of the patient. The modified scale includes 7 stages (1, 1.5, 2, 2.5, 3, 4 and 5) where stage 1 corresponds to unilateral involvement only and 5 to wheelchair bound or bedridden unless aided.

11.1.9 *Mini Mental Status Exam*

The Mini Mental Status Exam (MMSE) is a 30-point questionnaire used to measure cognitive impairment. The MMSE will be used to screen for dementia. Any score of 24 or more (out of 30) indicates a normal cognition. Below this, scores can indicate severe (≤9 points), moderate (10–18 points) or mild (19–23 points) cognitive impairment.

11.1.10 *Baseline symptoms*

A baseline symptom is defined as an event that occurs between the patient's signing of the ICF until the first administration of IMP (i.e. an event that occurs during the screening period). Such events are not AEs and will be recorded as baseline symptoms in the Medical History Log in the eCRF.

11.2 Assessments related to primary endpoints

11.2.1 *Adverse events*

The Principal Investigator is responsible for ensuring that all medical staff involved in the study is familiar with the content of this section and the content of the standard operating procedures (SOPs) of each site regarding emergencies.

11.2.1.1 Definition of adverse event

An AE is defined as any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Worsening of dyskinesias (except those associated with the 150% L-DOPA challenge) or PD symptoms compared to baseline will be reported as AEs.

11.2.1.2 Definition of serious adverse event

An SAE is any AE which:

- results in death,
- is life-threatening (this refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have led to death if the reaction was more severe),
- requires in-patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is an important medical event (IME) (this refers to a reaction that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent any of the other outcomes defined above).

Examples of IMEs are intensive treatment in an emergency room for allergic bronchospasm or blood dyscrasias, convulsions that do not result in hospitalization, development of drug dependency, and drug abuse.

Planned hospitalizations or surgical interventions for a condition that existed before the patient signed the ICF and that did not change in intensity are not SAEs.

If there is any doubt as to whether an AE meets the definition of an SAE, a conservative viewpoint must be taken, and the AE must be reported as an SAE.

11.2.1.3 Definition of adverse drug reaction

The term ADR is to be used whenever either the Investigator or Sponsor or designee assessed the AE as at least possibly related to the IMP.

11.2.1.4 Definition of serious adverse drug reaction

The term Serious Adverse Drug Reaction (SADR) is to be used whenever either the Investigator or Sponsor or designee assessed the SAE as at least possibly related to the IMP.

11.2.1.5 Definition of suspected unexpected serious adverse reaction

A SUSAR is any SADR whose nature or intensity is not consistent with the current Reference Safety Information (RSI) in the IB and therefore is assessed as unexpected.

11.2.1.6 Time period and frequency for collecting adverse events

All AEs (including SAEs) will be collected from the start of IMP administration until the end-of-study visit.

Any AE with start date on the day of IMP administration will, if possible, be recorded with start time.

At the end-of-study visit, information on new AEs or SAEs, if any, and stop dates for ongoing events must be recorded as applicable.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

11.2.1.7 Assessment of intensity

The grading of the intensity of AEs will follow the common terminology criteria for AEs (CTCAE) v5.0 [24]. Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline.

The Investigator must assess the intensity of an AE using the following definitions, and record it on the AE Log in the eCRF:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self- care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

**Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

***Self- care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*

11.2.1.8 Assessment of causal relationship

The Investigator must assess the causal relationship between an AE and the IMP using the definitions below and record it the AE Log of the eCRF:

Probable	The event has a strong temporal relationship to the IMP or recurs on re-challenge, and another etiology is unlikely or significantly less likely.
Possible	The event has a suggestive temporal relationship to the IMP, and an alternative etiology is equally or less likely.
Unlikely	The event has no temporal relationship to the IMP or is due to underlying/concurrent illness or effect of another drug (that is, there is no causal relationship between the IMP and the event).

An AE is considered causally related to the use of the IMP when the causality assessment is probable or possible.

11.2.1.9 Assessment of outcome

The Investigator must assess the outcome of an AE using the definitions below and record it on the AE Log of the eCRF:

Recovered/resolved	The patient has recovered completely, and no symptoms remain.
Recovering/resolving	The patient's condition is improving, but symptoms still remain.
Recovered/resolved with sequelae	The patient has recovered, but some symptoms remain (for example, the patient had a stroke and is functioning normally but has some motor impairment).
Not recovered/not resolved	The patient's condition has not improved and the symptoms are unchanged (for example, an atrial fibrillation has become chronic).
Fatal	
Unknown	

11.2.1.10 Reporting of action taken with study treatment

The Investigator must report the action taken with study treatment using the definitions below and record it on the AE Log of the eCRF:

Dose increased

Dose not changed

Dose rate reduced

Dose reduced

Drug interrupted

Drug withdrawn

Not applicable

Unknown

11.2.1.11 Collecting adverse events

AEs identified using any of the following methods will be recorded:

- AEs spontaneously reported by the patient.
- AEs observed by the Investigator or medical personnel.
- AEs elicited based on non-leading questions from the Investigator or medical personnel.

11.2.1.12 Recording adverse events

AEs must be recorded in the AE Log of the eCRF. The Investigator must provide information on the AE, preferably with a diagnosis or at least with signs and symptoms; start and stop dates, start and stop time; intensity; causal relationship to IMP; action taken, and outcome.

If the AE is serious, this must be indicated in the eCRF.

AEs, including out-of-range clinically significant clinical safety laboratory values, must be recorded individually, except when considered manifestations of the same medical condition or disease state; in such cases, they must be recorded under a single diagnosis.

11.2.1.13 Reporting of serious adverse events

SAE reporting should be performed by the Investigator within 24 hours of awareness via the eCRF. All available information regarding the SAE should be entered in the eCRF SAE form (i.e. term, intensity, causality, outcome, SAE criteria, action taken, narrative including rational for causality assessment) for the specific patient. By saving the event as "serious" in the eCRF and once the Investigator has signed-off of the event, an e-mail alert is automatically sent to predefined recipients to highlight that an SAE has been registered. The same information is automatically sent to sae@ctc-ab.se.

The SAE report is reviewed by a designated person at CTC AB's Pharmacovigilance department to ensure that the report is valid and correct. For fatal or life-threatening SAEs where important or relevant information is missing, immediate follow-up is undertaken and queries to the site are raised. Investigators or other site personnel should inform the Pharmacovigilance department of any follow-up information (including rational for changes, e.g. changes in causality assessment and intensity, that should be described in the SAE narrative) on a previously reported SAE immediately but no later than within 24 hours of awareness.

If the SAE report in the eCRF is updated and signed by the Investigator, a new e-mail alert will be sent.

If any additional documentation is required (e.g. autopsy report), CTC Pharmacovigilance will request this information from the study site.

In case the eCRF cannot be accessed, the SAE should be reported by manual completion of the paper SAE Form, provided in the Investigator Site File (ISF). The completed, signed and dated paper SAE Form should, within 24 hours, be scanned and e-mailed to:

Medical Monitor: [redacted]

A copy of the paper SAE form must also be e-mailed to CTC AB at: sae@ctc-ab.se.

The study site should notify the site Monitor via phone or e-mail about the submission of the SAE report. As soon as the site personnel have access to the eCRF, the SAE should be reported electronically as well.

11.2.1.14 Reporting of SUSARs to EudraVigilance, local competent authority and independent ethics committee

The term SADR is used whenever either the Investigator or Medical Monitor deems a blinded SAE as possibly or probably related to IMP. If an SADR is assessed as unexpected by the Medical Monitor, it is a potential SUSAR and under such circumstances an EudraVigilance reporter will be unblinded. In case the event is regarded as a SUSAR the EudraVigilance

reporter will report the SUSAR to the local competent authority (CA), via the EudraVigilance database, and to the independent ethics committee (IEC) in accordance with local regulations and CTC AB's SOPs within the following timelines:

- 7 calendar days if fatal or life-threatening (follow-up information within an additional 8 days)
- 15 calendar days if non-fatal and non-life-threatening (follow-up information as soon as possible)

The clock for expedited initial reporting (Day 0) starts as soon as the Sponsor becomes aware of an SAE. The date should be documented on an acknowledgement receipt.

The Medical Monitor is responsible for medical review of the SAE narrative in the Council for International Organizations of Medical Sciences (CIOMS) for (or equivalent) prior to expedited reporting.

The Sponsor has delegated to CTC AB the responsibility to report SUSARs to the EudraVigilance database.

The Sponsor or delegate is responsible for, once a year throughout the clinical study (or on request), submitting a safety report to the CA and the IEC taking into account all new available safety information received during the reporting period.

11.2.1.15 Treatment and follow-up of adverse events

Patients with AEs that occur during the study must be treated according to daily clinical practice at the discretion of the Investigator.

AEs must be followed up until resolution or to the end-of-study visit, whichever comes first. At the end-of-study visit, information on new AEs, if any, and stop dates for previously reported AEs must be recorded (if known). AEs assessed as stable by the Investigator at the end-of-study visit will not have to be followed up until resolution.

It is the responsibility of the Investigator to follow up on all SAEs until the patient has recovered, stabilized, or recovered with sequelae, and to report to the Sponsor all relevant new information using the same procedures and timelines as those for the initial report. Relevant information includes discharge summaries, autopsy reports, and medical consultation.

Patients who withdraw from the study due to an AE must be followed by the Investigator for 30 days after the last dose of NLX-112 or until the AE is considered resolved or stabilized.

11.2.1.16 Procedures in case of pregnancy

In case of pregnancy or suspicion of possible pregnancy of any female patients the study treatment must be stopped immediately, and the patient discontinued from participation in the study.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP may have interfered with the effectiveness of the contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even after the patient was discontinued from the study. The outcome of all pregnancies of a female partner to a male patient must also

be followed up and documented, yet the male patient does not need to be discontinued from the study.

Patients who withdraw from the study due to pregnancy will be followed until the resolution of the pregnancy. Follow-up for pregnancy will include regular documented patient contacts to ascertain the pregnancy status until the final outcome of the pregnancy is known.

All events of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as AEs. All outcomes of pregnancy must be reported to the Sponsor and the Principal Investigator on the pregnancy outcomes report form.

11.2.1.17 Treatment of overdose

An overdose is a dose in excess of the dose specified for each cohort in this clinical study protocol (CSP).

In cases of accidental overdose, standard supportive measures should be adopted as required.

An overdose should be documented as follows:

- An overdose with associated AE is recorded as the AE diagnosis/symptoms in the AE Log of the eCRF.
- An overdose without associated symptoms is only reported in the patient's medical records.
- Registered in the protocol deviations log.

No known antidote is available.

11.2.2 ***Physical examination***

The physical examination should include examination of the following: general appearance, head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, abdominal system, and nervous system.

Any abnormalities will be specified and documented as clinically significant (CS) or not clinically significant (NCS). Abnormal post-dose findings assessed by the Investigator as clinically significant will be reported as AEs.

11.2.3 ***Vital signs***

Blood pressure (systolic and diastolic) and pulse will be measured in sitting position after at least 5 minutes of rest and then again 3 minutes after standing upright to determine whether the patient has orthostatic hypotension (decrease in systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg within 2 minutes of the patient standing up, compared to the blood pressure obtained while in the sitting position). At screening and baseline (Visit 1 and Visit 2), the investigator should collect 3 assessments, each taken 15 to 20 minutes apart, in order to obtain an average value. All measurements and the calculated average value should be recorded in the eCRF. At other visits, one assessment is sufficient.

Respiratory rate will be assessed by routine methods. Body temperature will be measured orally using a digital thermometer.

Any vital signs outside the normal ranges at each site will be judged as NCS or CS. The assessment will be recorded in the eCRF. Post-dose vital signs judged as “abnormal, clinically significant” by the Investigator will be reported as AEs.

11.2.4 *Electrocardiogram*

Single 12-lead ECG will be recorded in supine position after at least 5 minutes of rest using an ECG machine. The following parameters will be recorded: rhythm, ventricular rate, PR interval, QRS duration, QT, QTcB, and QTcF. In case of an abnormal ECG, the ECG will be repeated once as judged by the Investigator. In case of a QTcF ≥500 ms, refer to the withdrawal criterion in Section 9.8.2.

Any abnormalities will be specified and documented as clinically significant or not clinically significant. Abnormal post-dose findings assessed by the Investigator as clinically significant will be reported as AEs.

11.2.5 *Columbia Suicide Severity Rating Scale (C-SSRS)*

The C-SSRS is an assessment tool designed to quantify the severity of suicidal ideation and behavior as rated by the investigator. The baseline scale will be used at screening (Visit) and the follow-up scale at all subsequent visits as specified in Table 8.1-1.

The scale contains 6 "yes" or "no" questions in which respondents are asked to indicate whether they have experienced several thoughts or feelings relating to suicide over the past month and behavior over their lifetime and past 3 months. Each question addresses a different component of the respondent's suicide ideation severity and behavior.

- Question 1: wish to be dead
- Question 2: non-specific suicidal thoughts
- Questions 3-5: more specific suicidal thoughts and intent to act
- Question 6: suicidal behavior over the respondent’s lifetime and past 3 months
- If the respondent answers "yes" to Question 2, he/she is instructed to answer Questions 3-5. If the respondent answers "no" to Question 2, he/she may skip to Question 6.

An answer of "yes" to any of the 6 questions may indicate a need for referral to a trained mental health professional and an answer of "yes" to questions 4, 5 or 6 indicate high-risk.

11.2.6 *Laboratory safety assessments*

Blood samples for analysis of clinical chemistry, hematology and coagulation parameters will be collected through venipuncture or an indwelling venous catheter and analyzed by routine analytical methods by local hospital laboratories. Urine analysis will be performed at the research clinic using dip sticks. Pregnancy test (urine) will be performed at the research clinic at screening.

All safety laboratory parameters are defined in Table 11.2-1 and will be assessed at time-points detailed in (Table 8.1-1). The safety laboratory results will be recorded in the eCRF by site personnel.

Any lab values outside the normal ranges will be judged as NCS or CS. The assessment will be recorded in the eCRF. Abnormal values assessed by the Investigator as clinically

significant will be reported as AEs. If an abnormal value is associated with corresponding clinical signs or symptoms, the sign/symptom should be reported as the AE.

Table 11.2-1 Safety laboratory parameters

Category	Parameter
Clinical chemistry	Alanine aminotransferase (ALT)
	Albumin
	Alkaline phosphatase (ALP)
	Aspartate aminotransferase (AST)
	Bilirubin (total and conjugated)
	Calcium
	Chloride
	C-reactive protein (CRP) (screening only)
	Creatine phosphokinase (CPK)
	Creatinine (eGFR included)
	Gamma glutamyl transpeptidase (GGT)
	Glucose
	Phosphate
	Potassium
	Sodium
	Urea (nitrogen)
	Uric acid
Hematology	Hematocrit
	Hemoglobin (Hb)
	Platelet count
	Red blood cell (RBC) count
	White blood cell (WBC) count with differential count
	Mean corpuscular volume (MCV)
	Mean corpuscular hemoglobin (MCH)
	Mean corpuscular hemoglobin concentration (MCHC)
Coagulation	Activated Partial Thromboplastin Time (APTT)
	Prothrombin Complex International Normalized Ratio (PK[INR])
Urinalysis (dip stick)	Bilirubin
	Blood
	Erythrocytes
	Glucose
	Ketones
	Leucocytes
	Nitrites
	pH
	Albumin
Pregnancy test	Urine pregnancy test at screening[1]

[1] Females of child-bearing potential only

11.3 Assessments related to secondary endpoints

An independent neurologist or the treating physician will rate patients at each clinical site. At each applicable visit (Visits 2, 6 and 7), the same rater (if possible) will conduct efficacy

assessments beginning 30 minutes after the patient has taken 150% of his or her regular L-DOPA dose, when the patient is ON and experiencing typical dyskinesia.

Efficacy in treating LID, as well as other non-motor symptoms of PD, will be assessed with the UDysRS, UPDRS, CGI-S, CGI-C, PDQ39, and a PD Home Dyskinesia Diary (electronic). Dyskinesia will also be monitored using a wearable dyskinesia assessment device. In addition, 2 exploratory scales, the KPPS and the ICIQ-OAB will assess potential treatment effects on various types of pain and on overactive bladder, respectively, and one assessment of sleep (the ESS) will be used to evaluate sleep quality, sleep disturbances and sleepiness while engaged in 8 activities.

The details of the rating scales, the patient diary, and the wearable dyskinesia assessment device are presented below.

11.3.1 *L-DOPA challenge*

The patient will take 150% of their normal L-DOPA dose 30 minutes prior to the start of efficacy assessments (UDysRS) at Day 1 (Visit 2), Day 28 (Visit 6) and Day 42 (Visit 7), see Table 8.1-1 and Section 11.3.2.

The challenge should be performed approximately 2 to 2.5 hours after the patient's morning dose (which is also generally around 150%).

Patients who use continuous intestinal levodopa infusion (Duodopa or Lecigon) should instead stop the infusion for 15-30 minutes before the administration of an oral levodopa dose equivalent to 300% of their hourly infusion levodopa equivalent dose (LED*). The time of the day and the time between stopping the pump and administering the oral dose should be the same on all assessments.

*) 100 mg Duodopa = 111 mg LED, 100 mg Lecigon = 148 mg LED

The maximum L-DOPA dose to be given is 250 mg.

The UDysRS (Parts III and IV) will be repeated 3 times after each L-DOPA challenge, 30 minutes apart, and will hence be performed approximately 30, 60 and 90 minutes after each challenge.

Should the Investigator consider it medically warranted to reduce the L-DOPA challenge in a specific patient for safety or tolerability reasons, this should be approved by the Sponsor prior to implementation. It is critical that the same dose is given at all visits with L-DOPA challenges for a given patient.

11.3.2 *Unified Dyskinesia Rating Scale (UDysRS)*

The UDysRS is a rating instrument designed to assess the core features of dyskinesia in Parkinson's Disease. The UDysRS consists of 4 parts:

- Part I, historical disability with regard to the patient's perceptions of the impact on activities of ADL of on-dyskinesia.
- Part II, historical disability with regard to the patient's perceptions of the impact on ADL of off-dystonia.
- Part III, objective impairment, which assesses severity of dyskinesia, affected body parts, and type of impairment (choreic vs. dystonic).

- Part IV, objective disability, based on an evaluation of Part III activities.

Each item in the UDysRS is scored from 0 to 4, with a possible maximum total score of 104.

The UDySRS assessment will be performed at baseline (Day 1, Visit 2), Day 28 and Day 42 (Visits 6 and 7), see Table 8.1-1, starting approximately 30 minutes after the L-DOPA challenge on these days. The UDysRS (Parts III and IV) will be repeated 3 times after each L-DOPA challenge, 30 minutes apart, and will hence be performed approximately 30, 60 and 90 minutes after each challenge.

The data for all 3 assessments performed at each visit will be entered in the eCRF and the Investigator will highlight which of the assessments, corresponding to the assessment where the patient had most severe dyskinesia, that will be used in the descriptive summaries of data.

The UDysRS assessments will be videotaped at Visits 2, 6 and 7. The video recordings are planned to be used as a backup to the standard investigator rating; for example, to ensure consistency between assessments in case several assessors are involved, or if other issues arise. It may be possible that all video recordings are assessed by a common central rater..

11.3.3 *PD Home Dyskinesia Diary*

A PD Home Dyskinesia Diary (electronic) will be completed by the patients and/or caregiver with concordance in ON time with dyskinesia between study staff and patient. The diary is integrated in the Kinesia 360 wearable dyskinesia assessment system (Section 11.3.6) and is based on the PD Home Diary developed by Hauser et al 2004 [26]. The diary will be used to score 5 different conditions in 30-minute time intervals during 2x24 hours prior to Visit 2, Visit 6 and Visit 7:

- ASLEEP;
- OFF;
- ON (i.e., adequate control of PD symptoms) without dyskinesia;
- ON with non-troublesome dyskinesia;
- ON with troublesome dyskinesia.

11.3.4 *Unified Parkinson's Disease Rating Scale (UPDRS)*

The UPDRS is one of the most widely-used rating scales employed in the assessment of Parkinson's disease. The UPDRS consists of 4 parts:

- Part I assesses non-motor experiences of daily living, such as cognitive impairment and depressed mood.
- Part II assesses motor experiences of daily living, such as speech and eating tasks.
- Part III is a motor examination conducted by the clinician, including assessments of symptoms such as rigidity and tremor.
- Part IV is an assessment of motor complications, such as time spent with dyskinesia and functional impact of dyskinesias.

Each item in the UPDRS is scored from 0 to 4, and the individual scores are summed to give a total score that indicates the severity of the disease, with a score of 0 indicating no disability and a score of 199 being the most severe (indicating total disability).

For timing of assessments, refer to Table 8.1-1.

11.3.5 *Clinical Global Impression of Severity and Change (CGI-S, CGI-C)*

The CGI-C is a clinician-oriented scale that assesses the total improvement in the patient's condition relative to the clinical global impression of severity (CGI-S) scale conducted at baseline. The CGI-C rates the patient's condition from 0 to 7, with a rating of 0 indicating "no assessment", a rating of 1 indicating "very much better", and a rating of 7 indicating "very much worse".

For timing of assessments, refer to Table 8.1-1.

11.3.6 *Wearable dyskinesia assessment device*

The Kinesia 360 (Great Lakes Neurotechnologies, Inc) wearable dyskinesia assessment system will be used to monitor dyskinesias. Wearable data collection of dyskinesias will take place during a 2-day period prior to the baseline visit (Visit 2) and a 2-day period prior to the clinic visits on Days 28 and 42 (Visits 6 and 7, respectively).

The Kinesia 360 motor assessment system provides low burden method for remote, continuous measurement of patient symptoms. Sensors worn on the wrist and ankle combined with a mobile application continuously record data for assessment of tremor, slowness, dyskinesia and mobility. Data from the motion sensors is uploaded to the Kinesia Web Portal and algorithms are used to detect symptoms and calculate severity scores every 2 minutes on a scale shown to be highly correlated with clinician ratings. Sensors record data all day and recharge overnight for extended home use.

Each patient will be trained and provided with a user guide in Swedish, sensors and a smartphone that is preloaded with the Kinesia 360 software app. The app guides patients through daily use and includes electronic diaries for capturing patient-reported outcomes (see Section 11.3.3) and a medication diary. The system also includes mobile device management to ensure that the software is always current.

Motion and diary data are transmitted to a secure cloud via mobile broadband for processing and storage in a 21 CFR Part 11 compliant database. Clinicians and researchers can access reports via the Kinesia web portal and view real-time patient compliance.

Each site will be trained by the manufacturer.

11.4 Assessments related to exploratory endpoints

11.4.1 *King's Parkinson's Disease Pain Scale (KKPS)*

The KPPS is a rater-interview-based scale conducted with the patient and caregiver (if available). It is a 14-item scale covering 7 domains of pain:

- Musculoskeletal pain
- Chronic pain
- Fluctuation-related pain
- Nocturnal pain
- Orofacial pain

- Edema/swelling; discoloration
- Radicular pain

Each item is scored by severity (0 - 3; none to very severe) multiplied by frequency (0 - 4; never to all the time), for an item sub score of 0-12, resulting in a total score from 0 to 168. Ratings are based on the previous month, or in the case of this study, the intervening period since the previous clinic visit (about 3 weeks). Treatment effects will be analyzed as change from baseline for total score and for individual pain domains.

For timing of assessments, refer to Table 8.1-1.

11.4.2 *Parkinson's Disease Questionnaire (PDQ39)*

The PDQ39-item patient reported outcome of health status and quality of life and is the most frequently used disease-specific health status measure for PD. The questionnaire assesses how often people affected by PD experience difficulties across 8 dimensions of daily living. The standard PDQ39 assesses quality of life over the previous month. In this study the initial time period assessed at the Baseline Visit will be the previous month, with subsequent assessments for the intervening period since the last clinic visit (about 3 weeks).

The 8 quality of life dimensions covered in the questionnaire are:

- Mobility (10 items #1-10)
- ADL (6 items #11-16)
- Emotional Well Being (6 items #17-22)
- Stigma (4 items #23-26)
- Social Support (3 items #27-29)
- Cognition (4 items #30-33)
- Communications (3 items #34-36)
- Bodily Discomfort (3 items #37-39)

Individual items are rated by the patient on a scale of 0 to 5. Dimension scores are calculated on a scale of 0 to 100. The total score and individual dimension scores will be assessed for change from baseline.

For timing of assessments, refer to Table 8.1-1.

11.4.3 *Hospital Anxiety Depression Scale (HADS)*

The HADS is used to determine the levels of anxiety and depression that a person is experiencing. The questionnaire consists of 7 items related to anxiety and 7 related to depression. Each item on the questionnaires is scored from 0-3, which means that a person can score between 0 and 21 for either anxiety or depression.

For timing of assessments, refer to Table 8.1-1.

11.4.4 *International Consultation on Incontinence Questionnaire Overactive Bladder Module (ICIQ-OAB)*

The ICIQ-OAB provides a brief and robust measure to assess the impact of symptoms of overactive bladder on quality of life and outcome of treatment. It is a 4-item patient reported outcome covering 4 domains of bladder function: frequency, nocturia, urgency, and urge urinary incontinence. Each item is scored by frequency of 0 - 4, for a total score of 0 - 16. Ratings will be based on the previous month or since the last clinic visit. Efficacy will be assessed as change from the baseline total score.

For timing of assessments, refer to Table 8.1-1.

11.4.5 *Epworth Sleepiness Scale (ESS)*

The ESS is a self-administered questionnaire with 8 questions. Respondents are asked to rate, on a 4-point scale (0 - 3), their usual chances of dozing off or falling asleep while engaged in 8 different activities. The ESS score (the sum of 8 item scores, 0 - 3) can range from 0 to 24. Ratings are based on the previous month, or in the case of this study, the intervening period since the previous clinic visit (about 3 weeks).

For timing of assessments, refer to Table 8.1-1.

11.4.6 *Plasma concentration of NLX-112*

Should it be deemed necessary by the Sponsor, the NLX-112 plasma concentration will be analyzed using blood taken at visits specified in Table 8.1-1. These plasma level checks may serve as a rough measure of compliance with the study medication.

Blood samples (5 mL) will be collected into tubes containing K2 EDTA and will be centrifuged at approximately 2000xg for 10 minutes at +4 °C. The resultant plasma will be transferred into 2 clean, labeled 2 mL tubes. All plasma samples will be stored in a - 20 °C freezer until shipment.

A samples will be transferred to the bioanalysis laboratory on dry ice. B samples will be shipped to the bioanalysis laboratory, upon instruction from the Sponsor, if they are required for repeat analysis.

11.5 Appropriateness of measurements

Methods used for safety assessments are commonly used in standard medical care and in clinical studies as are methods used for the preliminary assessment of efficacy.

12 PROCEDURES FOR BIOLOGICAL SAMPLES

12.1 Sample collection

The sample collection procedure for plasma concentration analysis of NLX-112 is described in Section 11.4.6.

Safety laboratory samples will be collected according to standard procedures.

12.2 Volume of blood

The anticipated volume of blood samples collected during the study from each patient will be approximately 100 mL, which is significantly less than volume drawn during a regular blood donation (450 mL).

12.3 Handling, storage and destruction of laboratory samples

Safety laboratory samples will be analyzed shortly after sample collection and these samples will not be stored. Any remains from the safety laboratory samples will be disposed of after analyses.

Samples collected for potential NLX-112 plasma concentration analysis are included in a biobank and will be stored at <-20°C until analyzed. The A samples will be destroyed by the bioanalysis lab and the B samples will be destroyed at each site after finalization of the CSR.

12.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

Each investigator keeps full traceability of collected biological samples from the patients while in storage at the research clinic until shipment and keeps documentation of receipt of arrival.

The sample receiver (the analytical laboratory) keeps full traceability of the samples while in their storage and during use until used or disposed of.

The Sponsor keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

12.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of biological samples donated, the samples will be disposed of /destroyed, if not already analyzed and documented.

The Principal Investigator will ensure that:

- Patient withdrawal of informed consent is notified immediately to Sponsor.
- Biological samples from the patient, if stored at the research clinic, are immediately identified, disposed of/destroyed and the action is documented.

The Sponsor has to ensure that the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed or returned to the research clinic and the action is documented.

13 QUALITY MANAGEMENT, QUALITY ASSURANCE AND QUALITY CONTROL

13.1 Quality management: critical process, system and data identification

During CSP development, the Sponsor will identify those processes, systems (facilities, computerized systems) and data that are critical to ensure human subject protection and the

reliability of trial results according to applicable SOPs and International Council for Harmonisation (ICH) E6 (R2) guidelines.

Identified risks, including risks associated with the Covid-19 (Coronavirus) pandemic, will be categorized separately from the CSP.

Sponsor oversight responsibilities, such as monitoring, AE reporting, safety monitoring, changes in investigators and key study team staff and quality assurance (QA) activities may need to be reassessed in relation to the Covid-19 pandemic and temporary, alternative proportionate mechanisms of oversight may be required.

13.2 Quality assurance and quality control

The Sponsor is responsible for implementing and maintaining QA and quality control (QC) systems with written SOPs with regards to management of identified risks, CSP compliance, good clinical practice (GCP) compliance and applicable regulatory requirements.

The Sponsor is responsible for securing agreements with involved subcontractors and to perform regular subcontractor oversight to ensure CSP compliance, GCP compliance and compliance with applicable regulatory requirements.

The Sponsor is responsible for implementing a risk-based validated electronic data capture (EDC) system and maintain SOPs for the whole life cycle of the system.

QC should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

The Sponsor has delegated the responsibilities outlined above to CTC AB whilst maintaining overall study oversight.

14 ETHICAL AND REGULATORY REQUIREMENTS

14.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki [27] and are consistent with ICH E6 (R2) GCP guidelines, EU Clinical Trials Directive, and applicable local regulatory requirements.

14.2 Ethics and regulatory review

The Principal Investigator is responsible for submission of the CSP, the patient information and ICF, any other written information to be provided to the patients and any advertisements used for recruitment of patients to applicable IEC for approval.

The Sponsor has delegated to CTC AB the responsibility to submit study documents to the applicable CA according to local regulatory requirements.

Approval must be obtained in writing from both IEC and CA before the first patient can be recruited.

The Sponsor will provide the CA, IEC and Principal Investigators with safety updates/reports according to local requirements. Progress reports and notifications of SUSARs will be provided to the IEC according to local regulations and guidelines.

14.3 Patient information and consent

It is the responsibility of the Investigator or an authorized associate to give each potential study patient (or the patient's legally acceptable representative and/or witness, as applicable) adequate verbal and written information before any study specific assessments are performed.

The information will include the objectives and the procedures of the study as well as any risks or inconvenience involved. It will be emphasized that participation in the study is voluntary and that the patient may withdraw from participation at any time and for any reason, without any prejudice. All patients will be given the opportunity to ask questions about the study and will be given sufficient time to consider participation before signing the ICF.

Before performing any study-related procedures the ICF must be signed and personally dated by the patient and by the Investigator. A copy of the patient information including the signed ICF will be provided to the patient.

Documentation of the discussion and the date of informed consent must be recorded in the source documentation and in the eCRF. The patient information sheet and the signed ICF should be filed by the Investigator for possible future audits and/or inspections.

The final approved version of the patient information and ICF must not be changed without approval from the Sponsor and the applicable IEC.

14.4 Patient information card

The patient will be provided with a Patient Information Card including the following information:

- That he/she is participating in a clinical study
- Patient study ID
- That he/she is treated with an IMP
- The name and phone number of the Investigator
- Name and address of the Sponsor

14.5 Patient data protection

The ICF includes information that data will be recorded, collected and processed and may be transferred to European Economic Area (EEA) or non-EEA countries. In accordance with the General Data protection Regulation (GDPR) (EU) 2016/679, the data will not identify any persons taking part in the study.

The potential study patient (or the patient's legally acceptable representative and/or witness, as applicable) should be informed that by signing the ICF he/she approves that authorized representatives from Sponsor and CTC AB, the concerned IEC and CA have direct access to

his/her medical records for verification of clinical study procedures. For further details on the patient information and ICF process, refer to Section 14.3.

The patient has the right to request access to his/her personal data and the right to request rectification of any data that is not correct and/or complete in accordance with GDPR (EU) 2016/679 and the request will be raised to the Principal Investigator.

The Investigator must file a Patient Identification List which includes sufficient information to link records, i.e. the eCRF and clinical records. This list should be preserved for possible future inspections/audits but must not be made available to the Sponsor except for monitoring or auditing purposes.

Personal data that are collected in the study such as health information and ethnicity are considered as sensitive personal data. This data will be pseudoanonymized, i.e. personally identifiable information (PII) will be removed and replaced by a unique patient ID and will be processed by the Sponsor and other involved parties during the study. After the study end, only anonymized data, i.e. aggregated data sets, can be used.

For this study, the Sponsor is the data controller of all data processed during the study (e.g. TMF, study reports) and CTC AB is the data processor. For data that are processed at the clinic(s) (e.g. medical records and ISF), each site is the data controller. Any subcontractors used in the study are data processors.

14.6 Changes to the approved clinical study protocol

Any proposed change to the approved final CSP (including appendices) will be documented in a written and numbered clinical protocol amendment. All substantial amendments to the protocol must be approved by the appropriate IEC and/or CA before implementation according to applicable regulations.

14.7 Audits and inspections

Authorized representatives of Sponsor, a CA, or an IEC may perform audits or inspections at the research clinic, including source data verification (SDV). The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH E6 (R2)GCP guidelines and any applicable regulatory requirements. The Investigator will contact the Sponsor immediately if contacted by a CA about an inspection at the center.

14.8 Insurance

Patients will be covered under Neurolixis' insurance policy through the Swedish Pharmaceutical Insurance (Läkemedelsförsäkringen). The certificate of insurance and an information leaflet containing essential information about the insurance coverage can be provided upon request. The participating patients are also protected in accordance with national regulations, as applicable.

15 STUDY MANAGEMENT

15.1 Training of study site personnel

Before enrolment of the first study patient, a Sponsor representative or delegate will perform a study initiation visit at the research clinic. The requirements of the CSP and related documents will be reviewed and discussed, and the investigational staff will be trained in any study specific procedures and system(s) utilized.

It is the responsibility of the Investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study and have a detailed knowledge of and training in the procedures that are to be executed by them. Any new information of relevance to the performance of this study must be forwarded to the staff involved in a timely manner.

The Investigator will keep a list of all personnel involved in the study together with their function and study related duties delegated. A Curriculum Vitae will be available for all staff to whom study-specific duties are delegated.

15.2 Clinical monitoring

The Sponsor is responsible for securing agreement from all involved parties to ensure direct access to all study related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by domestic and foreign regulatory authorities.

As defined in the risk-based monitoring (RBM) plan, approved by the Sponsor and provided separately, the responsible Monitor will periodically visit the study site at times agreed upon by the Investigator and the Monitor. Adaptations related to the on-site monitoring plan, when it is impossible or inappropriate to follow due to the Covid-19 pandemic, may be required such as supplementation with (additional/increased) centralized monitoring and central review of data if considered possible and meaningful. Results of adjusted monitoring/review measures should be reported to the Sponsor in monitoring reports and in the CSR. At the time of each monitoring visit, the role of the Monitor is (but not limited to) to:

- provide information and support to the investigational team.
- confirm that facilities and resources remain acceptable.
- confirm that the investigational team is adhering to the CSP, applicable SOPs, guidelines, manuals and regulatory requirements.
- verify that data are being accurately and timely recorded in the eCRFs and that IMP accountability checks are being performed.
- verify that data in the eCRF are consistent with the clinical records (SDV) in accordance with the RBM plan.
- verify that the correct informed consent procedure has been adhered to for participating patients.

- ensure that withdrawal of informed consent to the use of the patient's biological samples will be reported and biological samples are identified and disposed of/destructed accordingly, and that this action is documented and reported to the patient.
- verify that AEs are recorded and reported in a timely manner and according to the CSP.
- raise and escalate any serious quality issues, serious GCP breach and any data privacy breach to the Sponsor.

Centralized monitoring will also be performed continuously by study team members at CTC AB in accordance with the RBM plan.

When the study has been completed and all queries have been resolved and the database has been locked, the Monitor will perform a close-out visit.

15.3 Source data documents

A separate Origin of Source Data List will be generated for each site before start of enrolment, specifying the location of the source of derived information appearing in the eCRF. This document must be signed by the Principal Investigator and the Monitor to confirm agreement before start of recruitment.

Source documents are all documents used by the Investigator or hospital that relate to the patient's medical history, that verifies the existence of the patient, the inclusion and exclusion criteria, and all records covering the patient's participation in the trial. They include laboratory notes, memoranda, material dispensing records, patient files, etc. The eCRF may constitute source data if clearly defined in the Origin of Source Data List.

The Investigator should guarantee access to source documents to the Monitor, CAs and the IECs, if required.

15.4 Study agreements

The Principal Investigator must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study.

Agreements between Sponsor and CTC AB and site contracts must be in place before any study-related procedures can take place, or patients are be enrolled.

15.5 Study timetable and end of study

The study is expected to start in Q3 2021 and to be completed by Q4 2022.

A patient is considered to have completed the study if he/she has completed all visits in the study including.

The end of the study is defined as the date of the last visit of the last patient in the study.

15.6 Criteria for site termination

A specific site maybe terminated due to the following conditions:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled at that site.
- The Investigator does not meet an acceptable enrollment rate.
- The Investigator is not adhering to the protocol requirements.

If there are patients still active at a site that is being terminated, efforts will be made to transfer the patients to another participating site if feasible.

15.7 Termination of the study

The study may be terminated if evidence indicates that there is an unacceptable risk to the patients or if circumstances arise that make it impossible for the study to continue. If it is necessary to terminate the study, Neurolixis will formulate and communicate to the Investigators the plan for study termination and close out. Neurolixis may decide to delay or terminate the study at any time, or for any reason.

The IEC and CA should be informed promptly. Conditions that may warrant study termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study or potential study patients; or
- A decision by the Sponsor to suspend or discontinue development of the IMP.
- If the CA obtains information that raises doubts about the safety or scientific validity of the clinical study, the CA can suspend or prohibit the study. Before the CA reaches its decision, it shall, except where there is imminent risk, ask the Sponsor and/or the Investigator for their opinion, to be delivered within one week (Directive 2001/20/EC, Article 12, Section 1).

If the study is prematurely terminated or suspended for any reason, the Investigator/institution should promptly inform the study patients and should assure appropriate follow-up for the patients.

15.8 Reporting and publication

15.8.1 *Clinical study report*

A summarizing report must be submitted to the applicable CA and IEC within 12 months after completion of the study (in accordance with LVFS 2011:19, Chapter 9).

A CSR, in compliance with ICH-E3 guidelines, describing the conduct of the study, any statistical analyses performed and the results obtained, will be prepared by CTC AB. The report will be reviewed and approved by, as a minimum, the Coordinating Investigator, the Statistician and the Sponsor. The study results will be reported in the EudraCT database per applicable regulations within 12 months after completion of the study. Any work created in connection with performance of the study and contained in the data that can benefit from

copyright protection (except any publication by the Investigator as provided for below) shall be the property of Neurolixis as author and owner of copyright in such work.

15.8.2 *Annual safety report*

If the study duration exceeds one year, the Sponsor must submit development safety update report (DSUR) to the CA and to the IEC. The report shall summarize all pertinent safety information collected during the reporting period and contain an update of the risk-benefit evaluation if there has been any change since the approval of the clinical study.

15.8.3 *Confidentiality and ownership of study data*

Any confidential information relating to the IMP or the study, including any data and results from the study, will be the exclusive property of the Sponsor. The Investigator and any other persons involved in the study are responsible for protecting the confidentiality of this proprietary information belonging to the Sponsor.

15.8.4 *Publication*

All information, including but not limited to information regarding NLX-112 or the operations of Neurolixis, (e.g., patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, and formulation information) supplied by Neurolixis to the Investigator and not previously published, and any data generated as a result of this study, is considered confidential and remains the sole property of Neurolixis. The Investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the prior written consent of Neurolixis.

The Investigator understands that the information developed in the clinical study will be used by Neurolixis. in connection with the continued development of NLX-112, and thus may be disclosed as required to other clinical investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the Investigator is obligated to provide Neurolixis with all data obtained in the study.

Neurolixis shall have the right to publish data and information without approval from the Investigator. If an Investigator wishes to publish information from the study, a copy of the manuscript must be provided to Neurolixis for review before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by Neurolixis in writing, the Investigator will withhold any publication to allow for fi1ing of a patent application. Authorship of publications resulting from this study will be based on generally accepted criteria for major medical journals.

15.9 Archiving

The Principal Investigator is responsible for maintaining essential documents, (as defined in ICH E6 (R2) GCP guidelines, Section 8) for 10 years after finalization of the CSR. This includes any original source documents related to the study, the Patient Identification List (providing the sole link between named patient source records and anonymous eCRF data), the original signed ICFs and detailed records of disposition of IMP.

It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

The Sponsor will archive the TMF in accordance with ICH E6 (R2) GCP guidelines, Section 8 and applicable regulatory requirements.

The data from the eCRFs will be sent to the Sponsor and a copy will be sent to the clinic and filed in the Investigator Study File for archiving for 10 years after finalization of the CSR.

The completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the Sponsor.

16 DATA MANAGEMENT

The data management routines include procedures for handling of the eCRF, database set-up and management, data entry and verification, data validation, QC of the database, and documentation of the performed activities including information of discrepancies in the process. The database, data entry screens, and program will be designed in accordance with the CSP.

Data validation/data cleaning procedures are designed to assure validity and accuracy of clinical data. These procedures consist of computerized online edit checks identifying e.g. data values that are outside the allowed range and SAS-programmed batch checks on data exports. All study-specific and standard data validation programming will be tested prior to being used on final data.

Detailed information on data management will be described in a study-specific Data Management Plan (DMP).

16.1 The web-based eCRF

Clinical data will be entered into a 21 CFR Part 11-compliant eCRF (Viedoc™) provided by Viedoc Technologies AB. The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents or at bedside (if the eCRF data constitutes source data). Source data are to be defined at the site before inclusion of the first patient (Section 15.3).

Authorized site personnel designated by the Investigator will complete data collection. Appropriate training and security measures will be completed with the Investigator and all authorized trial site personnel prior to the trial being initiated and any data being entered into the system for any study patient.

16.2 The entering of data into the eCRF

All entries, corrections, and alterations are to be made by the Investigator or designee. Neither the Monitor nor any other study team member besides site staff can enter data in the eCRF. All data should be entered in English. The eCRFs should be completed as soon as possible during or after the patient's visit. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the Investigator or assigned clinical staff should record such information in the eCRF. The Investigator will be required to electronically sign

off the clinical data. This will be performed by means of the Investigator's unique User ID and password; date and time stamps will be added automatically at time of electronic signature.

16.3 The query process

The Monitor will review the eCRFs and evaluate them for completeness and consistency. Data in the eCRF will be compared with the respective source documents to ensure that there are no discrepancies for critical data as described in the RBM plan.

If corrections are needed, queries will be raised within the eCRF, either as a result of built-in edit checks or manually raised by the monitor. An appropriate member of the site staff will answer the queries in the eCRF either by correcting the data or by entering a response to the query. The monitor will either approve the answer/correction or re-issue the query.

16.4 Audit trail

All entries in the eCRF will be fully recorded in a protected audit trail. Once clinical data have been saved, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who made the change, together with time and date will be logged.

16.5 External data

External data consists of data that are not recorded in the eCRF. External data must be received in electronic format. Key variables are defined in order to uniquely identify each sample record. File and data formats are agreed with the external data provider.

External data in the current study include safety laboratory data, wearable data, electronic diary data and (if performed) NLX-112 plasma concentration data.

16.6 Medical coding

Medical coding will be performed by trained personnel at CTC AB. AEs and medical/psychiatric history verbatim terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; latest version available at eCRF setup). Prior and concomitant medications will be coded according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system. All coding will be approved by Sponsor prior to database lock.

16.7 Database lock

When all data have been entered and discrepancies solved, clean file will be declared, the

database will be locked, the code will be broken and the data will be analyzed.

17 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The principal features of the statistical analysis to be performed are described in this section. A more technical and detailed elaboration of the principal features will be presented in a separate Statistical Analysis Plan (SAP), which will be signed and approved prior to database lock. All analyses will be performed by CTC AB.

17.1 General

Continuous data will be presented in terms of evaluable and missing observations, arithmetic mean, standard deviation (SD), median, minimum and maximum value.

Categorical data will be presented as counts and percentages. When applicable, summary data will be presented by treatment, and by assessment time. Individual patient data will be listed by patient number, treatment, and, where applicable, by assessment time.

All descriptive summaries and statistical analyses will be performed using SAS Version 9.4 or later (SAS Institute, Inc., Cary, NC).

Baseline will be defined as the last non-missing data point prior to the first administration of IMP.

The primary objective of this study is to evaluate the safety and tolerability of NLX-112. The secondary objective is to evaluate preliminary efficacy endpoints, hence, statistical tests of efficacy outcomes will be for descriptive purposes and no adjustment for multiple tests will be performed.

No imputation of missing data will be performed.

All data will be listed by treatment and patient.

17.2 Determination of sample size

No formal sample size calculation has been performed. The sample size of 24 patients is considered sufficient to evaluate the primary objective and to allow for a preliminary efficacy evaluation.

17.3 Analysis populations

17.3.1 *Safety analysis set*

The safety analysis set will comprise all patients who received at least one dose of the IMP.

17.3.2 *Full analysis set*

The full analysis set (FAS) will comprise all randomized patients who were dosed and who provided at least one post-baseline assessment of the UDysRS.

17.3.3 *Per protocol set*

The per protocol set (PPS) will consist of all patients included in the FAS population who do not have any major protocol violations assessed to compromise the analysis of study data. All protocol violations will be judged as major or minor prior to database lock.

17.4 Description of study population

17.4.1 *Demographics and baseline characteristics*

Descriptive statistics for demographics, weight and height will be presented by treatment.

17.4.2 *Medical/psychiatric history and prior/concomitant medication*

Medical/psychiatric history will be presented by system organ class (SOC) and preferred term (PT) by treatment. Prior/concomitant medications will be presented by ATC level 1, 3 and 5 by treatment.

17.4.3 *Treatment compliance*

The number of patients treated in each treatment period and their individual dose will be listed.

Compliance will be presented using summary statistics per treatment (1-[number of study drugs returned/number of study drug delivered]).

17.5 Analysis of primary endpoints

The safety analyses will be based on the safety dataset.

17.5.1 *Adverse events*

An overview of all AEs, including SAEs, intensity, relationship to IMP, and deaths will be presented by treatment. Incidence of AEs and SAEs will be summarized by SOC and PT by treatment. Separate tables will be provided, if relevant, for serious AEs (SAEs) or events leading to withdrawal from study.

All AE data will be listed by patient and include the verbatim term entered by the Investigator.

17.5.2 *Physical examination*

Clinically significant and non-clinically significant abnormal findings will be specified and presented by patient and summarized by treatment.

Changes over time will be presented using shift tables, if considered appropriate.

17.5.3 *Vital signs*

Vital signs (systolic/diastolic blood pressure, orthostatic blood pressure, pulse, respiratory rate and body temperature) will be summarized by treatment. Data will be presented with absolute and percent change from baseline.

17.5.4 *12-lead ECG*

All ECGs will be categorized as ”normal”, ”abnormal, not clinically significant”, or ”abnormal, clinically significant” (as judged by the Investigator) and summarized by treatment using frequency tables.

Changes over time will be presented using shift tables, if considered appropriate.

17.5.5 *Columbia Suicide Severity Rating Scale (C-SSRS)*

C-SSRS data will be listed by patient and visit and summarized by treatment.

Changes over time will be presented using shift tables, if considered appropriate.

17.5.6 *Safety laboratory analyses*

Safety laboratory data will be summarized by treatment with absolute and percent change from baseline at each visit.

Abnormal, clinically significant values will be summarized separately, if considered appropriate.

17.6 Analysis of secondary endpoints

The efficacy analyses will be performed separately on both the FAS and PPS if deemed appropriate.

17.6.1 *Unified Dyskinesia Rating Scale (UDysRS) total score*

Change from baseline in the UDysRS total score to Visit 6 (Day 28) and Visit 7 (Day 42) respectively will be summarized using descriptive statistics. A Wilcoxon signed-rank test will be used to assess statistically significant differences between active treatment and placebo for each time point. The same analysis will be done for UDysRS total objective score Part III and IV only.

17.6.2 *ON Time Without Troublesome Dyskinesia*

Change from baseline in ON Time Without Troublesome Dyskinesia (ON Without Dyskinesia plus ON With Non-troublesome Dyskinesia) based on a PD Home Dyskinesia Diary (see Section 11.3.3) will be summarized using descriptive statistics for all assessment time points. A Chi-Square test will be used to assess statistically significant differences between active treatment and placebo for the whole study period.

17.6.3 *Unified Parkinson’s Disease Rating Scale (UPDRS)*

Change from baseline in UPDRS combined scores (Parts I, II, III and IV) to Visit 6 (Day 28) and Visit 7 (Day 42) respectively will be summarized using descriptive statistics. A Wilcoxon signed-rank test will be used to assess statistically significant differences between active treatment and placebo for each time point. The same analysis will be done for UPDRS Part III only.

17.6.4 *Clinical Global Impression of Change (CGI-C) in overall PD symptoms*

Change from baseline in CGI-C in overall PD symptoms to Visit 6 (Day 28) and Visit 7 (Day 42) respectively will be summarized using descriptive statistics. A Wilcoxon signed-rank test will be used to assess statistically significant differences between active treatment and placebo for each time point.

17.6.5 *Dyskinesia scores measured by a wearable dyskinesia assessment device*

Change from baseline in dyskinesia scores measured by the Kinesia 360 (Great Lakes Neurotechnologies, Inc) wearable dyskinesia assessment system to Visit 6 (Day 28) and Visit 7 (Day 42) respectively will be summarized using descriptive statistics. A Wilcoxon signed-rank test will be used to assess statistically significant differences between active treatment and placebo for each time point.

17.7 Analysis of exploratory endpoints

17.7.1 *King's Parkinson's Disease Pain Scale (KPPS) total score*

Change from baseline in the KPPS total score to Visit 6 (Day 28) and Visit 7 (Day 42) respectively will be summarized using descriptive statistics. A Wilcoxon signed-rank test will be used to assess statistically significant differences between active treatment and placebo for each time point.

17.7.2 *Parkinson's Disease Questionnaire (PDQ39) total score*

Change from baseline in the PDQ39 total score to Visit 6 (Day 28) and Visit 7 (Day 42) respectively will be summarized using descriptive statistics. A Wilcoxon signed-rank test will be used to assess statistically significant differences between active treatment and placebo for each time point.

17.7.3 *Hospital Anxiety Depression Scale (HADS)*

Change from baseline in the HADS to Visit 6 (Day 28) and Visit 7 (Day 42) respectively will be summarized using descriptive statistics. A Wilcoxon signed-rank test will be used to assess statistically significant differences between active treatment and placebo for each time point.

17.7.4 *International Consultation on Incontinence Questionnaire Overactive Bladder Module (ICIQ-OAB) total score*

Change from baseline in the ICIQ-OAB total score to Visit 6 (Day 28) and Visit 7 (Day 42) respectively will be summarized using descriptive statistics. A Wilcoxon signed-rank test will be used to assess statistically significant differences between active treatment and placebo for each time point.

17.7.5 *Epworth Sleepiness Scale (ESS)*

Change from baseline in the ESS to Visit 6 (Day 28) and Visit 7 (Day 42) respectively will be summarized using descriptive statistics. A Wilcoxon signed-rank test will be used to assess statistically significant differences between active treatment and placebo for each time point.

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19 SIGNATURES

19.1 Principal Investigator statement

I have read and understood this CSP and agree to conduct the study accordingly and to comply with the Investigator obligations stated in this CSP, GCP and applicable regulatory requirements.

Principal Investigator

Name	*Signature*	*Date*

Site

19.2 Signature page (approval of the clinical study protocol)

Sponsor signatory

[redacted]

Coordinating Investigator

[redacted]