CLINICAL STUDY PROTOCOL

A multicenter, international, open-label, safety study of ND0612, a solution of levodopa/carbidopa delivered via a pump system as a continuous subcutaneous infusion in subjects with advanced Parkinson's Disease (BeyoND)

Protocol Number:	ND0612H-012
EudraCT Number:	2015-005814-31
IND Number:	114367
Investigational Product:	ND0612; Levodopa/Carbidopa solution
Phase:	Phase IIb
Sponsor:	NeuroDerm Ltd. Ruhrberg Science building- Bell entrance - 4th floor 3 Pekeris St. Rehovot, 7670212 Israel
Contract Research Organization (CRO):	Syneos Health 1030 Sync Street Morrisville, NC, 27560 United States of America
Protocol Date:	Protocol V 1.0: 29 December 2015 Protocol V 2.0 (global Amendment 1): 14 June 2016 Protocol V 3.0 (global Amendment 2): 23 January 2017 Protocol V 4.0 (global Amendment 3): 17 August 2017 Protocol V 5.0 (global Amendment 4): 11 December 2017 Protocol V 6.0 (global Amendment 5): 20 March 2018 Protocol V 7.0 (global Amendment 6): 04 March 2019 Protocol V 8.0 (global Amendment 7): 12 March 2019 Protocol V 9.0 (global Amendment 8): 11 July 2019 Protocol V10.0 (global Amendment 9): 28 December 2020
Protocol Version:	Version 10.0 (28 December 2020)

1 PROTOCOL APPROVAL SIGNATURES

Protocol Title: **A multicenter, international, open-label, safety study of ND0612, a solution of levodopa/carbidopa delivered via a pump system as a continuous subcutaneous infusion in subjects with advanced Parkinson's Disease (BeyoND)**

Protocol Number: ND0612H-012

This study will be conducted in compliance with the clinical study protocol (and amendments), International Conference on Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

Sponsor Signatories

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3 SYNOPSIS

Protocol Number:

ND0612H-012

Title:

A multicenter, international, open-label, safety study of ND0612, a solution of levodopa/carbidopa delivered via a pump system as a continuous subcutaneous infusion in subjects with advanced Parkinson's Disease (BeyoND)

Investigational Product:

ND0612, a solution of levodopa/carbidopa (LD/CD) 60/7.5 mg/mL delivered continuously subcutaneously (SC) via an infusion pump system (CRONO TWIN ND), delivering daily doses of up to 720/90 mg LD/CD.

Study Centers:

About 65 international sites will participate in this study.

Phase:

Phase IIb (long-term safety study)

Objectives:

Primary Objective (assessed based on 12-month data):

- To assess the long-term safety (systemic and local) and tolerability of continuous SC infusion of ND0612. Assessment will be based on adverse events (AEs), with a focus on adverse events of special interest (AESI), i.e., infusion site reactions, cases of hypersensitivity, polyneuropathy. Tolerability will be assessed based on the percentage of subjects that complete the 12-month treatment period of the study and the percentage of subjects who discontinue from the 12-month treatment period due to an AE.

Further Safety Objectives (assessed based on 12-month data):

- To further assess the safety and tolerability of ND0612 including suicidality (Columbia - Suicide Severity Rating Scale [C-SSRS]), Questionnaire for Impulsive-Compulsive Disorders in PD-Rating Scale (QUIP RS), excessive daytime sleepiness (Epworth Sleepiness Scale [ESS]), vital signs, laboratory tests, and electrocardiogram (ECG) data.

Further Safety Objective (assessed based on data up to 102 months):

- To assess the long-term safety (systemic and local) and tolerability of continuous SC infusion of ND0612. Assessment will be based on AEs, with a focus on AESI, i.e., infusion site reactions, cases of hypersensitivity, polyneuropathy.

Exploratory Efficacy Objectives (assessed based on 12-month data):

The following exploratory efficacy objectives will be assessed separately for Cohort 1 (subjects who completed the treatment period of study ND0612H-006 within one month prior to enrolling to ND0612H-012) and for Cohort 2 (ND0612 naïve subjects and subjects who completed the treatment period of any ND0612 study more than one month before enrolling to ND0612H-012).

- To assess the efficacy of continuous SC infusion of 2 dosing regimens of ND0612 on daily "ON" time without troublesome dyskinesia based on home "ON/OFF" diaries
- To assess the efficacy of continuous SC infusion of 2 dosing regimens (see ‘Treatment’ section below for description of each regimen) of ND0612 on daily “OFF” time based on home “ON/OFF” diaries

- To assess the efficacy of continuous SC infusion of 2 dosing regimens of ND0612 on total daily dose of oral LD/DDI
- To assess the effect of continuous SC infusion of 2 dosing regimens of ND0612 on the motor score and activities of daily living (ADL) scores of the Unified Parkinson's Disease Rating Scale (UPDRS)
- To assess the effect of continuous SC infusion of 2 dosing regimens of ND0612 on the proportion of subjects with an improvement of ≥50% in "OFF" time based on home "ON/OFF" diaries
- To assess the effect of continuous SC infusion of 2 dosing regimens of ND0612 on "ON" time with troublesome dyskinesia (based on home "ON/OFF" diaries) in a subset of subjects who had more than 1 hour of troublesome dyskinesia at baseline.
- To assess the Clinical Global Impression (CGI: improvement and severity score assessed by investigator), Subject Global Impression (SGI-I: improvement score assessed by subject), Parkinson's Disease Sleep Scale (PDSS), the 39-Item PD Quality of Life [QoL] Questionnaire (PDQ-39) and the EQ-5D-5L QoL questionnaire.

Additional Objectives:

- To collect data on issues/problems of the pump system for a 12-month treatment period.
- To collect data on the user experience with the infusion pump, service, and support.

Study Design:

This is a multi-center, international, open-label, safety study of ND0612, a solution of levodopa/carbidopa (LD/CD) delivered via a pump system as a continuous SC infusion in subjects with advanced Parkinson's Disease (PD). Two cohorts of subjects are candidates for this study:

Cohort 1 - Subjects who completed treatment in study ND0612H-006 within one month prior to enrolling to ND0612H-012: The first cohort is comprised of subjects who recently completed the treatment period of the ND0612H-006 study. Prior to enrolling in this study subjects and study partners will provide informed consent and eligibility will be confirmed. Subjects should be considered capable of handling the procedures related to the administration of the SC infusion alone or with the assistance of a study partner. Subjects in Cohort 1 will remain on their assigned treatment regimen from study ND0612H-006 for 12 more months.

Subjects who enroll to ND0612H-012 immediately upon completion of the treatment period in ND0612H-006 will come in for their final treatment study visit and have all of the final study assessments completed for ND0612H-006. Afterwards, they may proceed directly to the Baseline visit of the current study.

Subjects in Cohort 1 who do not enroll to ND0612H-012 immediately upon completion of the treatment period in ND0612H-006 will perform the Baseline visit of ND0612H-012 in the morning, after having taken their standard anti-PD medication. During the visit the treatment with the pump system will be started. It is anticipated that subjects will down titrate their oral LD/ DDI (Dopa Decarboxylase Inhibition) based on the investigator's clinical judgment. Subjects may be asked to perform additional unscheduled visits in cases the investigator believes the subject's treatment requires additional titration to achieve stabilization.

Subjects will receive a phone call at Day 4, and return for in-clinic visits at Week 1, and Months 1, 2, 3, 4, 6, 9, and 12.

Cohort 2 – ND0612 naïve subjects and subjects who completed treatment in a ND0612 clinical study more than one month before screening: During the Screening visit the subjects and study partners will provide informed consent and eligibility will be confirmed. During the Screening Period subjects and study partners will be trained by a Home Nursing Service at their home setting on the administration of the SC infusion treatment alone or with the assistance of the study partner. The training will be performed in at least 4 separate sessions and for not less than 6 hours in total. Only subjects who are considered capable of handling these procedures alone or with the assistance of a study partner are eligible for study participation. Within 40 days of the Screening visit, subjects will return to the clinic for a Baseline visit (Day 1) in the morning, after having taken their standard anti-PD medication. During this visit, subjects will be randomized (at a 1:1 ratio) to one of two dosing regimens of ND0612 (see dosing regimens for descriptions of each regimen). Treatment with the pump system will start at the clinic visit.

On 08 December 2016, the Sponsor decided to switch all subjects who were treated with Regimen 2 to Regimen 1. Following this decision, ongoing subjects treated with Regimen 2 were to be switched at their next scheduled study visit to Regimen 1, and subjects not yet randomized were to be allocated Regimen 1 instead of being randomized.

Following the approval of Protocol amendment 2 (dated 23 January 2017) all new subjects who are enrolled in Cohort 2 will be assigned to treatment Regimen 3 (see dosing regimens for description of each regimen).

Subjects will return to the clinic on the next day (Day 2) so that the study staff can observe them and adjust their oral anti-PD medications, if necessary. It is anticipated that subjects will down titrate their oral LD/DDI based on the investigator's clinical judgment. Subjects may be asked to perform additional unscheduled visits in cases the investigator believes the subject's treatment requires additional titration to achieve stabilization. Subjects will remain on the assigned ND0612 dosing regimen for 12 months. During the treatment period, subjects will receive a phone call at Days 3, 4 and 6 and return for in-clinic visits at Week 1, and Months 1, 2, 3, 4, 6, 9, and 12.

For both cohorts:

If required, the subjects and their study partners will be trained and assisted at their homes during the first week of treatment by the Home Nursing Service on the proper operation of the pump system, including changing the infusion sets and syringes. One mandatory home visit will be performed during the first week, preferably on Day 3. Throughout the 12-month treatment period the Home Nursing Service will visit the subjects at their homes on a monthly basis. For both cohorts, adjustments of the oral anti-PD medication may be made via telephone contacts or during in-clinic unscheduled visits at the discretion of the investigator. Adjustment of the SC ND0612 treatment can be made at a scheduled or unscheduled in-clinic visit.

Study medication and ancillary supplies (i.e., infusion sets and syringes) will be dispensed at the site to the subjects or their study partners every month.

Subjects will be allowed to continue with study treatment for an optional treatment extension period of 24 more months in which clinic visits will be performed every 3 months (Months 15, 18, 21, 24, 27, 30, 33 and 36) to assess subject safety.

At the end of the optional treatment extension period, subjects will be allowed to continue with study treatment for another optional long-term treatment extension period up to Month 102 in which clinic visits will continue to be performed every 3 months up to Month 102, to assess subject long-term safety.

In the extension periods, subjects will be allowed to switch from Regimen 1 to Regimen 3 or from Regimen 3 to Regimen 1, according to the investigator's decision.

During the extension periods the sponsor may switch the infusion set used by the subjects to other commercially available or approved for use sets. If this will be the case, at their next scheduled clinic visit the subjects will receive an updated Operation Manual with the new infusion sets, and will be trained by the site staff on how to use the new infusion set. The subjects will use the new infusion set for 3 months and local safety assessments will be performed at the next scheduled clinic visit as at previous visits. Subjects may choose to continue with the new infusion set or switch back to the previous infusion set at any time.

Safety follow up visits will be performed 1, 2, and 3 months after the last study treatment.

Number of Subjects:

Approximately 210 subjects are planned to be treated in this safety study.

Treatment:

ND0612, is a LD/CD solution product, with an LD concentration of 60 mg/mL and CD concentration of 7.5 mg/mL administered by continuous subcutaneous infusion via two infusion sites using the CRONO TWIN ND infusion pump. Depending on the treatment regimen, the infusion rate on the pump may be programmed to automatically adjust for the night time hours when less LD/CD is administered at a fixed low infusion rate, and to the day time hours when higher doses are administered.

Treatment with ND0612 is initiated in the following steps:

1. Program the pump to deliver the infusion rates according to the assigned treatment regimen.
2. Initiate ND0612 while continuing adjunct oral LD/DDI, and gradually down titrating the oral LD dose. For subjects with a low baseline total dose of LD (≤ 700 mg per day), consider significantly reducing or stopping the oral LD/DDI that is taken as adjunct therapy upon initiation of ND0612 (please note the morning dose of Regimen 3 must be given). The ND0612 dose may also be down titrated.
3. For troublesome dyskinesia, or other troublesome levodopa related adverse reactions consider first reducing the dose of oral LD/DDI that is taken as adjunct therapy. If complications persist, the hourly high day rate of the ND0612 infusion may be down titrated.
4. Titrate the dose of adjunct oral LD/DDI, and the ND0612 dose based on the subject's individual clinical response and tolerability until a stable daily regimen is maintained.
5. Extra doses of oral LD/DDI can be used to manage “OFF” symptoms that are not controlled by the continuous ND0612 infusion

Study treatment will be administered by the study subjects and/or their study partners. Home nursing services will be used as needed in order to train the subjects and the study partners with the operation of the pump system and administration of the SC infusion during the screening period, during the first week of study treatment and once a month afterwards throughout the 12-month treatment period. Throughout the treatment period (up to Month 102), a helpline will be available for subjects/study partners to call at any time should they encounter any difficulties with the pump system.

Three dosing regimens of ND0612 will be studied

Regimen 1 – ND0612 solution will be infused subcutaneously via 2 infusion sites for 24 hrs continuously. Dosing will start at any time during the day which is convenient for the subject. The regimen will be comprised of two infusion rates: a fixed rate of 0.08mL/h for 6 hrs (22:00-4:00-low night rate), which will then change automatically to a rate of up to 0.64 mL/h for 18 hrs (4:00-22:00 high day rate) from two infusion sites in parallel, utilizing a pump system. The times for the automatic switch between the night and day rates may be configured by the investigator according to the subject's needs, however the total infusion volume during a 24 hr period will remain up to 12.00 ml (~6.00 ml from each infusion site) which is equivalent to 720 mg LD and 90 mg CD. The infusion sets and syringes will be changed at approximately the same time each day. Subjects will wear the infusion pump overnight while sleeping. Additional adjunct oral LD/DDI may be taken as needed.

Regimen 2 – ND0612 solution will be infused subcutaneously via 2 infusion sites for 14 hrs continuously. Dosing will start upon waking. The infusion will be set to a rate of 0.64 mL/h for 14 hrs (high rate) from two infusion sites in parallel, utilizing a pump system. The total infusion volume during the infusion period will be up to 8.96 ml (4.48 ml from each infusion site) which is equivalent to 537.6 mg LD and 67.2 mg CD. Subjects will remove the pump each evening at about 22:00 or their bedtime, whichever comes first. Subjects in this regimen will not wear the pump overnight and will change the infusion sets and syringes, applying new ones each morning. Subjects will also take an oral immediate release (IR) LD/CD dose of 150/15 mg at the time they start the SC treatment each morning. The Sponsor reserves the right to switch all subjects to one of the above 2 regimens. This decision will be made following the recommendation of the Oversight Committee that is following study ND0612H-006 and will be based on the safety, tolerability and efficacy results of these 2 regimens in the ND0612H-006 study. In this case,

ongoing subjects will be switched at their next scheduled study visit and subjects not yet randomized will be allocated to the selected regimen instead of being randomized. On 08 December 2016 the Sponsor made such a decision, and discontinued treatment Regimen 2. At that point, 12 subjects were included in Regimen 2, and all but 2 subjects (who had already been discontinued at that time) were transitioned to Regimen 1.

Regimen 3 – ND0612 solution will be infused subcutaneously via 2 infusion sites for 16 hrs continuously. Dosing will start upon waking. The infusion will be set to a rate of 0.75 mL/h for 16 hrs from two infusion sites in parallel, utilizing the pump system. The total infusion volume during the infusion period will be up to 12 ml (6 ml from each infusion site) which is equivalent to 720 mg LD and 90 mg CD. Subjects will remove the pump each night, after 16 hours of treatment or their bedtime, whichever comes first. Subjects in this regimen will not wear the pump overnight and will change the infusion sets and syringes, applying new ones each morning. Subjects will also take each morning oral LD/DDI (dose as needed according to investigator's assessment) at the time they wake up and start the SC treatment. Additional adjunct oral LD/DDI may be taken as needed.

Study Duration:

Planned enrollment duration: approximately 12 months

Treatment Period: 12 months of ND0612 continuous SC infusion

Optional Treatment Extension Period: Subjects will be allowed to continue with study treatment for an extension period of 24 more months (Months 12-36) during which they return for clinic visits every 3 months (Months 15, 18, 21, 24, 27, 30, 33 and 36).

Optional Long-Term Extension Period: At the end of the optional treatment extension period, subjects will be allowed to continue with study treatment for another optional long-term treatment extension period up to Month 102 during which they will return for clinic visits every 3 months up to Month 102.

Safety Follow-up Period: Safety follow up visits will be conducted for all subjects at 1, 2 and 3 months after last study treatment.

Study Population:

To be eligible for study entry subjects in Cohort 1 (previously completed the treatment period in protocol ND0612H-006 within one month prior to enrolling to ND0612H-012) must satisfy all of the following criteria:

1. Subject is able to, and has signed an Institutional Review Board/Ethics Committee (IRB/EC)-approved informed consent form (ICF).
2. Subject has completed the treatment period of study ND0612H-006 not more than one month prior to enrolling in ND0612H-012.
3. Willing and able to administer the SC infusion alone or with the assistance of a study partner and able to comply with the study specific procedures.

To be eligible for study entry subjects in Cohort 2 (ND0612 naïve subjects and subjects who completed treatment in a ND0612 clinical study more than one month before screening) must satisfy all of the following criteria:

1. Male and female PD subjects of any race aged at least 30 years who have signed an IRB/EC-approved ICF.
2. PD diagnosis consistent with the UK Brain Bank Criteria.
3. Modified Hoehn & Yahr scale in "ON" state of stage ≤3.
4. Taking at least 4 doses/day of LD/DDI (or at least 3 doses/day of Rytary) and taking, or have attempted to take, at least 1 other PD treatment for at least 30 days.
5. Subjects must be stable on their anti-PD medications for at least 30 days before Day 1.

6. Subjects may have had prior exposure to SC apomorphine injections/infusion but must have stopped continuous apomorphine administration at least 4 weeks before the screening visit. Treatment with apomorphine is prohibited during the entire ND0612 treatment period.
7. Must have a minimum of 2 hrs of "OFF" time per day with predictable early morning "OFF" periods as estimated by the subject.
8. Must have predictable and well-defined early morning "OFF" periods with a good response to LD for treatment of the early morning "OFF" in the judgement of the investigator.
9. Mini Mental State Examination (MMSE) score ≥26.
10. No clinically significant medical, psychiatric or laboratory abnormalities which the investigator judges would be unsafe or non-compliant in the study.
11. Female subjects must be surgically sterile (hysterectomy, bilateral oophorectomy, or tubal ligation), postmenopausal (defined as cessation of menses for at least 1 year), or willing to practice a highly effective method of contraception. All female participants must be non-lactating and non-pregnant and have a negative urine pregnancy test at Screening and at Baseline. Female subjects of childbearing potential must practice a highly effective method of contraception (e.g., oral contraceptives, intrauterine devices, partner with vasectomy), 1 month before enrollment, for the duration of the study, and 3 months after the last dose of study drug. Alternatively, true abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes active, the subject and sexual partner must comply with the contraceptive requirements detailed above.
12. Willing and able to administer the SC infusion alone or with the assistance of a study partner after a screening period of up to 40 days and willing and able to comply with study requirements.
13. Subjects should have a named study partner.

Subjects will be excluded from the study if one or more of the following criteria are applicable:

For Cohort 1 and Cohort 2, the following exclusion criterion applies:

1. Previously unable to tolerate ND0612 and/or have experienced intolerable adverse drug reactions associated with its use, regardless of the dosing regimen administered.

For Cohort 2, the following exclusion criteria apply:

1. Atypical or secondary parkinsonism.
2. Acute psychosis or hallucinations in past 6 months.
3. Any relevant medical, surgical, or psychiatric condition, laboratory value, or concomitant medication which, in the opinion of the Investigator makes the subject unsuitable for study entry or potentially unable to complete all aspects of the study.
4. Any malignancy in the 5 years prior to randomization (excluding basal cell carcinoma of the skin or cervical carcinoma in situ that have been successfully treated).
5. Positive serum serology for Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) or Human Immunodeficiency Virus (HIV) at the Screening visit.
6. Prior neurosurgical procedure for PD, or Duodopa treatment.
7. Subjects with a history of drug abuse or alcoholism within the past 12 months.
8. Clinically significant ECG rhythm abnormalities.
9. Renal or liver dysfunction that may alter drug metabolism including: serum creatinine >1.3 mg/dL, serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 x upper limit of normal (ULN), total serum bilirubin >2.5 mg/dL.
10. Current participation in a clinical trial with an investigational product or past participation within the last 30 days before Day 1.

Safety and Tolerability Assessment:

The primary endpoint in this study is a safety endpoint assessing the long-term safety (systemic and local) and tolerability of continuous SC infusion of ND0612 throughout the 12-month treatment period. Assessments, which constitute the primary endpoint of this study, will be based on AEs, with a focus on AESI, which will include infusion site reactions, hypersensitivity and polyneuropathy. Visual Analogue Scale (VAS) for pain assessment will also be used as primary measure. Tolerability will be assessed based on percentage of subjects completing 12 months of treatment in the trial, and the percentage of subjects who discontinued from the 12-month treatment period due to an AE.

Dopaminergic side effects including orthostatic blood pressure and changes in electrocardiogram (ECG) will be reviewed.

Safety and tolerability will furthermore be assessed based on laboratory parameters, vital signs, physical and neurological examination, assessment of suicidal behavior and ideation, assessment of excessive sleepiness, and assessment of impulsive compulsive behavior. The percentage of subjects that complete the 12-month study will be assessed.

For the subjects who continue to the optional treatment extension period only, and subjects who continue to the optional long-term treatment extension period, systemic and local safety of continuous SC infusion of ND0612 will also be assessed after up to 102 months of treatment based on AEs, with a focus on AESI, i.e., infusion site reactions, cases of hypersensitivity, polyneuropathy.

Efficacy Endpoints:

The exploratory efficacy endpoints assessed for 12 months of treatment are:

- Change in daily “ON” time without troublesome dyskinesia (defined as the sum of "ON" time without dyskinesia and “ON” time with non-troublesome dyskinesia) from Baseline to the 12-month visit based on home "ON/OFF" diaries.
- Change in daily “OFF” time from Baseline to the 12-month visit, based on home "ON/OFF" diaries
- Change in total daily dose of oral LD/DDI from Baseline to the 12-month visit.
- Proportion of responders at the 12-month visit based on daily “OFF” time recorded in home "ON/OFF" diaries. A responder is defined as a subject that experiences ≥50% reduction in “OFF” time from Baseline.
- Change in daily “ON” time with troublesome dyskinesia in a subset of subjects who had more than 1 hour of troublesome dyskinesia at Baseline, based on home "ON/OFF" diaries from Baseline to the 12-month visit.
- Change in PDQ-39 scores from Baseline to the 12-month visit.
- Change in EQ-5D-5L scores from Baseline to the 12-month visit.
- Change in UPDRS Part II (ADL) from Baseline to the 12-month visit.
- Change in CGI-Severity and CGI-Improvement from Baseline to the 12-month visit.
- Change in SGI-Improvement from Baseline to the 12-month visit.
- Change in PDSS total score from Baseline to the 12-month visit.
- Change in UPDRS Part III (motor score) from Baseline to the 12-month visit.
- Change from baseline to month 12 in percentage of “OFF” time and percentage of ‘Good’ ON during the first 3 hours since the subject is awake after 06:00 (6 am)
- Change from baseline to month 12 in ND0612 total dose
- Proportion of patients who reduced ND0612 total dose at any time during the study

Efficacy assessment:

Efficacy will be assessed based on daily "ON" time without troublesome dyskinesia and "OFF" time during waking hours as determined from "ON/OFF" home diary entries. Efficacy will be further explored using PDQ-39 (QoL), EQ-5D-5L (QoL), rating of PD (UPDRS), CGI for severity and improvement, and sleep assessment (PDSS).

Assessment of issues/problems in the infusion pump system:

Number of issues/problems in the pump system and number of subjects with at least one event/problem will be determined for the 12-month treatment period.

User experience assessment:

The user experience with the infusion pump, service, and support will be assessed by an optional questionnaire.

Statistical Analysis:

The All Enrolled Set will consist of all enrolled subjects. The Safety Set will consist of all enrolled subjects receiving at least 1 dose of study drug (ND0612). The modified Intention-to-Treat (mITT) Set will include all enrolled subjects who have valid efficacy data at baseline and at least once after the baseline. Analysis of the safety and tolerability data will be based on the Safety Set. The analysis of the efficacy data will be based on the mITT Set. The earlier version of this protocol included a randomization of the subjects to Regimen 1 or Regimen 2. Unless stated otherwise, the subjects who received Regimen 2 and were switched to Regimen 1 during the study conduct will be included in the Regimen 1 group.

The analyses related to the primary objective will include the study data up to the Month 12 visit. A separate analysis will be conducted based on the data up to 102 months. In addition, safety snapshot data in between the above mentioned time periods may be summarized during the study conduct for regulatory purposes.

The analysis of the safety data will be based on data accumulated from the present study. For safety, Cohort 1 and Cohort 2 will be analyzed jointly (for Regimen 1) and separately. For efficacy, Cohort 1 and Cohort 2 will be analyzed separately (where applicable). Baseline values for Cohort 1 will be derived from the ND0612H-006 study.

The safety data will be summarized both for the total Safety Set and broken down by the treatment regimen (Regimen 1 or Regimen 3). An additional safety analysis will be conducted by excluding the safety data from the subjects who received Regimen 2 during the period when these subjects received Regimen 2 (i.e. by excluding the data captured after the first dose of Regimen 2 until the switch to Regimen 1)

All safety data will be summarized using either summary statistics or frequency tabulations, as appropriate to the type of data. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be grouped by system organ class (SOC) and preferred term (PT) and summarized as described above. Only treatment emergent AEs will be summarized. Treatment emergent AEs (TEAEs) are defined as all AEs that start or worsen on or after the start of first study drug administration in the present study and before the start of the optional treatment extension (for the 1 year analysis). For patients who do not participate in the optional treatment extension, events that start >28 days after the last dose of study medication will not be defined as TEAEs. In addition to the frequency counts and percentages, the TEAEs will be presented as annualized rates. The annualized rates will be calculated by the total number of reported AEs divided by the total exposure time measured as the total subject years of exposure to the study medication.

Primary safety analyses will be based on TEAEs with a focus on AESI, i.e., infusion site reactions, hypersensitivity and polyneuropathy. Summaries of total number of cases will be presented as number of events, event rates adjusted to exposure and patient counts and percentages. For hypersensitivity and polyneuropathy, summaries will be broken down by outcomes (unknown, recovered, not yet recovered, recovered with sequelae and death); time to onset will be presented by Kaplan Meier figures, and with descriptive statistics. The Visual Analogue Scale (VAS) pain score will be summarized with descriptive statistics by visit and treatment group, changes from baseline will be summarized and the proportion of patients with a VAS pain score >0 mm or ≥40 mm will be tabulated by visit and treatment group.

Tolerability will be assessed based on percentage of subjects that complete the 12-month treatment period (or long term extension) of the study and the percentage of subjects who discontinue from the 12-month treatment period (or long term extension) due to a TEAE. Time (days) from enrolment to discontinuation will be illustrated as Kaplan-Meier curves by treatment regimen. Subjects who complete the study will be right censored at the date of last dose of study treatment during the 12-month study period (or long term extension). Time to discontinuation will also be explored by recruitment wave 1 and 2 following corrective actions for patients' retention.

Safety data from the treatment extensions up to Month 102 will be combined with the safety data of the main study and will be analyzed similarly.

The analysis of the efficacy data will focus on estimating the changes from baseline of the present study. The efficacy data will be summarized for both the total mITT Set and broken down by the treatment regimen. Cohort 1 and Cohort 2 will be summarized separately (where applicable).

The change from Baseline to Month 12 and to the other visits within each treatment regimen in daily "ON" time without troublesome dyskinesia will be estimated using a Mixed Model for Repeated Measures (MMRM) including response data from all scheduled post-baseline visits with no imputation for missing data. The changes from Baseline within each treatment regimen and the comparison between the regimens will be estimated, separately for each scheduled study visit, from the same MMRM using contrasts. The treatment regimen (Regimen 1 or Regimen 3, when applicable), visit and the interaction between treatment regimen and visit (if applicable) will be included as fixed factors in the MMRM together with the baseline value as covariate. The analysis for the "ON/OFF" home diary, will be performed only for Cohort 2. Changes from baseline will be summarized also the overall data.

All further efficacy endpoints will be analyzed in a similar manner (for both cohorts where applicable), using either an MMRM analysis for continuous endpoints or descriptive statistics for categorical endpoints. Sensitivity analyses of efficacy data will be conducted by excluding the subjects who were randomized to receive Regimen 2.

The endpoint of issues/problems in the infusion pump system will be summarized using descriptive statistics.

A Data Monitoring Committee (DMC) consisting of clinical experts will review the data periodically, with particular emphasis on local skin safety and tolerability.

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5 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the plasma concentration vs. time curve
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C-SSRS	Columbia - Suicide Severity Rating Scale
CD	Carbidopa
CGI	Clinical Global Impression
CRO	Contract Research Organization
DDI	Dopa Decarboxylase Inhibitor
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EQ-5D-5L	EuroQol Group 5-dimensions, 5-level Quality of Life questionnaire
ESS	Epworth Sleepiness Scale
FDA	Food And Drug Administration
Gamma GT	Gamma Glutamyltranspeptidase
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
hr(s)	Hour(s)
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus Antibody
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Immediate Release
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LD	Levodopa
MedDRA	Medical Dictionary For Regulatory Activities
mITT	Modified Intention-to-Treat
mL/µL	Milliliter/Microliter
MMSE	Mini Mental State Examination
mmHg	Millimeter(s) of Mercury
MMRM	Mixed Model for Repeated Measures
n	Number of subjects with an observation
N	Number of subjects in the dataset or population
PD	Parkinson’s Disease
PDQ-39	39-Item Parkinson's Disease Quality of Life Questionnaire
PDSS	Parkinson’s Disease Sleep Scale
PK	Pharmacokinetics

PT	Preferred Term
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale
QoL	Quality of Life
SAE	Serious Adverse Event
SGI-I	Subject Global Impression of Improvement
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
SD	Standard Deviation
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	Half-Life
TEAE	Treatment emergent Adverse Event
ULN	Upper Limit of Normal
UPDRS	Unified Parkinson Disease Rating Scale
USA	United States of America
VAS	Visual Analogue Scale
WHO	World Health Organization

DEFINITION OF TERMS

“OFF” state	Phase with no response to medication and significant motor symptoms
“ON” state	Phase with good response to medication and few symptoms

6 INTRODUCTION

6.1 Background

Parkinson's disease (PD) is a neurodegenerative movement disorder characterized by tremor, bradykinesia, muscular rigidity, and gait impairment as a result of marked dopamine deficiency in the basal ganglia of the brain due to the loss of dopaminergic neurons [1, 2]. Dopamine itself does not cross the blood-brain barrier, but its metabolic precursor, levodopa (LD), can permeate into striatal tissue and has, therefore, been an important drug in the treatment of the disease. For the past 40 years, LD (or L-Dopa) has remained the most effective therapy for the treatment of PD.

Under normal conditions, there is a low but continuous release of dopamine in the brain with superimposed bursts of increased release. However, LD has a short half-life ($t_{½}$) in plasma that, even under the best common current standard of care, results in pulsatile dopaminergic stimulation which differs from the physiological pattern of neurotransmitter secretion. The pulsatile manner in which LD or other short-acting dopaminergic agents stimulate striatal dopamine receptors is a key in the priming of the basal ganglia for induction of motor complications [3, 4, 5, 6, 7], i.e. motor fluctuations and dyskinesia that can represent a source of significant disability for the subjects, resulting in reduced overall effectiveness after 2 or 3 years of treatment. Carbidopa (CD) was developed to attenuate the adverse effects of LD therapy, such as nausea and vomiting as well as neurological deficits [8]. Proposed mechanisms include gastrointestinal dopa decarboxylase inhibition (DDI) to increase bioavailability, systemic DDI to decrease the plasma clearance, and brain capillary DDI to promote entry of L-dopa into brain tissue. Attempts are being made to provide more sustained dopamine concentrations in the central nervous system, known as continuous dopaminergic stimulation, by using novel LD preparations [2, 5, 9]. The current available long acting oral LD therapies failed to reduce the risk of motor complications in controlled trials [10, 11, 12]. In contrast, long lasting and dramatic reductions in motor complications associated with reduced dyskinesias and "OFF" periods (phases with no response to medication and significant motor symptoms) have been observed in PD subjects when treated with continuous infusion of LD (intravenous or intraduodenal) or dopamine agonists [1, 6, 8, 11, 13]. Unfortunately, the infusion approaches to date have inherent limitations in that they are neither convenient nor practical treatment options and dopamine agonists fail to reach the efficacy of LD and bear major adverse effects [14].

Levodopa and CD have been used extensively in humans by the oral route. NeuroDerm, Ltd. (NeuroDerm) is developing combination products comprising an LD/CD solution for continuous subcutaneous (SC) administration via different infusion pump systems for the treatment of idiopathic PD. The LD/CD solution contains 60 mg/mL LD and 7.5 mg/mL of CD.

ND0612 is being developed for patients with LD-responsive PD who do not have satisfactory control of debilitating motor fluctuations and hyper-/dyskinesia despite optimized treatment with commercially available PD products.

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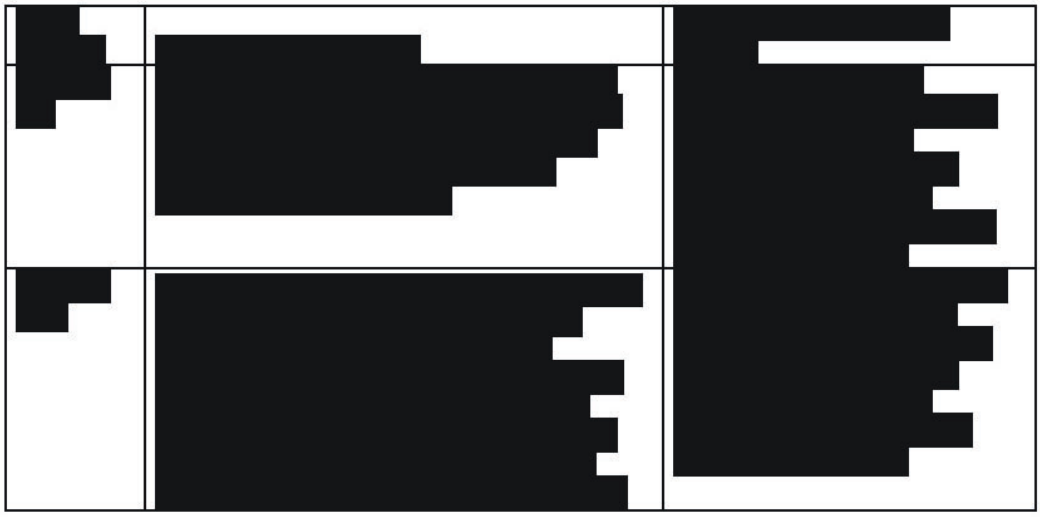

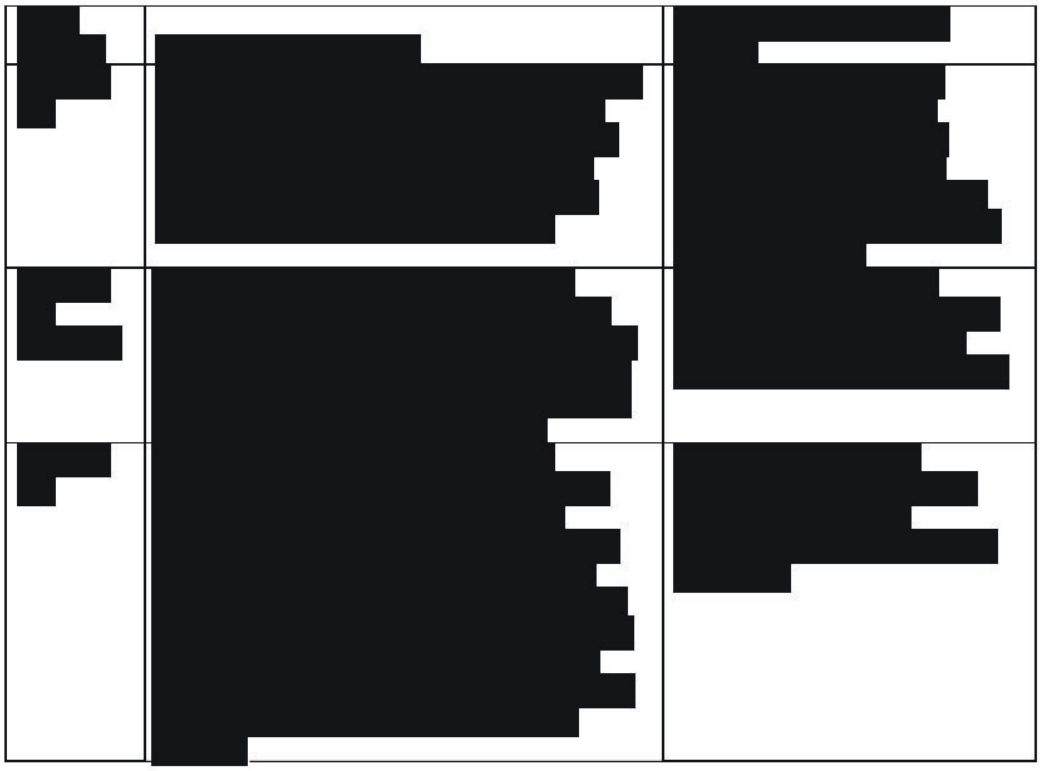


Study

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Eight completed clinical studies have evaluated a wide range of ND0612 exposures in healthy volunteers and patients with PD. LD and CD PK have been extensively evaluated, and safety and tolerability of infusions (with daily change of infusion sites) has been demonstrated with regard to both ND0612 study drug and the SC delivery system.

6.5 Study Plan

This Phase IIb open-label safety study is conducted in approximately 210 subjects who belong to 1 of 2 cohorts:

Cohort 1 includes subjects with advanced PD who are currently being treated (within the past month) with ND0612 in study ND0612H-006. They were planned to remain on the treatment regimen that they received in the ND0612H-006 study. From 08 December 2016 onwards, all subjects who were treated with Regimen 2 were to be switched to Regimen 1 and newly enrolled subjects were allocated to Regimen 1 (see Section 8.4.5 for details).

Cohort 2 includes subjects with advanced PD who completed any ND0612 study more than one month ago, or were not previously enrolled in any of the ND0612 protocols ("ND0612 naive subjects"). Cohort 2 subjects were randomized (1:1 ratio) to treatment regimens 1 or 2 (described below and in Section 8.1.1) up to 08 December 2016. After this date, all Cohort 2 subjects were allocated to Regimen 1 instead of being randomized (see Section 8.4.5 for details). After the implementation of Protocol amendment 2, all subjects enrolled in Cohort 2 receive Regimen 3. Total enrolment will be approximately 210 subjects.

The study will primarily investigate the safety (with a focus on local safety) and tolerability of continuous SC infusion of 3 dosing regimens of ND0612; efficacy will be assessed in an exploratory manner. Regimen 1 will employ continuous infusion for 24 hrs using a low infusion rate at night and a higher rate at daytime, resulting in a daily dose of 720 mg LD and 90 mg CD and additional oral LD/DDI as needed. Regimen 2 will employ infusion for 14 hrs only during daytime (at an infusion rate of 0.64 mL/hr; daily dose: 537.6 mg LD and 67.2 mg CD) with supplemental administration of oral immediate release (IR) LD/CD (150/15 mg) in the mornings. Regimen 3 will employ infusion for 16 hrs only during daytime (at an infusion rate of 0.75 mL/hr; daily dose: 720 mg LD and 90 mg CD) with supplemental administration of oral LD/DDI in the mornings and additional oral LD/DDI as needed.

For Cohort 2, subjects and study partners will receive training on administration of the SC infusions during the screening period by the Home Nursing Service. During the Baseline visit (Day 1) the site staff will supervise the administration of the infusion.

For both cohorts, if required, subjects and their study partners will be trained and assisted at their homes during the first week of treatment by the Home Nursing Service on the correct administration technique. One mandatory home visit will be performed during the first week, preferably on Day 3. Throughout the 12-month treatment period the Home Nursing Service will visit the subjects at their homes on a monthly basis.

For both cohorts, during the treatment period (up to Month 102), a helpline will be available for subjects/study partners to call at any time should they encounter any difficulties with the pump system.

The planned treatment duration for all regimens is 12 months with in-clinic visits at Week 1, Month 1, Month 2, Month 3, Month 4, Month 6, Month 9 and Month 12.

Subjects will be allowed to continue with study treatment for an optional treatment extension period of 24 more months in which clinic visits will be performed every 3 months to assess subject safety. Subjects will be offered another optional long-term treatment extension period up to Month 102. During this long-term extension period, clinic visits will continue to be performed every 3 months to assess subject long-term safety.

Safety follow-up visits will be performed 1, 2 and 3 months after the last SC administration of the study drug.

This will be the third study to assess the administration of the ND0612 solution using different dosing regimens in a home setting, with the focus of the current study being on the safety of long-term home administration. Additionally, the study will explore the need for dose adjustments e.g., up and down titrations of the study drug and/or a need for additional oral anti-PD treatment.

7 STUDY OBJECTIVES

7.1 Primary Objective

The primary objective of the study is to assess the long-term safety (systemic and local) and tolerability of continuous SC infusion of ND0612 for 12 months. Assessment will be based on adverse events (AEs), with a focus on adverse events of special interest (AESI), i.e., infusion site reactions, cases of hypersensitivity, polyneuropathy.

Tolerability will be assessed based on percentage of subjects that complete the 12-month treatment period of the study and the percentage of subjects who discontinue from the 12-month treatment period due to an AE.

7.2 Further Safety Objectives

Further safety objectives are to further assess the safety and tolerability of 12-months of ND0612 treatment including suicidality (Columbia – Suicide Severity Rating Scale [C-SSRS]), Questionnaire for Impulsive-Compulsive Disorders in PD-Rating Scale (QUIP RS), excessive daytime sleepiness (Epworth Sleepiness Scale [ESS]), vital signs, laboratory tests, and electrocardiogram (ECG) data.

Systemic and local long-term safety and tolerability of continuous SC infusion of ND0612 will also be assessed based on data up to 102 months of treatment. Assessments will be based on AEs, with a focus on AESI, i.e. infusion site reactions, cases of hypersensitivity, polyneuropathy.

7.3 Efficacy Objectives

The following exploratory efficacy objectives will be assessed for a 12-month treatment period, separately for Cohort 1 (subjects who completed the treatment period of study ND0612H-006 within one month prior to enrolling to ND0612H 012) and Cohort 2 (ND0612 naïve subjects and subjects who completed the treatment period of any ND0612 study more than one month before screening of ND0612H-012):

- To assess the efficacy of continuous SC infusion of 2 dosing regimens of ND0612 on daily "ON" time without troublesome dyskinesia (defined as the sum of "ON" time without dyskinesia, and "ON" time with non-troublesome dyskinesia) based on home "ON/OFF" diaries
- To assess the efficacy of continuous SC infusion of 2 dosing regimens of ND0612 on daily “OFF” time based on home “ON/OFF” diaries
- To assess the efficacy of continuous SC infusion of 2 dosing regimens of ND0612 on total daily dose of oral LD/DDI
- To assess the effect of continuous SC infusion of 2 dosing regimens of ND0612 on the motor score and ADL scores of the UPDRS

- To assess the effect of continuous SC infusion of 2 dosing regimens of ND0612 on the proportion of subjects with an improvement of ≥50% in “OFF” time based on home "ON/OFF" diaries

- To assess the effect of continuous SC infusion of 2 dosing regimens of ND0612 on “ON” time with troublesome dyskinesia time (based on home "ON/OFF" diaries) in a subset of subjects who had more than 1 hour of troublesome dyskinesia at baseline.

- To assess the CGI (improvement and severity score assessed by investigator), Subject Global Impression (SGI-I: improvement score assessed by subjects), PDSS, the PDQ-39 and the EQ-5D-5L.

Efficacy analyses will be exploratory only; no formal hypothesis testing will be performed in this study.

7.4 Additional Objectives

Additional exploratory objectives are:

- To collect data on issues/problems of the pump system for a 12-month treatment period

- To collect data on the user experience with the infusion pump, service, and support

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan: Description

8.1.1 Study Design

A multi-center, international, open-label, safety study of ND0612, a solution of LD/CD delivered via a pump system as a continuous SC infusion in subjects with advanced PD. The study will assess safety, tolerability, and efficacy of 2 dosing regimens (Regimen 1 and 2) of ND0612 compared to standard oral LD/DDI (Baseline) in advanced PD subjects. Two cohorts of subjects are candidates for this study:

Cohort 1 includes subjects with advanced PD who completed the treatment period in study ND0612H-006 within one month prior to enrollment in ND0612H-012. The subjects who completed treatment in study ND0612H-006 and who are considered capable of handling the procedures related to the administration of the SC infusion alone or with the assistance of a study partner can either roll-over directly to the current study or roll-over within a month time window. In the current study, subjects were to receive the same treatment regimen that they received in the ND0612H-006 study (including any up- or down-titrations performed in study ND0612H-006). On 08 December 2016, the Sponsor decided to switch all subjects who were treated with Regimen 2 to Regimen 1. Following this decision, ongoing subjects treated with Regimen 2 were to be switched at their next scheduled study visit to Regimen 1. Subjects may proceed directly to the Baseline visit of the current study (which may be the same as the end of treatment period visit for the ND0612H-006 protocol); a Screening Visit is not necessary.

Subjects in Cohort 1 who do not enroll to ND0612H-012 immediately upon completion of the treatment period in ND0612H-006 will perform the Baseline visit of ND0612H-012 in the morning, after having taken their standard anti-PD medication. During the visit, treatment with the pump system will be started. It is anticipated that subjects will down titrate their oral LD/DDI based on the investigator's clinical judgment. Subjects may be asked to perform additional unscheduled visits in cases the investigator believes the subject's treatment requires additional titration to achieve stabilization.

Cohort 2 includes subjects with advanced PD who completed ND0612 studies more than one month ago, or were not previously enrolled in any of the ND0612 protocols ("ND0612 naive subjects"). They will be seen for a Screening visit, during which they will provide informed consent and eligibility will be confirmed. Subjects and study partners will be trained by home nurses in their home setting on the administration of the SC infusion alone or with the assistance of the study partner between Screening and Baseline visit. The training will be performed in at least 4 separate sessions and for not less than 6 hours in total. Only subjects who are considered capable of handling these procedures alone or with the assistance of a study partner are eligible to be treated in this study. Within 40 days of the Screening visit, subjects will return to the clinic for a Baseline visit in the morning, having taken their standard anti-PD medication. During this visit, subjects were to be randomized at a 1:1 ratio to 1 of 2 dosing regimens

(Regimen 1 or Regimen 2) of ND0612 (see below for a description of each regimen). Following 08 December 2016, all subjects who were treated with Regimen 2 were to be switched to Regimen 1 at their next scheduled study visit, and subjects not yet randomized were to be allocated Regimen 1 instead of being randomized. Following the approval of Protocol amendment 2 (dated 23 January 2017) all new subjects who are enrolled in Cohort 2 will be assigned to treatment Regimen 3.

Treatment with the pump system will start at the clinic visit. The subject, in conjunction with the investigator, will determine whether or not the subject requires subsequent oral LD/DDI dose. It is anticipated that subjects will down titrate their oral LD/DDI as the LD/CD plasma levels reach steady state. Subjects will return to the clinic the next day so that the study staff can observe them and the investigator assess if the subject's treatment has been stabilized.

For both cohorts, the subjects and their study partner may be trained again during the first week of treatment by the Home Nursing Service on the proper operation of the pump system, including changing the infusion sets and syringes. During the treatment period (up to Month 102), a helpline will be available for subjects/study partners to call at any time should they encounter any difficulties with the pump system.

All subjects should remain on the assigned dosing regimen for one year. They will receive a phone call at Day 4 (and Days 3 and 6 for Cohort 2) and return for in- clinic visits at Week 1 and at Months 1, 2, 3, 4, 6, 9, and 12 for assessment of safety and efficacy variables. Subjects requiring modifications to their oral anti-PD medication to control their motor symptoms may add whichever medication the investigator determines to be the most clinically appropriate. Adjustments of the oral anti-PD medication may be made via telephone contacts or at an unscheduled visit at the discretion of the investigator. Adjustment of the SC treatment can be made at a scheduled or unscheduled in-clinic visit. For Cohort 2 subjects it is foreseen that the subjects' oral LD/DDI and other anti-PD medication will be titrated during the early weeks of the study based on the investigator's clinical judgment.

Subjects will be allowed to continue with study treatment for 24 more months (optional treatment extension period) and return for in-person visits every 3 months (Months 15, 18, 21, 24, 27, 30, 33 and 36). At the end of the 36-month treatment period, subjects will be offered an additional option to continue with study treatment up to Month 102 and continue to return for in-person visits every 3 months up to Month 102 (optional long-term extension period). Safety follow-up visits will occur 1, 2, and 3 months after the last SC infusion of ND0612 or after early termination. In both extension periods, subjects will be allowed to switch from Regimen 1 to Regimen 3 or from Regimen 3 to Regimen 1, according to the investigator's decision.

Regimen 1 (24 hour continuous infusion at a high infusion rate during the waking hours and a low infusion rate at night): Dosing will start at any time during the day which is convenient for the subject. The regimen will be comprised of two infusion rates: a rate of 0.08mL/h for 6 hrs (22:00-4:00-low night rate), which will then change automatically to a rate of 0.64 mL/h for 18 hrs (4:00-22:00-high day rate) from two infusion sites in

parallel, utilizing a pump system. The pump will automatically change the infusion rates according to the actual time. The times for the automatic switch between the night and day rates may be configured by the investigator according to the subject's needs, however the total infusion volume during a 24 hr period will remain 12.00 ml (~6.00 ml from each infusion site) which is equivalent to 720 mg LD and 90 mg CD. The infusion sets and syringes will be changed at approximately the same time each day. Subjects will wear the infusion pump overnight while sleeping. Additional oral LD/DDI may be taken as needed.

Regimen 2 (14 hours of continuous infusion at a high infusion rate during the waking hours only with supplemental oral 150 mg/15 mg LD/CD IR in the morning):
Dosing will start upon waking. The infusion will be set to a rate of 0.64 mL/h for 14 hrs (high rate) from two infusion sites in parallel, utilizing a pump system. The total infusion volume during the infusion period will be up to 8.96 ml (~4.48 ml from each infusion site) which is equivalent to 537.6 mg LD and 67.2mg CD. Subjects will remove the pump each evening at about ~22:00 or their bedtime, whichever comes first. Subjects in this regimen will not wear the pump overnight and will change the infusion sets and syringes, applying new ones each morning. Subjects will also be administered an oral IR LD/CD dose of 150/15 mg at the time they start the SC treatment. Additional oral LD/DDI may be taken as needed.

Following the recommendation of the Oversight Committee that is following study ND0612H-006 based on the safety, tolerability and efficacy results of these 2 regimens in the ND0612H-006 study, the sponsor decided to switch all Regimen 2 ongoing subjects at their next scheduled study visit to Regimen 1 and all subjects not yet randomized were to be allocated to Regimen 1 instead of being randomized.

Regimen 3 (16 hours of continuous infusion at a high infusion rate during the waking hours only with supplemental oral LD/DDI in the morning and as needed); All Cohort 2 subjects that are enrolled after Protocol amendment 2 will be allocated to Regimen 3:
Dosing will start upon waking. The infusion will be set to a rate of 0.75 mL/h for 16 hrs from two infusion sites in parallel, utilizing the pump system. The total infusion volume during the infusion period will be up to 12 ml (6 ml from each infusion site) which is equivalent to 720 mg LD and 90 mg CD. Subjects will remove the pump each night, after 16 hours of treatment or at their bedtime, whichever comes first. Subjects in this regimen will not wear the pump overnight and will change the infusion sets and syringes, applying new ones each morning. Subjects will also take each morning oral LD/DDI (dose as needed according to investigator's assessment) at the time they wake up and start the SC treatment. Additional adjunct oral LD/ DDI may be taken as needed.

During the Baseline Visit the administration of the infusion and the operation of the pump system will be performed by the subject/study partner and supervised by the study staff. Subjects/study partners will be provided instructions and training on the operation of the pump system including changing the infusion sets and syringes.

Subjects will record prolonged temporary discontinuations (over 3 hours) of study drug infusion in a Pump Diary. In case of any problem in the pump system that cannot be fixed within 3 hours the subjects should contact the Investigator, and resume a regimen of oral LD/CD until the study drug administration can be continued. The Sponsor's Device Service Manager or Training Manager may be called on from time-to-time to trouble-shoot issues that may arise in connection with the use of the infusion pump system, and may need to be directly involved in research activities in order to ensure the ongoing well-being of the trial subjects and efficient device development.

All subjects will keep an "ON/OFF" home diary; entries will be made for the 2 days before the in-clinic visits on Baseline, and Months 1, 3, 6, 9 and 12. Additionally, diaries will be completed for the 2 days before the in-clinic visits at Months 18, 24, 30, and 36 of the extension period. Subjects will be contacted by phone prior to each of these visits to remind them to enter the data in the "ON/OFF" home diary. At the conclusion of the study, subjects will be restarted on their standard anti-parkinsonian treatments. An Early Termination visit is to be conducted for subjects who discontinue study participation prematurely, whenever possible.

A Data Monitoring Committee (DMC) consisting of clinical experts will review the data periodically, with particular emphasis on local skin safety and tolerability (see Section 10.3 for further details).

8.1.1.1 Guidelines for Management of the Infusion Sites

The following measures are recommended for the selection and management of infusion sites: The recommend infusion sites are the abdomen (including flanks), and outer thighs. Alternative subcutaneous infusion sites may be used per the investigator recommendation. Needle length may be adjusted by the investigator accordingly. Infusion site locations should be changed on a daily basis. It is recommended that new infusion sets are applied at a different application site in a systematically rotating manner (as indicated in Operation Manual for the study) to avoid returning to the same application site for at least 2 weeks. The location of the infusion sites, and insertion date should be marked on a schematic map that will be provided to subjects and their study partners.

- The following criteria should be considered when choosing an infusion site:
  - Avoid sites that are within 5 cm from the umbilicus.
  - Avoid sites over skin nodules, or over areas with erythema or edema.
  - Avoid sites that are under a waistband of clothing, or constant rubbing (e.g., the inner thighs).
  - Avoid sites that are over bone, blood vessels, scar tissue, body piercing or tattoos.
  - The distance between the 2 simultaneous infusion sites should be at least 5 cm.

- Prior to inserting the cannula, hands should be washed and a clean working environment ensured. The site should be cleaned with 2 sterile prep pads or alcohol swabs taking care to wipe in same direction, e.g., left to right. The insertion should be done only after the area has completely dried.

In order to prevent inadvertent dislocation of the cannula it is important to properly fixate the infusion set to the skin with adhesive dressing. The adhesive dressing should be placed on dry skin. In certain cases, shaving of body hair may be required to securely attach the cannula to the skin.

Prior to the daily removal of the cannulas, the hands should be washed. After the cannulas removal, the infusion sites should be cleaned with a non-alcoholic pad. If possible, it is recommended to change the cannulas following a shower during which the infusion site is cleaned with soap and water.

The study subjects/study partners should be instructed to inspect the infusion pump system during the day to assure that the study drug is administered (drug level in the syringes is decreasing), and no signs of leakage are seen.

In case of a leakage from a cannula, both cannulas should be removed promptly and the pump disconnected. The skin that was exposed to the drug solution should be cleaned with water and a new infusion set inserted at a different infusion site location. In case the insertion of the new infusion set cannot be performed in a timely manner (approximately 3 hours), the subjects should contact the Investigator, and resume a regimen of oral LD/DDI as instructed by the Investigator. The pump should be kept dry at all times.

Additional safety measures should be taken in case of an infusion site infection, such as abscess or cellulitis, in order to minimize the risk of recurrence of the infection:

- Cultures should be taken from the nostrils, the sub-mammary and inguinal folds in order to identify subjects who are staphylococcus aureus (staph) carriers. Topical antibiotic treatment should be applied to subjects who are identified as staph carriers. It is recommended to refer the patients who had an infusion site infection to a consultant (e.g., dermatologist) to assist in the identification and decolonization of staph carriers.
- Every day, before inserting new infusion cannulas, subjects should clean the intended infusion site with antibacterial soaps, such as Betadine (polyvidone iodine) or Hibiclens (chlorhexidine gluconate), according to the manufacturer's guidelines. After this cleaning step, the site should also be cleaned with 2 sterile prep pads or alcohol swabs as described above.

8.1.1.2 Study Partners and Study Assistance

Subjects in this study should have a named study partner who may help them with the study procedures. The study partner can be a spouse, relative, friend, neighbor or caregiver. During the screening period, the subjects in Cohort 2 and their study partners will be provided with training, support and assistance by a home nurse in the procedures to be performed during the treatment period related to handling of the infusion pump, syringes, and infusion sets. Only subjects capable of performing the required procedures alone or with the help of their study partner will be eligible for treatment within this study.

A helpline will be available for subjects/study partners to call at any time should they encounter any difficulties with the pump system.

8.1.2 Schedule of Assessments

The schedule of planned study assessments is shown in the following flow chart. Assessments in shaded columns are for Cohort 2 only.

	Cohort 2[a]	All	Cohort 2[a]	All Subjects (Cohorts 1 & 2)									As Needed
Period/Visit	SCR	BSL[b]	Clinic visit 1a	Phone calls	Clinic visit 1b	Clinic visits 2 to 7	Clinic visit (End of M12 Treat-ment)	Safety F/U 1	Safety F/U 2,3[c]	Optional Treatment Extension[d, aa]	Optional Long-Term Treatment Extension[e,aa]	ET[f]	UN[g]
Duration	≤40 days	~6 hrs	~2 hrs	~10 min	~2 hrs	~2 hrs	~2 hrs	~4 hrs	~1 hr	~1 hr	~1 hr	~4 hrs	~1 hr
Visit/Phase Descriptor	SCR	BSL	Safety	Safety	Safety	Safety	Safety	Safety	Safety	Safety	Safety	Early Term.	Safety/ dose ad-justments
Study day (D)/ study week (W)/ study month (M)		D 1	D2	D3,4,6[h]	D7/ W1	M1, 2, 3, 4, 6, 9	M12	M13, M37, or M103[i]	M14,15, or M38, M39, or M104, M105	M15, 18, 21, 24, 27, 30, 33, 36	M39 up to Month 102 (every 3 months)		TBD
Visit Window (days)	-40			±1	±1	±3	±3	±3	±5	±5	±5		
Informed consent	X	X											
Inclusion/exclusion criteria	X	X[j]											
Modified Hoehn & Yahr (inclusion criterion)	X												
MMSE (exclusion criterion)	X												
Demographic data	X												
Medical history	X												
Prior and/or concomitant medication review	X	X	X	X	X	X	X	X		X	X	X	X
Urine pregnancy test[k]	X	X				X	X	X	X	X	X	X	X

	Cohort 2[a]	All	Cohort 2[a]	All Subjects (Cohorts 1 & 2)									As Needed
Period/Visit	SCR	BSL[b]	Clinic visit 1a	Phone calls	Clinic visit 1b	Clinic visits 2 to 7	Clinic visit (End of M12 Treatment)	Safety F/U 1	Safety F/U 2,3[c]	Optional Treatment Extension[d, aa]	Optional Long-Term Treatment Extension[e,aa]	ET[f]	UN[g]
Duration	≤40 days	~6 hrs	~2 hrs	~10 min	~2 hrs	~2 hrs	~2 hrs	~4 hrs	~1 hr	~1 hr	~1 hr	~4 hrs	~1 hr
Visit/Phase Descriptor	SCR	BSL	Safety	Safety	Safety	Safety	Safety	Safety	Safety	Safety	Safety	Early Term.	Safety/ dose adjustments
Study day (D)/ study week (W)/ study month (M)		D 1	D2	D3,4,6[h]	D7/ W1	M1, 2, 3, 4, 6, 9	M12	M13, M37, or M103[i]	M14,15, or M38, M39, or M104, M105	M15, 18, 21, 24, 27, 30, 33, 36	M39 up to Month 102 (every 3 months)		TBD
Visit Window (days)	-40			±1	±1	±3	±3	±3	±5	±5	±5		
Vital signs[l]	X	X	X		X	X	X	X		X	X	X	X
Body weight and height[m]	X	X			X	X	X	X				X	X
12-lead ECG[n]	X				X	X	X	X[ag]				X[f]	X
Serology	X												
Serum biochemistry and hematology tests	X	X			X	X	X	X[o]				X[f]	X
Blood test for vitamin B6, vitamin B12 and folate										X[ae]	X[ae]		X
Urinalysis (dipstick)	X	X			X	X	X	X[o]				X[f]	X
Physical examination	X	X						X				X	
Neurological examination	X	X						X				X	
C-SSRS	X	X			X	X[p]	X	X				X	
QUIP-RS	X	X			X	X	X	X				X	
Epworth Sleepiness Scale		X			X	X	X	X				X	

	Cohort 2[a]	All	Cohort 2[a]	All Subjects (Cohorts 1 & 2)									As Needed
Period/Visit	SCR	BSL[b]	Clinic visit 1a	Phone calls	Clinic visit 1b	Clinic visits 2 to 7	Clinic visit (End of M12 Treat-ment)	Safety F/U 1	Safety F/U 2,3[c]	Optional Treatment Extension[d, aa]	Optional Long-Term Treatment Extension[e,aa]	ET[f]	UN[g]
Duration	≤40 days	~6 hrs	~2 hrs	~10 min	~2 hrs	~2 hrs	~2 hrs	~4 hrs	~1 hr	~1 hr	~1 hr	~4 hrs	~1 hr
Visit/Phase Descriptor	SCR	BSL	Safety	Safety	Safety	Safety	Safety	Safety	Safety	Safety	Safety	Early Term.	Safety/ dose ad-justments
Study day (D)/ study week (W)/ study month (M)		D 1	D2	D3,4,6[h]	D7/ W1	M1, 2, 3, 4, 6, 9	M12	M13, M37, or M103[i]	M14,15, or M38, M39, or M104, M105	M15, 18, 21, 24, 27, 30, 33, 36	M39 up to Month 102 (every 3 months)		TBD
Visit Window (days)	-40			±1	±1	±3	±3	±3	±5	±5	±5		
PDSS		X			X	X[p]	X					X	
PDQ39		X			X	X[p]	X					X	
EQ-5D-5L		X				X[p]	X					X	
Global Impression of Improvement (CGI –I, SGI-I) (Investigator, Subject, respectively)					X	X[p]	X					X	
Clinical Global Impression of Severity (CGI-S) (Investigator)		X			X	X[p]	X					X	
UPDRS Parts I, II, III & IV		X[b]			X	X[p]	X					X	
Randomization to treatment regimen for Cohort 2. Subjects rolling-over from ND0612H-006 study stay on their treatment regimen		X											

	Cohort 2[a]	All	Cohort 2[a]	All Subjects (Cohorts 1 & 2)									As Needed
Period/Visit	SCR	BSL[b]	Clinic visit 1a	Phone calls	Clinic visit 1b	Clinic visits 2 to 7	Clinic visit (End of M12 Treatment)	Safety F/U 1	Safety F/U 2,3[c]	Optional Treatment Extension[d, aa]	Optional Long-Term Treatment Extension[e,aa]	ET[f]	UN[g]
Duration	≤40 days	~6 hrs	~2 hrs	~10 min	~2 hrs	~2 hrs	~2 hrs	~4 hrs	~1 hr	~1 hr	~1 hr	~4 hrs	~1 hr
Visit/Phase Descriptor	SCR	BSL	Safety	Safety	Safety	Safety	Safety	Safety	Safety	Safety	Safety	Early Term.	Safety/ dose adjustments
Study day (D)/ study week (W)/ study month (M)		D 1	D2	D3,4,6[h]	D7/ W1	M1, 2, 3, 4, 6, 9	M12	M13, M37, or M103[i]	M14,15, or M38, M39, or M104, M105	M15, 18, 21, 24, 27, 30, 33, 36	M39 up to Month 102 (every 3 months)		TBD
Visit Window (days)	-40			±1	±1	±3	±3	±3	±5	±5	±5		
Intake of standard LD/DDI therapy[q]	X	(X)[q]	(X)[q]				X	X	X				
Initiate subcutaneous infusion of ND0612 in clinic		X											
Home Nursing Service train subject and/or study partner at their home on proper use of the infusion pump[r]	X	X	X		X	X							
Infusion Site Assessment [t]		X	X		X	X	X	X	X	X	X	X	X
Dispense 1-month supply of study medication, infusion sets & syringes[u]		X				X	X			X (not M36[ac])	X (not M 102)		
Provide subjects with training on the use of the "ON/OFF" diary and the Pump diary	X[v]	X											

	Cohort 2[a]	All	Cohort 2[a]	All Subjects (Cohorts 1 & 2)									As Needed
Period/Visit	SCR	BSL[b]	Clinic visit 1a	Phone calls	Clinic visit 1b	Clinic visits 2 to 7	Clinic visit (End of M12 Treat-ment)	Safety F/U 1	Safety F/U 2,3[c]	Optional Treatment Extension[d, aa]	Optional Long-Term Treatment Extension[e,aa]	ET[f]	UN[g]
Duration	≤40 days	~6 hrs	~2 hrs	~10 min	~2 hrs	~2 hrs	~2 hrs	~4 hrs	~1 hr	~1 hr	~1 hr	~4 hrs	~1 hr
Visit/Phase Descriptor	SCR	BSL	Safety	Safety	Safety	Safety	Safety	Safety	Safety	Safety	Safety	Early Term.	Safety/ dose ad-justments
Study day (D)/ study week (W)/ study month (M)		D 1	D2	D3,4,6[h]	D7/ W1	M1, 2, 3, 4, 6, 9	M12	M13, M37, or M103[i]	M14,15, or M38, M39, or M104, M105	M15, 18, 21, 24, 27, 30, 33, 36	M39 up to Month 102 (every 3 months)		TBD
Visit Window (days)	-40			±1	±1	±3	±3	±3	±5	±5	±5		
Provide subjects with home "ON/OFF" diary and Pump diary	X[v]	X			X	X	X			X[ab]			
Phone call 3 days before each visit to remind subject to complete the "ON/OFF" diary		X				X[p]	X			X[s]		X[x]	
Subjects to complete "ON/OFF" diary during the waking day for the 2 days prior to the visit.		X[w]				X[p]	X			X[s]		X[x]	
Subject returns drug (used and unused), pump, unused infusion sets & syringes (drug accountability)					X	X	X[y]			X[y]	X	X	X
Adverse event recording including SAEs and AESIs	X	X	X	X	X	X	X	X		X	X	X	X

	Cohort 2[a]	All	Cohort 2[a]	All Subjects (Cohorts 1 & 2)									As Needed
Period/Visit	SCR	BSL[b]	Clinic visit 1a	Phone calls	Clinic visit 1b	Clinic visits 2 to 7	Clinic visit (End of M12 Treatment)	Safety F/U 1	Safety F/U 2,3[c]	Optional Treatment Extension[d, aa]	Optional Long-Term Treatment Extension[e,aa]	ET[f]	UN[g]
Duration	≤40 days	~6 hrs	~2 hrs	~10 min	~2 hrs	~2 hrs	~2 hrs	~4 hrs	~1 hr	~1 hr	~1 hr	~4 hrs	~1 hr
Visit/Phase Descriptor	SCR	BSL	Safety	Safety	Safety	Safety	Safety	Safety	Safety	Safety	Safety	Early Term.	Safety/ dose adjustments
Study day (D)/ study week (W)/ study month (M)		D 1	D2	D3,4,6[h]	D7/ W1	M1, 2, 3, 4, 6, 9	M12	M13, M37, or M103[i]	M14,15, or M38, M39, or M104, M105	M15, 18, 21, 24, 27, 30, 33, 36	M39 up to Month 102 (every 3 months)		TBD
Visit Window (days)	-40			±1	±1	±3	±3	±3	±5	±5	±5		
Return Subject to Standard LD/DDI dose[z]							X			X[ad]	X	X	
User experience questionnaire [af]										X	X		

Abbreviations: AESI=adverse event of special interest; BSL=Baseline; BP=blood pressure; CGI= Clinical Global Impression, C-SSRS=Columbia Suicide Severity Rating Scale; DDI = Dopa Decarboxylase Inhibitor; ECG=electrocardiogram; EQ-5D-5L=EuroQol 5-dimensions, 5-level Quality of Life Questionnaire ESS=Epworth Sleepiness Scale; ET=Early Termination; FU=Follow-up; IR=immediate release; LD/CD = Levodopa/Carbidopa; MMSE=Mini-Mental State Examination; PDQ-39=Parkinson's Disease Quality of Life Questionnaire-39 ; PDSS=Parkinson's Disease Sleep Scale; QUIP-RS= Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale; SAE=serious adverse event; SGI=Subject Global Impression; SCR=Screening; UPDRS=Unified Parkinson Disease Rating Scale; UN=unscheduled visit; term=termination.

Notes:

a. All subjects in Cohort 2 (subjects who completed ND0612 studies more than one month ago or who have not previously participated in any of the approved ND0612 protocols). These assessments are not necessary for subjects in Cohort 1.
b. For Cohort 1 subjects the assessments can be taken at the Day 28 visit of study ND0612H-006. For Motor (UPDRS part III), the last assessment performed on Day 28 of study ND0612H-006 will be used.
c. Safety visits will be scheduled at M 14 and M 15 for subjects stopping treatment at M 12 (or 2 and 3 months after early termination). For subjects who continue treatment until M 36, such visits will be scheduled for M 38, and M 39 (or 2, and 3 months after early termination in the optional extension phase). For subjects who continue treatment until M 102, such visits will be scheduled for M 104, and M 105(or 2, and 3 months after early termination in the optional long-term extension phase).
d. Subjects will be allowed to continue with study treatment for an optional treatment extension period of 24 more months in which clinic visits will be performed every 3 months to assess subject safety (visits scheduled for M15, M18, M21, M24, M27, M30, M33, M36).
e. Subjects will be allowed to continue with study treatment for another optional long-term extension period of up to Month 102 in which clinic visits will be performed every 3 months to assess subject long-term safety (visits scheduled for M39, M42, M45, M48, M51, M54, M57, M60, M63, M66, M69, M72, M75, M78, M81, M84, M87, M90, M93, M96, M99, M102).
f. An early termination visit should be performed for subjects who discontinue prematurely, whenever possible. Early termination visit procedures should also be performed for any subject who prematurely discontinues from the optional treatment extension period or optional long-term extension period. For early termination visits during the extension periods, safety laboratory tests (blood chemistry, hematology and dipstick urinalysis) and 12-lead ECG should be done at the investigator's discretion, and data will be analysed locally (i.e., not at a central lab/by central reader).
g. Subjects that complete the study and have unresolved nodules/skin problems will continue to be seen for unscheduled visits to evaluate the skin until the nodules/skin problems resolve or there are sequelae. Subjects requiring up or down titrations of study drug must be seen for an unscheduled visit to have the pump flow rate adjusted. Assessments will be performed at the investigator's discretion and may include one or more of the safety assessments described for this study.
h. At Days 3 and 6, phone calls are only made for Cohort 2 subjects. If phone calls fall on a weekend, they will be rescheduled for a time before or after the weekend, whichever is earlier.
i. Four weeks after the last study treatment, i.e., in Month 13 (for subjects not continuing to optional treatment extension), Month 37 (for subjects completing optional treatment extension but not continuing to long-term treatment extension), Month 103 (after completion of long-term treatment extension), or 4 weeks after the early termination visit.
j. For Cohort 1 only
k. Urine pregnancy test for all female subjects of childbearing potential only. A dipstick urine pregnancy test will be performed at the study site for all female subjects as part of the Screening and Baseline assessments prior to enrolment, at subsequent visits starting with Month 1, at the time of premature withdrawal (if applicable). At Months 5, 7, 8, 10, 11 the subjects will perform a home pregnancy test. Additional tests may be performed at any time during the study and up to 3 months after the last dose of study drug if required by local legislation. During the optional treatment and the optional long-term treatment extension period, monthly urine pregnancy tests will be performed either during study visits or at home for months without study visits.
l. Vital signs include supine (for at least 5 minutes) and standing BP, pulse rate, and body temperature.

m. Height will be recorded at the Screening Visit only.
n. 12-lead ECG should be recorded. In the event of possible ECG findings, additional ECG readings could be added at follow-up visits. For Cohort 1 subjects rolling-over directly from study ND016H-006, the results of the ECG performed at Day 28 of the ND0612H-006 study must be reviewed during the baseline visit of the ND0612H-012 study to ensure no exclusionary abnormalities are present.
o. At the safety follow-up visit, blood samples for serum biochemistry and hematology tests and samples for urinalysis must only be obtained if in the opinion of the investigator there were clinically significant results that require further follow-up. For safety follow-up visits after the optional extension period and the optional long-term extension period, optional safety laboratory data will be analysed locally (i.e., not at a central lab/by central reader).
p. Will not be performed at the Months 2 and 4 visits.
q. Starting on Day 1, subjects' standard oral LD/DDI dose will be down titrated at the discretion of the investigator.
r. Subjects and their study partner in Cohort 2 will already be trained on the administration of the SC infusion during the screening period. For this purpose, a pre-programmed, locked pump will be dispensed at the screening visit (to be returned at the baseline visit). The training will be performed in at least 4 separate sessions and for not less than 6 hours in total. Only subjects considered capable of handling these procedures alone or with the assistance of a study partner are eligible to be treated in this study. For both cohorts, if required, the subjects and/or their study partners will be trained and assisted at their homes during the first week of treatment by the Home Nursing Service on the proper operation of the pump system, including changing the infusion sets and syringes. One home visit during the first week is mandatory and should be performed preferably on Day 3. Throughout the 12-month treatment period the Home Nursing Service will visit the subjects at their homes on a monthly basis to provide training and assistance with the handling of the pump system.
s. Will be performed every 6 months during the extension period, at the Month 18, 24, 30, and 36 visits.
t. Infusion site assessment will be performed and all infusion site reactions (whether or not considered to be clinically significant by the investigators) will be reported as AESI.
u. At the clinic visits, the sites will supply drug supply for 1 month to the subjects. When clinic visits are more than one month apart the site will dispense study drug and clinical supplies for 1 month to the subject or the study partner at a clinic visit dedicated to study medication dispensing. Alternative means for medication distribution (e.g., via courier) may be used following regulatory and EC approval.
v. "ON/OFF" diary only, not Pump diary
w. Subjects in Cohort 1 will perform the Baseline motor assessment on the "ON/OFF" diary on study Days 2 and 3.
x. If possible, i.e. when the Early termination visit was scheduled a few days in advance.
y. If subjects continue treatment beyond Month 12, drug accountability will be performed but the pump and accessories will be left with the subject.
z. At Month 12, Month 36, or the Early termination visit, subjects who do not continue on their study regimen will be returned to their standard LD/DDI dose from the baseline visit after they have completed ND0612 continuous infusion. At Month 102, subjects will be prescribed an appropriate LD/DDI dose as determined by the investigator.

aa. During the extension period the sponsor may switch the infusion set used by the subject to other commercially available or approved for use sets. If this will be the case, subjects will receive the new infusion set at their next scheduled clinic visit. The subjects will use the new infusion set for 3 months and at the next clinic visit local safety assessments with the new infusion set will be performed. Subjects may choose to continue with the new infusion set or switch back to the previous infusion set at any time.
ab. Dispense ON/OFF diary at M15, M21, M27 and M33 only.
ac. Subjects continuing to the long-term treatment extension period will receive a 1-month supply of study medication, infusion sets and syringes.
ad. Not for subjects continuing to the long-term treatment extension period.
ae. Collect blood sample for vitamin B6, vitamin B12 and folate every 6 months during extension periods (M18, M24, M30 and M36 during treatment extension; M42, M48, M54, M60, M66, M72, M78, M84, M90, M96, and M102 during long-term treatment extension).
af. Subjects who consent to participate in this non-mandatory activity will receive the questionnaire at a site visit during the optional treatment extension period or the optional long-term extension period. They will be asked to complete the questionnaire once during the next scheduled visit at the site.
ag. For safety follow-up visits after the optional extension period and the optional long-term extension period, 12-lead ECG data will be analysed locally (i.e., not at a central lab/by central reader)

8.2 Discussion of Study Design

An open-label design in which subjects are randomized to 1 of 2 treatment regimens (Cohort 2) or continue on 1 of these regimens (Cohort 1) from a previous clinical study (ND0612-006) was chosen for this Phase IIb safety study.

Following the recommendation of the ND0612-006 oversight committee the sponsor decided to discontinue Regimen 2 treatment on 08 December 2016. The decision was based on interim data from ND0612-006 that suggested that Regimen 2 (14 hr at a rate of 0.64 mL/hr) is suboptimal in respect to the therapeutic response as reflected by the daily "OFF" time, and therefore assessment of its long-term safety is not relevant. The sponsor decided to further evaluate an optimized daily treatment regimen of 16 hr at a rate of 0.75 mL/hr, and introduced treatment Regimen 3 in Protocol amendment 2.

Clinical studies have demonstrated that ND0612, at concentrations of up to 60 mg/mL LD and 14.0 mg/mL CD, can be administered for a continuous 24 hr period in healthy subjects and patients with PD and produce clinically relevant plasma concentrations of LD and CD with modest intersubject variability. This appears to be accomplished with minimal local dermal toxicity and with only mild and expected systemic toxicity. Total daily doses of ND0612 over 24 hrs have ranged to as high as 720 mg LD and 90 mg CD in study ND0612H-005, which was well-tolerated without significant AEs. This exposure is the same as the planned daily exposure of 720 mg LD/90 mg CD over 24 hrs in the current study for Regimen 1. Based on clinical experience so far, the local infusion site safety profile of ND0612 is favorable, local transient findings do generally not impact the subjects' general well-being and the drug's tolerability.

The variables used for assessing safety, tolerability, and efficacy are standard measures in clinical studies in PD subjects.

Subjects will be followed for at least 12 months to ensure that long-term safety and tolerability data can be collected. A special focus will be on local tolerability to ensure sufficient data for the evaluation of long-term local reactions at the infusion sites are being collected.

8.3 Selection of Study Population

8.3.1 Number of Planned Subjects

The aim is to include approximately 210 subjects who received study drug (ND0612) overall. This number of subjects should be sufficient for the evaluation of long-term safety and tolerability with a focus on local tolerability at the infusion sites. No formal sample size evaluation has been conducted. Rescreening is allowed in this study (see Section 9.1.1).

The study is planned to be conducted in about 65 study sites globally.

8.3.2 Inclusion Criteria

To be eligible for study entry subjects in **Cohort 1** (previously completed the treatment period in protocol ND0612H-006 within one month prior to enrolling to ND0612H-012) must satisfy all of the following criteria:

1. Subject is able to, and has signed an Institutional Review Board/Ethics Committee (IRB/EC)-approved informed consent form (ICF).

2. Subject has completed the treatment period of study ND0612H-006 not more than one month prior to enrolling in ND0612H-012.

3. Willing and able to administer the SC infusion alone or with the assistance of a study partner and able to comply with the study specific procedures.

To be eligible for study entry subjects in **Cohort 2** (ND0612 naïve subjects and subjects who completed treatment in a ND0612 clinical study more than one month before screening) must satisfy all of the following criteria:

1. Male and female PD subjects of any race aged at least 30 years who sign an IRB/EC-approved ICF.

2. PD diagnosis consistent with the UK Brain Bank Criteria.

3. Modified Hoehn & Yahr scale in "ON" state of stage ≤3.

4. Taking at least 4 doses/day of LD/DDI (or at least 3 doses/day of Rytary) and taking, or have attempted to take, at least one other PD treatment for at least 30 days.

5. Subjects must be stable on their anti-PD medications for at least 30 days before Day 1.

6. Subjects may have had prior exposure to SC apomorphine injections/infusion but must have stopped continuous apomorphine administration at least 4 weeks before the screening visit. Treatment with apomorphine is prohibited during the entire ND0612 treatment period.

7. Must have a minimum of 2 hrs of "OFF" time per day with predictable early morning "OFF" periods as estimated by the subject.

8. Must have predictable and well defined early morning "OFF" periods with a good response to LD for treatment of the early morning "OFF" in the judgement of the investigator.

9. Mini Mental State Examination (MMSE) score ≥26.

10. No clinically significant medical, psychiatric or laboratory abnormalities which the investigator judges would be unsafe or non-compliant in the study.

11. Female subjects must be surgically sterile (hysterectomy, bilateral oophorectomy, or tubal ligation), postmenopausal (defined as cessation of menses for at least 1 year), or willing to practice a highly effective method of contraception. All female participants must be non-lactating and non-pregnant and have a negative urine pregnancy test at Screening and at Baseline. Female subjects of childbearing potential must practice a highly effective method of contraception (e.g., oral contraceptives, intrauterine devices, partner with vasectomy), 1 month before enrollment, for the duration of the study, and 3 months after the last dose of study drug. Alternatively, true abstinence is acceptable when it is in line with the subject's preferred and usual lifestyle. If a subject is usually not sexually active but becomes active, the subject and sexual partner must comply with the contraceptive requirements detailed above.

12. Willing and able to administer the SC infusion alone or with the assistance of a study partner after a screening period of up to 40 days and willing and able to comply with study requirements.

13. Subjects should have a named study partner.

8.3.3 Exclusion Criteria

Subjects in **Cohort 1** and **Cohort 2** will be excluded from the study if one or more of the following criteria listed below are applicable.

1. Previously unable to tolerate ND0612 and/or have experienced intolerable adverse drug reactions associated with its use, regardless of the dosing regimen administered.

For **Cohort 2** the following exclusion criteria apply:

1. Atypical or secondary parkinsonism.

2. Acute psychosis or hallucinations in past 6 months.

3. Any relevant medical, surgical, or psychiatric condition, laboratory value, or concomitant medication which, in the opinion of the Investigator makes the subject unsuitable for study entry or potentially unable to complete all aspects of the study.

4. Any malignancy in the 5 years prior to randomization (excluding basal cell carcinoma of the skin or cervical carcinoma in situ that have been successfully treated).

5. Positive serum serology for Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) or Human Immunodeficiency Virus (HIV) at the Screening visit.

6. Prior neurosurgical procedure for PD, or Duodopa treatment

7. Subjects with a history of drug abuse or alcoholism within the past 12 months.

8. Clinically significant ECG rhythm abnormalities.

9. Renal or liver dysfunction that may alter drug metabolism including: serum creatinine >1.3 mg/dL, serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 x upper limit of normal (ULN), total serum bilirubin >2.5 mg/dL.

10. Current participation in a clinical trial with an investigational product or past participation within the last 30 days before Day 1.

8.3.4 Removal of Subjects from Therapy or Assessments

A subject may withdraw or be withdrawn from the study for the following reasons:

- Subject withdraws consent, without the need to justify the decision
- Use of non-permitted concomitant therapy
- Non-compliance with the study drug or study schedule
- Lost to follow-up
- Pregnancy
- Occurrence of AEs not compatible with the continuation of subject participation in the study, in the investigator's opinion, or unacceptable to the subject to continue:
    - AE - Infusion site reaction
    - AE – Other
- Investigator request to remove subject
- Lack of efficacy
- Sponsor request to remove subject or to terminate entire study
- Other; reasons have to be documented clearly in the source documents and electronic case report form (eCRF)

If the reason for early treatment discontinuation is "subject withdrew consent" or "other", the site will be asked to rule out the possibility of an AE. If an AE leads to study discontinuation, "AE – Infusion site reaction" or "AE – Other" should be chosen as the discontinuation reason instead of "subject withdrew consent" or "other".

Subjects who are withdrawn from the study and/or study treatment will not be replaced. Subjects are free to withdraw from the study at any time without prejudice to further treatment. The reason(s) for withdrawal will be documented in the eCRF.

Subjects withdrawing from the study will be encouraged to complete the same final evaluations as subjects completing the study according to this protocol, particularly

safety evaluations. The aim is to record data in the same way as for subjects who completed the study.

Reasonable efforts will be made to contact subjects who are lost to follow-up. These efforts will be documented in the subject's file.

The sponsor has the right to terminate the study at any time in case of serious AEs (SAEs) or if special circumstances concerning the study drug or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

A DMC will meet periodically to review the accumulating safety data of the study and to provide a recommendation on study continuation or Early termination in case there is a concern regarding safety (see Section 10.3).

Pregnancy

Subjects will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the investigator, who will withdraw a pregnant subject from the study without delay and report the pregnancy within 24 hrs of first knowledge using a pregnancy report form. Upon discontinuation from the study, only those procedures that would not expose the subject to undue risk will be performed. The investigator should also be immediately notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject is found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and after delivery, the status of mother and child will be reported to the sponsor after delivery.

Full details will be recorded on the withdrawal page of the eCRF.

8.4 Investigational Products

8.4.1 Investigational Products Administered

ND0612, a LD/CD solution, with a LD concentration of 60 mg/mL and CD concentration of 7.5 mg/mL will be administered in this clinical study using an infusion pump system, CRONO Twin ND, for daily doses up to 720 mg LD/ 90 mg CD (12 mL).

Three dosing regimens of ND0612 will be studied in this study as described in Section 8.1.1 (see also dosing table in Section 8.4.7).

The ND0612 infusion pump system is comprised of a pump CRONO TWIN ND, manufactured by CANE for ambulatory use, two 10 mL syringes, and two infusion sets, which are commercially available or approved for use and are assembled from a tube and a cannula. Additional ancillary supplies may be provided as needed.

The study site staff will program the infusion rates and time of administration data in the pumps, and will be trained for reprograming infusion rates for up and down titration purposes.

The cannulas should be inserted into the SC layer. The recommended infusion sites are in the abdomen (including flanks) and outer thighs. It is recommended to insert the cannula with the assistance of an insertion device. During the treatment initiation, this will be supervised by the study site staff. During the treatment period subjects/study partners will handle the administration of the infusion and the operation of the pump system after having been provided with appropriate training. Refer to Section 8.1.1.1 for instructions regarding management of the infusion sites.

Treatment with ND0612 will be initiated in the following steps:

1. Program the pump to deliver the infusion rates according to the assigned treatment regimen
2. Initiate ND0612 while continuing adjunct oral LD/DDI, and gradually down titrating the oral LD dose. For subjects with a low baseline total dose of LD (≤ 700 mg per day), consider significantly reducing or stopping the oral LD/DDI that is taken as adjunct therapy upon initiation of ND0612 (please note the morning dose of Regimen 3 must be given). The ND0612 dose may also be down titrated (refer to Section 8.4.9.3 for further instructions).
3. For troublesome dyskinesia, or other troublesome levodopa related adverse reactions consider first reducing the dose of oral LD/DDI that is taken as adjunct therapy. If complications persist, the hourly high day rate of the ND0612 infusion may be down titrated.
4. Titrate the dose of adjunct oral LD/DDI, and the ND0612 dose based on the subject's individual clinical response and tolerability until a stable daily regimen is maintained.
5. Extra doses of oral LD/DDI can be used to manage “OFF” symptoms that are not controlled by the continuous ND0612 infusion

ND0612 dose may be decreased if required per the Investigator’s decision. In the event a subject experiences dopaminergic complications, oral LD/DDI taken as additional therapy (if any) should be reduced/stopped first. If complications persist, the hourly high infusion rate may be down titrated. Every 0.05 ml/h increment is equivalent to ~50 mg LD reduction per day. There is no cap to the number of dose reductions a subject may require. Subjects tolerating a dose reduction for 72 hours may attempt to up-titrate again. Subjects must come to the clinic for any up or down titrations as the pump must be reprogrammed to accommodate the new flow rate.

Abrupt discontinuation or significant dose reductions of the study treatment should be avoided. The study drug dosing should be gradually reduced.

In case of any problem in the pump system that cannot be fixed within 3 hours, the subjects should contact the Investigator and the helpline, and resume a regimen of oral LD/DDI until the study drug administration can be continued.

Study drug and clinical supplies for 1 month will be dispensed on the clinic visits at Baseline and Months 1, 2, 3, 4, 6, 9. On months 5, 7, 8, 10, 11, study drug and clinical supplies for 1 month will be dispensed to the subject, or the study partner at a clinic visit dedicated to study medication dispensing, Alternative means of medication distribution (e.g., via courier) may be used following regulatory and EC approval.

8.4.2 Identity of Investigational Products

Characteristics of test product:

Substance: Levodopa/carbidopa

Pharmaceutical form: solution for infusion supplied in a glass vial closed with a rubber stopper.

Manufacturer: CATALENT Indiana LLC
1300 South Patterson Drive, Bloomington, IN 47403, USA

Unit Strength: LD 60 mg/mL / CD 7.5 mg/mL

Route of administration: SC infusion (rates and duration of infusion depending on regimen)

The study drug ND0612 will be manufactured and imported according to the applicable regulatory requirements.

The study drug ND0612 will be infused using a pump system; CRONO TWIN ND pump system, manufactured by CANE. The pump system is comprised of a pump, two special syringes and two infusion sets with an insertion device.

8.4.3 Study Drug Packaging and Labeling

The secondary packaging and labeling of study drug will be performed by PCI - Packaging Coordinators Inc. (Rockford office: 4545 Assembly Drive, Rockford, IL 61109, USA).

All packaging and labeling operations for study drug will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

Distribution and Shipment:

ND0612 will be shipped frozen to the study site (or Central Pharmacy, where applicable), under the sponsor's responsibility. All study drugs will be packed in

appropriate storage boxes. If, upon arrival at the investigational site, the study drugs appear to be damaged, the sponsor or designee should be contacted immediately. Each shipment of study drug for the study will contain a shipment form describing the content of shipment. This form will assist in maintaining current and accurate inventory records. When a shipment is received, the investigator or designee will acknowledge receipt of the study drugs by signing the relevant shipping documents and recording arrival of the shipment in the Interactive Web Response System (IWRS).

Storage Conditions for ND0612

ND0612 will be kept at the site in a freezer at -20º C ±5 ºC in a secure, limited-access, controlled storage area.

Only authorized personnel will have access to the study drugs. The study site personnel at each site or Central Pharmacy will be responsible for correct storage and handling of the study drugs.

Study drug is packed in drug kits. Each kit will contain 72 drug vials. Each drug kit will be labelled with the protocol number, storage information, warning language (i.e., as required by local legislation for investigational drug products), dosing and storage instructions. The kit should be taken out of the freezer at least 4 hours before dispensing and kept at room temperature. Before dispensing or shipping of study drug kits, the dispensing study staff member or Central Pharmacy staff will write on the label the Subject's Study ID number and the last date to use after thawing.

Once study drug is dispensed or shipped to a subject, it may be shipped at ambient temperatures from the site or Central Pharmacy to the subject's home and stored at home at room temperature (15°C-30°C, 59°F-86°F), out of the reach of children. The study drug should NOT be placed in the refrigerator. Storage at room temperature must not exceed 35 days from thawing day. Before use, the vials should be tilted gently to verify that the content is uniform and is a clear slightly yellowish to yellowish solution without visible particles.

8.4.4 Direct-to-Patient (Supplies) Model

In case a study site is unavailable to receive IP shipments and/or dispense IP to subjects, a Central Pharmacy may be used (where regulatory applicable) to perform these activities directly to subject's home. A designated courier approved by the Sponsor will ship the required supplies. When this option will be applicable, specific procedures of working with a Central Pharmacy will be specified in a specific clinical supplies manual for the Central Pharmacy.

8.4.5 Method of Assigning Subjects to Treatment Groups

The original plan in this study was that subjects in Cohort 1 remain on the regimen they received in study ND0612H-006; subjects in Cohort 2 were to be randomized to one of the two treatment regimens (Regimen 1 or 2) at a ratio of 1:1. Following the recommendation of the ND0612H-006 oversight committee, the sponsor decided to discontinue Regimen 2 treatment on 08 December 2016. At that point 12 subjects were included in Regimen 2, and all but 2 subjects (who had already been discontinued at that time) on Regimen 2 were transitioned to Regimen 1. The sponsor decided to further evaluate an optimized daily treatment regimen (Regimen 3) of 16 hr at a rate of 0.75 mL/hr; after Protocol amendment 2, all newly enrolled subjects in Cohort 2 were to receive Regimen 3.

Each subject will receive a unique subject number when study staff enter them into the IWRS after they have provided informed consent. Subjects will retain their assigned subject number for the duration of the study; the subject numbers consist of a 3-digit site number and a 3-digit sequential number (i.e., xxx-xxx). Every subject must provide informed consent before any study procedures are conducted. Every subject that provides informed consent must be entered into the IWRS system regardless of eligibility. All subjects who are consented will also have their data entered into the electronic data capture (EDC) system. Subjects who are screen failures will only need to have limited data entered, including the reason for failing screening.

Subjects will enter the treatment period after all screening procedures (if applicable) and baseline assessments have been performed and eligibility for the study has been confirmed. Enrolled subjects who terminate their study participation for any reason, regardless of whether any study medication was received or not, will retain their screening number and randomization number (if applicable) and the study staff will need to enter the information into the IWRS to discontinue the subject's participation in the study.

Randomization was performed in Cohort 2 before implementation of Protocol amendment 2 as follows. In order to ensure a balanced treatment allocation, subjects in Cohort 2 were to be randomized in a 1:1 ratio to receive either Regimen 1 or Regimen 2. A stratification by region was performed. IWRS assigned a unique randomization ID for each randomized subject and assigned subjects to a treatment regimen based on the pre-defined randomization schedule. Syneos Health biostatistics prepared the master randomization schedule, which was imported into the IWRS using a validated program.

Subjects who are withdrawn from the study and/or study treatment will not be replaced.

The Sponsor reserves the right to switch all subjects to one of the above 2 regimens, based on the results of the ND0612H-006 study. In this case, ongoing subjects will be switched at their next scheduled study visit and subjects not yet randomized will be allocated to the selected regimen instead of being randomized. Such a decision was taken on 08 December 2016, when Regimen 2 was discontinued.

8.4.6 Selection of Doses in the Study

A rationale for the selection of doses in this study is provided in Section 8.2.

8.4.7 Selection and Timing of Dose for Each Subject

The daily dosing in the study regimens is summarized in Table 2 (below). Dose adjustments can be made as described in Section 8.4.9.2.

Table 2 Summary of ND0612 SC and oral LD/CD dosing regimens

Treatment	Formulation LD/CD	No. of Infusion Sites	Infusion Rate	Total Volume (mL/24h)	Total LD Dose (mg/24h)	Total CD Dose (mg/24h)	Timing	Oral LD/DDI	Wear Pump Over-night
Regimen 1	60/7.5 mg/mL	2	0.08 mL/hr for 6 hrs 0.64 mL/hr for 18 hrs	12.00	720	90	Start at any convenient time on Day 1; exchange of infusion sets at about 24-hr intervals[1]	As needed	Yes
Regimen 2[2]			0.64 mL/hr for 14 hrs	8.96	537.6	67.2	Start in the morning of Day 1; end after 14 hrs or bedtime (whichever occurs first)	Yes: morning dose of LD/CD 150 mg/15 mg and additional LD/DDI as needed	No
Regimen 3[3]			0.75 mL/hr for 16 hrs	12	720	90	Start at any convenient time on Day 1; exchange of infusion sets at 24-hr intervals	Yes: morning dose of LD/DDI and additional LD/DDI as needed[4]	No

[1] Pump automatically alternates from low infusion rate to high infusion rate

[2] Regimen 2 was discontinued on 08 December 2016 and all ongoing subjects who were treated with this regimen were switched to Regimen 1.

[3] Introduced with Protocol amendment 2.

[4] The investigator will determine the dose of daily oral LD/DDI based on the subject's needs.

8.4.8 Blinding

No blinding is foreseen in this open-label study.

8.4.9 Prior and Concomitant Therapy

Any medication taken in addition to the study medication has to be documented in the eCRF with details on the drug, dose, date and reason for prescription.

To be eligible for entering this study, subjects in Cohort 2 have to take at least 4 doses/day of LD (or at least 3 doses/day of Rytary).

Subjects furthermore have to take, or have attempted to take, at least one other PD treatment for at least 30 consecutive days. Subjects must be stable on their anti-PD medications for at least 30 days before Day 1.

Women of childbearing potential who take oral contraception have to continue taking it throughout the whole study.

8.4.9.1 Prohibited Medication/Therapy

If a subject receives prohibited concomitant medication, which cannot be discontinued or reduced, the subject must not enter the trial. If during the study the use of any prohibited medication becomes necessary, the subject will be withdrawn from further participation in the trial. If a subject is withdrawn during the treatment period, the assessments of the Early termination visit have to be performed for this subject.

Subjects may have had prior exposure to SC apomorphine injections/infusion but must have stopped continuous apomorphine infusion administration at least 4 weeks before the screening visit. Treatment with apomorphine is prohibited during the entire ND0612 treatment period. Prior or concomitant neurosurgical procedures for PD or duodopa treatment are also forbidden.

8.4.9.2 Rescue Medication and Additional Anti PD Therapy

Regimen 3 includes a mandatory morning oral dose of LD/DDI. The dose is to be determined by the investigator based on subject's need and may be adjusted during the study.

During the study, subjects who have intolerable "OFF" periods in the clinical judgement of the investigator may receive supplemental oral LD/DDI and/or entacapone as rescue therapy.

Subjects may receive supplemental oral LD/DDI therapy and/or entacapone during the study. Changes can only be made by the investigator and may be initiated via a telephone call or an unscheduled visit if warranted. If the use of rescue medication

continues over an extended period of time, this medication is considered additional PD therapy, and will be recorded by site staff on the eCRF, including date, time, dose and reason.

8.4.9.3 Down Titration of Study Drug During the Treatment Period of the Study

ND0612 dose may be decreased if required per the Investigator's decision. In the event a subject experiences dopaminergic complications in the opinion of the clinical investigator, oral LD/DDI or entacapone taken as additional therapy (if any) should be reduced/stopped first. If complications persist, the hourly high infusion rate may be down titrated. Every 0.05 mL/hr increment of ND0612 infusion rate is equivalent to ~50 mg LD reduction per day. There is no limitation to the number of dose reductions a subject may require. Subjects not tolerating a dose reduction may attempt to up-titrate again. Both down and up titrations of study drug and additional therapy are at the discretion of the investigator. The morning dose of oral LD/CD IR in Regimen 3 is not to be reduced. Subjects must come to the clinic for any up or down titrations of the study drug as the pump must be reprogrammed to accommodate the new flow rate.

Subjects with a low total dose of LD at baseline (≤ 700 mg per day) should receive special consideration. In such cases, upon initiation of SC infusion on Day 1, oral LD/DDI may be significantly reduced or stopped (please note the morning dose of Regimen 3 must be taken); the ND0612 hourly high infusion rate may be down titrated as well.

8.4.10 Study Drug Accountability and Treatment Compliance

Drug accountability measures will be performed as described in Section 13.1.

During the study visit the investigator and/or site coordinator will assess the subject's compliance with the prescribed regimen for the study medication. This will include checks of protocol compliance and use of study drug in order to assess the reliability of subject-generated data. Subjects who fail to comply with the study requirements may be withdrawn from the study, following consultation with the sponsor.

Compliance with the dosing regimen will be determined by performing study drugs accountability of returned study drugs used and unused. The number of used, unused and lost vials and/or containers will be recorded on the accountability forms by site personnel.

9 TIMING OF STUDY PROCEDURES

Subjects will provide written informed consent before any study related procedures are performed.

The planned study assessments are detailed in Section 8.1.2.

9.1 Pre-treatment

9.1.1 Screening Visit (for Cohort 2 only; up to 40 days before Day 1)

Subjects in Cohort 1 do not need to repeat screening procedures.

Before performing any study activity, the subject will be thoroughly informed on all aspects of the study. The subject will be requested to sign an EC/IRB approved ICF, after which a screening number will be assigned to the subject. The consent process for this study will include a video demonstration of the handling of the drug-pump system to aid in the subject's consideration of this aspect of the study.

Subjects will be assessed for study eligibility by the investigator at the screening visit(s). Screening procedures can be performed over several days. The maximal interval between the screening and baseline visits is 40 days. The following screening procedures will be performed:

- Informed consent
- Review of inclusion/exclusion criteria (including MMSE assessment and modified Hoehn & Yahr staging; see Appendices 17.1 and 17.2, respectively)
- Demographic data collection.
- Complete medical history, including disease history
- Review of prior and concomitant medication review (including anti-PD medication)
- Urine pregnancy test for female subjects of childbearing potential
- Vital signs (including supine [after resting for at least 5 min] and standing blood pressure (BP), pulse rate, and body temperature
- Body weight and height
- 12-lead ECG recording (single). In the event of possible ECG findings by the central ECG assessor, additional ECG reads could be added at follow-up visits as deemed necessary.
- Safety laboratory tests, including blood chemistry, hematology, serology, and dipstick urinalysis (see Section 10.1.2 for details)

- Physical and neurological examination
- Assessment of suicidality using C-SSRS (see Section 10.1.8 and Appendix 17.3)
- Assessment of impulsive-compulsive disorders in PD using the QUIP-RS (see Section 10.1.10 and Appendix 17.4)
- Recording of AEs (starting from signing of the ICF).
- Dispense home "ON/OFF " diary (see Section 10.2.1.1 and Appendix 17.12)
- Training of subjects and study partners on motor state assessment and recording using the home "ON/OFF" diary
- Dispense pre-programmed, locked pump for training purposes.

During the Screening Period subjects and study partners in Cohort 2 will be trained by a Home Nursing Service at their home setting on the administration of the SC infusion treatment alone or with the assistance of the study partner. The training will be performed in at least 4 separate sessions and for not less than 6 hours in total using a pre-programmed, locked pump. Only subjects who are considered capable of handling these procedures alone or with the assistance of a study partner can continue with this study.

After completion of all the testing for the assessment of eligibility, it will be decided by the investigator whether the subject is eligible for the study. For a subject to be eligible all inclusion criteria must be met and none of the exclusion criteria must apply. Therefore, all the results from the screening procedures must be available before determining a subject's eligibility.

This study permits the re-screening of a subject who has been found non-eligible when the reason for failure has been temporary and expected to resolve. If re-screened, the subject must be re-consented and receive a new screening number.

Subjects eligible for the study will be provided with home "ON/OFF" diaries after having received training on the use of these diaries. Subjects will be reminded of their next visit by phone 3 days before Day 1 so they can enter data on "ON/OFF" time for the 2 days before Day 1 (see Section 10.2.1.1).

Eligible subjects will return to the clinic for the Day 1 visit.

9.2 Treatment Period

9.2.1 Day 1 (Baseline Visit and Start of Treatment)

For subjects in Cohort 1 rolling-over directly, the Baseline visit can be conducted together with the Day 28 visit in study ND0612H-006. For Motor (UPDRS part III), the last assessment performed on Day 28 of study ND0612H-006 will be used as baseline assessment for the current study. The results of the ECG performed at Day 28 of the ND0612H-006 study must be reviewed during the baseline visit of the ND0612H-012 study to ensure no exclusionary abnormalities are present.

The following **Baseline assessments** will be performed:

Subjects in Cohort 1 will provide informed consent at Day 1 and will be provided with the “ON/OFF” diaries and with training on the use of the home diary. The Baseline "ON/OFF" assessment for Cohort 1 will be performed on Days 2 and 3. The subsequent "ON/OFF" diary assessments will be completed 2 days prior to each subsequent visit.

Up to 08 December 2016, subjects in Cohort 2 were randomized to Regimen 1 or 2 at a 1:1 ratio. After this date (pending implementation of Protocol Amendment 1), all subjects on Regimen 2 were switched to Regimen 1. After implementation of Protocol amendment 2, all subjects in Cohort 2 will receive Regimen 3.

The following procedures will be conducted for ALL subjects:

- Reassessment of eligibility against inclusion/exclusion criteria
- Review of concomitant medication (including anti-PD medication)
- Urine pregnancy test for female subjects of childbearing potential
- Vital signs (including supine [after resting for at least 5 min] and standing BP, pulse rate, and body temperature
- Body weight
- Safety laboratory tests, including blood chemistry, hematology, and dipstick urinalysis (see Section 10.1.2 for details)
- Physical and neurological examination
- Assessment of suicidality using C-SSRS (see Section 10.1.8 and Appendix 17.3)

- Assessment of impulsive-compulsive disorders in PD using the QUIP-RS (see Section 10.1.10 and Appendix 17.4)
- Assessment of excessive daytime sleepiness using ESS (see Section 10.1.9 and Appendix 17.5)
- PD rating using UPDRS Parts I, II, III and IV (see Section 10.2.1.2 and Appendix 17.6)
- Completion of the PDQ-39 (QoL) (see Section 10.2.1.5 and Appendix 17.7)
- Completion of the EQ-5D-5L (QoL) (see Section 10.2.1.6 and Appendix 17.8)
- Assessment of sleep using the PDSS (see Section 10.2.1.4 and Appendix 17.9)
- Assessment of Clinical Global Impression of disease severity by investigator or designee using CGI-S (see Section 10.2.1.3 and Appendix 17.10.1)
- Cohort 2: Collection of "ON/OFF" home diary. Entries will be reviewed for completeness and accuracy and data recorded in the eCRF.
- Cohort 1: Dispense "ON/OFF" home diary for entry of baseline motor assessment that will be performed on Days 2 and 3
- Dispense new "ON/OFF" home diary (see Section 10.2.1.1 and Appendix 17.12) Pump diary (see Section 10.1.11 and Appendix 17.13)
- Provide training on Pump diary use
- Administration of standard LD/DDI therapy throughout the day until infusion is started
- SC infusion will be started at the clinic at a convenient time on Day 1 for subjects on all regimens. The SC infusion will be applied by subject or study partner with the supervision of the study site staff. Infusion site assessments will be performed and infusion site reactions will be reported as AESI (see Section 10.1.3)
- Recording of AEs including SAEs and AESIs
- Dispensing of study medication and clinical supplies for 1 month
- Subjects will leave the clinic with their infusion pump attached, programmed according to the assigned regimen, and locked, and a supply of infusion sets and syringes sufficient for 1 month

- On the Baseline visit only, additional supply of infusion sets & syringes for 30 extra days will be dispensed to serve as back up for the 12-month treatment period

Subjects and study partners will be instructed to continue administration of the study drug at their homes according to their assigned regimen, and to contact the helpline if they need assistance. Home visits by the Home Nursing Service may be performed as needed during the first 7 days of treatment to provide additional training on the use of the infusion pump system including the application of infusion sites and the changing of the syringes and infusion sets. One home visit during the first week of study treatment is mandatory and should be performed preferably on Day 3.

9.2.2 Day 2

All subjects in Cohort 2 will return to the clinic on Day 2. Subjects in Cohort 1 who perform the completion visit of ND0612H-006 on the same day as the baseline visit of ND0612H-012 do not need to perform this visit. The subjects will arrive to the site after they have administered the study drug at a new infusion site.

The following procedures will be performed on Day 2:

- Concomitant medication review (including anti-PD medication). The investigator will determine if any changes need to be made to the subject's other anti-PD medications, including oral LD/DDI.
- Vital signs (including supine [after resting for at least 5 min] and standing BP, pulse rate, and body temperature
- Infusion site assessments will be performed on Day 2 and infusion site reactions will be reported as AESI (see Section 10.1.3)
- Recording of AEs including SAEs and AESIs
- Recording of study treatment temporary interruptions

9.2.3 Week 1 to Month 12

After the baseline visit (Cohort 1) or the Day 2 visit (Cohort 2), subjects will continue into the 12-month treatment phase of the study. The following procedures will be performed during the treatment period:

- SC infusion will be continued according to the assigned treatment regimen with the infusion set and syringe changed daily.

- Subjects will enter data on "ON/OFF" time for the 2 days before the Months 1, 3, 6, 9, and 12 visits using the "ON/OFF" diary (see Section 10.2.1.1).

On Day 4 all subjects and on Days 3 and 6 subjects in Cohort 2 will be contacted by phone to document AEs and to review concomitant medication (including anti-PD medication). It will be determined if any changes need to be made to the subject's other anti-PD medications, including oral LD/DDI. If these phone calls fall on a weekend, they will be rescheduled for before or after the weekend, whichever is earlier. Three days before each of the visits on Month 1, 3, 6, 9, or 12, subjects will receive reminder phone calls to ensure they enter the diary data.

On **Week 1** as well as **Month 1, 2, 3, 4, 6, 9, and 12** (End of 12-month treatment), a clinic visit will be scheduled with the following additional procedures:

- Drug accountability review of used and unused study medication; subjects are to bring their supplies to all clinic visits.
- Concomitant medication review (including anti-PD medication). The investigator will determine if any changes need to be made to the subject's other anti-PD medications including oral LD/DDI, and record all changes on the eCRF.
- Urine pregnancy test for female subjects of childbearing potential will be performed at all clinic visits but Week 1. To ensure monthly testing, the site will provide the subject with home urine pregnancy kits at the Month 4 visit. The subject will perform these tests at home on Months 5,7,8,10,11, and the site will contact the subject by phone and report the results of the monthly home tests on the source documentation. Additional pregnancy tests can be performed during the treatment period and up to 3 months after last dose of study drug if required by local legislation.
- Vital signs (including supine [after resting for at least 5 min] and standing BP, pulse rate, and body temperature
- Body weight
- 12-lead ECG recording (single). In the event of possible ECG findings by the central ECG assessor, additional ECG reads could be added at follow-up visits as deemed necessary.
- Safety laboratory tests, including blood chemistry, hematology, and dipstick urinalysis (see Section 10.1.2 for details)
- Assessment of suicidality using C-SSRS (Week 1 and Months 1, 3, 6, 9 12 only; see Section 10.1.8 and Appendix 17.3)

- Assessment of impulsive-compulsive disorders in PD using the QUIP-RS (see Section 10.1.10 and Appendix 17.4)
- Assessment of excessive daytime sleepiness using ESS (see Section 10.1.9 and Appendix 17.5)
- Completion of the PDQ-39 (QoL) (Week 1 and Months 1, 3, 6, 9 12 only; see Section 10.2.1.5 and Appendix 17.7)
- Completion of the EQ-5D-5L (QoL) (Months 1, 3, 6, 9 12 only; see Section 10.2.1.6 and Appendix 17.8)
- Assessment of sleep using the PDSS (Week 1 and Months 1, 3, 6, 9 12 only; see Section 10.2.1.4 and Appendix 17.9)
- Assessment of Clinical Global Impression of disease severity by investigator or designee using CGI-S (Week 1 and Months 1, 3, 6, 9 12 only; see Section 10.2.1.3 and Appendix 17.10.1)
- Assessment of Global Impression of improvement by subject and investigator using CGI-I and SGI-I, respectively (Week 1 and Months 1, 3, 6, 9 12 only; see Section 10.2.1.3, Appendix 17.10.1, and Appendix 17.10.2)
- PD rating using UPDRS Parts I, II, III and IV (Week 1 and Months 1, 3, 6, 9 12 only; see Section 10.2.1.2 and Appendix 17.6)
- Infusion site assessments will be performed and infusion site reactions will be reported as AESI (see Section 10.1.3)
- Recording of AEs including SAEs and AESIs
- Subjects will be provided with infusion sets, syringes and study medication sufficient for 1 month (not at Week 1).
- Home diary entries will be reviewed for completeness and accuracy
- Study treatment temporary interruptions will be recorded
- New home diaries (“ON/OFF” diary and Pump diary) will be dispensed (not at study end)
- Subjects will be prescribed an appropriate LD/DDI dose as determined by the investigator at the end of the 12-month treatment period visit (Month 12) and will return the infusion pump to the site. Subjects will be allowed to continue with study treatment for an optional treatment extension period and have clinic

visits every 3 months for another 24 months at Months 15, 18, 21, 24, 27, 30, 33 and 36.

Subjects that require additional modifications to their anti-PD medications after Week 1 may have their anti-PD medications adjusted via phone calls or unscheduled visits as determined by the investigator.

In case of any problem in the pump system that cannot be fixed within 3 hours the subjects should contact the Investigator, and resume a regimen of oral LD/DDI until the study drug administration can be continued.

Subjects and/or their study partners will be trained and assisted at their homes during the first week of treatment by the Home Nursing Service on the proper operation of the pump system, including changing the infusion sets and syringes. Throughout the 12-month treatment period the Home Nursing Service will visit the subjects at their homes on a monthly basis.

Throughout the treatment period (up to Month 102), a helpline will be available for subjects/study partners to call at any time should they encounter any difficulties with the pump system.

When clinic visits are more than 1 month apart, the site will dispense study drug and clinical supplies for 1 month to the subject, or the study partner at additional clinic visits dedicated to study medication dispensing. Alternative means for medication distribution (e.g., via courier) may be used following regulatory and EC approval.

A DMC consisting of clinical experts and NeuroDerm representatives will review the data periodically, with particular emphasis on local skin safety and tolerability.

9.2.4 Safety Follow-up Visit 1 (1 Month after Last Study Treatment)

Subjects will return to the clinic 1 month after the completion of the last study treatment for a safety follow-up visit. This will be at Month 13 for subjects who choose not to continue treatment in the optional treatment extension period, or Month 37 for subjects who continue treatment in the treatment extension period, or Month 103 for subjects who continue treatment in the long-term treatment extension period. In case of early termination, this visit is to be scheduled about 1 month after the Early termination visit. The following procedures are scheduled for this visit:

- Concomitant medication review (including anti-PD medication).
- Urine pregnancy test for female subjects of childbearing potential

- Vital signs (including supine [after resting for at least 5 min] and standing BP, pulse rate, and body temperature
- Body weight
- 12-lead ECG recording (single)
- Safety laboratory tests, including blood chemistry, hematology, and dipstick urinalysis (see Section 10.1.2 for details) if deemed necessary by the investigator to follow-up on earlier clinically significant findings
- Physical and neurological examination
- Assessment of suicidality using C-SSRS (see Section 10.1.8 and Appendix 17.3)
- Assessment of impulsive-compulsive disorders in PD using the QUIP-RS (see Section 10.1.10 and Appendix 17.4)
- Assessment of excessive daytime sleepiness using ESS (see Section 10.1.9 and Appendix 17.5)
- Infusion site assessments will be performed and infusion site reactions will be reported as AESI (see Section 10.1.3)
- Recording of AEs (including SAEs and AESIs)

For safety follow-up visits after the optional extension period and the optional long-term extension period, 12-lead ECG and optional safety laboratory test data (blood chemistry, hematology, and dipstick urinalysis) will be analysed locally (i.e., not at a central lab/by central reader).

9.2.5 Safety Follow-up Visits 2 and 3 (2 and 3 Months after Last Study Treatment)

Additional safety visits will be scheduled for all subjects 2 and 3 months after the last study dose. This will be Month 14 and Month 15 for subjects with treatment up to Month 12 who chose not to continue to the optional treatment extension period. For subjects stopping treatment at Month 36 after the optional treatment extension, such visits will be scheduled at Month 38 and Month 39. For subjects stopping treatment at Month 102 after the optional long-term treatment extension period, such visits will be performed at Month 104 and Month 105. In case of early termination, these visits will be performed 2 and 3 months after early termination.

Assessments will be limited to:

- Urine pregnancy test for female subjects of childbearing potential if required by local legislation.

- Infusion site assessments will be performed and infusion site reactions will be reported as AESI (see Section 10.1.3)

9.2.6 Optional Treatment Extension Period (Visits Months 15, 18, 21, 24, 27, 30, 33, 36)

Subjects will be allowed to continue with study treatment for an optional treatment extension period of 24 more months in which clinic visits will be performed every 3 months.

Assessments will be limited to:

- Urine pregnancy tests for female subjects of childbearing potential will be performed at all clinic visits. The site will provide the subject with monthly home urine pregnancy kits. The subject will perform these tests at home on a monthly basis, and the site will contact the subject by phone and report the results of the monthly home tests on the source documentation.
- Vital signs (including supine [after resting for at least 5 min] and standing BP, pulse rate, and body temperature)
- Infusion site assessments will be performed and infusion site reactions will be reported as AESI (see Section 10.1.3)
- Blood test for vitamin B6, vitamin B12 and folate (Months 18, 24, 30, 36 only)
- Recording of AEs including SAEs and AESIs
- Home diary "ON/OFF" diary entries will be reviewed for completeness and accuracy
- New home "ON/OFF" diary will be dispensed (at Months 15, 21, 27, and 33 only). New pump diary will be dispensed at every extension period visit (Months 15, 18, 21, 24, 27, 30, and 33).
- Concomitant medication review (including anti-PD medication).
- Subjects will be provided with infusion sets, syringes and study medication sufficient for 1 month
- Drug accountability review of used and unused study medication; subjects are to bring their supplies to all clinic visits
- Optional: user experience questionnaire (see Section 10.3 and Appendix 17.14)

As the clinic visits are more than 1 month apart, the site will dispense study drug and clinical supplies for 1 month, as well as the home diaries (when applicable), to the subject or the study partner at additional clinic visits dedicated to study drug dispensing. Alternative means for study drug distribution (e.g., via courier) may be used following regulatory and EC approval.

Subjects will enter data on "ON/OFF" time for the 2 days before the Month 18, 24, 30, and 36 visits using the "ON/OFF" diary (see Section 10.2.1.1).

Three days before each of the visits on Months 18, 24, 30, and 36, subjects will receive reminder phone calls to ensure they enter the diary data.

In the extension period, subjects will be allowed to switch from Regimen 1 to Regimen 3 or from Regimen 3 to Regimen 1, according to the investigator's decision.

During the extension period the sponsor may switch the infusion set used by the subjects to other commercially available or approved for use sets. If this will be the case, at their next scheduled clinic visit the subjects will receive an updated Operation Manual with the new infusion sets, and will be trained by the site staff on how to use the new infusion set. The subjects will use the new infusion set for 3 months and local safety assessments will be performed at the next scheduled clinic visit as at previous visits. Subjects may choose to continue with the new infusion set or switch back to the previous infusion set at any time.

Subjects will be allowed to continue with study treatment for an optional long-term treatment extension period with clinic visits every 3 months up to Month 102. Subjects who do not continue to the optional long-term treatment extension period will be prescribed an appropriate commercial LD/DDI dose as determined by the investigator at the end of the last visit they attend and will return the infusion pump to the site.

9.2.7 Optional Long-Term Extension Period (visits every 3 months starting at Month 39 up to Month 102)

Subjects will be allowed to continue with study treatment for another optional long-term extension period up to Month 102, during which clinic visits will continue to be performed every 3 months.

Assessments will be limited to:

- Urine pregnancy tests for female subjects of childbearing potential will be performed at all clinic visits. The site will provide the subject with monthly home urine pregnancy kits. The subject will perform these tests at home on a monthly basis, and the site will contact the subject by phone and report the results of the monthly home tests on the source documentation.
- Vital signs (including supine [after resting for at least 5 min] and standing BP, pulse rate, and body temperature)

- Infusion site assessments will be performed and infusion site reactions will be reported as AESI (see Section 10.1.3)
- Blood test for vitamin B6, vitamin B12, and folate will be performed every 6 months from Month 42 up to 102 months, where applicable
- Recording of AEs including SAEs and AESIs
- Concomitant medication review (including anti-PD medication)
- Subjects will be provided with infusion sets, syringes and study medication sufficient for 1 month
- Drug accountability review of used and unused study medication (vials containing particles will be counted separately); subjects are to bring their supplies to all clinic visits
- Optional: in case the subjects did not complete the user experience questionnaire during the optional treatment extension period, they will be asked to complete it during the optional long-term extension period (see Section 10.3 and Appendix 17.14)
- Other assessments may be done at the investigator's discretion

As the clinic visits are more than 1 month apart, the site will dispense study drug and clinical supplies for 1 month to the subject, or the study partner at additional clinic visits dedicated to study medication dispensing. Alternative means for medication distribution (e.g., via courier) may be used following regulatory and EC approval.

In the long-term extension period, subjects will also be allowed to switch from Regimen 1 to Regimen 3, or from Regimen 3 to Regimen 1, according to the investigator's decision.

At the end of the long-term extension period visit (Month 102) subjects will return the infusion pump to the site and will be prescribed an appropriate commercial LD/DDI dose as determined by the investigator.

The sponsor may terminate the optional long-term extension period at any time for safety and/or medical reasons, or if special circumstances concerning the investigational product (or the company itself) occur, making further treatment of subjects impossible. In this event, the site/investigator(s) will be informed of the reason for termination of the optional long-term extension period.

9.2.8 Early Termination Visit

Subjects who decide not to continue with the study procedures or who are withdrawn from the study should complete an early termination visit.

Procedures at the early termination visit are the same as mentioned in Section 9.2.3 for the Month 12 visit, with the addition of a neurological and a physical examination. Subjects will be prescribed an appropriate commercial LD/DDI dose as determined by the investigator and will return the infusion pump system to the site.

Early termination visits should also be performed for any subject who prematurely discontinues from the optional treatment extension period and the optional long-term extension period. For early termination visits during the extension periods, safety laboratory tests (blood chemistry, hematology, and dipstick urinalysis) and 12-lead ECG recordings should be done at the investigator's discretion and associated data will be analysed locally (i.e., not at a central lab/by a central reader).

Reasons for withdrawal of the subject before completion of the study must be stated in the eCRF and in the site source documentation for all study subjects who were enrolled in the study. The sponsor should be informed of all subjects who are withdrawn due to AEs.

An in-person safety follow-up visit should take place 1, 2 and 3 months after the actual discontinuation of the study drug. See Section 9.2.4 and Section 9.2.5 for procedures at the safety follow-up visits.

9.2.9 Unscheduled Visits

An Unscheduled visit may be performed at any time during the study at the subject's request or as deemed necessary by the investigator. Unscheduled visits will be scheduled e.g., if pump rate adjustments become necessary (see Section 8.4.9.2), when the subject has tolerability problems or has to down titrate the investigational treatment. Subjects should be advised that if tolerability problems continue then they should contact their investigator who may then withdraw them from the study. Subjects that complete the study and have unresolved nodules/skin problems at the last safety follow up visit will continue to be followed as considered necessary by the investigator.

At a minimum, concomitant medication data, AEs, and the date and reason for the Unscheduled visit will be recorded at this visit. Infusion site assessments will be performed and all infusion site reactions will be reported as AESI (see Section 10.1.3), whether or not considered clinically significant by the investigator.

When a subject attends an Unscheduled Visit between the scheduled visits they should be instructed to attend their next visit according to the study schedule as planned.

9.2.10 Duration of Treatment

The planned duration of treatment is 12 months of infusion with ND0612 in this study. At the end of the 12-month treatment period, an optional extended treatment period can be chosen by the subjects for an additional 24 months. If the product is not available on the market at the end of the 36-month treatment period, an optional long-term treatment extension period can be chosen by the subjects up to Month 102.

10 SAFETY AND EFFICACY VARIABLES

The planned schedule of assessments is in Section 8.1.2.

10.1 Safety Assessments

10.1.1 Adverse Events

Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product 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 (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. AEs will be elicited by asking the subject a nonleading question, for example, "Have you experienced any new or changed symptoms since we last asked/since your last visit?" AEs should be reported in the appropriate section of the eCRF.

Assessment of Severity

Each AE will be assigned a category by the investigator as follows:

Mild:	An AE that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.
Moderate:	An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
Severe:	An AE that prevents normal everyday activities; treatment or other intervention usually needed.

If there is a change in severity of an AE, it must be recorded as a separate event.

Assessment of Causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the study drug. Investigators should use their knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study drug. Causality should be assessed using the categories presented below:

Related: Adverse event judged by the investigator as having a reasonable suspected causal relationship to the investigational medicinal product

Unrelated: Adverse event judged by the investigator as NOT having a reasonable suspected causal relationship to the investigational medicinal product

Action Taken

The investigator will describe the action taken in the appropriate section of the eCRF, as follows:

Action Taken:

- None
- Study Drug Stopped
- Study Drug temporarily interrupted
- Concomitant medication
- Other

Action Taken with Study Treatment:

- Dose Increased
- Dose Not Changed
- Dose Reduced
- Drug Interrupted
- Drug Withdrawn
- Not Applicable
- Unknown

Recording and Follow-up of Adverse Events

Adverse events will be recorded from informed consent to the final safety follow-up visit or the Early termination visit (if applicable). Subjects should be followed up for 3 months after receiving the last dose of study drug, and any AEs that occur during this time should be reported according to the procedures outlined above.

The subject will be followed as part of this protocol for 3 months after the last dosing.

All investigators should follow up subjects with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic.

Documentation and Reporting of Adverse Events

AEs should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant eCRF pages. The following data should be documented for each AE:

- Description of the symptom event
- Classification of "serious" or "not serious"
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken
- Causal relationship
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

10.1.1.1 Adverse Events of Special Interest

Adverse events of special interest (AESI) include the following:

- Infusion site reactions
- Cases of hypersensitivity (e.g., diffuse skin rash, anaphylaxis and angioedema).
- Polyneuropathy

A dermatology examination is mandatory for the following 2 cases:

1. Infusion site reactions reported as SAE leading to withdrawal
2. Infusion site reactions reported as SAE requiring additional medical/surgical treatment

Additionally, the Investigator may refer to a dermatologist any infusion site reactions reported as an SAE or AE. The skin lesions should be photographed before and after treatment, if feasible.

The dermatologist consultant will document any relevant information of the lesion including pictures of the lesions.

10.1.1.2 Serious Adverse Events

Serious Adverse Event Definition

An SAE is any untoward medical occurrence or effect that, at any dose,

- Results in death.
- Is life-threatening (an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred, i.e., it does not include a reaction that might have caused death if it had occurred in a more serious form).
- Requires or prolongs inpatient hospitalization. (Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing non-worsening condition is not, however, considered an AE. The details of such hospitalizations must be recorded on the medical history or physical examination page of the eCRF).
- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions).
- Results in a congenital anomaly/birth defect.

In addition, medical and scientific judgement is required to decide if prompt notification is required in situations other than those defined for SAEs above. This may include any event that the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the subject or required intervention to prevent 1 of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the investigational product.

Reporting of Serious Adverse Events

Any SAE must be reported by the investigator if it occurs during the clinical study or within 28 days of receiving the study drug, whether or not the SAE is considered to be related to the investigational product. An SAE report consists of the SAE form, the AE form, and the concomitant medication form. A copy of these forms must be emailed **within 24 hrs** for the attention of the product safety scientist at:

Email: safetyreporting@syneoshealth.com

E-mail is the preferred reporting tool. In addition, sending reports by fax is also possible via the Global SAE Fax Line: 1-877-464-7787.

The investigator should not wait to receive additional information to document fully the event before notification of a SAE, though additional information may be requested.

Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time after cessation of study drug administration and linked by the investigator to this study, should be reported to the study monitor.

NeuroDerm will be notified of reported SAEs by the Syneos Health Pharmacovigilance Group as per the safety management plan. The sponsor and/or Syneos Health will promptly notify all relevant investigators and the regulatory authorities of findings that could adversely affect the safety of subjects, impact on the conduct of the study or alter the EC/IRB approval/favorable opinion of the study. In addition, Syneos Health, on behalf of the sponsor, will expedite the reporting to all concerned investigators, to the ECs/IRBs, where required, and to the regulatory authorities of all adverse reactions that are both serious and unexpected.

Details of the procedures to be followed if a pregnancy occurs are provided in Section 8.3.4.

10.1.1.3 Unexpected Adverse Reactions

Unexpected Adverse Reaction Definition

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of the study drug at any dose that is not consistent with the applicable product information (i.e., investigators brochure [15]).

All suspected unexpected serious adverse reactions (SUSARs) to ND0612 will be the subject of expedited reporting. The sponsor and/or Syneos Health shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and EC/IRB within 7 days after knowledge by the sponsor of such a case and that relevant follow up information is communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and EC/IRB within 15 days after knowledge by the sponsor of such a case. All investigators should follow up SUSARs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic.

Competent authorities and ECs/IRBs will be notified of all SAEs and SUSARs according to ICH-GCP and local legislation.

10.1.2 Clinical Laboratory Evaluation

The safety laboratory tests will include hematology, blood chemistry, and dipstick urinalysis. Samples will be taken according to the schedule of assessments in Section 8.1.2 and as outlined in Section 9.

Laboratory tests will include:

Hematology: white cell count and differential count, red cell count, hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, platelet count

Clinical Chemistry: sodium, potassium, chloride, glucose, blood urea nitrogen (BUN), creatinine, calcium, phosphate, bilirubin, alkaline phosphatase, gamma glutamyl transpeptidase (gamma GT), AST, ALT, total protein, albumin, and cholesterol

Urinalysis: pH, protein, glucose, ketones, urine microscopic (if required): white blood cell count, red blood cell count, casts

In addition, blood tests for vitamin B6, vitamin B12 and folate will be performed during the extension periods according to the schedule of assessments in Section 8.1.2.

Urine pregnancy tests will be performed for all female subjects of childbearing potential according to the schedule of assessments in Section 8.1.2 and as outlined in Section 9.

Serology will be performed at the screening visit only to detect: Hepatitis B Surface Antigen (HBsAg), HCV and HIV.

The hematology and clinical chemistry laboratory analyses will be performed at a central laboratory (Covance Central Laboratory Services, see Section 2) with the following exception: Data from safety laboratory tests (blood chemistry, hematology, and dipstick urinalysis) will be analysed locally at the Month 103 Safety Follow-up visit (see Section 9.2.4) and for early termination visits during the long-term extension period (see Section 9.2.8).

Reference ranges will be used by the investigator to assess the laboratory data for clinical significance and pathological changes.

The total amount of blood sampled is 50 ml during the 12-month treatment period and an additional 82.5 ml during the optional extension periods, including the long-term extension period. The calculated amount excludes optional safety samplings at safety follow-up visits, early termination samplings, as well as repeat and unscheduled samplings.

10.1.3 Local Safety

An assessment of each SC infusion site (i.e., local safety of the skin at all application sites) will be made by a nurse or physician at all clinic visits during the treatment period and the optional treatment extension periods.

All infusion site reactions will be reported as an AESI (whether or not considered clinically significant by the investigator), and assigned a severity category by the Investigator as mild/ moderate/ severe.

The reason for early termination will be captured by differentiating it in the eCRF as follows: (1) AE due to infusion site reactions or (2) AE for other reasons.

Pain will be assessed with the Visual Analogue Scale (VAS) score (see Appendix 17.11).

Instructions for patients: Consider the infusion sites. The left hand side of the scale indicates no pain and the right hand side of the scale indicates the worst possible pain; please mark with a single vertical line on the scale what level of pain you are feeling now.

Burden of local skin reactions will be determined by the patient and physician assessment.

A dermatology examination is mandatory for the following 2 cases:

1. Infusion site reactions reported as SAE leading to withdrawal
2. Infusion site reactions reported as SAE requiring additional medical/surgical treatment

Additionally, the Investigator may refer to a dermatologist any infusion site reactions reported as SAE or AE. The skin lesions should be photographed before and after treatment, if feasible.

A dermatologist may perform skin biopsies, according to the dermatologist's judgement.

10.1.4 Vital Signs

Vital signs: heart rate, standing and supine (after resting for at least 5 min) BP, weight and height (only at screening) will be measured at Screening, Day 1, Week 1, Months 1, 2, 3, 4, 6, 9, 12, during both optional extension periods, and Early Termination visit (if applicable).

10.1.5 Physical Examination

A physical examination will be performed by the investigator at Screening, Day 1, the 1-month safety follow-up visit, and the Early termination visit (if applicable). Any changes during the treatment period will be recorded on the eCRF.

10.1.6 Neurological Examination

A neurological examination will be performed by an investigator who is a neurologist by medical training at Screening, Day 1, the 1-month safety follow-up visit, and the Early termination visit (if applicable). Any changes during the treatment period will be recorded on the eCRF.

10.1.7 12-lead ECG

A resting 12-lead ECG will be performed at Screening and the clinic visits on Week 1, Months 1, 2, 3, 4, 6, 9, 12, Safety FU visit 1, and Early Termination visit (if applicable). In the event of possible ECG findings, additional ECG reads can be added at follow-up visits. The ECG evaluation will be performed centrally by Biomedical Systems (see Section 2) with the following exception: ECG data obtained at the safety follow-up visits after the extension periods (see Section 9.2.4) and at early termination visits during the extension periods (see Section 9.2.8) will be analysed locally. ECG abnormalities will be recorded on the eCRF.

10.1.8 Assessment of Suicidal Ideation and Behavior (C-SSRS)

Suicidal ideation and behavior will be assessed using the "Screening" part of the C-SSRS at Screening, and the "Since Last Visit" part of the C-SSRS on Day 1, Week 1, Months 1, 3, 6, 9, 12, the Safety FU visit 1, and the Early termination visit (if applicable).

Each part of the C-SSRS consists of 3 question groups (suicidal ideation, intensity of ideation, suicidal behavior). It will be administered by individuals who have been trained in its administration. Ultimately, the presence of suicidality depends on clinical judgment (see Appendix 17.3).

10.1.9 Assessment of Excessive Daytime Sleepiness (ESS)

Assessments of excessive daytime sleepiness using the Epworth Sleepiness Scale (ESS; see Appendix 17.5) will be performed on scheduled clinic visits on Day 1, Week 1, Months 1, 2, 3, 4, 6, 9, 12, Safety FU 1, and Early Termination visit (if applicable).

The ESS is an effective instrument used to measure average daytime sleepiness. The ESS differentiates between average sleepiness and excessive daytime sleepiness that requires intervention. The subject self-rates on how likely it is that he/she would doze in 8 different situations. Scoring of the answers is 0-3, with 0 being "would never doze"

and 3 being “high chance of dozing”. A sum of 10 or more from the 8 individual scores reflects above normal daytime sleepiness and need for further evaluation [23].

10.1.10 Assessment of Impulsive-Compulsive Disorders in PD-Rating Scale (QUIP-RS)

The QUIP-RS, see Appendix 17.4) is designed to measure severity of symptoms and support a diagnosis of impulse control disorders and related disorders in PD. It assesses gambling, sexual, buying, and eating behaviors, other compulsive behaviors and compulsive medication use on a scale from 0 (“never”) to 4 (“very often”). The QUIP-RS will be applied on scheduled clinic visits on Day 1, Week 1, Months 1, 2, 3, 4, 6, 9, 12, Safety FU 1, and Early Termination visit (if applicable).

10.1.11 Infusion Pump System Issues/Problems, and Temporary Interruptions in Study Drug Infusion

Infusion pump system issues/problems will be reported to the helpline, and will be documented on a Service Report which will be forward by the helpline to the site. Temporary discontinuations of study drug infusion of more than 3 hours will be recorded by the subject in a Pump Diary (see Appendix 17.13). Infusion pump system issues/problems, and temporary interruptions in study drug infusion will be transferred to the relevant eCRF pages by site staff. The following data should be documented in the eCRF for each infusion pump system event: date and time, description, action taken, and association with AE.

10.2 Efficacy Measurements Assessed

10.2.1 Efficacy Variables

10.2.1.1 “ON/OFF” Home Diary

Subjects will record their assessment of motor state every 30 minutes during waking hours for the 2 days prior to the following visits: Baseline, Months 1, 3, 6, 9, and 12 and the Early termination visit (if possible), as well as at Months 18, 24, 30, and 36 of the extension period. Motor State will be documented in Hauser's Parkinson's Disease Home Diary ("ON/OFF" home diary; see Appendix 17.12) [16, 17]), a validated and widely accepted tool for the assessment of "ON" and "OFF" efficacy endpoints in PD clinical trials. Motor state will be classified as “OFF”, “ON” without dyskinesia, “ON” with non-troublesome dyskinesia, “ON” with troublesome dyskinesia or “asleep”. At the corresponding study visits, the data will be transferred to the eCRF by study site staff. It should be noted that the Baseline motor state assessment for subjects in Cohort 1 will be reported by the subject on Days 2 and 3 following the initiation of this study.

Subjects and their study partners will be trained on the use of this diary during the screening period (Cohort 2) or at study baseline (Cohort 1).

Diary entries will allow the calculation of waking hours.

10.2.1.2 Unified Parkinson's Disease Rating Scale

The UPDRS [18] is divided into 4 parts. Part I is designed to rate mentation, behavior and mood (questions 1-4). It is to be collected as historical information without direct relevance to "ON" or "OFF" periods experienced by the Subject. Part II (questions 5-17) is also historical information. Part III (questions 18-31) is done as a motor examination at the time of a visit as defined in this protocol. Part IV (questions 32-42) is historical information designed to rate complications of therapy.

The various items to be rated are scored using a 5-point system (i.e., 0 is normal and 4 indicates a severe abnormality; see Appendix 17.6).

UPDRS assessment will be performed on Day 1, Week 1, Months 1, 3, 6, 9, 12 and the Early termination visit.

Whenever feasible, UPDRS sections II to IV should be assessed by the same assessor in an individual subject.

10.2.1.3 Clinical Global Impression

Severity of illness and global improvement will be rated by the investigator or designee separately on Day 1 (only severity of illness), Week 1, Months 1, 3, 6, 9, 12 and the Early termination visit (if applicable) using the CGI (see Appendix 17.10.1) [19]. The CGI-S employs a 7-point scale with 1 being "not at all ill" and 7 being "among the most severely ill subjects" for severity rating; the CGI-I employs a 7-point scale with 1 being "very much improved" and 7 being "very much worse" for improvement rating. Whenever feasible, assessments should be made by the same assessor in an individual subject.

An assessment of the subjects Global Impression of Improvement will be performed on Day 1, Week 1, Months 1, 3, 6, 9, 12 and the Early termination visit using the SGI-I, an adaptation of the CGI-I using the same 7-point scale (see Appendix 17.10.2).

10.2.1.4 Parkinson's Disease Sleep Scale (PDSS-2)

The quality of night sleep will be rated by the subjects at clinic visits on Day 1, Week 1, Months 1, 3, 6, 9, 12, and Early Termination visit (if applicable) using the PDSS-2 (see Appendix 17.9). The PDSS-2 includes questions addressing 15 commonly reported symptoms associated with sleep disturbance in PD [20].

10.2.1.5 Quality of Life in Parkinson's Disease (PDQ-39)

Their perception of QoL will be rated by the subjects on Day 1, Week 1, Months 1, 3, 6, 9, 12 and the Early termination visit (if applicable) using the PDQ-39 ([21] see

Appendix 17.7) a 39-item questionnaire with 8 discrete scales: mobility (10 items), ADL (6 items), emotional well-being (6 items), stigma (4 items), social support (3 items), cognitions (4 items), communication (3 items), and bodily discomfort (3 items).

Subjects are asked to think about their health and general well-being and to consider how often in the last month they have experienced certain events (e.g., difficulty walking 100 yards). Subjects are asked to indicate the frequency of each event by selecting 1 of 5 options (Likert Scale): never/occasionally/sometimes/often/always or cannot do at all.

10.2.1.6 EQ-5D-5L Quality of Life Questionnaire

Their perception of general QoL will furthermore be rated by the subjects on Day 1, Months 1, 3, 6, 9, 12 and the Early termination visit (if applicable) using the EQ-5D-5-L questionnaire ([22] see Appendix 17.8). The EQ-5D-5L consists of 2 pages, the EQ-5D-5L descriptive system and the EQ VAS. The descriptive system comprises 5 dimensions (mobility, self care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. The EQ VAS records the respondent's self-rated health on a 20 cm vertical VAS with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'. This information can be used as a quantitative measure of health as judged by the individual respondents.

10.3 Other Assessments

The subject will be asked to complete a short questionnaire regarding the overall user experience with the infusion pump, service, and support (see Section 17.14). Subjects who consent to participate in this non-mandatory activity will receive the questionnaire at a site visit during the optional treatment extension period or the optional long-term extension period, respectively. They will be asked to complete the questionnaire once during the next scheduled visit at the site.

10.4 Data Monitoring Committee

To enhance the safety and integrity of the study data a DMC consisting of clinical experts (a neurologist, a dermatologist, and a statistician) will meet periodically to review the accumulating safety data for the study and to provide a recommendation on study continuation or early termination of the study in case there is a concern regarding safety with particular emphasis on local skin safety and tolerability. The specific responsibilities and composition of the committee are outlined in a separate document,

the Committee Charter, which will also include details of the outputs provided for the DMC meetings.

10.5 Appropriateness of Measurements

The safety and efficacy assessments planned for this study are widely used and generally recognized as reliable, accurate and relevant to the disease condition.

11 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

The analyses related to the primary objective will include the study data up to the Month 12 visit. A separate analysis will be conducted based on the data up to 102 months. In addition, safety snapshot data in between the above-mentioned time periods may be summarized during the study conduct for regulatory purposes.

The analysis of the safety data will be based on data accumulated from the present study. For safety, Cohort 1 and Cohort 2 will be analyzed jointly (for Regimen 1) and separately. For efficacy, Cohort 1 and Cohort 2 will be analyzed separately (where applicable). Baseline values for Cohort 1 will be derived from the ND0612H-006 study.

The safety data will be summarized for both the total Safety Set and broken down by the treatment regimen (Regimen 1 or Regimen 3). An additional safety analysis will be conducted by excluding the safety data from the subjects who received Regimen 2 during the corresponding treatment period (i.e., the data captured after the first dose of Regimen 2 until the switch to Regimen 1 will be excluded).

A fully detailed Statistical Analysis Plan (SAP) will be produced and finalized after finalizing the protocol and before any data base lock. The SAP will detail the implementation of all the planned statistical analyses in accordance with the protocol. Any deviations from the statistical analyses planned in the protocol will be documented in the SAP and any deviations from the statistical analyses planned in the SAP will be documented in the final clinical study report.

All data will be listed. In general, data will be summarized using either descriptive statistics (number of non-missing observations, mean, median, standard deviation (SD), standard error of the mean (SEM), minimum and maximum for continuous data) or frequency counts and percentages for categorical data.

In general, Baseline will be defined for each subject and will be defined as the last available, valid, non-missing assessment before the start of first study drug (ND0612) administration within the current study (ND0612H-012) or before the start of first study drug administration in study ND0612H-006 (for cohort 1) Unknown, Not Done, Not Applicable and other classifications of missing data will not be considered when calculating baseline observations. However, valid categorical observations will be considered for baseline calculations. All analyses will be based on the absolute changes from Baseline (not percentage), unless stated otherwise.

11.1.1 Datasets or Populations Analyzed

The All Enrolled Set will consist of all enrolled subjects. All listings will be produced for the All Enrolled Set.

The Safety Set will consist of all subjects receiving at least 1 dose of study drug (ND0612). The Safety Set will be used for all summaries of safety and tolerability data. In addition, summaries of baseline and demographic data will also be produced for the Safety Set.

The modified Intention-to-Treat (mITT) Set will include all enrolled subjects who have valid efficacy data at baseline and at least once after the baseline. The efficacy analysis will be based on the mITT Set. The mITT Set will be used for all summaries and analyses of efficacy data.

The earlier version of this protocol included a randomization of subjects to Regimen 1 or Regimen 2. Unless stated otherwise, the subjects who received Regimen 2 and were switched to Regimen 1 during the study conduct will be included in the Regimen 1 group.

11.1.2 Demographic and Other Baseline Characteristics

All baseline and demographic summaries will be produced for the mITT Set and the Safety Set.

Subject disposition will be summarized by treatment regimen and will include the total number of subjects enrolled into the study and in all analysis sets. The number of subjects prematurely discontinuing from the study and/or study drug, along with the reason for early discontinuation will be summarized. Furthermore, the number of subjects screened, number of subjects who failed the screening and the reasons for exclusion will be summarized.

A consort diagram will be provided.

11.1.3 Safety Variables

11.1.3.1 Primary Outcome Measures

The primary objective of the study is to assess the long-term safety (systemic and local) and tolerability of continuous SC infusion of ND0612 throughout the 12-month treatment period. Assessments, which constitute the primary endpoint of this study, will be based on AEs, with a focus on AEs of special interest (AESI) which will include infusion site reactions, hypersensitivity and polyneuropathy. VAS for pain assessment will also be used as primary measure. Tolerability will be assessed based on percentage of subjects completing 12 months of treatment in the trial, and the percentage of

subjects who discontinued from the 12-month treatment period due to a treatment emergent AE (TEAE).

11.1.3.2 Secondary Safety Measures

The secondary safety endpoints to be assessed for the 12-month treatment period include:

- Assessment of suicidal behavior and ideation (C-SSRS responses, including the number of subjects experiencing at least 1 event of suicidal ideation, at least 1 event of suicidal behavior, at least 1 event of suicidal ideation or behavior and self-injurious behavior without suicidal intent, changes from Baseline in C-SSRS categories (No Suicidal Ideation or Behavior, Suicidal Ideation and Suicidal Behavior) and changes from Baseline in C-SSRS suicidal ideation)
- Assessment of impulsive compulsive behavior (QUIP-RS total scores)
- Epworth Sleepiness Scale (ESS total score)
- Vital signs with a focus on orthostatic BP (possible dopaminergic side effect)
- Laboratory data (hematology and biochemistry), including dipstick urinalysis results evaluation
- 12-lead ECG parameters, including ECG interpretation of clinical significance
- Physical examination
- Prior and concomitant medications

The definition of the other safety endpoints and the corresponding analyses will be detailed in the SAP.

11.1.4 Primary Analyses

11.1.4.1 Methods of Analysis

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be grouped by system organ class (SOC) and preferred term (PT) and summarized by treatment regimen. Only treatment emergent AEs (TEAEs) will be summarized. TEAEs are defined as all AEs that start or worsen on or after the start of first study drug administration in the present study and before the start of the optional treatment extension (for the 1-year analysis). It is assumed that AEs that started in study ND0612H-006 will not be recorded on the case report form of the present study (unless the event in question worsened during the present study), as these

events will not be TEAEs in the present study. For subjects who do not participate in the optional treatment extension, events that start >28 days after the last dose of study medication will not be defined as TEAEs.

The summary tables will present the frequency and percentage of total subjects and number of events, by SOC and by PT.

For the summaries of AEs, subjects who experience the same AE (in terms of the MedDRA PT) more than once will only be counted once for that event in the number of subjects but all occurrences of the same event will be counted in the number of events. In addition, separate summaries will be provided for AEs by severity and relationship to study drug, as well as separate summaries for AEs leading to study drug discontinuation and SAEs.

In addition to the frequency counts and percentages, the AEs will be presented as annualized rates. The annualized rates will be calculated by the total number of reported AEs divided by the total exposure time, measured as the total subject years of exposure to the study medication.

The below listed summaries will be produced for the Safety Set. In general, all safety endpoints will be summarized using either summary statistics or frequency tabulations, as applicable to the type of data.

11.1.4.1.1 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) will include the following:

- Infusion site reactions
- Cases of hypersensitivity (e.g. diffuse skin rash, anaphylaxis and angioedema).
- Polyneuropathy

11.1.4.1.2 Analyses of Infusion Site Reactions

- Summaries for total infusion site reactions, both as number of events, event rates adjusted to exposure and patient counts and percentages will be provided.

11.1.4.1.3 Hypersensitivity Analyses

- Summaries for total number of hypersensitivity cases (by SOC and PT), will be presented as number of events, event rates adjusted to exposure and patient counts and percentages.

- Time to onset of hypersensitivity will be presented by Kaplan Meier figures. In these analyses, the patients who did not experience hypersensitivity will be right censored at the time of the last visit.

- Time from onset of hypersensitivity to resolution will be presented with descriptive statistics. Unresolved cases will be right censored at the last visit.

- Summaries for total number of hypersensitivity will be broken down by outcomes (unknown, recovered, not yet recovered, recovered with sequelae and death) and will be presented as number of events, event rates adjusted to exposure and patient counts and percentages.

11.1.4.1.4 Polyneuropathy Analyses

- Summaries for total number of polyneuropathy cases (by SOC and PT), will be presented as number of events, event rates adjusted to exposure and patient counts and percentages.

- Time to onset of polyneuropathy will be presented by Kaplan Meier figures. In these analyses, the patients who did not experience polyneuropathy will be right censored at the time of the last visit.

- Time to from onset of polyneuropathy to resolution will be presented with descriptive statistics

- Summaries for total number of polyneuropathy will be broken down by outcomes (unknown, recovered, not yet recovered, recovered with sequelae and death) and will be presented as number of events, event rates adjusted to exposure and patient counts and percentages.

11.1.4.1.5 VAS Score for Pain

The VAS pain score will be summarized with descriptive statistics by visit and treatment group. In addition, the changes from baseline will be summarized. Furthermore, the proportion of patients with a VAS pain score >0 mm or ≥40 mm will be tabulated by visit and treatment group.

11.1.4.1.6 Tolerability

Tolerability will be assessed based on percentage of subjects that complete the 12-month treatment period (or long-term extension) of the study and the percentage of subjects who discontinue from the 12-month treatment period (or long-term extension) due to a TEAE. Time (days) from enrolment to discontinuation will be illustrated as Kaplan-Meier curves by treatment regimen. Patients who complete the study will be right censored at the date of last dose of study treatment during the 12-month study period (or long-term extension). Time to discontinuation will also be explored by recruitment wave 1 and 2 following corrective actions for patients' retention.

Local safety expressed by erythema, edema and Draize scores as well as assessment of nodules and hematomas (number and severity) will be listed but not summarized.

The safety data from the treatment extensions up to Month 102 will be combined with the safety data of the main study and will be analyzed similarly as defined above.

11.1.4.2 Secondary Safety Analysis

The definition of the other safety endpoints and the corresponding analyses will be detailed in the SAP.

11.1.4.3 Efficacy Variables

Efficacy will be assessed for the 12-month treatment period based on daily “ON” time without troublesome dyskinesia and daily “OFF” time as determined from “ON/OFF” home diary entries. Efficacy will be further explored using PDQ 39 (PD-QoL), EQ-5D-5L (general QoL), rating of PD (UPDRS), CGI for severity and improvement, and sleep assessment (PDSS).

The analysis of the efficacy data will focus on estimating the changes from baseline of the present study. The efficacy data will be summarized for both the total mITT Set and broken down by the treatment regimen (when applicable). Cohort 1 and Cohort 2 will be summarized separately (where applicable).

11.1.4.3.1 Definition of Efficacy Endpoints

The exploratory efficacy endpoints assessed for 12 months of treatment are:

- Change in daily “ON” time without troublesome dyskinesia (defined as the sum of "ON" time without dyskinesia and “ON” time with non-troublesome dyskinesia) from Baseline to the 12-month visit based on home "ON/OFF" diaries.
- Change in daily “OFF” time from Baseline to the 12-month visit, based on home "ON/OFF" diaries.
- Change in total daily dose of oral LD/DDI from Baseline to the 12-month visit.
- Proportion of responders at the 12-month visit based on daily “OFF” time recorded in home "ON/OFF" diaries. A responder is defined as a subject that experiences ≥50% reduction in “OFF” time from Baseline.
- Change in daily “ON” time with troublesome dyskinesia in a subset of subjects who had more than 1 hour of troublesome dyskinesia at Baseline, based on home "ON/OFF" diaries from Baseline to the 12-month visit.

- Change in PDQ-39 scores from Baseline to the 12-month visit.
- Change in EQ-5D-5L scores from Baseline to the 12-month visit.
- Change in UPDRS Part II (ADL) from Baseline to the 12-month visit.
- Change in CGI-Severity and CGI-Improvement from Baseline to the 12-month visit.
- Change in SGI-Improvement from Baseline to the 12-month visit.
- Change in PDSS total score from Baseline to the 12-month visit
- Change in UPDRS Part III (motor score) from Baseline to the 12-month visit.
- Change from baseline to month 12 in percentage of "OFF" time and percentage of 'Good' ON during the first 3 hours since the subject is awake after 06:00 (6 am)
- Change from baseline to month 12 in ND0612 total dose
- Proportion of patients who reduced ND0612 total dose at any time during the study

The first efficacy endpoint of the change from Baseline to Month 12 in daily "ON" time without troublesome dyskinesia will be based on subject diary data. This will be a within group analysis for each treatment regimen. Subjects will provide data on daily "ON" and "OFF" time for the 2 days prior to the following visits: Baseline (Cohort 2 only), Months 1, 3, 6, 9, and 12 and the Early termination visit (if applicable) and additionally at Months 18, 24, 30, and 36 of the extension period. Subjects in Cohort 1, will be excluded from this analysis.

11.1.4.3.2 Methods of Analysis

All efficacy summaries and analyses will be produced for the mITT Set.

For the efficacy endpoints, continuous data will be summarized at each protocol scheduled time point, by treatment regimen, using summary statistics. Actual values and changes from Baseline will be presented. All categorical endpoints will be summarized at each protocol scheduled time point, by randomized treatment regimen, using frequency tabulations.

As the primary purpose of this study is to explore the 2 treatment regimens with regards to efficacy and safety and not to perform confirmatory analyses comparing the treatment

regimens, there will be no formal hypothesis testing performed and adjustments for multiplicity are not required.

The change from Baseline to Month 12 and to the other visits within each treatment regimen in daily "ON" time without troublesome dyskinesia will be estimated using a Mixed Model for Repeated Measures (MMRM) including response data from all scheduled post-baseline visits with no imputation for missing data. The changes from Baseline within each treatment regimen and the comparison between the Regimens will be estimated, separately for each scheduled study visit, from the same MMRM using contrasts. . The treatment regimen (Regimen 1 or Regimen 3, when applicable), visit and the interaction between treatment regimen and visit (if applicable) will be included as fixed factors in the MMRM together with the baseline value as covariate. The analysis for the "ON/OFF" home diary, will be performed only for cohort 2. Changes from baseline will be summarized also the overall data. There will be no random effects. An unstructured covariance structure will be assumed, and the denominator degrees of freedom will be computed using the Kenward-Roger method.

The changes in "ON" time without troublesome dyskinesia will be estimated both as hours (normalized to 16 hours of awake time) and as a proportion out of awake time.

In general, all further efficacy endpoints will be summarized and analyzed using either a MMRM analysis, as described above, for continuous endpoints or descriptive statistics for categorical endpoints. Sensitivity analyses of efficacy data will be conducted by excluding the subjects who were randomized to receive Regimen 2. The definition of the endpoints and the statistical analyses will be detailed in the SAP.

Data collected in the extension period will be analyzed similarly as for the 12-month period.

11.1.5 Other Variables

The number of issues/problems in the pump system and number of subjects with at least one event/problem will additionally be analyzed using descriptive statistics.

11.1.6 Interim Analyses

There are no formal interim analyses planned for this study. The data of the 12-month treatment period (including all data from the safety follow-up visits after treatment termination that will be available at the time of the database lock) will be used for the primary analysis and reporting for this study.

A DMC (see Section 10.3) consisting of clinical experts will review the data periodically, with particular emphasis on local skin safety and tolerability.

11.1.7 Handling of Missing Data

For the analysis of the AEs, the incomplete follow-up will be taken into account by summarizing the data as annualized rates in addition to the frequency counts and percentages. The analysis of the annualized rates takes into account the actual duration of the exposure to the study treatment.

For the efficacy analyses of continuous endpoints, likelihood-based modeling approach (MMRM) will be used to handle incomplete data.

All withdrawals will be included in all analyses up to the time of withdrawal. Subjects who are withdrawn prematurely from study drug and/or the study will be included in all analyses regardless of the duration of treatment. In general, there will be no imputation for missing data, unless otherwise specified.

11.2 Determination of Sample Size

A sample size of approximately 210 treated subjects was considered appropriate for evaluating the long-term safety and tolerability of ND0612 administered at the 2 study regimens, Regimen 1 and Regimen 3, with a focus on local tolerability at the infusion sites. No formal sample size evaluation has been conducted. Since the maximum size of Cohort 1 is limited (36 subjects were to be treated in study ND0612H-006) the majority of subjects will be included in Cohort 2.

11.3 Protocol Deviations

Protocol deviations will be defined in the SAP.

12 QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audit during the course of the study by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

12.2 Monitoring

Data for each subject will be recorded in an eCRF. Data collection must be completed for each subject who signs an ICF and is administered study drug.

In accordance with GCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

The investigator must permit the monitor, the EC/IRB, the sponsor's internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs.

12.3 Data Management and Coding

Syneos Health will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures (SOPs) of the data management and biostatistics departments of Syneos Health.

Study centers will enter data directly into an EDC system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be Food and Drug Administration (FDA) CFR 21 Part 11 compliant.

Medical coding will use MedDRA for concomitant diseases (Medical History) and AEs and WHO Drug for medications.

Missing or inconsistent data will be queried within the EDC system in writing to the investigator for clarification. Subsequent modifications to the database will be documented.

13 RECORDS AND SUPPLIES

13.1 Drug Accountability

Study drugs accountability records must be maintained at the site at all times. Receipt of study drugs will be recorded. All study drugs, used and unused, should be checked and recorded by designated site personnel on a full accountability log. Dispensing of study drug and the pump system will be documented in the subject's source records and on the accountability form.

Upon the monitor's visit at the site, accountability of the returned study drugs and returned pump systems should be performed and recorded by the monitor. The subject number, the dispensing and return dates, batch number, pump serial number and quantity of study drugs returned by the subject will be checked for correctness and recorded on appropriate accountability forms.

During the study, all study drugs (used and unused vials and containers) and the corresponding accountability forms must be returned to the sponsor by the monitor for reconciliation and destruction. The study monitor will also perform an inventory of study drug and pump systems at the close-out visit for the study site. All discrepancies must be accounted for and documented. The original corresponding records must be kept at the study sites and photocopies will be sent to the Sponsor.

Drug accountability records will also be kept for oral LD/CD IR provided to the subjects in Regimen 2.

13.2 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between Syneos Health and NeuroDerm Ltd.

14 ETHICS

14.1 Independent Ethics Committee or Institutional Review Board

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate EC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the investigator. Any necessary extensions or renewals of EC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the EC/IRB together with the approved ICF must be filed in the study files.

The investigator will report promptly to the EC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the EC/IRB as required. On completion of the study, the EC/IRB will be notified that the study has ended.

14.2 Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

14.3 Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, ICH-GCP guidelines, appropriate Food and Drug Administration Code of Federal Regulations (FDA-CFRs) and the applicable national and local laws and regulatory requirements.

14.4 Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The investigator is responsible for ensuring that no subject undergoes any study related examination or activity before that subject has given written informed consent to participate in the study.

The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study. Subjects will be required to

sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the subject ICF will be provided to the subject or their authorized representative.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be approved by the EC(s)/IRB(s) (and regulatory authorities, if required). The study subjects will be informed about this new information and re-consent will be obtained.

The subject's study partner will have to also sign the ICF after having been informed about the study and the study partner's responsibilities.

14.5 Subject Confidentiality

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the EC(s)/IRB(s) approving this research, and the US FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality and the privacy of the subjects to the extent permitted by the applicable law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act [24], and the General Data Protection Regulation (GDPR) applicable to national and/or local laws and regulations on personal data protection.

15 REPORTING AND PUBLICATION, INCLUDING ARCHIVING

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last subject), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the study center when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

Study results will be published according to local legislation. The sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies must not be published separately.

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17 APPENDICES