

PROTOCOL PD0049

A MULTICENTER, OPEN-LABEL, TWO-ARM STUDY TO EVALUATE THE IMPACT OF USING WEARABLE DEVICES IN ADDITION TO STANDARD CLINICAL PRACTICE ON PARKINSON'S SUBJECT SYMPTOMS MANAGEMENT

PHASE 4

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LIST OF ABBREVIATIONS

ADE	adverse device event
AE	adverse event
ANCOVA	analysis of covariance
APP	application, application software
ATC	Anatomical Therapeutic Chemical
CDMS	clinical data management system
CG	Control Group
CI	confidence interval
CRO	contract research organization
DBS	Deep Brain Stimulation
ECG	electrocardiogram
eCRF	electronic Case Report form
EG	Experimental Group
ES	Enrolled Set
FAS	Full Analysis Set
FDA	Food and Drug Administration
GLNT	Great Lakes Neuro Technologies, Inc.
H ₀	null hypothesis
H _a	alternative hypothesis
ICF	Informed Consent form
ICH-GCP	International Council for Harmonisation-Good Clinical Practice
IMP	investigational medicinal product
IRB	Institutional Review Board
ISO	International Organization for Standardization
MedDRA	Medical Dictionary for Regulatory Activities
n	number
PDQ-39	39-Item Parkinson's Disease Questionnaire
PPS	Per-Protocol Set
PS	Patient Safety
RLS	restless leg syndrome
SAE	serious adverse event

SAP	Statistical Analysis Plan
SD	standard deviation
SOP	Standard Operating Procedure
SS	Safety Set
TEAE	treatment-emergent adverse event
UPDRS	Unified Parkinson's Disease Rating Scale

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1 SUMMARY

PD0049 is a pilot study to investigate whether motor symptoms in subjects with Parkinson's disease who start treatment with Neupro[®] can be improved by using wearable devices. Specifically, this study focuses on investigating how to optimize the evaluation of motor symptoms in subjects with Parkinson's disease aiming at enabling Investigators to optimize subjects' Neupro dosing regimens and ensure better patient outcomes in a timelier manner.

In this study, 2 Kinesia devices (Kinesia-ONE and Kinesia-360) will be employed to record specific motor symptoms. Approximately 40 subjects with Parkinson's disease of any stage will be randomized (1:1 ratio) to either the Control Group or the Experimental Group. Specific motor tasks will be measured in all subjects with Kinesia-ONE on Day 1. In contrast to subjects randomized to the Control Group, subjects randomized to the Experimental Group will also use the Kinesia-360 device for home-based self-recording of their motor symptoms.

All subjects will start Neupro treatment at a dose of either rotigotine 2mg/24h or 4mg/24h (according to the disease stage of the subject), which will then be adjusted based on symptom assessment either via standard care alone (Control Group) or via a combination of standard care and evaluation of the recordings made available by the Kinesia wearable technologies (Experimental Group). The Neupro dosing regimen used in PD0049 follows standard of care, and is in line with the approved dosing regimen for rotigotine in the treatment of Parkinson's disease (ie, up to 8mg/24h, depending on the stage of the disease).

PD0049 starts with in-clinic Screening activities, assessments (including recording of Baseline motor symptoms via Kinesia-One), and training in the use of Kinesia-360 devices (for subjects randomized to the Experimental Group only) on Day 1, followed by 3 days at home: During this period, subjects randomized to the Experimental Group will use the Kinesia-360 device to record their motor symptoms (on Days 2 and 3). Subjects allocated to the Control Group will start treatment with Neupro preferably on Day 1 (but no later than Day 4); subjects allocated to the Experimental group will start treatment with Neupro on Day 4. There are no required visits from Week 2 up to Week 12 (Visit 2). However, Investigators and subjects in the Experimental Group are encouraged to discuss by phone Kinesia-360 motor symptom reports and needs for any changes in Neupro dosing. Subjects of either group return to the clinic for final assessments and reporting of adverse events (AEs) and concomitant medications at Week 12. The individual duration of study participation may last up to 12 weeks.

A primary objective of PD0049 is to evaluate whether Parkinson's disease motor symptoms in subjects starting Neupro can be improved by using feedback of motor symptom data from the Kinesia-360 wearable technology presented to subjects and Investigators in addition to standard clinical practice as compared with only standard clinical practice. A primary objective is to evaluate whether a clinician is more likely to determine a Neupro dosing regimen that improves a subject's Parkinson's disease motor symptoms when using motor symptom data collected with the Kinesia-360 wearable technology in addition to standard clinical practice as compared with only standard clinical practice. Another primary objective is to evaluate whether subjects with Parkinson's disease are more likely to continue the usage of Neupro if Parkinson's disease motor symptom data collected using the Kinesia wearable technology is used to provide the subjects with feedback on the status of their Parkinson's disease motor symptoms and is used in addition to standard of care for titrating their Neupro dosing regimen. Other objectives include to evaluate

the quality of life and engagement in the management and treatment of their disease within subjects in either group, as well as to evaluate the safety of Neupro. The corresponding variables to be assessed to meet the study objectives are described in detail in [Section 4](#).

2 INTRODUCTION

Neupro is approved for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease as monotherapy (ie, without levodopa) or in combination with levodopa, ie, over the course of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or "on-off" fluctuations).

Dosing in patients with early-stage Parkinson's disease consists of a single daily dose initiated at rotigotine 2mg/24h and then increased in weekly increments of rotigotine 2mg/24h to an effective dose up to a maximum dose of rotigotine 6mg/24h. Rotigotine 4mg/24h may be an effective dose in some patients. For most patients an effective dose is reached within 3 or 4 weeks at doses of rotigotine 6mg/24h. The maximum approved dose is rotigotine 6mg/24h (NEUPRO [package insert]. 2016 [[Section 15](#)]).

Dosing in patients with advanced-stage Parkinson's disease with fluctuations consists of a single daily dose that should be initiated at rotigotine 4mg/24h and then increased in weekly increments of rotigotine 2mg/24h to an effective dose up to a maximum dose of rotigotine 8mg/24h. Rotigotine 4mg/24h or rotigotine 6mg/24h may be effective doses in some patients. For most patients with advanced-stage Parkinson's disease, an effective dose is reached within 3 to 7 weeks at doses of rotigotine 8mg/24h. The maximum approved dose is rotigotine 8mg/24h (NEUPRO [package insert]. 2016 [[Section 15](#)]).

Optimal patient outcomes may be expected only when the clinician is able to prescribe a customized, optimal dosing regimen for patients with Parkinson's disease. Clinicians employ various measures to diagnose Parkinson's disease and its severity in order to prescribe the optimal dosing regimen for the patient. Key amongst these measures is an evaluation of the severity of the motor symptoms (eg, dyskinesia, gait, tremor, rigidity, and posture) associated with Parkinson's disease. The quality of this evaluation (ie, quantification of movement) is critical to an accurate diagnosis of the evaluation of severity of the motor symptoms and is currently limited by the ability of the Clinician (through manual manipulation and observation) to accurately measure the various physical manifestations of motor symptoms associated with Parkinson's disease. Ultimately, the quality of the evaluation of the motor symptoms may determine whether the Clinician is able to prescribe the optimal dosing regimen for the patient.

New, wearable technologies that allow for accurate, consistent, and ongoing measurement of motor activity under ambulatory conditions in patients with Parkinson's disease may provide the Clinician with additional motor symptom data that the Clinician could use to make more accurate evaluations of the motor symptoms associated with Parkinson's disease, thereby providing the patient with the optimal Neupro dosing regimen and ensuring better patient outcomes in a more timely manner.

The focus of this 12-week study is on optimizing patients' response to Neupro by using a commercially available wearable device to optimize the evaluation of motor symptoms and to improve customized dosing.

3 STUDY OBJECTIVES

3.1 Primary objectives

The primary objectives of this study are to:

- Evaluate whether Parkinson's disease motor symptoms in subjects starting Neupro can be improved by using feedback of motor symptom data from the Kinesia-360 wearable technology presented to subjects and Investigators in addition to standard clinical practice as compared with only standard clinical practice.
- Evaluate the Neupro dosing regimen when using feedback of motor symptom data collected with the Kinesia-360 wearable technology in addition to standard clinical practice as compared with only standard clinical practice.
- Evaluate whether subjects with Parkinson's disease are more likely to continue the usage of Neupro if Parkinson's disease motor symptom data collected using the Kinesia-360 wearable technology is used to provide the subjects with feedback on the status of their Parkinson's disease motor symptoms and is used in addition to standard of care for titrating their Neupro dosing regimen.

3.2 Other objectives

Other objectives of this study are to:

- Evaluate whether the quality of life of subjects with Parkinson's disease can be improved by using the Kinesia-360 wearable technology to collect motor symptom data in addition to standard clinical practice as compared with only standard clinical practice to titrate the Neupro dosing regimen.
- Evaluate whether subjects with Parkinson's disease are more actively engaged in the management and treatment of their disease with Neupro therapy with the use of the Kinesia-360 wearable technology as compared to without the use of the Kinesia-360 wearable technology.
- Evaluate the safety of Neupro.

4 STUDY VARIABLES

4.1 Efficacy variables

4.1.1 Primary efficacy variables

The efficacy variables of this study are:

- Change from Baseline (Visit 1/Week 1) to Visit 2 (Week 12/3 months after start of treatment with Neupro) in Unified Parkinson's Disease Rating Scale (UPDRS) Part III Motor Score.
- Change from Baseline (Visit 1/Week 1) to Visit 2 (Week 12) in Kinesia-ONE variables:
 - finger tapping speed score
 - rest tremor score
 - averaged finger tapping speed and resting tremor scores
 - postural tremor score
 - finger tapping amplitude score
 - hand grasp speed score
 - hand grasp amplitude score
 - rapid alternating movement speed score
 - rapid alternating amplitude score
 - dyskinesia score
- Neupro dose per 24h at Visit 2 (Week 12)
- Number of Neupro dose changes during the study (between Visit 1 and Visit 2)
- Discontinuation of treatment with Neupro during the course of the study

4.1.2 Other efficacy variables

- Change from Baseline to Visit 2 in the motor scores derived from the Kinesia-360 wearable technology by time (weekly/monthly) and by Neupro dose level (mg/24h) for the Experimental Group in:
 - average daily tremor score
 - average daily slowness score
 - average daily dyskinesia score
 - percent wear-time tremor detected
 - percent wear-time dyskinesia detected
 - percent wear-time user not moving
 - percent wear-time user was walking score
 - percent wear-time user active but not walking

- number of steps per hour while wearing device
- Change from Baseline to Visit 2 (Week 12) in the 39-Item Parkinson's Disease Questionnaire (PDQ-39) scores.
- Change from Baseline to Visit 2 (Week 12) in subject engagement questionnaire scores.

4.2 Safety variables

Safety variable is:

- Occurrence of AEs

5 STUDY DESIGN

5.1 Study description

PD0049 is a multicenter, open-label, two-arm, 12-week study in subjects with Parkinson's disease. On Day 1, eligible subjects will be randomized to either the Control Group or the Experimental Group in a 1:1 fashion. In both groups, subjects will use the Kinesia-ONE wearable device in-clinic at Visit 1 and Visit 2 for recording of specific motor symptoms, and subjects randomized to the Experimental Group will also use the Kinesia-360 wearable device at home while awake for continuous measurement of motor symptoms. The Investigator will use these symptom data to provide feedback to subjects on their motor symptoms and to supplement standard of care to titrate the optimal dose of Neupro for any given subject. In the Control Group, subjects will not use any wearable device at home, and the Investigator will use only standard of care to titrate the optimal Neupro dose.

Subjects in the Control Group and the Experimental Group will start treatment with Neupro 2mg/24h or 4mg/24h (at the Investigator's discretion and according to the disease stage of the subject) preferably on Day 1 (but no later than Day 4) or Day 4, respectively. Evaluations conclude 12 weeks after the start of treatment with Neupro (ie, at Visit 2).

The decision to prescribe Neupro must be made by the Investigator independent of his/her decision to include the subject in the study. The subject's treatment/Neupro intake must be within the terms of the marketing authorization; Neupro will not be supplied by UCB.

A schedule of study assessments is presented in [Table 5-1](#); for a detailed rationale of the study design see [Section 5.3](#).

5.1.1 Study duration per subject

Each subject's participation is approximately 12 weeks.

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

5.1.2 Planned number of subjects and sites

This study will be conducted in approximately 6 sites and will include a total of approximately 40 subjects (20 subjects in the Experimental Group and 20 subjects in the Control Group). Of note, a single site will not randomize more than 20 subjects.

5.1.3 Anticipated regions and countries

This study will be conducted in the US.

5.2 Schedule of study assessments

A schedule of assessments planned for both the Control Group and the Experimental group is presented in [Table 5-1](#).

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Table 5–1: Schedule of study assessments

Assessments	In Clinic		At Home					In Clinic
	SCREENING	BASELINE						EOS/EW
	Visit 1						Visit 2	
	Day 1	Day 2-3	Day 4	Week 2	Week 3	Week 4	Week 11	Week 12 (±3 days)
Written informed consent	X							
Demographic data (incl. height and weight)	X							X ^a
Kinesia-ONE subject assessments (measured in triplicate)	X ^b							X
UPDRS	X							X
Patient engagement questionnaire	X							X
PDQ-39	X							X
Verification of inclusion/exclusion criteria	X							
Randomization	X							
C Group: Start treatment with Neupro 2mg or 4mg preferably on Day 1 but no later than Day 4 (dose adjustments during study are performed per standard of care)		X						X
C Group: Record Neupro dose		X						X
E Group: Kinesia-360 device training and distribution of equipment	X							
E Group: Subject wears Kinesia-360 wrist and ankle devices on Days 2 and 3 at home for baseline			X					
E Group: Start treatment with Neupro 2mg or 4mg on				X				

Day 4								
E Group: Record Neupro dose ^c			X					X
E Group: Reminder phone calls from site to subject at beginning of Weeks 2, 3, 4 and 11 (remind subject to charge devices and wear devices on at least 2 consecutive days during Weeks 2, 3, 4 and 11)				X ^d	X ^d	X ^d	X ^d	
E Group: Subject wears Kinesia-360 wrist and ankle devices on at least 2 consecutive days at home				X	X	X	X	
E Group: Subject and Investigator access Kinesia-360 device reports (subjects via device app, Investigators via GLNT web portal)					X			X
E Group: Investigator combines standard of care with Kinesia-360 motor symptom reports to adjust Neupro dose and is encouraged to contact the subject by phone to discuss motor symptom reports and potential Neupro dose adjustments anytime between V1 and V2 based on clinical judgment					X			
E Group: Subject returns Kinesia-360 device equipment to site								X
Record adverse events	X							X
Record concomitant medications	X							X

APP=application; C Group=Control Group; E Group=Experimental Group; EOS=End of Study; EW=Early Withdrawal; GLNT=Great Lakes Neuro Technologies, Inc.; PDQ-39=39-Item Parkinson's disease questionnaire; UPDRS=Unified Parkinson's Disease Rating Scale; V=visit

^a Only weight at V2.

^b The average of the triplicate resting tremor scores and triplicate finger tapping scores from Kinesia-ONE must be >1.0 to be eligible for inclusion in this study.

^c Subjects in the Experimental Group will be prompted to record Neupro dose in device app during each use of Kinesia-360 between V1 and V2.

^d Subjects in the Experimental Group are to use Kinesia-ONE on at least 2 consecutive days during Weeks 2, 3, 4 and 11, but are free to use the device as often as they like between these time points prior to Visit 2.

5.3 Rationale for study design and selection of dose

The Neupro dosing regimen used in PD0049 follows standard of care, and is in line with the approved dosing regimen for rotigotine in the treatment of Parkinson's disease (ie, up to 8mg/24h, depending on the stage of the disease).

As described in [Section 2](#), the focus of this study is on optimizing the benefits of Neupro in patients with Parkinson's disease by using wearable devices to help the Investigator optimize the evaluation of motor symptoms and improve customized dosing.

To that end, PD0049 employs Kinesia wearable technologies that allow for accurate, consistent, and ongoing measurement of motor activity under ambulatory conditions to provide the Investigator with additional information to further enhance his/her ability to evaluate subjects' motor symptoms more accurately and, via providing the patient with the optimal Neupro dosing regimen, ensure better patient outcomes in a more timely manner. Both Kinesia devices will be used in accordance with their labelled instructions.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. Subject is newly prescribed Neupro and is expected to commence Neupro treatment. Historical Neupro treatment is permitted.
2. An Institutional Review Board (IRB) approved written Informed Consent form (ICF) is signed and dated by the subject, before any study-related procedures.
3. Subject is considered reliable and capable of adhering to the protocol, visit schedule, completion of the diary, and using Kinesia devices according to the judgment of the Investigator.
4. Male or female subject, ≥ 18 years of age at the time of the Screening Visit.
5. Subject has Parkinson's disease, defined by the cardinal sign, bradykinesia, plus the presence of at least 1 of the following: tremor at rest, rigidity or impairment of postural reflexes, and without any other known or suspected cause of Secondary Parkinsonism.
6. Subject experiences motor symptoms associated with Parkinson's disease that are not sufficiently controlled by current therapy. The average of the triplicate resting tremor scores and triplicate finger tapping scores from Kinesia-ONE (6 scores in total) must be >1.0 .

6.2 Exclusion criteria

Subjects are not permitted to enroll in the study if any of the following criteria is met:

1. Subject is currently participating in any study with an investigational medicinal product (IMP) or investigational device.
2. Subject has any medical, neurological or psychiatric condition (eg, previous stroke, bipolar disorder, dementia, hallucinations, psychosis or severe depression, and drug or alcohol abuse) which, in the opinion of the Investigator, could jeopardize or would compromise the subject's ability to participate in this study.

3. Subject with Deep Brain Stimulation (DBS) device implant.

6.3 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care.

Subjects should be withdrawn from the study if any of the following events occur:

1. Subject develops an illness that would interfere with his/her continued participation.
2. Subject is noncompliant with the study procedures in the opinion of the Investigator.
3. Subject withdraws his/her consent.
4. The sponsor or a regulatory agency requests withdrawal of the subject.

For assessments to be performed in case of an Early Withdrawal, refer to [Table 5-1](#).

Investigators should attempt to obtain information on subjects in the case of withdrawal or discontinuation. For subjects considered as lost to follow up, the Investigator should make an effort (at least 1 phone call and 1 written message to the subject), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents) to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for discontinuing the subject, including the date of discontinuation, must be recorded in the source documents. The electronic Case Report form (eCRF) must document the primary reason for withdrawal or discontinuation.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a subject in advance.

For handling of dropouts, refer to [Section 12.6](#).

7 MEDICINAL PRODUCT AND DEVICE

7.1 Description of medicinal product

Neupro (rotigotine) is a nonergolinic dopamine agonist for the treatment of the signs and symptoms of Parkinson's disease and Restless Legs Syndrome (RLS). Neupro elicits its beneficial effect on Parkinson's diseases by activation of the D3, D2 and D1 receptors of the caudate-putamen in the brain.

Neupro (Anatomical Therapeutic Chemical [ATC] code: N04BC09) is available as a transdermal system in six dosages. In the current study, Neupro is to be applied as prescribed by the Investigator and based on instructions provided in the patient leaflet/package insert (NEUPRO [package insert], 2016 [[Section 15](#)]).

7.2 Devices

In the present study, all subjects will use the Kinesia-ONE device in-clinic during the Screening Visit for specific motor tasks/for recording of specific baseline motor symptoms. Subjects randomized to the Experimental Group will also use the Kinesia-360 device at home for continuous measurement of motor symptoms.

Kinesia-360 is intended to monitor physical motion and muscle activity to quantify kinematics of movement disorder symptoms such as tremor, and assess activity in any instance where

quantifiable analysis of motion and muscle activity is desired. Kinesia Regulatory Certifications: Kinesia-One and Kinesia-360 have received US Food and Drug Administration (FDA) 510K clearance to market (06 Apr 2007), Conformité Européen Mark (European Medical Device Directive 93/42/EEC), Canadian Medical Device Conformity Assessment Systems, Australian Therapeutic Goods Association Certification, and International Organization for Standardization (ISO) 13485 (2003). Kinesia-One and Kinesia-360 are tested to International Electrotechnical Commission 60601 Standards, comply with Federal Communications Commission Part 15 Rules, and are Health Insurance Portability and Accountability Act compliant, and FDA Part 11 compliant for Electronic Data Capture in Clinical Trials.

7.2.1 Description of devices

Kinesia-ONE Wearable Sensor uses a subject-worn finger sensor and iPad mini application (APP) to objectively measure specific motor tasks related to Parkinson’s disease symptoms such as tremor, bradykinesia (slowed movements), and dyskinesia (involuntary movements) in the Investigator’s office. Subjects should wear the Kinesia-ONE device on the most affected side.

Kinesia-360 Wearable Sensor includes a wrist and ankle device, along with a cell phone, which is also APP-based, and is designed for continuous day time monitoring of Parkinson’s disease symptoms. Subjects will wear Kinesia-360 while they go about their daily lives, and symptom severity is continually captured to enable objective assessment of Parkinson’s disease symptoms. Subjects should wear the Kinesia-360 device bands on the most affected side.

Symptom data recorded by either device, as well as the corresponding data reports, will be made available to the Investigators through a web portal.

The following variables will be derived from either Kinesia device to be used in PD0049:

Kinesia-ONE	Kinesia-360
Change from Baseline to Visit 2 (Week 12) in the following Kinesia-ONE measures, which will be averaged from triplicate repeated assessments at a measurement point:	Change from Baseline to Visit 2 (Week 12) in the following Kinesia-360 measures, which will be averaged from 2 consecutive days of wear:
Resting tremor score	Average daily tremor score
Postural tremor score	Average daily slowness score
Finger tapping speed and amplitude scores	Average daily dyskinesia score
Hand grasps speed and amplitude scores	% wear-time tremor was detected
Rapid alternating movements speed and amplitude scores	% wear-time dyskinesia was detected
Dyskinesia score	% wear-time user was not moving
	% wear-time user was walking

	% wear-time user was active, but not walking
	Number of steps/h while wearing the device

7.2.2 Packaging and labeling of the Kinesia devices

The sites will receive uniquely numbered wearable sensor devices (Kinesia-ONE and Kinesia-360) for use in the study. The devices will be provided in the intended final packaging.

7.2.3 Storage requirements

Sensor devices must be stored in a secured area with limited access at the Investigators' sites.

7.2.4 Device accountability

Great Lakes Neuro Technologies, Inc. (GLNT) will supply the wearable sensor devices and associated equipment / software. The Investigator must ensure that the devices are used only in accordance with the manufacturer's instructions. A device accountability form will be used to record the receipt and return dates of the wearable sensor devices and associated equipment/ software. In addition, dispensing and returning information on a by-subject basis will be completed. This form will serve as source documentation during the course of the study. Details of any device lost, not used, disposed of at the study site, or returned to the Sponsor must also be recorded. The Investigator, after completion of the study, will ensure that all devices are returned to GLNT.

7.3 Concomitant medications/treatments

Subjects will continue with their usual treatment. All medications/treatments (ie, Parkinson's disease medications and others), including dosages, will be recorded in the appropriate study documents (ie, eCRF and source document).

Investigators are encouraged to adjust, if needed, the Neupro dose to optimize Parkinson's disease symptoms. Back-titration of the Neupro dose in case of AEs is allowed as per standard of care.

Subjects are encouraged not to change the dosages of any concomitant medications during the study. There are no prohibited medications defined for this study.

7.3.1 Rescue medication

Not applicable.

7.4 Blinding

Not applicable.

7.5 Randomization and numbering of subjects

Subjects will be randomized (1:1) to either the Control Group (without Kinesia-360 device to measure motor symptoms at home) or the Experimental Group (with Kinesia-360 device to measure motor symptoms at home) during the Screening Visit (Visit 1). The randomization will be stratified by site. A randomization list for each site with a block size of 4 will be provided to

the site. Each subject will receive a 5-digit number assigned at Screening that serves as the subject identifier throughout the study.

8 STUDY PROCEDURES BY VISIT

Prior to the start of any study-related examinations or procedures, the written ICF must be signed and personally dated by the subject. The person (Investigator [or designee]) who conducted the informed consent discussion will document their informed consent process with his/her signature.

8.1 Visit 1 /Screening

The Screening examinations will be completed within 4 days, the first of which will take place at the study site (in clinic) and will include the following:

Day 1, in clinic:

- Sign ICF
- Control Group and Experimental Group: Subject wears Kinesia-ONE sensor on the most affected side in the clinic to measure specific motor tasks in triplicate. Calculation of the average of triplicate resting tremor scores and triplicate finger-tapping speed scores (ie, 6 scores in total) must be >1.0 for subject inclusion in the study.
- Verification of inclusion/exclusion criteria and collection of demographic data (including weight and height)
- PDQ-39
- Investigator performs UPDRS assessment
- Patient Engagement Questionnaire
- Randomization (Control Group [without Kinesia-360 device use at home]/Experimental Group [with Kinesia-360 device use at home])
- Experimental Group: Trained in-clinic on Kinesia-360 device (and sent home with the device)
- Control Group: Start treatment with Neupro as prescribed (preferably on Day 1, but no later than Day 4); record date and dose
- Control Group and Experimental Group: Recording of AEs and concomitant medications

8.2 Week 1

Day 2 and 3, home:

- Experimental Group: Subject wears Kinesia-360 wrist and ankle devices on Days 2 and 3 at home for baseline
- Experimental Group: Recording of concomitant medications and Neupro dose via APP

Day 4, home:

- Experimental Group: Start treatment with Neupro as prescribed; record date and dose via APP

- Experimental Group: Recording of concomitant medications

8.3 Weeks 2, 3, and 4

Control Group, home:

- Investigator uses standard of care to adjust Neupro dose as needed.
- Phone contact initiated by subject or Investigator as needed. Documentation of any contact or dosage adjustment.

Experimental Group, home:

- Subject uses Kinesia-360 at least on 2 consecutive days at home weekly to measure motor symptoms.
- Subject accesses Kinesia-360 motor symptom reports on device following each day of measurements.
- Investigator receives Kinesia-360 motor symptom reports via web portal following each day of measurements.
- Investigator combines standard of care with weekly Kinesia-360 motor symptom reports to adjust Neupro dose as needed.
- Phone contact initiated by subject or Investigator as needed and dispatch of Kinesia-360 motor symptom reports. Documentation of any contact or dosage adjustment.
- Recording of concomitant medications and Neupro dose via APP.
- A reminder phone call from the site to the subject each week during Weeks 2, 3, and 4 to ensure the subject will perform the protocol-requested Kinesia-360 assessments on 2 consecutive days per week. In addition, the subject should be reminded to charge the device and phone batteries the night prior to assessments.

8.4 Week 5 up to Week 12

Control Group, home:

- Treatment of subjects as per standard of care.
- Phone contact initiated by subject or Investigator as needed. Documentation of any contact or dosage adjustment.

Experimental Group, home:

- A reminder phone call from the site to the subject during the week prior to Visit 2 to ensure the subject will perform the protocol-requested Kinesia-360 assessments on 2 consecutive days. In addition, the subject should be reminded to charge the device and phone batteries the night prior to assessments.
- Optional: Subject may use Kinesia-360 as desired between Week 5 and Visit 2 (Week 12).
- Subject receives Kinesia-360 motor symptom reports on device following each day of measurements.

- Investigator receives Kinesia-360 motor symptom reports via web portal and by email following each day of measurements.
- Treatment of patients as per standard of care and dispatch of any Kinesia-360 motor symptom report.
- Phone contact initiated by subject or Investigator as needed and dispatch of Kinesia-360 motor symptom reports. Documentation of any contact or dosage adjustment.

8.5 Visit 2 (End of Study Visit) (Week 12 ±3 days)

Visit 2 represents the 3 month (from first Neupro dose) Follow-Up Visit.

Control Group and Experimental Group, in clinic:

- Control Group and Experimental Group: Subject wears Kinesia-ONE sensor in the clinic on the same side assessed at Visit 1 to measure specific motor tasks in triplicate.
- Investigator performs UPDRS assessment
- Patient Engagement Questionnaire
- Record Neupro dose
- Complete questionnaire (PDQ-39)
- Recording of AEs and concomitant medications

Experimental Group, in clinic:

- Return Kinesia-360 equipment to site

8.6 Early Withdrawal Visit

In case of an Early Withdrawal Visit, the same assessments as planned for Visit 2 shall be performed (see [Section 8.5](#)).

9 ASSESSMENT OF EFFICACY

9.1 Inclusion criteria threshold related to tremor and/or bradykinesia

Based on prior experience with studies involving dopaminergic therapies, GLNT expects bradykinesia and tremor to improve when using Neupro during PD0049. At Screening (ie, on Day 1), Investigators will perform the Kinesia-ONE assessment battery in triplicate on the more affected side of the body of each subject. As subjects will be on their individual Parkinson's disease medication when entering the study, they will likely be in a relative "on" state. However, since these subjects will be newly prescribed Neupro as their Parkinson's disease symptoms are not sufficiently controlled by their current therapy, it is likely that 1 or more symptoms will be present at Screening. To ensure subjects have sufficient room to improve, the inclusion criteria for this study include the presence of tremor and/or bradykinesia at Screening as measured by Kinesia-ONE. Specifically, based on experience in prior studies, the average of the triplicate resting tremor scores and the triplicate finger tapping scores (6 scores in total, averaged for 1 single score) must be >1.0 at Screening for subjects to be eligible for inclusion in this study (see Section 6.1, inclusion criterion #6).

9.1.1 Unified Parkinson's Disease Rating Scale

The change from Baseline to Visit 2 (Week 12) in Part III UPDRS Motor Score will be utilized as a primary efficacy variable.

The UPDRS is a comprehensive assessment of symptoms in subjects with Parkinson's disease. If possible, the same Investigator will perform both UPDRS assessments on a given subject. In PD0049, Parts I, II, and IV of the UPDRS will be used for the assessment of other efficacy variables.

9.1.2 39-Item Parkinson's Disease Questionnaire

Another efficacy variable to be assessed is the change from Baseline to Visit 2 (Week 12) in PDQ-39 questionnaire scores.

In Parkinson's disease, the PDQ-39 is the most widely used subject-reported rating scale endpoint in clinical studies.

10 ASSESSMENT OF SAFETY

10.1 Adverse events

10.1.1 Definitions

10.1.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that 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 (investigational) product, whether or not related to the medicinal (investigational) product.

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the ICF), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no Neupro was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which Neupro is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the Investigator from the subject's history or the pre-Neupro Period.

10.1.1.2 Serious adverse event

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. A serious adverse event (SAE) must meet 1 or more of the following criteria:

- Death
- Life-threatening

(Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)

- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious

(Important medical events may include, but are not limited to, potential Hy's Law, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

- Initial inpatient hospitalization or prolongation of hospitalization

(A patient admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, important medical event].

Hospitalizations for reasons not associated with the occurrence of an AE [eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner] do not qualify for reporting. For example, if a subject has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE, since there is no AE upon which to assess the serious criteria. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.)

10.1.1.3 Adverse events of special interest

Not applicable.

10.1.2 Procedures for reporting and recording adverse events and other safety related information

The Investigator is requested to instruct participating subjects of the need to inform them of any AE or other safety related information during the study, regardless of the relationship to medication, device use, or study procedures.

The subject will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs. For example:

“Did you notice anything unusual about your health (since your last visit)?”

In addition, the Investigator should review any self-assessment procedures (eg, diary cards) employed in the study.

10.1.2.1 Description of adverse events

When recording an AE, the Investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the subject's own words on his/her own records (eg, diary card) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the AE eCRF (including judgment of relationship to Neupro) are described in the eCRF Completion Guidelines.

10.1.2.2 Rule for repetition of an adverse event

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- The outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of "worsening"
- The AE verbatim term being the same for the first and repeated AE, so that the repeated AE can be easily identified as the worsening of the first one

Details for completion of the AE are described in the eCRF Completion Guidelines.

10.1.2.3 Reporting of serious AEs (related or not to Neupro)

An Investigator shall submit to UCB a report of any SAE experienced by a study subject, whether or not considered related to the participation in the study (ie, associated or not with Neupro) within 24 hours after the Investigator first learns of the event using the appropriate form.

Every effort shall be made to report the following information: date of AE, treatment/action taken, resolution, assessment of both the seriousness and the relationship to Neupro.

10.1.2.4 Device reporting

Great Lakes Neuro Technologies, Inc. will follow FDA medical device reporting requirements per 21CFR803. Sites will report adverse device effects and device deficiencies directly to GLNT ([REDACTED]: Office: [REDACTED] [9:00am – 5:00pm EST]; Mobile: [REDACTED] [after business hours]; email: [REDACTED]). An adverse device event (ADE) is defined as any AE related to the use of a device. A device deficiency is defined as inadequacy of a device with respect to its identity, quality, durability, reliability, safety, or performance. Great Lakes Neuro Technologies, Inc. will share this information with UCB.

10.1.3 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow up. This follow-up requirement applies to AEs and SAEs.

If an AE is ongoing at the end of the study for a subject, follow up should be provided until resolution/stable level of sequelae is achieved, or until the Investigator no longer deems that it is clinically significant, or until the subject is lost to follow up. If no follow up is provided, the Investigator must provide a justification. The follow up will usually be continued for 30 days after the subject has discontinued treatment with Neupro.

Information on SAEs obtained after clinical database lock will be captured through the Patient Safety (PS) database without limitation of time.

10.1.4 Pregnancy and breastfeeding

Investigators are required to report pregnancy of a subject, pregnancy of a subject's partner, and a subject who is breastfeeding using the Pregnancy Report and Outcome form for postmarketing cases. The procedure for reporting a pregnancy or breastfeeding is identical to the procedure for reporting safety relevant information (see [Section 10.1.2.3](#)).

The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the same form in which the Investigator has to report on the health of the mother and of the child. Every reasonable attempt should be made to follow the development and health of the child for at least 30 days after birth for any significant medical issues or development delay.

If the subject is lost to follow up and/or refuses to give information, written documentation of attempts to contact the subject needs to be provided by the Investigator and filed at the site.

In cases where the partner of a male subject enrolled in this study becomes pregnant, the Investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that should be available in the Investigator's site file. The Investigator will complete the Pregnancy Report and Outcome form for postmarketing cases and send it to UCB only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form.

10.1.5 Overdose of medicinal product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

Further details on Neupro overdosing can be found in the label (NEUPRO [package insert]. 2016 [[Section 15](#)]).

10.2 Laboratory measurements

Not applicable.

10.3 Other safety measurements

10.3.1 Rate of discontinuation of treatment with Neupro

The comparison of the rate of discontinuation of treatment with Neupro during the course of the study for the Control Group and the Experimental Group is one of the safety variables in PD0049.

Subjects who discontinue treatment with Neupro are encouraged to attend an Early Withdrawal Visit (see [Section 8.6](#)). For subjects randomized to the Experimental Group, discontinuation of treatment with Neupro can also be captured via the Kinesia-360 diary medication section within the respective APP.

11 STUDY MANAGEMENT AND ADMINISTRATION

11.1 Adherence to protocol

The Investigator should not deviate from the protocol. However, the Investigator should take any measure necessary in deviation from or not defined by the protocol in order to protect clinical study subjects from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IRB, or sponsor.

After implementation of such measure, the Investigator must notify the Clinical Project Manager of the sponsor within 24 hours and follow any local regulatory requirements.

11.2 Monitoring

UCB (or designee) will monitor the study to meet the sponsor's monitoring Standard Operating Procedures (SOPs), International Council for Harmonisation-Good Clinical Practice (ICH-GCP) guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by UCB to a Contract Research Organization (CRO) or a contract monitor.

The Investigator and his/her staff are expected to cooperate with UCB (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The Investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB review, and regulatory inspection(s).

The Investigator will allow UCB (or designee) to periodically review all eCRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authorities regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

11.2.1 Definition of source data

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, electrocardiogram (ECG) or other printouts, completed scales, or quality of life questionnaires. Source documents should be kept in a secure, limited access area.

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the subject's source documents. The Investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records, such as Holter monitor records or electroencephalogram records, must be saved and stored as instructed by UCB (or designee).

11.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents, unless otherwise specified in [Section 11.2.1](#).

11.3 Data handling

11.3.1 Case Report form completion

The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the Investigator's review and approval (by means of a password/electronic signature) will be reapproved by the Investigator.

The Investigator should maintain a list of personnel authorized to enter data into the eCRF.

Detailed instructions will be provided in the eCRF Completion Guidelines.

11.3.2 Database entry and reconciliation

Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. The data are entered into the eCRFs once and are subsequently verified.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

11.3.3 Subject Screening and Enrollment log/Subject Identification Code list

The subject's screening and enrollment will be recorded in the Subject Screening and Enrollment Log.

The Investigator will keep a Subject Identification Code list. This list remains with the Investigator and is used for unambiguous identification of each subject.

The subject's consent and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

11.4 Termination of the study

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the Investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB should also be informed and provided with reason(s) for the termination or suspension by the sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of the Kinesia devices and other material in accordance with UCB procedures for the study.

11.5 Archiving and data retention

The Investigator will maintain adequate records for the study, including eCRFs, medical records, Informed Consent documents, device dispensing and disposition records, safety reports, information regarding participants who discontinued, device distribution, and other pertinent data.

All essential documents are to be retained by the Investigator for at least 5 years after the final study report or first publication of the study results becomes available, whichever comes later. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB. The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the sponsor's trial master file.

11.6 Audit and inspection

The Investigator will permit study-related audits mandated by UCB, after reasonable notice, and inspections by domestic or foreign regulatory authorities.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of Neupro have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB SOPs, ICH-GCP, and applicable regulatory requirements.

The Investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the Investigator will immediately inform UCB (or designee).

11.7 Good Clinical Practice

Noncompliance with the protocol, ICH-GCP, or local regulatory requirements by the Investigator, institution, institution staff, or designees of the sponsor will lead to prompt action by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

12 STATISTICS

A description of statistical methods follows and will be described in more detail in the Statistical Analysis Plan (SAP).

12.1 Definition of analysis sets

Four analysis sets will be defined for this study: the Enrolled Set (ES), the Safety Set (SS), the Full Analysis Set (FAS), and the Per-Protocol Set (PPS).

The ES will consist of all subjects who signed the ICF.

The SS will consist of all subjects who received at least 1 dose of Neupro. The SS will be used for the analysis of all demographic, disposition, and safety data.

The FAS will consist of all subjects who have at least 1 valid Baseline and at least 1 valid post-Baseline efficacy measurement. The FAS will be used for the analysis and presentation of the efficacy data. In the case of misallocation, subjects will be primarily analyzed according to Kinesia-360 application (yes/no). However, if applicable, sensitivity analysis will also be performed according to the randomized group.

The PPS will consist of those subjects in the FAS who do not have any important protocol deviations that would have an impact on the efficacy variables. The PPS will be used for sensitivity analysis.

12.2 General statistical considerations

All analyses will be performed using SAS[®] version 9.3 or higher (SAS Institute, Cary, NC, USA). Continuous variables will be summarized by visit (where applicable) with the statistics including the number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by visit (where applicable) with frequency counts and percentages.

Unless otherwise specified, the comparisons will be for outcomes in subjects with Parkinson's disease in the Experimental Group (optimal Neupro dosing regimen will be titrated using motor symptom data collected with the Kinesia-360 wearable technology in addition to standard clinical practice) versus outcomes in subjects with Parkinson's disease in the Control Group (optimal Neupro dosing regimen will be titrated using only standard clinical practice). It is obvious that Kinesia-360 based efficacy data will be presented for the Experimental group only.

Unless otherwise specified, the level of significance for all tests will be 0.05. All statistical tests are 2-sided; however, they are exploratory only and p-values <0.05 do not indicate statistical significance, since no alpha adjustment will be performed.

All data recorded in the eCRF, APP, and questionnaires will be listed.

12.3 Planned efficacy analyses

12.3.1 Analysis of the efficacy variables

The efficacy variables, change from Baseline to Visit 2 (for all efficacy variables not based on Kinesia-360) will be analyzed utilizing an analysis of covariance (ANCOVA) with Baseline as a covariate, "center" as factor, and "group" as main factor. The 2 groups are the Experimental Group (EG) and the Control Group (CG).

The 2-sided null and alternative hypotheses are:

- Null hypothesis (H_0): EG=CG
- Alternative hypothesis (H_a): EG≠CG

EG: Represents the change from Baseline to Visit 2 for subjects in the Experimental Group.

CG: Represents the change from Baseline to Visit 2 for subjects in the Control Group.

The efficacy analysis will be performed on the FAS and observed cases will be utilized. The group effect will be estimated and presented with 95% 2-sided confidence intervals (CIs) and p-values.

The PPS will be used for sensitivity analysis on selected efficacy variables.

12.3.2 Other efficacy analyses

Kinesia-360-based efficacy data will be presented descriptively for the Experimental Group. Due to repeated measurements (during titration weekly and during maintenance), comparisons will be performed by time point and also by dose, if applicable (dependent on number of subjects in respective dose groups). Optional time points might also be subject to analysis (dependent on number of subjects at respective time points or windows for time points).

12.4 Planned safety analyses

12.4.1 Safety analyses

All analyses of safety data will be performed on the SS.

The incidence of subjects with treatment-emergent AEs (TEAEs) and/or SAEs will be determined. Furthermore, the absolute and relative frequencies for subjects with a given TEAE with respect to the preferred term according to the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA[®]) will be determined within each study part and system organ class. Additional tables will include, but are not limited to, summaries of TEAEs by maximum event intensity and causal relationship to Neupro. The actions taken for each AE, the time of onset of the AE, and the duration of each AE will be listed.

Further details will be provided in the SAP.

12.5 Handling of protocol deviations

Important protocol deviations are identified as part of the data cleaning process in the Data Cleaning Plan. Ongoing data cleaning meetings will be held throughout the duration of the study. Objectives of these meetings include to review and update (if necessary) the important protocol deviations and discuss exclusion of subjects from analysis populations. Furthermore, overall trends in protocol deviations will be discussed at the Data Evaluation Meeting. Through this ongoing data cleaning and evaluation process, all decisions regarding important protocol deviations and exclusions from analysis populations are made on an ongoing basis.

12.6 Handling of dropouts or missing data

In general, there will be no imputation of missing data.

12.7 Planned interim analysis and data monitoring

Not applicable.

12.8 Determination of sample size

Due to the character of the study, no formal sample size estimation can be performed. A sample size of approximately 40 will be regarded to be sufficient to get an impression of the effect of the device on the efficacy variables.

13 ETHICS AND REGULATORY REQUIREMENTS

13.1 Informed consent

Subject's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the subject in both oral and written form by the Investigator (or designee). Each subject will have the opportunity to discuss the study and its alternatives with the Investigator.

Prior to participation in the study, the ICF should be signed and personally dated by the subject, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The subject or his/her legal representative must receive a copy of the signed and dated ICF. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB review, and regulatory inspection.

If the ICF is amended during the study, the Investigator (or the Sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended ICF by the IRB and use of the amended form.

All studies conducted at centers in the US must include the use of a Health Insurance Portability and Accountability Act Authorization form.

The subject may withdraw his/her consent to participate in the study at any time. A subject is considered as enrolled in the study when he/she has signed the ICF. An eCRF must not be started, nor may any study specific procedure be performed for a given subject, without having obtained his/her written consent to participate in the study.

13.2 Subject identification cards

Upon signing the ICF, the subject or legal representative will be provided with a subject identification card in the language of the subject. The Investigator will fill in the subject identifying information and medical emergency contact information. The Investigator will instruct the subject to keep the card with him/her at all times.

13.3 Institutional Review Boards

The study will be conducted under the auspices of an IRB and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator(s)/UCB will ensure that an appropriately constituted IRB that complies with applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator/UCB will

forward copies of the protocol, ICF, Investigator's Brochure, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB for its review and approval.

Before initiating a study, the Investigator will have written and dated full approval from the responsible IRB for the protocol and all other documents submitted to the IRB.

The Investigator will also promptly report to the IRB all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

The Investigator will not make any changes in the study or study conduct without IRB approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the Investigator to obtain an expedited review by the IRB as allowed.

As part of the IRB requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IRB (based on IRB requirements), at intervals appropriate to the degree of subject risk involved, but no less than once per year. The Investigator should provide a final report to the IRB following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active Investigators in accordance with applicable regulatory requirements. The appropriate IRB will also be informed by the Investigator or the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, Investigators are to provide the Sponsor (or its representative) with evidence of such IRB notification.

13.4 Subject privacy

UCB staff (or designee) will affirm and uphold the subject's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the subject number assigned at Screening.

The Investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB, or representatives of regulatory authorities will be allowed to review that portion of the subject's primary medical records that directly concerns this study (including, but not limited to, admission/discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports for deaths occurring during the study).

13.5 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IRB, and the regulatory authorities (if required), prior to being implemented.

14 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in the Investigator and/or CRO agreements, as applicable.

15 REFERENCES

NEUPRO [package insert]. Smyrna, GA: UCB Inc.; 2016

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16 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

Printed name

Date/Signature

17 SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

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PD0049 Protocol

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[REDACTED]	Clinical Approval	16-Dec-2016 19:08 GMT+01
[REDACTED]	Clinical Approval	20-Dec-2016 13:54 GMT+01

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