Statistical Analysis Plan

Sponsor Name: NeuroDerm. Mitsubishi Tanabe Pharma Group Company

STATISTICAL ANALYSIS PLAN

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)

Study ND0612H-012

Phase IIb

Date: 27-AUG-2019

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Prepared by: [redacted] Biostatistics, Senior Consultant

Version Control

Version:	**Version Date:**	
Draft 1.0	20 December 2017	Final Draft
Draft 1.1	28 December 2018	New template and add more efficacy analyses
Final 2.0	24 February 2019	Final Draft
Draft 2.1	28 March 2019	Change Efficacy meausres and safety measures to match 317 study following FDA input
Final 3.0	28 May 2019	Final Signed
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STATISTICAL ANALYSIS PLAN APPROVAL FORM

Study No.: ND0612H-012

StudyTitle: 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)

Statistical Analysis Plan for:

☐ Interim Analysis ☐ Integrated Summary of Efficacy

☒ Final Analysis ☐ Integrated Summary of Safety

Version Date: Date 27-AUG-2019
(DD-MMM-YYYY)

Author: [redacted] Biostatistics, Senior Consultant

I confirm that I have reviewed this document and agree with its content.

APPROVALS	
[redacted] Biostatistics, Senior Consultant	04-Sep-2019 **Date (dd-Mmm-yyyy)**
[redacted] BMedSc, DMD Medical Director NeuroDerm	04-Sep-2019 **Date (dd-Mmm-yyyy)**
[redacted] PhD ~~Sr. Director~~, Global Clinical Program Leader Head of Phase-1 & Clinical Pharmacology NeuroDerm	04-Sep-2019 **Date (dd-Mmm-yyyy)**

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GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CD	Carbidopa
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
C-SSRS	Columbia Suicide Severity Rating Scale
DDI	Dopa Decarboxylase Inhibitor
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ESS	Epworth Sleepiness Scale
HLGT	High Level Group Term
IR	Immediate Release
IWRS	Interactive Web Response System
LD	Levodopa
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intention-to-Treat
MMRM	Mixed Model for Repeated Measures
MMSE	Mini–Mental State Examination
PD	Parkinson's Disease
PDSS	Parkinson's Disease Sleep Scale
PDQ-39	39-Item Parkinson's Disease Quality of Life Questionnaire
PT	Preferred Term
QoL	Quality of Life

Abbreviation	Description
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SEM	Standard Error of Mean
SGI-I	Subject's Global Impression of Improvement
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TEAE	Treatment emergent adverse event
UPDRS	Unified Parkinson's Disease Rating Scale
WHO-DD	World Health Organization Drug Dictionary

1. PREFACE

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for NeuroDerm clinical trial ND0612H-012 (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)), and was written in accordance with SOP 002 - Statistical Analysis Plan (NStat – [redacted] Procedure). The structure and content of this SAP provides sufficient details to meet the requirements identified by the FDA and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): E9 Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association, and the Royal Statistical Society, for statistical practice.

The following documents were reviewed in preparation of this SAP:

- Clinical Study Protocol ND0612H-012 Version 9.0 (global Amendment 8): issued on, July 11th 2019
- Case report form (CRF) for ND0612H-012
- ICH E9 Guidance on Statistical Principles for Clinical Trials.
- ICH E3 Structure and Content of Clinical Study Reports (CSRs)

This SAP describes the statistical analyses as it is foreseen before final database lock. The SAP will serve as a complement to the study protocol and supersedes it in case of differences between the SAP and the statistical sections of the protocol. In case of major differences, e.g. changes in the analysis related to the primary endpoint, a protocol amendment will be considered. The SAP may be updated during the study conduct and will be finalized before final database lock.

Based on FDA correspondences dated 27th of March 2019, Neuroderm was advised to focus its safety analysis on AE of Special Interest (AESI), specifically for Infusion Site Skin Reactions (ISR's). In addition, all cases of hypersensitivity reactions (e.g., diffuse skin rash, anaphylaxis and angioedema) should be considered AESI. Cases of Polyneuropathy were also considered as AESI.
The above feedback from FDA was further endorsed by a dermatology advisory board and by the Data Monitoring Committee of the current study. As a result, Neuroderm decided to change the primary analysis from its initial focus on Local safety expressed by scores for erythema, edema, draize as well as assessment of nodules and hematomas to the above recommended AESI's analyses.

1.1. Scope

Study ND0612H-012 consists of two parts:

- The main study: all subjects will participate in the 12-month main study. The data from the main study will be included in the final study report and will constitute the primary analysis of the study. This Statistical Analysis Plan (SAP) covers the main study only. The primary analysis based on the data from the main study will be conducted once all subjects have completed the final treatment visit (Month 12 visit) of the main study.

- The optional treatment extension period: Subjects are allowed to continue to an extension period. This SAP does not cover this extension period. A separate SAP will define the analyses of the data from the optional treatment extension period.

1.2. Responsibilities

The Study Statistician will be responsible for the statistical analysis planning. A Contract Research Organization (CRO) selected by NeuroDerm will be responsible for the execution of all statistical programming deliverables. The Study Statistician will have the overall accountability for the statistical programming deliverables for final analysis as well as for ongoing data to the Data Monitoring Committee (DMC).

2. STUDY OBJECTIVES

2.1. Primary Objective (assessed based on 12-month data)

The primary objective of the study is to assess the long-term safety (systemic and local) and tolerability of continuous subcutaneous (SC) infusion of ND0612. Assessment will be based on adverse events (AEs) reporting, with a focus on reports of infusion site skin reactions and infusion site inspections for erythema, edema, pain, hematoma and nodules and other local pathologies (local safety). 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 a TEAE.

2.2. Secondary Objectives - (assessed based on 12-month data)

Secondary safety objectives of the study include assessments of 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.

2.3. Exploratory Objectives

Exploratory efficacy objectives will be to assess the following:

- To assess the efficacy of continuous SC infusion of 2 dosing regimens of ND0612 on daily ON time without troublesome dyskinesia (“GOOD ON“) 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 patient completed home “ON/OFF” diaries
- To assess the efficacy of continuous SC infusion of 2 dosing regimens of ND0612 on daily “ON“ time without any dyskinesia based on home “ON/OFF“ diaries
- To assess the effect of ND0612 on morning “OFF” time using subject-completed “ON/OFF” diary assessments of motor function.
- To assess the effect of continuous SC infusion of 2 dosing regimens of ND0612 on the motor and Activities of Daily Living (ADL) sub-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 "ON/OFF" home 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.

2.4. Additional Objective

The additional objective of the study is to collect data on malfunctions of the pump system.

3. STUDY DESIGN

3.1. General Design and Study Schema

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 PD.

For study procedures, see protocol section 8.1.2.

Two cohorts of subjects are candidates for this study:

- **Cohort 1-** subjects with advanced PD 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. Those subjects can either roll-over directly to the current study or roll-over within a month time window while receiving the same treatment regimen that they received in the ND0612H-006 study.

    - The First type includes subjects who enroll to ND0612H-012 immediately upon completion of the treatment period in ND0612H-006. Those subjects will come in for their final treatment study visit and have all of the final study assessments completed for ND0612H-006 and may proceed directly to the Baseline visit of the current study (ND612H-012). A Screening Visit is not necessary.

    - The second type includes subjects who completed the treatment period in study ND0612H-006 within one month prior enrollment to ND0612H-012. Those subjects will perform the Baseline visit of ND0612H- 012 in the morning, after having taken their standard anti-PD medication. During this 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.

    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** – subjects with advanced PD who are naïve to ND0612s or subjects who completed treatment in the ND0612-006 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. Within 28 days of the Screening visit, subjects will return to the clinic for a Baseline visit in the morning, after having taken their standard anti-PD medication. During this visit, subjects were either randomized at a 1:1 ratio to Regimen 1 or

Regimen 2 (before Amendment 1), allocated to Regimen 1 (after Amendment 1, before Amendment 2) or allocated to Regimen 3 (after Amendment 2).

Treatment with the pump system will start at the clinic visit. 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 where the investigator believes that additional titration is required to achieve stabilization. Subjects will remain on the assigned ND0612 dosing regimen for 12 months.

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.

For both cohorts: 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 and 24, 27, 30,33 and 36) to assess subject safety.

3.2. Primary and Additional Measures and Endpoints

3.2.1. 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 AE's of special Interest (AESI's) which will include Infusion Site Reactions (ISR's), 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 TEAE.

The definitions and analyses of these safety endpoints are provided in Section 7 of this SAP

3.2.2. Secondary Safety Measures

The additional secondary safety outcome measures include:

- Suicidality (C-SSRS)
- Questionnaire for Impulsive-Compulsive Discorder (QUIP-RS)
- Excessive daytime sleepiness (ESS)
- Vital signs, including evaluation of orthostatic hypotension
- Laboratory tests

- ECG data.

The definitions and analyses of these safety measures are provided in Section 7.5 of this SAP.

8.3

3.2.3. Exploratory Efficacy Measures and Endpoints

Exploratory efficacy objectives will be to assess for Cohort 1 and Cohort 2 efficacy trends based on assessments made on "ON/OFF" home diary (cohort 2 only), PDQ-39, EQ-5D-5L (cohort 2 only), UPDRS Part II, UPDRS Part III, CGI-Severity, CGI-Improvement , SGI-Improvement, Morning Akinesia and PDSS. Twenty four hours "ON/OFF" home diaries were assessed only for 012 study while in-clinic diaries were assessed in 006 study. Therefore, cohort 1 will be excluded from the "ON/OFF" time analyses.

The following exploratory efficacy endpoints will be evaluated:

3.2.3.1. Change in daily "ON" time without troublesome dyskinesia ("GOOD ON") from Baseline to the 12-month visit, based on patients completed "ON/OFF" home diaries

- Subjects will record their assessment of motor state every 30 minutes during waking hours for the 2 days prior to the following visits: Baseline, Week 1, Months 1, 3, 6, 9, and 12 (and on early termination visit if possible). Motor State will be documented in these diaries as "OFF", "ON" without dyskinesia, "ON" with non-troublesome dyskinesia, "ON" with troublesome dyskinesia or "asleep".

- The validity of the diary entries will be checked prior to including a diary day in the summary calculations. Only valid diary days will be included in the diary summarizations. The diary endpoints will be derived as defined below.

  - A day will be considered as being valid if at least 44 of the 48 half hour periods during the day have been completed per instructions.

  - Each half hour period entry (Asleep, "OFF", "ON" without dyskinesia, "ON" with non-troublesome dyskinesia, or "ON" with troublesome dyskinesia) is considered valid if only one entry has been checked. The entry will not be used if no responses are checked or more than one response is checked. However, if the proportion of entries rejected due to multiple checked responses is large (>2% of all completed half-hour periods in the total study data), sensitivity analysis will be performed by using the worst case out of the entries that had been checked. The worst case will be defined in the following order: "OFF", "ON" with troublesome dyskinesia, "ON"

with non-troublesome dyskinesia, "ON" without dyskinesia, Asleep. If there are duplicate entries (i.e., multiple entries recorded with same date and time interval), the worst entry will be used for the date and time interval in question. The worst entry will be selected in the order defined above.

- The diary day data expressed as hours will be normalized to 16 waking hours per day: The daily "ON" time without troublesome dyskinesia ("GOOD ON") will be extrapolated to a 16 hour period by determining the proportions of "ON" time without troublesome dyskinesia among accurately recorded entries, excluding Asleep time and missing/non-valid recordings, and by multiplying this proportion by 16 hours. In addition, daily "ON" time without troublesome dyskinesia will be expressed as the percentage (%) of daily "ON" time without troublesome dyskinesia during waking hours (by multiplying the proportion by 100). However, only a single p-value applicable to both the percentage and number of hours will be reported.

- The mean daily "ON" time without troublesome dyskinesia ("GOOD ON") prior to each visit will be calculated as mean value of the valid days documented in the patient's diary prior to that visit. In case there are gaps within the 2 days preceding the visit, the last 2 recorded days before the visit will be used regardless of the gaps (as long as all days are within 7 days from the visit). If there are more than 2 valid days, only the last 2 days will be used. If there is only 1 valid day, the data from this day will be used.

- The Baseline for the home diary for subjects in Cohort 2 is defined as 2 consecutive days prior to the Baseline visit. The diaries collected at the subsequent visits after baseline will be used as response variables.

3.2.3.2. Change in daily "OFF" time based on home "ON/OFF" diaries from Baseline to the 12-month visit.

- The daily "OFF" time will be derived similarly as the daily "ON time without troublesome dyskinesia in 3.2.3.1.

3.2.3.3. Change in daily "ON" time without any dyskinesia (troublesome or non-troublesome) based on home "ON/OFF" diaries from Baseline to the 12-month visit.

- The daily "ON" time without any dyskinesia will be derived similarly as the daily "ON time without troublesome dyskinesia time in 3.2.3.1.

3.2.3.4. Change from baseline to month 12 in percentage of "OFF" time during the first 3 hours since the subject is awake after 06:00 (6 am), based on subject's "ON/OFF" diary assessments on the 3 consecutive days before the visit.

- Subject will be declared as 'awake' if found not 'asleep' for at least 2 hours after 06:00 (6 am)
- This endpoint will be derived similarly as the daily "ON time without troublesome dyskinesia in 3.2.3.1. However, only data recorded after 06:00 (6 am) will be used for derivation. At least 5 out of 6 half-hour periods (3 hours) are required to be completed, in order to classify a diary day as valid.

3.2.3.5. Change in total ND0612 total dose from baseline to month 12

3.2.3.6. Proportions of patients who reduced their total ND0612 total dose during 12 month of treatment

3.2.3.7. Proportion of responders at the 12-month visit based on daily "OFF" time recorded in "ON/OFF" diaries. A responder is defined as a subject that experiences ≥50% reduction in "OFF" time from Baseline.

- The daily "OFF" time will be calculated as defined in 3.2.3.2. The percentage reduction will be calculated as $(OFF_{Month\ 12} - OFF_{baseline})/ OFF_{baseline} * 100$. The subjects will be dichotomized as having a percentage reduction of ≥50% versus a reduction of <50%.The patients with missing "OFF" time will be imputed with last available 'OFF' time value. .

3.2.3.8. 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.

- The daily "ON" time with troublesome dyskinesia will be derived similarly as the daily "ON time without troublesome dyskinesia in 3.2.3.1.

3.2.3.9. Change in PDQ-39 summary index and the 8 dimension scores from Baseline to the 12 month visit

- The PDQ-39 questionnaire provides scores on eight dimensions as outlined below:

- mobility (10 items, #1 to 10)
- activities of daily living (6 items, #11 to 16)
- emotional well-being (6 items, #17 to 22)
- stigma (4 items, #23 to 26)
- social support (3 items, #27 to 29)
- cognitions (4 items, #30 to 33)
- communication (3 items, #34 to 36)
- bodily discomfort (3 items, #37 to 39).

Items are scored from 0 (never) to 4 (always). Dimension scores are obtained by dividing the sum of the item scores by the maximum possible score for any given dimension and expressing this as a percentage. For example:

- mobility = (sum of scores of #1 to 10)/(4 x 10) x 100
- activities of daily living = (sum of scores of #11 to 16)/(4 x 6) x 100.

For social support, if the response indicates that a patient does not have a spouse or partner for #28, social support can be calculated as [(sum of scores of #27 and 29)/(4 x 2) x 100].

A summary index is then calculated as the sum of the total score of the dimensions divided by the number of dimensions, i.e. (sum of dimension scores / 8). If any item score is missing, the relevant dimension score and the summary index will be missing.

3.2.3.10. Change in EQ-5D-5L scores from Baseline to the 12 month visit

- The EQ-5D is a utility scale consisting of three components: health state dimensions, health state thermometer scale and health state index.

- The health state dimensions will be described by the 5 dimensions of the EQ-5D (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension has 5 response choices, listed in order of increasing severity.
- The health state thermometer scale asks respondents to rate their present health status on a 0 to 100 visual analog scale (VAS). The change from Baseline visit to the 12 month visit in the VAS scores will be evaluated.
- The health state index score will be calculated using the dimension scores from the 5 dimensions, ranging between 1.0 (best imaginable health) and -0.594 (worst imaginable health). The change from Baseline visit to the 12 month visit

in the health state index score will be evaluated.

3.2.3.11. Change in UPDRS Part II (ADL) from Baseline to the 12 month visit.

- The UPDRS part II (ADL) score will be calculated as the sum of the individual items 5-17. Missing individual items will not be imputed. If there is at least 1 missing item, the corresponding sum score will be set as missing.

3.2.3.12. Change in CGI-Severity (CGI-S) and CGI-Improvement (CGI-I) from Baseline to the 12 month visit

- The CGI-I scores will be categorized as improvements (very much improved, much improved, minimally improved) or non-improvements (no change, minimally worse, much worse, very much worse). For descriptive statistics, in case the CGI-I score is missing (or "Not assessed") but the visit in question was done, the last non missing available data will be used for incomplete data.

- The changes from Baseline in CGI-S score will be categorized as improvements if the value at the visit in question is better than the baseline value. If the value at the visit in question is same or worse than the baseline value, the change is categorized as a non-improvement. "Normal, not at all ill" is considered as the best value and "Among the most extremely ill" the worst. For descriptive statistics, in case the post-baseline CGI-S score is recorded as "Not assessed", but the visit in question was done, the last non missing available data will be used for incomplete data. In case the baseline value is missing or recorded as "Not assessed", the change will be set as missing.

3.2.3.13. Change in SGI-Improvement from Baseline to the 12 month visit.

- This variable will be derived in a similar way as CGI-I described in 3.2.3.12.

3.2.3.14. Change in PDSS total score from Baseline to the 12 month visit.

- Each of the 15 items is scored on a 5-point scale (from 0 indicating no symptoms to 4 indicating maximum symptoms). The total score is calculated as a sum score of the 15 items. In case a single item is missing, the total score will be set as missing.

3.2.3.15. Change in UPDRS Part III (motor score) from Baseline to the 12 month visit.

- The UPDRS part III (motor) score will be calculated as the sum of the individual items 18-31. UPDRS scores will be gathered during visit but not at pre-specified time points. Missing individual items will not be imputed. If there is at least 1 missing item, the corresponding sum score will be set as missing.

3.2.3.16. Change in ND0612 Dose - Data on ND0612 dose reduction will be assessed as change from baseline in total daily of LD dose**.**

3.2.4. Additional Outcome Measures

- Data on malfunctions of the pump system will be evaluated as additional endpoints. The influence of the pump system malfunctions on the safety of ND0612 will be evaluated by capturing data on the date of malfunctions, including the description of the malfunction, association to an AE and action taken.

3.3. Determination of Sample Size

A sample size of 120-170 treated subjects is considered appropriate for evaluating the long-term safety and tolerability of ND0612 (administered as one of two regimens) with a focus on local safety at infusion sites. No formal sample size evaluation has been conducted. Since the maximum size of Cohort 1 is limited (36 subjects are to be treated in study ND0612H-006) the majority of subjects who completed the ND0612H-012 study will be included in Cohort 2.

3.4. Treatment Assignment & Blinding

This study investigates three dosing regimens of ND0612:

- Regimen 1 – ND0612 solution will be infused subcutaneously via 2 infusion sites for 24 hours 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 hours (22:00-4:00-low night rate), which will then change automatically to a rate of up to 0.64 mL/h for 18 hours (4:00-22:00 high day rate). The dose will be delivered via two infusion sites in parallel, utilizing a pump system. The total infusion volume during a 24 hr period will be up to 12.00 ml (~6.00 ml from each infusion site) and deliver 720 mg LD and 90 mg CD.

- Regimen 2 – ND0612 solution will be infused subcutaneously via 2 infusion sites for 14 hours continuously. Dosing will start upon waking. The infusion will be set to a rate of 0.64 mL/h for 14 hours (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 delivery of 537.6 mg LD and 67.2 mg CD over the course of 14 hours. On 08 December 2016 the Sponsor made a decision to discontinue treatment Regimen 2

and switched all subjects who were receiving Regimen 2 to Regimen 1 at their next scheduled visit.

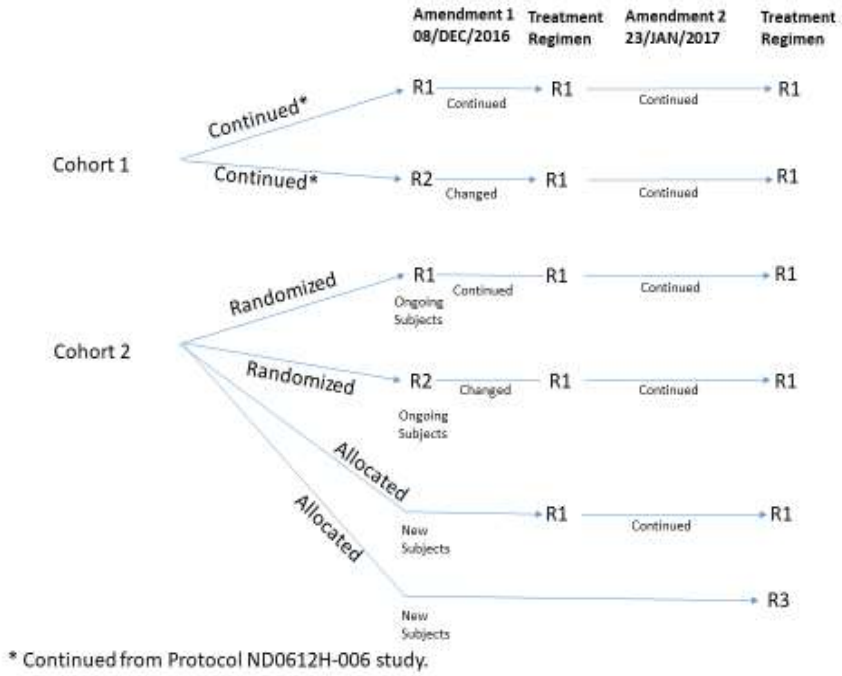
- Regimen 3 – ND0612 solution will be infused subcutaneously via 2 infusion sites for 16 hours continuously. Dosing will start upon waking. The infusion will be set to a rate of 0.75 mL/h for 16 hours from two infusion sites in parallel, utilizing the pump system. The total infusion volume during the 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.

On 08 December 2016 (Amendment 1), 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. Ongoing subjects in cohort 1 who were treated with Regimen 2 were to be switched at their next scheduled study visit to Regimen 1. Subjects in cohort 2 who were not yet randomized were to be allocated to Regimen 1 instead of being randomized.

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

Unless stated otherwise, the subjects who received Regimen 2 and were switched to Regimen 1 during the study and will be included in the Regimen 1 group.

Figure 1: ***Cohorts and Regimen Changes following Protocol Amendments***



3.5. Sequence of Planned Analyses

3.5.1. Interim Analyses

No interim analysis is planned for this study.

3.5.2. Final Analyses and Reporting

All final, planned analyses identified in this SAP will be performed only after the last patient has completed 12 months. Database lock will not be performed until this SAP has been signed and approved. Any exploratory analyses completed to support study analyses, which were not identified in this SAP, will be documented and reported in appendices to the CSR.

The safety data from the optional treatment extension will be combined with the safety data of the main study and will be analyzed similarly as defined below using the Follow-up Safety Set. These analyses will be defined in more detail in a separate SAP for the optional treatment extension period.

4. ANALYSIS SETS

The following analysis sets will be defined:

4.1. All screened subjects

This Analysis set consists of all patients who underwent screening and will be used for summary of disposition and data listings.

4.2. Intention-to-Treat (ITT):

The ITT set will include all subjects who were randomized (before Amendment 1) or enrolled (after Amendment 1) to the study. The subjects will be grouped according to the randomized (before Amendment 1) or allocated (after Amendment 1) treatment regimen.

4.3. Safety Set:

The Safety Set will consist of all subjects (cohort 1 and cohort 2) receiving at least 1 dose of study drug (ND0612). The subjects will be grouped according to the treatment regimen actually received. The Safety Set will be used for all summaries of safety and tolerability data.

4.4. Modified Intention-to-Treat (mITT) Set:

The mITT is a subset of the ITT analysis set. The mITT Set for cohort 2 will include subjects having ON/OFF Home diary data at baseline and at least one valid post-baseline measurement. The mITT Set for in cohort 1 will include subjects having UPDRS (part III) efficacy data at baseline and at least one valid post-baseline UPDRS (part III) measurement. The subjects will be grouped according to the randomized (before Amendment 1) or allocated (after Amendment 1) treatment regimen. The mITT Set will be used for all summaries and analyses of efficacy data.

Unless stated otherwise, the subjects who received Regimen 2 and were switched to Regimen 1 during the study will be included in the Regimen 1 group. However, sensitivity analyses will be conducted by excluding the subjects who were randomized to receive Regimen 2, as specified later in this SAP.

4.5. Sub-group Analysis Sets

The following subgroups may be explored, e.g. for the “ON” time without troublesome dyskinesia:

- Patients with the baseline “ON” time without troublesome dyskinesia less than or equal to the median versus patients with baseline “ON” time without troublesome dyskinesia above the median
- Patients with low total daily levodopa dose at baseline (<400 mg) versus patients with high total daily levodopa dose at baseline (≥400 mg)
- Non-elderly (<65 years) versus elderly (≥65 years) patients
- Male versus female patients
- Patients with 1 hour or more of troublesome dyskinesia at baseline vs. Patients with less than 1 hour.
- Patients enrolled in USA versus EU+Israel (Eastern+Western+Israel)

In case any subgroup analysis will be performed, the corresponding demographic and baseline data will be summarized.

5. GENERAL ASPECTS FOR DATA ANALYSIS

5.1. General Methods

All data from all patients entered into the study will be included in patient data listings. The listings will be sorted by center, and patient number (and by visit, if applicable).

The data will be summarized using either descriptive statistics (number of non-missing observations, mean, median, SD, standard error of the mean (SEM), minimum and maximum) for continuous data or frequency counts and percentages for categorical data. For visit-specific data, the number of subjects with non-missing observations at the visit in question will be used as the denominator for percent calculations. Unknown, Not Done, Not Applicable and other classifications of missing data will not be considered.

The summaries will be broken down by treatment regimen (Regimen 1, Regimen 3) and by visit, as applicable. For demographic and other baseline characteristics and selected safety data, an overall column will be displayed in addition to the data broken down by the treatment regimen. Unscheduled or repeated assessments will not be included in summary tables but will be included in listings.

5.2. Baseline Definition

In general, Baseline will be defined for each subject 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). The analyses involving calculation of change from baseline will be based on the actual changes from baseline (not percentage), unless stated otherwise.

5.3. Significance level

Significance testing will be 2-sided using $\alpha = 0.05$. All p-values will be nominally described and no adjustment to multiple comparison will be performed.

5.4. Handling Withdrawals and Missing Data

In general, there will be no imputation for missing data, unless otherwise specified

The primary objective of this study is safety. Safety data will not be subject to any imputation and will be summarized on an observed case basis. 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 endpoint, the missing data will be handled as follows:

- For patients who withdraw from the study, data at the early termination visit will be excluded from the by-visit summaries but will be included in the closest visit in case this visit was missing.
- For the continuous efficacy endpoints, likelihood-based modeling approach will be used to handle incomplete data. For this purpose, Mixed Model for Repeated Measures (MMRM) will be applied, see section 8.2.1.
- For categorical efficacy endpoints, the last non missing available data will be used for 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.

5.5. Study Days and Visit Windows

Study days will be numbered relative to the first day of study drug administration. The start of treatment (day 1) is defined as the date on which a patient takes the first dose of study drug, as recorded in CRF. Days will be numbered relative to study start (ie, ..., –2, –1, 1, 2, ...; with day 1 being the start of study drug and day –1 being the day before the start of study drug).

The study data will be summarized as collected at the scheduled study visits regardless of visit window violations. For by-visit summaries, if there are multiple assessments at a post-baseline visit, then the last non-missing assessment at that visit will be used for the summary.

5.6. Pooling of Centers

The randomization (before Amendment 1) was stratified by region (Region 1 (Israel+USA) and Region 2 (Europe). Because there was no randomization in this study after Amendment 1, the region is not included in the statistical models. As the center is not included as a factor in any of the statistical models, pooling of centers is not applicable.

6. STUDY POPULATION

6.1. General

All Enrolled patients will be included in all study population summaries unless otherwise noted. Summaries will be presented by treatment group and overall unless otherwise noted.

6.2. Patient Disposition

The patient disposition will be summarized as follows and presented for each treatment regimen (Regimen 1 or Regimen 3) and overall, and for each cohort and overall. The percentages will be calculated from the ITT set, unless otherwise specified.

- The number of patients screened (i.e. the number of patients in the Screened Set)
- The number (%) of patients who failed screening (% calculated from the Screened Set), including the distribution of reasons for failing the screening
- The number of patients who enrolled to the study (i.e. the number of patients in the ITT Set)
- The number (%) of patients in the mITT and Safety sets
- The number of patients who were randomized (before Amendment 1), classified by the randomized dosing regimen (Regimen 1 or Regimen 2).
- The number of patients who received at least one dose of Regimen 2
- The number of patients who were switched from Regimen 2 to Regimen 1
- The number of patients who received at least one dose of Regimen 3
- The number (%) of patients who completed the 12-month treatment
- The number (%) of patients who discontinued the study prematurely including the distribution of reasons for premature discontinuations.

  In addition, a CONSORT diagram will be provided.

6.3. Demographic and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively for the ITT, mITT and Safety sets by treatment regimen and overall, and for each cohort and overall. In general, Baseline data for cohort 1 will be taken from 006 baseline visit while for cohort 2 baseline data will be taken from 012 baseline visit.

- Demographics: continuous: age, height, weight, Body Mass Index (BMI); categorical: age categorized as <65 years versus ≥65 years, BMI<20 vs BMI≥20, gender, race, country and region defined as Israel+Europe or USA (categorical)
    - The age will be calculated as the difference in days between the date of birth and date of screening and converted to years by dividing the number of days by 365.25. In case the exact birth day is missing, day 15 will be used. The BMI will be calculated as weight (kg) divided by squared height (m^2).
- PD history (time since diagnosis of PD, time since onset of motor fluctuations, time since onset of dyskinesia) will be summarized as continuous variables
    - The times will be calculated as differences in days between the date of diagnosis/onset and the date of screening. The missing diagnosis/onset day will be replaced by 15. In case the month is missing, it will be replaced by 6. The days will be converted to years by dividing the number of days by 365.25.
- Cognitive status: total score of Mini–Mental State Examination (MMSE), summarized as a distribution of values 30, 29, 28, 27, 26 and ≤25. If baseline MMSE is not available in the current study, the baseline MMSE from study ND0612H-006 will be used instead
- Modified Hoehn and Yahr scale stage, summarized as categorical variable. If baseline Hoehn and Yahr scale stage is not available in the current study, the baseline Hoehn and Yahr scale stage from study ND0612H-006 will be used instead
- Baseline UPDRS scores: Sum of UPDRS Part I (Mentation, Behavior and Mood, items 1-4), Part II (Activities of Daily Living, items 5-17), Part III (Motor Examination, items 18-31), Part IVA (Dyskinesia sum score, items 32-35) and Part IVB (Fluctuation sum score, items 36-39)
    - Each sum score will be calculated as the sum of the individual items. Missing individual items will not be imputed. If there is at least 1 missing item, the corresponding sum score will be set as missing

- Baseline ON time without troublesome dyskinesia determined by "ON/OFF" diary (defined as the sum of ON time without dyskinesia and ON time with non-troublesome dyskinesia)
    - For derivation, see section 3.2.3

- Baseline "OFF" time as determined by "ON/OFF" diary (continuous)
    - For derivation of the "OFF" time, see section 3.2.3

- Baseline ON time without dyskinesia as determined by "ON/OFF" diary (continuous)
    - For derivation, see section 3.2.3.

- Baseline ON time with Troublesome dyskinesia as determined by "ON/OFF" diary (continuous)

- Total daily levodopa dose as IR levodopa equivalent dose (continuous); total administered daily levodopa dose (without conversion); total administered daily levodopa dose (without conversion) categorized as <400 mg or ≥400 mg,); daily levodopa dosing frequency (categorical); patients using COMT inhibitors, patients using carbidopa or benserazide as DDI. For conversion factors, see Table 1.

Table 1 - IR levodopa Equivalent Dose Conversion Factors

Previous medication	**LD Conversion factor**
LD+Opicapone	×1.4
LD+Entacapone	×1.33
LD+Tolcapone	×1.5
Stalevo	×1.33
Benserazide Methyldopa: Aldomet, Aldoril, Dopamet, Dopegyt DL-x-Difluoromethyl DOPA (DFMD) 3',4',5,7-Tetrahydroxy-8-methoxyisoflavone	×1
Controlled-release (CR) or Extended release (ER) Levodopa (e.g. Rytary, Numient)	×0.7

6.4. Medical History and Concomitant Diseases

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The medical history data will be summarized with frequencies and percentages of patients with at least one medical history item, and patient frequencies and percentages on the System Organ Class (SOC) and Preferred Term (PT) levels. The number of events will also be summarized. The table will be sorted by overall descending frequency of SOC and then, within a SOC, by overall descending frequency of PT. The summary of medical history data will be done for the Safety set broken down by treatment group.

6.5. Medications

6.5.1. Prior Medications

All medications will be classified using the Anatomical Therapeutic Chemical (ATC) classification codes and preferred drug names from the World Health Organization Drug Dictionary ((WHO-DD, version from June 2016)). Medications with a stop date before the first date of study drug dosing in this study will be considered prior medications. Summaries of PD prior medications will be presented in tabular form using the ATC Level 4 and preferred term. Other prior medications will be presented in tabular form using the ATC Level 1, ATC Level 2, and Preferred Term (PT). Frequencies and percentages of patients receiving medications will be presented by treatment regimen and overall. The tables will be sorted by overall descending frequency of ATC Level(s) and then, within an ATC Level, by overall descending frequency of PT.

- For derivation and dates imputation see section 6.5.2 in concomitant medication

6.5.2. Concomitant Therapy or Medication

Medications with start date or stop date on or after the first date of study drug dosing or ongoing at study completion will be considered concomitant medications.

Separate summaries of concomitant PD treatment medications (medications which start with ATC code N04) will be presented in tabular form using the ATC Level 4 and preferred term. Other concomitant medications will be presented in tabular form using the ATC Level 1, ATC Level 2, and Preferred Term (PT). Frequencies and percentages of patients receiving medications will be presented by treatment group and overall. The tables will be sorted by overall descending frequency of ATC Level(s) and then, within an ATC Level, by overall descending frequency of PT.

If the medication start date is incomplete, then it will be imputed as follows for the purpose of determining concomitant use:

- If the start date is completely missing, the start date will be equal to the first dose date. However, if the stop date is not missing and is before the first dose date, then the stop date will be used instead.
- If the start day is missing, the first day of the month will be used.
- If the start day and month are missing, then the first day of the first month (January) will be used.

If the medication stop date is partial, then it will be imputed as follows for the purpose of determining concomitant use:

- If the stop date is completely missing and the medication is not ongoing, the stop date will be equal to the last dose date or date of completion/withdrawal, whichever is the latest.
- If the stop day is missing, the last day of the month will be used.
- If the stop day and month are missing, then the last day of the last month (December) will be used.

The summary of prior and concomitant medications will be done for the Safety set broken down by treatment group.

6.6. Electrocardiography

Electrocardiogram findings (normal, abnormal, and missing) at baseline will be summarized using descriptive statistics.

6.7. Physical Examinations

Physical examinations will be summarized at screening and Baseline. An abnormality at screening should be collected as a part of medical history.

6.8. Protocol Deviations

The important protocol deviations in the study will be listed.

7. SAFETY

7.1. General

All safety 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.

Cohort 1 and Cohort 2 will be analyzed jointly and separately. This analysis will include the following treatment groups:

- Cohort 1, Regimen 1
- Cohort 2, Regimen 1
- Cohort 2, Regimen 3
- Cohort 2, Total
- Cohort 1+2 combined, Regimen 1
- Cohort 1+2 combined, Total

An additional safety analysis will be conducted by excluding the safety data from the patients who received Regimen 2 during the period when these patients received Regimen 2 (i.e. by excluding the data captured after the first dose of Regimen 2 until the switch to Regimen 1). This additional analysis will be done at least for extent of exposure, tolerability and selected adverse event summaries. The safety data from the optional treatment extension will be combined with the safety data of the main study and will be analyzed similarly as defined below using the Follow-up Safety Set. These analyses will be defined in more detail in the separate SAP of the optional treatment extension period.

7.2. Study Drug Administration

Duration of treatment (days treated) is the number of days on treatment based on the first and last days of treatment with the study drug (last day of study drug – first day of study drug + 1).

The following information will be summarized by treatment regimen and overall.

- The number of patients exposed to study treatment
- Mean Duration of exposure (days)

- Total exposure to study treatment, expressed as person years (sum of exposure to study treatment over all patients, classified by treatment regimen)
- Number of patients who reduced ND0612 dose and the mean reduction from baseline to each visit

7.3. Primary Analyses

7.3.1. Adverse Events of Special Interest (AESI)

Adverse Events of Special Interest (AESI) will include the following:

- Injection Site Reactions (ISR's)
- Cases of Hypersensitivity (e.g. diffuse skin rash, anaphylaxis and angioedema).
- Polyneuropathy (EMG-ENG & Vit B: 6 and 12, Folate and Homocysteine)

7.3.1.1. ISR Analyses

- Summaries for total ISR's, both as number of events, event rates adjusted to exposure and patient counts and percentages will be provided.

7.3.1.2. 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.

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

- 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.

7.3.2. 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.

7.3.3. Additional Local Safety Measures.

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.

7.3.4. Adverse Events

Adverse events will be coded using MedDRA. Adverse events will be grouped by SOC and preferred term (PT). Only treatment emergent adverse events will be summarized. Treatment Emergent Adverse Events (TEAEs) are defined as all AEs that start (or worsen) on or after the start of first study drug administration in this study and before the start of the optional treatment extension. 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 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. The summary tables will present the frequency and percentage of total subjects and number of events, by SOC and by PT.

For tables of incidence 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.

Events with a missing start time, but with a start date equal to the date of first dose of study treatment after baseline will be considered treatment-emergent. If the AE start date is incomplete, it will be imputed as follows for the purpose of determining TEAE:

- If the start date is completely missing, the start date will be equal to the date of the first dose of study treatment. However, if the stop date is not missing and is before the date of the first dose of study treatment, then the stop date will be used instead.
- If the start day is missing, but the month and year are not missing and are equal to the month and year of the first study dose, then this event will be considered as TEAE.
- If the start day and month are missing, then the first day of the first month (January) will be used.

The original date and time will be shown on all listings of AEs. Listings will be provided for all AEs, serious AEs, AEs leading to study treatment discontinuation, AEs leading to dose adjustment/temporary withdrawal and deaths.

The following summaries will be provided:

- A table of the overall incidence (number and percentage) of patients reporting TEAEs and the number of TEAE events and event rates adjusted to exposure, drug-related TEAEs, severe TEAEs, serious TEAEs, TEAEs leading to study treatment discontinuation, TEAEs leading to dose adjustment/temporary withdrawal, and TEAEs leading to death
- TEAEs by SOC and PT, both as number of events, event rates adjusted to exposure and patient counts and percentages
- TEAEs by PT, both as number of events, event rate adjusted to exposure, patient counts, sorted by descending frequency of patients reporting TEAEs in Regimens 1
- Drug-related TEAEs by PT, both as event, event rate adjusted to exposure and patient counts and percentages
- Severe TEAEs by PT, both as event ,event rate adjusted to exposure and patient counts and percentages

- Drug-related TEAEs by SOC, PT and severity both, as event, event rate adjusted to exposure and patient counts and percentages
- Serious TEAEs by PT, both as event, event rate adjusted to exposure and patient counts and percentages
- TEAEs leading to study treatment discontinuation, both as event, event rate adjusted to exposure and patient counts and percentages
- TEAEs leading to dose adjustment/temporary withdrawal, both as event, event rate adjusted to exposure and patient counts and percentages
- TEAEs classified by SOC, PT and the time of onset both as event, event rate adjusted to exposure and patient counts and percentages. For this summary, the time of onset will be classified as <7 days, 7-30 days or >30 days

In addition, the following analyses will be performed for the most common or relevant TEAEs (at least for the 10 most commonly reported PTs in both regimens 1 and 3 including also dyskinesia in case it is not among the 10 most common ones):

  - The time to first onset of each TEAE within each treatment group will be summarized with Kaplan-Meier methods. In these analyses, the patients who did not experience the AE in question will be censored at the time of the last visit. Separate Kaplan-Meier plots (including separate curve for each treatment group) will be done for each PT.

7.4. Tolerability and Treatment Compliance

7.4.1. Tolerability

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 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. Time to discontinuation will also be explored by recruitment wave 1 and 2 following corrective actions for patients' retention.

7.4.2. Treatment Compliance

The proportion of used medication out of scheduled medication will be calculated based on the actual daily administered LD dose of ND0612 and summarized with descriptive statistics. The scheduled daily medication dose will be 720 mg LD for Regimen 1 and Regimen 3 and 537.6 mg LD for Regimen 2. The total scheduled dose will be calculated as duration of treatment (as calculated in section 7.2) multiplied by the scheduled daily dose.

In addition, the number and proportion of patients with at least one prolonged treatment interruption (over 3 hours, as recorded on the corresponding CRF page) and the total number of prolonged treatment interruptions will be tabulated.

7.5. Secondary Safety Analyses

C-SSRS: The C-SSRS is a measure of suicidal ideation and behavior. The rating scale has 4 general categories: suicidal ideation, intensity of ideation, suicidal behavior, and actual attempts. All C-SSRS data will be listed. The frequency and percentage of patients with each response for suicidal ideation, intensity of ideation, and suicidal behavior items will be summarized as appropriate by visit.

QUIP: The QUIP is an instrument used to measure the extent of impulsive and compulsive behaviors in PD patients. The QUIP has 3 sections: Section 1 assesses any impulsive control disorder (gambling, sexual, buying, and eating disorders); Section 2 assesses other compulsive behaviors (punding, hobbyism, and walkabout); and Section 3 assesses compulsive medication use. All QUIP scores (A: gambling, B: sex, C: buying, D: eating, total ICD score (A-D), E: hobbyism-punding, F: PD medication use and total QUIP score (A-F)) will be summarized with descriptive statistics by visit. In addition, the changes from baseline will be summarized.

ESS: The ESS is used to determine the level of daytime sleepiness. There are 8 situations listed for which patients rate their likelihood of dozing or sleeping (0=would never doze or sleep, 1=slight chance of dozing or sleeping, 2=moderate chance of dozing or sleeping, and 3=high chance of dozing or sleeping). The total score is the sum of 8 item scores and can range between 0 and 24. If any item score is missing, the total score will be missing. The higher total score indicates the higher level of daytime sleepiness. A score of 10 or more is considered sleepy, and a score of 18 or more is very sleepy. The ESS score will be summarized with descriptive statistics by visit. In addition,

the proportion of patients who are sleepy (score of 10 or more) or very sleepy (score of 18 or more) will be tabulated by visit and treatment group.

The influence of the pump system malfunctions on the safety of ND0612 will be evaluated by capturing data on the date and time of malfunctions, including the description of the malfunction, association to an AE and the action taken. All data collected for the pump system malfunctions will be listed. In addition, the following will be tabulated by treatment group:

- The number of pump system malfunctions and the number of subjects with at least one pump system malfunction
- The number of pump system malfunctions associated with an AE and the number of subjects with at least one pump system malfunction associated with an AE
- The distribution of the actions taken regarding the malfunctions (both as subject and event counts).

7.5.1. Clinical Laboratory Evaluations

All laboratory data (hematology and biochemistry), including dipstick urinalysis results will be summarized with descriptive statistics (continuous variables) or as distributions (categorical variables) by visit and treatment group. In addition, the changes from baseline will be summarized as well as the number and percentage of patients with normal or abnormal (i.e., out of reference range) values at each visit for each parameter by treatment group. The out-of-range values will be further classified as clinically significant and clinically not significant based on the investigator's interpretation.

Furthermore, values of selected laboratory parameters will be classified as potentially clinically significant using the following criteria and tabulated in addition to the criteria for abnormality and clinical significance defined above:

- Albumin-L (< 2.5 g/dl)
- Alkaline Phosphatase-H (> 400 U/L)
- Bilirubin, total-H (> 2 mg/dl)
- BUN-H (> 30 mg/dl)
- Calcium-L (< 7 mg/dl)
- Calcium-H (> 12 mg/dl)
- Cholesterol-H (> 300 mg/dl)
- Creatinine-H (> 2 mg/dl)
- GGT-H (> 3XULN)
- Glucose-L (< 50 mg/dl)
- Glucose-H (> 250 mg/dl)
- Phosphorus-L (< 2.0 mg/dl)
- Phosphorus-H (> 5.0 mg/dl)
- Potassium-L (< 3.0 mmol/L)
- Potassium-H (> 5.5 mmol/L)
- SGOT/AST-H (> 3XULN)
- SGPT/ALT-H (> 3XULN)
- Sodium-L (< 130 mmol/L)
- Sodium-H (> 150 mmol/L)

7.5.2. Vital Signs

Vital sign measurements include heart rate (HR), supine and standing blood pressure (BP) (both systolic and diastolic), body temperature, and weight. Furthermore, supine minus standing blood pressure (both systolic and diastolic) will be calculated. The data will be summarized with descriptive statistics by visit and treatment group. In addition, the changes from baseline will be summarized with descriptive statistics.

Furthermore, to identify potentially clinically significant vital signs, the following criteria will be used and tabulated as a shift table by visit:

- Systolic Blood Pressure: <90 mmHg (low), 90-140 mm Hg (normal), >140 mmHg (high)
- Diastolic Blood Pressure: <90 mmHg (low), 90-100 mmHg (normal), >100 mmHg (high)
- Heart Rate: <60 beats per minute (low), 60-100 beats per minute (normal), >100 beats per minute (high).

Orthostatic hypotension will be defined as a reduction in systolic BP of 20 mmHg or more, and/or a reduction in diastolic BP of 10 mmHg or more, for the standing measurement compared to the supine measurement. The proportion of patients with orthostatic hypotension will be tabulated as a shift table by visit and treatment group.

7.5.3. ECG

The ECGs will be assessed by the investigator and deemed “Normal”, “Abnormal, not clinically significant” and “Abnormal, clinically significant” and tabulated by visit and treatment group.

In addition, the numerical ECG data generated by the central ECG laboratory will be summarized by descriptive statistics for each parameter by visit and treatment group. Also the changes from baseline will be summarized.

The QTc intervals fulfilling the following criteria will be tabulated separately using Fridericia’s correction:

- Values >500 msec
- Values increasing >15% from baseline if baseline value is ≥440 msec
- Values increasing >30% from baseline if baseline value is <440 msec

- Values increasing >30 msec from baseline
- Values increasing >60 msec from baseline.

7.5.4. Physical Examination

Abnormal physical examination findings will be listed and summarized by visit and treatment group. The abnormal values will be further classified as clinically significant and not clinically significant based on the investigator's interpretation. In addition to the summary, all abnormal findings classified as clinically significant will be listed.

8. EFFICACY

8.1. General

For the efficacy endpoints, continuous data will be summarized at each protocol scheduled visit, 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 visit, by treatment regimen, using frequency tabulations.

As the primary and secondary purpose of this study is to explore the 2 treatment regimens with regards to safety and efficacy 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 analyses of the efficacy data will focus on estimating the changes from baseline of the present study for cohort 2 and from baseline of 006 study for cohort 1. Cohort 1 and Cohort 2 will be analyzed separately and combined. Data from Cohort 2 will be summarized by treatment group (Regimen 1 or Regimen 3), i.e. the summaries of efficacy data will include the following groups: Cohort 1/Regimen 1, Cohort 2/Regimen 1 and Cohort 2/Regimen 3. For the combined cohort analysis Regimen 1 and Regimen 3. The mITT set will be used for all efficacy analyses.

Sensitivity analyses of efficacy data will be conducted by excluding the patients who were randomized to receive Regimen 2. These analyses will be done for the “ON” time without troublesome dyskinesia.

8.2. Exploratory Efficacy Variable(s) and Analysis

8.2.1. Change in daily “ON” time without troublesome dyskinesia (“GOOD ON”) from Baseline to each visit

The changes from baseline to all post-baseline visits within each treatment regimen and the difference between the 2 treatment regimens in “GOOD ON” time (defined as the sum of "ON" time without dyskinesia and “ON” time with non-troublesome dyskinesia) will be estimated using a Mixed Model for Repeated Measures (MMRM). The model includes response data from all post-baseline visits with no imputation for missing data. The “GOOD ON” time at baseline will be included as a covariate and the treatment regimen (Regimen 1 or Regimen 3), visit (Month 1, 3, 6, 9 or 12) and the interaction between treatment regimen and visit will be included as fixed factors in the model. An unstructured covariance structure will be assumed and the denominator degrees of freedom will be computed using the Kenward-Roger method. In case the model will not converge

with the unstructured covariance structure, the heterogeneous compound symmetry (CSH) and the heterogeneous Toeplitz structure (TOEPH) will be used instead (in that order). Both the changes from baseline within each treatment regimen and the difference between the regimens will be estimated, separately for each visit, from the same MMRM using contrasts. Since ON/OFF diaries were assessed differently for Cohort 1, this cohort will be excluded from the model.

The changes in "GOOD ON" time will be estimated both as hours (normalized to 16 hours of awake time) and as a percentage out of awake time during the 24 hours of data collection. However, only one p-value will be provided due to the fact that the p-values will be identical.

The SAS code planned for the analysis is outlined below.

```
PROC MIXED DATA=DATA;
CLASS TRTP AVISIT USUBJID;
MODEL CHG=BASE TRTP AVISIT TRTP*AVISIT / SOLUTION DDFM=KR;
REPEATED AVISIT / SUBJECT=USUBJID TYPE=UN;
LSMEANS TRTP*AVISIT / PDIFF CL;
WHERE AVISIT IN ('MONTH 1', 'MONTH 3', 'MONTH 6', 'MONTH 9', 'MONTH 12' ) AND COHORT=2;
RUN;
```

8.2.2. Change in daily "OFF" time based on home "ON/OFF" diaries from Baseline to the 12-month visit

The daily "OFF" time will be analyzed similarly as the "GOOD ON" time replacing baseline "GOOD ON" time with baseline "OFF" time as covariate.

8.2.3. Change in daily "ON" time without any dyskinesia (troublesome or non-troublesome) based on home "ON/OFF" diaries from Baseline to the 12-month visit.

The daily "ON" time without any dyskinesia will be analyzed similarly as the "GOOD ON" time replacing baseline "GOOD ON" time with baseline "ON" time without any dyskinesia as covariate.

8.2.4. 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.

The proportion of patients fulfilling the response criterion will be tabulated by visit. In addition, cumulative percentage of patients with reduction in "OFF" time normalized to a 16-hour waking day will be plotted as a function of percent reduction in "OFF" time from baseline to Month 12..

8.2.5. 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.

The daily "ON" time with troublesome dyskinesia in the subset of subjects who had more than 1 hour of troublesome dyskinesia at Baseline will be analyzed similarly as the "GOOD ON" time replacing baseline "GOOD ON" time with baseline "ON" time with troublesome dyskinesia as covariate.

8.2.6. Change in PDQ-39 summary index and the 8 dimension scores from Baseline to the 12-month visit

The PDQ-39 summary index and the 8 dimension scores will be analyzed similarly as the "GOOD ON" time replacing baseline "GOOD ON" time with baseline PDQ-39 as covariate.

8.2.7. Change in EQ-5D-5L scores from Baseline to the 12-month visit

The health state dimensions will be evaluated by presenting the distribution of responses separately for each of the 5 dimensions at each visit. In addition, the categorical changes (improved, same, and worsened) will be summarized for each of the 5 dimensions at each visit. The VAS score and the health state index score will be analyzed similarly as the "GOOD ON" time replacing baseline "GOOD ON" time with baseline VAS or health state index score as covariate

8.2.8. Change in UPDRS Part II (ADL) from Baseline to the 12-month visit.

The UPDRS Part II (ADL) score change from baseline will be analyzed similarly as the "GOOD ON" time replacing baseline "GOOD ON" time with baseline UPDRS Part II as covariate.

8.2.9. Change in CGI-Severity (CGI-S) and CGI-Improvement (CGI-I) from Baseline to the 12-month visit

The distribution of categorized data (Improvement, non-improvement) will be summarized for each visit using frequencies and percentages. In addition, the distribution of the original uncategorized values will be summarized with frequencies and percentages.

8.2.10. Change in SGI-Improvement from Baseline to the 12-month visit.

The SGI-I will be analyzed similarly as the CGI-I.

8.2.11. Change in PDSS total score from Baseline to the 12-month visit.

The PDSS total score will be analyzed similarly as the "GOOD ON" time replacing baseline "GOOD ON" time with baseline PDSS as covariate.

8.2.12. Change in UPDRS Part III (motor score) from Baseline to the 12-month visit.

The UPDRS Part III (Motor) score will be analyzed similarly as "GOOD ON" time replacing baseline "GOOD ON" time with baseline UPDRS Part III score as covariate.

8.2.13. Morning Akinesia: Change from baseline to month-12 in percentage of "OFF" time during the first 3 hours since the subject is awake after 06:00 (6 am)

The change from baseline to month 12 in percentage of "OFF" time during the first 3 hours since the subject is awake after 06:00 (6 am) will be analyzed similar to the "GOOD ON" endpoint replacing baseline "GOOD ON" time with percentage of OFF during the first 3 hours since the subject is awake at baseline.

8.3. Subgroup analysis

Subgroup analyses will be performed for factors defined in section 4.5 of this document. Each subgroup will be analyzed separately for each regimen in "GOOD ON" time endpoint using MMRM model similar to the model specified in section 8.2.1 including additional fixed factors for the subgroup variable and 2 level interaction terms between the visit, and subgroup variable. The influence of each subgroup on the change from baseline will be investigated per visit using the p-values for the interaction terms. In addition, forest plot depicting the LS mean changes and 95% CI for each subgroup will be displayed.

```
PROC MIXED DATA=DATA;
CLASS SUBGROUP AVISIT USUBJID;
MODEL CHG=BASE SUBGROUP AVISIT SUBGROUP*AVISIT / SOLUTION DDFM=KR;
REPEATED AVISIT / SUBJECT=USUBJID TYPE=UN;
LSMEANS SUBGROUP*AVISIT / PDIFF CL;
WHERE AVISIT IN ('MONTH 1', 'MONTH 3', 'MONTH 6', 'MONTH 9', 'MONTH 12' ) AND COHORT=2;
BY TRTP;
RUN;
```

9. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS® version 9.3 or higher

10. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

- The version of SAP (3.0) was based on Clinical Study Protocol ND0612H-012 Version 8.0 (global Amendment 7): issued on 12 March 2019. At the time when the SAP version 3.0 was finalized, the sponsor endorsed FDA recommendation of a change in the safety primary analyses which were not yet reflected in the protocol. This change was intended to be introduced in a later protocol amendment
- The version of SAP (4.0) was based on Clinical Study Protocol ND0612H-012 Version 9.0 (global Amendment 8): issued on 11 July 2019. There are no changes from this current SAP version (4.0) to the amended protocol (V9.0).