STATISTICAL ANALYSIS PLAN

Study: PD0049

Product: Rotigotine transdermal system

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

SAP/Amendment Number	Date
Final SAP	14 Jun 2017
Amendment 1	31 Jan 2018

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LIST OF ABBREVIATIONS

ADaM	Analysis Data Model
AE	adverse event
ANCOVA	analysis of covariance
APP	application, application software
BMI	body mass index
BSA	body surface area
CG	Control Group
CI	confidence interval
cm	centimeters
EG	Experimental Group
EOS	end of study
ES	Enrolled Set
EW	Early withdrawal
FAS	Full Analysis Set
FDA	Food and Drug Administration
GLNT	Great Lakes NeuroTechnologies, Inc.
H_0	null hypothesis
H_a	alternative hypothesis
HLT	high level term
ICF	Informed Consent form
ICH	International Council for Harmonization
in	inches
lb	pounds
kg	kilograms
MedDRA	Medical Dictionary for Regulatory Activities
PAM-13	13-Item Patient Activation Measure
PDQ-39	39-Item Parkinson's Disease Questionnaire
PPS	Per-Protocol Set
PT	preferred term
Q1	first (25th percent) quartile

Q3	third (75th percent) quartile
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
SDTM	Study Data Tabulation Model
SS	Safety Set
TEAE	treatment-emergent adverse event
UPDRS	Unified Parkinson's Disease Rating Scale
WHODD	World Health Organization Drug dictionary

1 INTRODUCTION

This Statistical Analysis Plan (SAP) defines the scope of statistical analyses and provides a detailed description of methodology for the statistical analyses to support the final clinical study report for PD0049.

The SAP is based on the clinical study protocol, dated 16 Dec 2016.

The content of this SAP is in compliance with the International Council for Harmonization (ICH) / Food and Drug Administration (FDA) E9 Guidance documents.

2 PROTOCOL SUMMARY

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

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

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

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

2.1 Study objectives

2.1.1 Primary objectives

The primary objectives of this study are to:

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

2.1.2 Other objectives

Other objectives of this study are to:

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

2.2 Study variables

2.2.1 Efficacy variables

2.2.1.1 Primary efficacy variables

The primary efficacy variables of this study are:

- Change from Baseline (Visit 1/Week 1) to Visit 2 (Week 12/3 months after start of treatment with Neupro) in Unified Parkinson's Disease Rating Scale (UPDRS) Part III Motor Score
- Change from Baseline (Visit 1/Week 1) to Visit 2 (Week 12) in Kinesia-ONE variables:
  - finger tapping speed score
  - rest tremor score
  - averaged finger tapping speed and resting tremor scores
  - postural tremor score
  - finger tapping amplitude score
  - hand grasp speed score

  - hand grasp amplitude score
  - rapid alternating movement speed score
  - rapid alternating amplitude score
  - dyskinesia score
  - kinetic tremor score
  - rapid alternating movement rhythm score
  - hand movements rhythm score
  - finger tapping rhythm score
  - average Kinesia-ONE score
- Neupro dose per 24h at Visit 2 (Week 12)
- Number of Neupro dose changes during the study (between Visit 1 and Visit 2)
- Discontinuation of treatment with Neupro during the course of the study

2.2.1.2 Other efficacy variables

Other efficacy varibles are:

- Change from Baseline to Visit 2 in the motor scores derived from the Kinesia-360 wearable technology by time (weekly/monthly) for the Experimental Group in:
  - average daily tremor score
  - average daily slowness score
  - average daily dyskinesia score
  - percent wear-time tremor detected
  - percent wear-time dyskinesia detected
  - percent wear-time user not moving
  - percent wear-time user was walking score
  - percent wear-time user active but not walking
  - number of steps per hour while wearing device
- Number of days on Kinesia-360 device
- Change from Baseline to Visit 2 (Week 12) in the 39-Item Parkinson's Disease Questionnaire (PDQ-39) scores.
- Change from Baseline to Visit 2 (Week 12) in subject engagement questionnaire scores.

2.2.2 Safety variable

Safety variable is:

- Occurrence of AEs

2.3 Study design and conduct

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

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

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

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

Each subject's participation is approximately 12 weeks. The end of the study is defined as the date of the last visit of the last subject in the study.

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

A schedule of study assessments is presented in Table 2–1 :

Table 2–1: Schedule of study assessments

	In Clinic	At Home						In Clinic
	SCREENING	BASELINE						EOS/EW
	Visit 1							Visit 2
Assessments	**Day 1**	**Day 2-3**	**Day 4**	**Week 2**	**Week 3**	**Week 4**	**Week 11**	**Week 12 (±3 days)**
Written informed consent	X							
Demographic data (incl. height and weight)	X							X[a]
Kinesia-ONE subject assessments (measured in triplicate)	X[b]							X

Table 2–1: Schedule of study assessments

	In Clinic	At Home						In Clinic
	SCREENING	BASELINE						EOS/EW
	Visit 1							Visit 2
Assessments	**Day 1**	**Day 2-3**	**Day 4**	**Week 2**	**Week 3**	**Week 4**	**Week 11**	**Week 12 (±3 days)**
UPDRS	X							X
Patient engagement questionnaire	X							X
PDQ-39	X							X
Verification of inclusion/exclusion criteria	X							
Randomization	X							
C Group: Start treatment with Neupro 2mg or 4mg preferably on Day 1 but no later than Day 4 (dose adjustments during study are performed per standard of care)	X							X
C Group: Record Neupro dose	X							X
E Group: Kinesia-360 device training and distribution of equipment	X							
E Group: Subject wears Kinesia-360 wrist and ankle devices on Days 2 and 3 at home for baseline		X						
E Group: Start treatment with Neupro 2mg or 4mg on Day 4			X					
E Group: Record Neupro dose[e]			X					X
E Group: Reminder phone calls from site to subject at beginning of Weeks 2, 3, 4 and 11 (remind subject to charge devices and wear devices on at least 2 consecutive				X[d]	X[d]	X[d]	X[d]	

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	In Clinic	At Home						In Clinic
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Assessments	**Day 1**	**Day 2-3**	**Day 4**	**Week 2**	**Week 3**	**Week 4**	**Week 11**	**Week 12 (±3 days)**
days during Weeks 2, 3, 4 and 11)								
E Group: Subject wears Kinesia-360 wrist and ankle devices on at least 2 consecutive days at home				X	X	X	X	
E Group: Subject and Investigator access Kinesia-360 device reports (subjects via device app, Investigators via GLNT web portal)		X						X
E Group: Investigator combines standard of care with Kinesia-360 motor symptom reports to adjust Neupro dose and is encouraged to contact the subject by phone to discuss motor symptom reports and potential Neupro dose adjustments anytime between V1 and V2 based on clinical judgment		X						
E Group: Subject returns Kinesia-360 device equipment to site								X
Record adverse events	X							X
Record concomitant medications	X							X

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

[a] Only weight at V2.

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

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

[d] Subjects in the Experimental Group are to use Kinesia-360 on at least 2 consecutive days during Weeks 2, 3, 4 and 11, but are free to use the device as often as they like between these time points prior to Visit 2.

2.4 Determination of sample size

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

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

The statistical analyses will be performed by Chiltern. Computations and generation of outputs will be performed using SAS® (Statistical Analysis System, SAS-Institute, Cary, NC, USA) Version 9.3 or above. All tables and listings will use Courier New font size 9.

For continuous data in general, summary statistics (n [number of available measurements], arithmetic mean, standard deviation (SD), median, minimum, and maximum) will be presented by group. For selected variables, the first (25th percent) quartile (Q1) and the third (75th percent) quartile (Q3) may also be presented (for patient reported outcomes).

Mean, SD, median and quartiles will be displayed to 1 more decimal place than collected in the source data. Derived variables in general will display the mean, SD and median to 1 more decimal place than the variables used in the derivation (i.e. a change from Baseline will be reported to the same precision as the Baseline data). However, a special rule can be defined as needed for appropriate reporting.

For descriptive statistics of continuous variables by visit, the change from Baseline and actual value at the given time point will be displayed. The change from Baseline is the post-Baseline value minus the Baseline value. If the Baseline or post-Baseline value is missing, then the change from Baseline is set to missing. Percent change from Baseline is the change from Baseline divided by Baseline and multiplied by 100. If the Baseline value is 0 and the post-Baseline value is also 0, then the percent change from Baseline is set to 0. If the Baseline value is 0 and the post-Baseline value is non-zero, then the percent change from Baseline is set to missing. If the Baseline value is missing, the percent change from Baseline is set to missing.

Frequency tables (frequency counts and percentages) will be presented for categorical data. If there are no missing values then the missing row can be removed. If there are missing values (including missing a single assessment or entire visit), then include the missing row with the frequency count and percentage. If there are no subjects in a specific CRF category, then that row will be retained and 0 presented in the table. In general, percentages will be calculated based on the utilized analysis set. However, in the case of subgroup analyses, the N of the subgroup will be used as denominator.

Unless stated otherwise, all inferential statistical tests will be 2-sided and conducted at the 0.05 alpha level. P-values will be presented to 3 decimal places.

All data in the database (ADaM) will be presented in by-subject data listings, and sorted by group, site, subject number, variable (where applicable), and visit (where applicable). All listings

will include repeated and unscheduled measurements. Such measurements will appear in chronological order. In all the listings dates will be presented in the format 'YYYY-MM-DD' and times will be presented in 24h clock format as 'hh:mm'. The visit dates and phone contact dates will be presented in a listing. This includes the scheduled phone contacts in the Experimental Group and the unscheduled phone contacts in both groups. As scheduled phone contacts in the Experimental Group were consistently reported on both the form for scheduled contacts as well as on the unscheduled telephone log, duplicate phone contacts will be removed at the SDTM level. It will be considered at the SDTM level that the scheduled phone contacts do not appear twice, unless two or more phone contacts were documented as conducted on the same day.

All tabulations will be sorted by variable and visit. Only scheduled visits will be included in the tabulation. Categorical data will be summarized by visit, using the number and percentage of subjects in each category. Percentages will be based on the corresponding population size (i.e., the denominator of percentages should match the sample size in the column header), unless otherwise noted via footnote in the applicable summary table. Percentages will be presented to 1 decimal place. For data points with n=0 (i.e., no subjects in the applicable category), no value for percentage of subjects will be displayed.

3.2 General study level definitions

3.2.1 Analysis time points

3.2.1.1 Relative Day

The relative day of a visit or an event with respect to the first administration of study medication (i.e. first patch application of Neupro) will be presented in subject data listings. Relative days will be calculated as follows:

- If the start (stop) date occurred prior to the first application of study medication, the relative day is calculated as start (stop) date minus date of first patch application. That means that in subject data listings, relative days based on this situation will be preceded by a '-'.
- If the start (stop) date occurred on or after the first application of study medication but prior to the last patch application, the relative day is calculated as start (stop) date minus date of first patch application + 1.
- If the start (stop) date occurred after the date of last patch application, the relative day is calculated as start (stop) date minus date of last patch application + 1. In subject data listings, relative days based on this situation will be preceded by a '+'.

Relative days will not be presented for partial or missing dates.

3.2.1.2 End date of the Treatment Period

The end date of the Treatment Period will be either the date of Visit 2 for subjects completing the Treatment Period, or the date of the Early Withdrawal for subjects who discontinued during the Treatment Period. If a subject does not have a Visit 2/EW, then the date of last known dose of study medication during the Treatment Period will define the end date of the Treatment Period.

3.2.2 Study periods

The following study periods are defined for the classification by study period:

- Pretreatment Period: Prior to the date of first administration of study medication
- Treatment Period: On or after the date of first administration of study medication and prior to or on the date of last administration of study medication during the Treatment Period.

3.2.3 Mapping of assessments performed at Early Withdrawal Visit

Efficacy and safety assessments at an Early Withdrawal Visit that correspond to a scheduled visit (Visit 2) will be summarized at the scheduled visit (Visit 2) if the assessment was scheduled to occur at that visit.

3.2.4 Rescreening

Rescreening was not foreseen in the clinical study protocol. However one subject was rescreened. In this case, the initial screening is documented with a different subject number than the second screening and following visits of this same subject. The fact that a rescreened subject has 2 different subject numbers is not accounted for in the analysis, which means that the subject will be counted twice in the tables based on the Enrolled Set. This was decided to be acceptable due to the exploratory nature of this study, and will not impact the efficacy and safety analysis.

3.3 Definition of Baseline values

Baseline values for efficacy and safety variables will be determined from the last available value on or before the day of the first patch application, unless otherwise noted for a specific type of data. In general, Baseline values will be the values collected at Visit 1.

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary efficacy outcomes for an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. All important deviations will be identified and documented prior to database lock to confirm exclusion from analysis sets.

3.5 Analysis sets

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

3.5.1 Enrolled Set

The ES will consist of all subjects who signed the Informed Consent form (ICF).

3.5.2 Safety Set

The SS will consist of all subjects who received at least 1 dose of Neupro. A subject who received Neupro after screen failing is not considered as treated within the study and therefore not included in the SS. The SS will be used for the analysis of all demographic, disposition, and safety data.

3.5.3 Full Analysis Set

The FAS will consist of all subjects who have at least 1 valid Baseline and at least 1 valid post Baseline efficacy measurement. That means, subjects in FAS have non-missing values at Visit 1

and at Visit 2 either for the UPDRS Part III Motor Score or for at least one Kinesia-ONE variable or for Neupro dose per 24h.

The FAS will be used for the analysis and presentation of the efficacy data. In the case of misallocation, subjects will primarily be analyzed according to Kinesia-360 application (yes/no). However, if applicable, sensitivity analysis will also be performed according to the randomized group.

3.5.4 Per Protocol Set

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

3.6 Treatment assignment and treatment groups

Eligible Subjects will be randomized to either the Control Group or the Experimental Group. In the Control Group, optimal Neupro dosing regimen will be titrated using standard clinical practice only. In the Experimental Group, optimal Neupro dosing regimen will be titrated using motor symptom data collected with the Kinesia-360 wearable technology in addition to standard clinical practice.

Comparisons between Control Group and Experimental Group will be performed for outcomes where data are available for both groups, e.g. Kinesia-ONE data, and questionnaires. Kinesia-360 data however are only available for subjects in the Experimental Group, and will therefore be presented only for this group.

3.7 Center pooling strategy

No pooling of centers is planned for this study.

3.8 Coding dictionaries

All AEs will be coded for analysis according to the Medical Dictionary for Regulatory Activities (MedDRA)® coding dictionary, using the latest version available. Prior and concomitant medications will be coded for analysis using the latest version of the World Health Organization Drug dictionary (WHO-DD).

3.9 Changes to protocol-defined analyses

Additional Kinesia-ONE scores which were not prespecified in the clinical study protocol are provided by the vendor. These will be analyzed in the same way as the prespecified variables.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

The continuous efficacy variables, change from Baseline to Visit 2 (for all efficacy variables not based on Kinesia-360) will be analyzed utilizing an analysis of covariance (ANCOVA) with Baseline as a covariate, “center” as factor, and “group” as main factor. The adjustments for baseline value and center are included, as these variables may have a systematic impact on the efficacy outcome.

4.2 Handling of dropouts or missing data

Subjects who prematurely discontinue the study will be evaluated based on the data collected at the Withdrawal Visit. The Withdrawal Visit data will be used similar to Visit 2 data.

Adverse events with missing intensity will be assumed to be severe. Adverse events with missing relationship to study medication per the investigator will be assumed to be related.

For analyses of AEs and concomitant medication usage, a complete date must be established in order to correctly identify the AE or medication as occurring during treatment or not. For purposes of imputing missing components of partially-reported start and stop dates for AEs and for medication use, the algorithms listed below will be followed. Start and stop dates of AEs or concomitant medication will be displayed as reported in the subject data listings (i.e., no imputed values will be displayed in data listings).

- Missing start day, but month and year present: If the start of study medication occurred in the same month and year as the occurrence of the AE/concomitant medication, the start day of the event/concomitant medication will be assigned to the day of first application of study medication. Otherwise the start day will be set to the 1st day of the month.
- Missing start day and month, but year present: If the start of study medication occurred in the same year as the occurrence of the AE/concomitant medication, the start day and month will be assigned to the date of first application of study medication. Otherwise the start day and month will be set to January 1st.
- Missing end day, but month and year present: The end day will be set to the last day of the month.
- Missing end day and month, but year present: If the maximum of the subject's date of study termination or the date equivalent to 30 days after the subject's last application of study medication is the same year as the occurrence of the AE/Concomitant medication, then the end day and month will be set to the maximum of the date of study termination or the date equivalent to 30 days after last application of study medication. Otherwise the end day will be set to December 31st of the given year.

4.3 Interim analyses and data monitoring

No formal interim analysis is planned for PD0049. Also, no specific data monitoring, steering, or evaluation committee is planned for this study.

4.4 Multicenter studies

No multicenter analyses are planned. Therefore, this section is not applicable for this study.

4.5 Multiple comparisons/multiplicity

All statistical tests are considered exploratory, and calculated p-values <0.05 do not indicate statistical significance, since no alpha adjustment will be performed.

4.6 Use of an efficacy subset of subjects

The FAS will be used as primary analysis set for efficacy analyses. The primary efficacy analyses will be repeated for the PPS. The PPS will be used to evaluate subjects who have efficacy data and are reasonably compliant with the conditions of the study. This analysis set will

provide additional information on the efficacy analysis and will describe findings in a subset of subjects who more closely followed the intentions of the study protocol.

4.7 Active-control studies intended to show equivalence

This section is not applicable for this study.

4.8 Examination of subgroups

No subgroups are defined for this study.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

Subject disposition will be summarized on all subjects screened. The number of subjects screened, in addition to the number and percentage of those subjects who were screen failures, broken down by primary reason for screen failure, will be presented.

A summary of disposition of subjects will be provided for all screened subjects. The date of first subject in, date of last subject out, number of subjects screened, and the number of subjects in each analysis set by group and for all subjects will be summarized overall and by investigator site. Subjects who transferred sites will be summarized according to their original site.

A summary of disposition of analysis sets will be provided for the SS. Additionally, a summary of disposition and discontinuation reasons will present the number and percentage of subjects starting the study, completing the study, and discontinuing the study with primary reason for discontinuation.

A summary of discontinuations due to AEs for the SS will present the number and percentage of subjects who discontinued this study due to AEs broken down by type of AE.

The following listings will be provided: study eligibility criteria text, subjects who did not meet study eligibility criteria, subject disposition, subject analysis sets, Neupro discontinuation and visit dates.

5.2 Protocol deviations

Important protocol deviations defined in the protocol-specific document, and additionally identified at the data evaluation meetings, will be listed. In addition, the number and percentage of subjects with at least 1 important protocol deviation will be summarized overall and by category of important protocol deviation for the SS. The number and percentage of subjects with no important protocol deviations will also be summarized for the SS. These will be summarized by group and for all subjects overall. A listing of important protocol deviations will be provided.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

Tables with descriptive statistics and listings will be given for the demographic variables age, gender, weight and height at Baseline, race, ethnicity, and body mass index (BMI). Demographic characteristics will be summarized for all study defined analysis sets, and presented in a listing.

The calculation of age is based on the date of informed consent and the date of birth. If the date of birth is incomplete, it will be completed with January as imputed month if month is missing and it will be completed with 1 as imputed day of birth if day is missing. Age is calculated as follows: Age (years) = ([Date of Informed Consent] – [Imputed Date of Birth]) / 365.25. It will be summarized as a continuous variable and as a categorical variable based on the categories: <65 years, 65-<85 years, ≥85 years, also based on the categories: <65 years, ≥65 years, and also based on the categories: <75 years, ≥75 years.

Weight recorded in pounds (lb) will be converted to kilograms (kg) as weight(lb)*0.4536kg/lb.

Height recorded in inches (in) will be converted to height in centimeters (cm) as height(in)*2.54cm/in.

The BMI will be calculated using the following formula (Keys et al, 1972):

$$\mathrm{BMI\,(kg/m^2)} = 10000 * \frac{\mathrm{weight\,(kg)}}{\left[\mathrm{height\,(cm)}\right]^2}$$

6.2 Other Baseline characteristics

The disease stage of Parkinson's Disease at Baseline can be assessed by the given start dose of Neupro at either 2mg/24h or 4mg/24h. The start dose of Neupro is tabulated within the study medication summary.

6.3 Medical history and concomitant diseases

Medical history data and concomitant diseases data are not collected. Therefore this section is not applicable.

6.4 Prior and concomitant medications

Medications will be considered as prior if the start date of the medication is before the date of first patch administration. Medications will be considered as concomitant if they are taken at least once in the treatment period starting with the first patch administration and ending after the last patch administration during the study. Medications starting prior to first patch administration and continuing into the treatment period will be considered both prior and concomitant medication.

In case of partial or missing dates the rules described in Section 4.2 will be applied.

Prior and concomitant medications will be summarized separately for the SS. The number and percentage of subjects who used prior and concomitant medications, respectively, will be presented according to the anatomical main group (level 1), the pharmacological subgroup (level 3), and the preferred term.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

A calculation of treatment compliance will not be performed. This is due to the nature of this pilot study. Subjects in both treatment arms are treated using standard clinical practice only, there is no fixed mandatory dosing scheme to be followed. Also, no diary data or drug accountability data is collected. Data on Neupro dosing is recorded on the concomitant medication pages of the CRF only. Given this, an appropriate measure for treatment compliance could not be identified.

8 EFFICACY ANALYSES

The efficacy analysis will be performed on the FAS and observed cases will be utilized. The PPS will be used for sensitivity analysis on selected efficacy variables.

8.1 Statistical analysis of the primary efficacy variables

The change from Baseline to Visit 2 in the primary efficacy variables will be analyzed for differences among the treatment groups using analysis of covariance (ANCOVA) with treatment group and center as factors and the corresponding baseline variable as a covariate. The 95% confidence interval (CI) on the calculated least square mean difference between experimental group and control group in change from baseline in the primary efficacy variables will also be reported.

8.1.1 Derivations of primary efficacy variables

8.1.1.1 Unified Parkinson's Disease Rating Scale Part III

The Unified Parkinson's Disease Rating Scale (UPDRS; Movement Disorder Society Task Force on Rating Scales for Parkinson's disease, 2003) consists of 4 parts: Part I of UPDRS assesses mentation, behavior, and mood. Part II of the UPDRS assesses the subject's activity of daily living. Part III assesses motor function. Part IV assesses complications of therapy.

The UPDRS Part III (motor subscale) will be measured in the "on" state and consists of 27 items and sub-items scored between 0 and 4. It includes speech, facial expression, tremor at rest (face, right hand, left hand, right foot, left foot), action or postural tremor of hands (right and left), rigidity (neck, extremities), finger taps (right and left), hand movements (right and left), rapid alternating movements of hands (right and left), leg agility (right and left), arising from chair, posture, gait, postural stability, body bradykinesia, and hypokinesia (14 items, 27 questions = 108 points maximum). The sum score will be calculated as sum of the 27 individual scores. If one or more items are missing, the sum score will also be missing.

8.1.1.2 Kinesia-ONE variables

The Kinesia-ONE data includes the following variables collected at Baseline and at Visit 2:

- finger tapping speed score
- rest tremor score
- averaged finger tapping speed and resting tremor scores
- postural tremor score
- finger tapping amplitude score

- hand grasp speed score
- hand grasp amplitude score
- rapid alternating movement speed score
- rapid alternating amplitude score
- dyskinesia score
- kinetic tremor score
- rapid alternating movement rhythm score
- hand movements rhythm score
- finger tapping rhythm score

These scores are all calculated as an average from triplicate repeated assessments at a measurement point.

In addition, a composite Kinesia-ONE score will be calculated as the average of following scores:

- finger tapping speed score
- rest tremor score
- postural tremor score
- kinetic tremor score
- finger tapping amplitude score
- finger tapping rhythm score
- hand grasp speed score
- hand grasp amplitude score
- hand grasp rhythm score
- rapid alternating movement speed score
- rapid alternating amplitude score
- rapid alternating rhythm score

The composite score will only be calculated if at least 50% of the scores are available.

8.1.1.3 Number of Neupro dose changes

The number of Neupro dose changes is derived as the sum of all Neupro dose changes during the treatment period and includes any increase or decrease of dose, irrespective of the dose level. If a dose level change, e.g. from 2mg/24h to 4mg/24h, occurs multiple times, it is counted as often as it occurs.

8.1.2 Primary analysis of the primary efficacy variables

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

The 2-sided null and alternative hypotheses are:

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

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

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

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

The single items of UPDRS Part III and the sum score will be presented in listings, the sum score will be summarized by group, and the change from Baseline to Visit 2 in UPDRS Part III score will be analyzed using ANCOVA.

The change from Baseline to Visit 2 in each of the Kinesia-ONE scores will be analyzed using ANCOVA.

The Neupro dose per 24h at Visit 2 will be summarized by group, as well as the Neupro starting dose per 24h. Both assessments of Neupro dose will be related in a shift table by group. In addition, Neupro dose and Neupro dose change will be tabulated as continuous variable.

The number of Neupro dose changes after first administration until Visit 2 will be summarized by group.

The comparison of the rate of discontinuation of treatment with Neupro during the course of the study for the control group and the experimental group will be performed using logistic regression with factors for treatment and center.

8.1.3 Secondary analyses of the primary efficacy variables

Not applicable.

8.1.4 Supportive and sensitivity analyses of the primary efficacy variables

The primary analyses (ANCOVA and corresponding summary statistics) will be repeated for the PPS on observed cases.

In case of misallocation to treatment groups, the primary analyses will be repeated for the FAS as randomized.

8.2 Analysis of other efficacy variables

8.2.1 Kinesia-360 motor scores

Kinesia-360-based efficacy data will be presented descriptively for the Experimental Group. Due to repeated measurements (during titration weekly and during maintenance), comparisons will be

performed by time point and also by dose, if applicable (dependent on number of subjects in respective dose groups). Optional time points might also be subject to analysis (dependent on number of subjects at respective time points or windows for time points).

Change from Baseline to Week 2, Week 3, Week 4, Week 7/8, and Week 11 in the motor scores derived from the Kinesia-360 wearable technology by Neupro dose level (mg/24h) for the Experimental Group will be summarized for following scores:

- average daily tremor score
- average daily slowness score
- average daily dyskinesia score
- percent wear-time tremor detected
- percent wear-time dyskinesia detected
- percent wear-time user not moving
- percent wear-time user was walking score
- percent wear-time user active but not walking
- number of steps per hour while wearing device

The average daily scores of tremor, slowness and dyskinesia will be derived from the 2-minutes interval data. Only those 2-minutes interval data records, when the device was not paused, will be considered. For each day, starting at 0:00 until 23:58, the available non-paused 2-minutes interval scores of tremor (and similarly for slowness and dyskinesia) will be selected and the arithmetic mean of these will be calculated which results in the average daily scores.

The percent wear-times and number of steps per hour will be derived from the daily Kinesia-360 data. Multiple records per day will be averaged and weighted by wear-time.

These daily scores will be used to derive the scores per visit week. The daily scores will be averaged from 2 consecutive days of wearing in the respective assessment week. Assessments on study day 8 to 14 are eligible for Week 2 scores, assessments on study day 15 to 21 are eligible for Week 3 scores, assessments on study day 22 to 28 are eligible for Week 4 scores, assessments on study day 43 to 56 are eligible for Week 7/8 scores, and assessments on study day 71 to 77 are eligible for Week 11 assessments. The Week 7/8 is an artificially added Week, which considers the data collected on voluntary basis during that time interval, and therefore might have sparse data. If more than 2 consecutive assessments are available for Week 7/8, the latest 2 consecutive values will be considered. The same applies for the assessments in Week 2, Week 3, Week 4, and Week 11: If more than 2 consecutive assessments are available per week, the latest 2 consecutive values will be considered.

In addition, the maximum relative day of Kinesia-360 usage will be listed, and the number of days the subject used the Kinesia-360 device will be calculated by subject and summarized.

8.2.2 Parkinson's Disease Questionnaire (PDQ-39)

The Parkinson's Disease Questionnaire (PDQ-39; Jenkinson, 1997) is a simple questionnaire that assesses health related quality of life in individuals with PD. The answer categories are coded as follows: 0=never, 1=occasionally, 2=sometimes, 3=often, 4=always or cannot do at all. It

provides scores in 8 scales: mobility (questions 1-10), activities of daily living (questions 11-16), emotions (questions 17-22), stigma (questions 23-26), social support (questions 27-29), cognition (questions 30-33), communication (questions 34-36), and bodily discomfort (questions 37-39). It is designed for self-completion by subjects and should take only a few minutes for the subject to complete.

For each of the 8 domains a score will be calculated: The coded answer categories of the corresponding domain questions will be added. This domain raw value will be multiplied with 100 and divided by the maximum domain raw value (e.g. 4*10=40 for the 10 questions of mobility domain). This transformation gives domain scores between 0 and 100.

Domain scores will only be calculated if at least 50% of items on the scale have been answered. If this is the case, the missing items, if any, will be replaced with the overall mean of the item, and the corresponding domain score will be calculated based on the replaced questions.

The social support domain consists of questions 27, 28, and 29. If respondents indicate that they do not have a spouse or partner on question 28 then social support will be calculated as follows: social support = (sum of questions 27 + 29) / (4 * 2) * 100.

Individual questions will be summarized categorically, and the domain scores will be tabulated using continuous summary statistics by visit.

A sum score, calculated by adding together the 8 domain scores and dividing the sum by 8, will also be presented using continuous summary statistics by visit (including change from baseline values).

8.2.3 Patient Activation Measure (PAM-13)

The Patient Activation Measure (PAM-13) quantifies the extent to which people are informed about and involved in their health care. The answer categories are coded as follows: 1=disagree strongly, 2=disagree, 3=agree, 4=agree strongly.

A sum score will be calculated by adding together the coded answer categories of the 13 items, and then transforming to a scale from 0 to 100 using the formula 100*(sum of items - 13)/(52-13).

The sum score will only be calculated if at least nine questions have been answered. If this is the case, the missing items, if any, will be replaced with the overall mean of the item, and the sum score will be calculated based on the replaced items.

The individual questions will be summarized categorically, and the sum score will be presents using continuous summary statistics by visit (including change from baseline values).

8.2.4 Unified Parkinson's Disease Rating Scale Parts I, II, IV

The UPDRS Part I (Mentation, Behavior, and Mood) includes intellectual impairment, thought disorder, depression, and motivation/initiative (4 questions=16 points maximum).

The UPDRS Part II (Activities in Daily Living) consists of 13 items scored between 0 and 4. It includes speech, salivation, swallowing, handwriting, cutting food and handling utensils, dressing, hygiene, turning in bed and adjusting clothes, falling (unrelated to freezing), freezing when walking, walking, tremor, and sensory complaints related to Parkinsonism (13

questions=52 points maximum). The sum score will be calculated as the sum of the 13 individual scores. If one or more items are missing, the sum score will also be missing.

The UPDRS Part IV (Complications of Therapy) consists of 11 questions. It includes dyskinesias, duration, disability, painful dyskinesias, early morning dystonia, clinical fluctuations, presence of anorexia, nausea or vomiting, sleep disturbance, and symptomatic orthostasis (11 questions).

The single items of UPDRS Parts I, II, and IV, and the sum scores will be presented in listings. The UPDRS Part IV will be presented separately for each item, the sum scores of UPDRS Part I and II will be summarized by group, and the change from Baseline to Visit 2 in UPDRS Part II score will be analyzed using ANCOVA as described in Section 8.1.2 .

9 PHARMACOKINETICS AND PHARMACODYNAMICS

9.1 Pharmacokinetics

Not applicable.

9.2 Pharmacodynamics

Not applicable.

10 SAFETY ANALYSES

In general, safety analyses will be conducted with the SS as randomized.

10.1 Extent of exposure

The overall duration of exposure is defined as the date of last patch administration minus the date of the first patch application + 1 day. The overall exposure duration will be summarized using descriptive statistics for the subjects.

10.2 Adverse events

Adverse events with start date prior to first administration of study medication are defined as pre-treatment AEs. No summaries of these events will be provided, they are included in listings.

Treatment emergent AEs are all AEs starting on or after the date of first study medication and up to 30 days after the last dose of study medication. Also AEs with an earlier onset are treatment emergent, if the intensity worsened during the treatment period. AEs occurring more than 30 days after the last dose will not be considered treatment emergent.

For AEs with a partial start date, the imputation rules as described in Section 4.2 will be applied. If a start date is completely missing, then the AE will be considered treatment-emergent unless the AE end date is on or before the first date of study medication. Duration should not be calculated if there is missing stop date information.

Treatment emergent adverse events (TEAE) will be tabulated by MedDRA system organ class (SOC), high level term (HLT) and preferred term (PT). The number and percentage of subjects experiencing each event at least once will be summarized in addition to the number of events. In summaries of TEAEs by relationship and intensity, respectively, the number of events will not be presented.

All summaries will be sorted alphabetically by SOC and HLT and by descending frequency of PT in the Experimental Group within HLTs. If there is more than one PT with the same frequency in the Experimental Group these events will be sorted alphabetically.

Tables showing TEAEs, serious TEAEs, non-serious TEAEs, TEAEs leading to discontinuation of study medication, TEAEs by maximum intensity, TEAEs by maximum relationship, and TEAEs including subject numbers will be provided. The table showing AEs leading to study discontinuation will also be provided for the ES. A glossary of MedDRA terms and associated investigator provided terms for all adverse events will be presented. Individual subject data listings will be presented for all AEs, serious TEAEs, TEAEs leading to withdrawal of study medication, and TEAEs with fatal outcome.

10.3 Clinical laboratory evaluations

Not applicable.

10.4 Other observations related to safety

10.4.1 Weight

Weight recorded in pounds (lb) will be converted to kilograms (kg) as described in Section 6.1 . Summary statistics of the actual values and change from Baseline values of body weight will be presented by visit in the SS.

10.4.2 Other safety variables

The comparison of the rate of discontinuation of treatment with Neupro during the course of the study for the Control Group and the Experimental Group is one of the safety variables. This is described in Section 8.1.2 .

11 REFERENCES

Jenkinson C., Fitzpatrick R., Petro V., Greenhall R., and Hyman N. (1997) The Parkinson's Disease Questionnaire (PDQ-39). Development and validation of a Parkinson's Disease summary index score. Age Ageing, 26:353-357.

Keys A; Fidanza F; Karvonen M; Kimura N; Taylor H. Indices of relative weight and obesity. Journal of Chronic Diseases 1972, 25 (6–7): 329–43.

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12 APPENDICES

Not applicable.

13 AMENDMENT(S) TO THE STATISTICAL ANALYSIS PLAN (SAP) (IF APPLICABLE)

13.1 AMENDMENT 1

Rationale for the amendment

The SAP was amended after the Data Evaluation Meeting, to specify the SS more precisely, to define the handling of question 28 of PDQ-39, to describe the derivation of Kinesia-360 scores in more detail, and to correct the subgroup level of concomitant medications presented. In addition, new Kinesia variables, and the handling of rescreened subjects and of phone contacts has been added.

Modifications and changes

Changes in section 2.1

Following text before section 2.1.1 was removed in order to keep this section consistent with the clinical study protocol:

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

Changes in section 2.2.1.1

The primary efficacy variables of this study are:

- Change from Baseline (Visit 1/Week 1) to Visit 2 (Week 12/3 months after start of treatment with Neupro) in Unified Parkinson's Disease Rating Scale (UPDRS) Part III Motor Score
- Change from Baseline (Visit 1/Week 1) to Visit 2 (Week 12) in Kinesia-ONE variables:
  - finger tapping speed score
  - rest tremor score
  - averaged finger tapping speed and resting tremor scores
  - postural tremor score
  - finger tapping amplitude score
  - hand grasp speed score

  - hand grasp amplitude score
  - rapid alternating movement speed score
  - rapid alternating amplitude score
  - dyskinesia score
- Neupro dose per 24h at Visit 2 (Week 12)
- Number of Neupro dose changes during the study (between Visit 1 and Visit 2)
- Discontinuation of treatment with Neupro during the course of the study

Has been changed to:

The primary efficacy variables of this study are:

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

Changes in section 2.2.1.2

Other efficacy varibles are:

- Change from Baseline to Visit 2 in the motor scores derived from the Kinesia-360 wearable technology by time (weekly/monthly) for the Experimental Group in:
  - average daily tremor score
  - average daily slowness score
  - average daily dyskinesia score
  - percent wear-time tremor detected
  - percent wear-time dyskinesia detected
  - percent wear-time user not moving
  - percent wear-time user was walking score
  - percent wear-time user active but not walking
  - number of steps per hour while wearing device
- Change from Baseline to Visit 2 (Week 12) in the 39-Item Parkinson's Disease Questionnaire (PDQ-39) scores.
- Change from Baseline to Visit 2 (Week 12) in subject engagement questionnaire scores.

Has been changed to:

Other efficacy varibles are:

- Change from Baseline to Visit 2 in the motor scores derived from the Kinesia-360 wearable technology by time (weekly/monthly) for the Experimental Group in:
  - average daily tremor score
  - average daily slowness score
  - average daily dyskinesia score
  - percent wear-time tremor detected
  - percent wear-time dyskinesia detected
  - percent wear-time user not moving
  - percent wear-time user was walking score
  - percent wear-time user active but not walking
  - number of steps per hour while wearing device
- **Number of days on Kinesia-360 device**
- Change from Baseline to Visit 2 (Week 12) in the 39-Item Parkinson's Disease Questionnaire (PDQ-39) scores.
- Change from Baseline to Visit 2 (Week 12) in subject engagement questionnaire scores.

Changes in section 3.1

Following sentences were added to the penultimate paragraph of section 3.1:

The visit dates and phone contact dates will be presented in a listing. This includes the scheduled phone contacts in the Experimental Group and the unscheduled phone contacts in both groups. As scheduled phone contacts in the Experimental Group were consistently reported on both the form for scheduled contacts as well as on the unscheduled telephone log, duplicate phone contacts will be removed at the SDTM level. It will be considered at the SDTM level that the scheduled phone contacts do not appear twice, unless two or more phone contacts were documented as conducted on the same day.

Changes in section 3.2

Following subsection 3.2.4 was added at the end of section 3.2:

3.2.4 Rescreening

Rescreening was not foreseen in the clinical study protocol. However one subject was rescreened. In this case, the initial screening is documented with a different subject number than the second screening and following visits of this same subject. The fact that a rescreened subject has 2 different subject numbers is not accounted for in the analysis, which means that the subject will be counted twice in the tables based on the Enrolled Set. This was decided to be acceptable due to the exploratory nature of this study, and will not impact the efficacy and safety analysis.

Changes in section 3.5.2

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

Has been changed to:

The SS will consist of all subjects who received at least 1 dose of Neupro. **A subject who received Neupro after screen failing is not considered as treated within the study and therefore not included in the SS.** The SS will be used for the analysis of all demographic, disposition, and safety data.

Changes in section 3.9

Not applicable.

Has been changed to:

Additional Kinesia-ONE scores which were not prespecified in the clinical study protocol are provided by the vendor. These will be analyzed in the same way as the prespecified variables.

Changes in section 5.1

The following listings will be provided: study eligibility criteria text, subjects who did not meet study eligibility criteria, subject disposition, subject analysis sets, study discontinuation and visit dates.

Has been changed to:

The following listings will be provided: study eligibility criteria text, subjects who did not meet study eligibility criteria, subject disposition, subject analysis sets, **Neupro** discontinuation and visit dates.

Changes in section 6.1

The calculation of age is based on the date of informed consent and the date of birth. If the date of birth is incomplete, it will be completed with January as imputed month if month is missing and it will be completed with 1 as imputed day of birth if day is missing. Age is calculated as follows: Age (years) = ([Date of Informed Consent] – [Imputed Date of Birth]) / 365.25. It will be summarized as a continuous variable and as a categorical variable based on the categories: <65 years, ≥65 years, and also based on the categories: <75 years, ≥75 years.

Has been changed to:

The calculation of age is based on the date of informed consent and the date of birth. If the date of birth is incomplete, it will be completed with January as imputed month if month is missing and it will be completed with 1 as imputed day of birth if day is missing. Age is calculated as follows: Age (years) = ([Date of Informed Consent] – [Imputed Date of Birth]) / 365.25. It will be summarized as a continuous variable and as a categorical variable **based on the categories: <65 years, 65-<85 years, ≥85 years, also** based on the categories: <65 years, ≥65 years, and also based on the categories: <75 years, ≥75 years.

Changes in section 6.4

Prior and concomitant medications will be summarized separately for the SS. The number and percentage of subjects who used prior and concomitant medications, respectively, will be presented according to the anatomical main group (level 1), the pharmacological subgroup (level 2), and the preferred term.

Has been changed to:

Prior and concomitant medications will be summarized separately for the SS. The number and percentage of subjects who used prior and concomitant medications, respectively, will be presented according to the anatomical main group (level 1), the pharmacological subgroup (level **3**), and the preferred term.

Changes in section 8.1.1.2

The Kinesia-ONE data includes the following variables collected at Baseline and at Visit 2:

- finger tapping speed score
- rest tremor score
- averaged finger tapping speed and resting tremor scores
- postural tremor score
- finger tapping amplitude score
- hand grasp speed score
- hand grasp amplitude score
- rapid alternating movement speed score
- rapid alternating amplitude score
- dyskinesia score

These scores are all calculated as an average from triplicate repeated assessments at a measurement point.

Has been changed to:

The Kinesia-ONE data includes the following variables collected at Baseline and at Visit 2:

- finger tapping speed score
- rest tremor score
- averaged finger tapping speed and resting tremor scores
- postural tremor score
- finger tapping amplitude score
- hand grasp speed score
- hand grasp amplitude score
- rapid alternating movement speed score
- rapid alternating amplitude score
- dyskinesia score
- **kinetic tremor score**
- **rapid alternating movement rhythm score**
- **hand movements rhythm score**
- **finger tapping rhythm score**

These scores are all calculated as an average from triplicate repeated assessments at a measurement point.

In addition, a composite Kinesia-ONE score will be calculated as the average of following scores:

- **finger tapping speed score**
- **rest tremor score**
- **postural tremor score**
- **kinetic tremor score**
- **finger tapping amplitude score**
- **finger tapping rhythm score**
- **hand grasp speed score**
- **hand grasp amplitude score**
- **hand grasp rhythm score**
- **rapid alternating movement speed score**

- **rapid alternating amplitude score**
- **rapid alternating rhythm score**

The composite score will only be calculated if at least 50% of the scores are available.

Changes in section 8.1.2

The Neupro dose per 24h at Visit 2 will be summarized by group, as well as the Neupro starting dose per 24h. Both assessments of Neupro dose will be related in a shift table by group.

The number of Neupro dose changes after first administration until Visit 2 will be summarized by group.

The comparison of the rate of discontinuation of treatment with Neupro during the course of the study for the control group and the experimental group will be performed using logistic regression with factors for treatment and center.

Has been changed to:

The Neupro dose per 24h at Visit 2 will be summarized by group, as well as the Neupro starting dose per 24h. Both assessments of Neupro dose will be related in a shift table by group. **In addition, Neupro dose and Neupro dose change will be tabulated as continuous variable.**

The number of Neupro dose changes after first administration until Visit 2 will be summarized by group.

The comparison of the rate of discontinuation of treatment with Neupro during the course of the study for the control group and the experimental group will be performed using logistic regression with factors for treatment and center.

Changes in section 8.2.1

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

Change from Baseline to Week 2, Week 3, Week 4, Week 7/8, and Week 11 in the motor scores derived from the Kinesia-360 wearable technology by Neupro dose level (mg/24h) for the Experimental Group will be summarized for following scores:

- average daily tremor score
- average daily slowness score
- average daily dyskinesia score
- percent wear-time tremor detected
- percent wear-time dyskinesia detected
- percent wear-time user not moving
- percent wear-time user was walking score

- percent wear-time user active but not walking
- number of steps per hour while wearing device

The scores will be averaged from 2 consecutive days of wearing in the respective assessment week. Assessments on study day 8 to 14 are eligible for Week 2 scores, assessments on study day 15 to 21 are eligible for Week 3 scores, assessments on study day 22 to 28 are eligible for Week 4 scores, assessments on study day 43 to 56 are eligible for Week 7/8 scores, and assessments on study day 71 to 77 are eligible for Week 11 assessments. The Week 7/8 is an artificially added Week, which considers the data collected on voluntary basis during that time interval, and therefore might have sparse data. If more than 2 consecutive assessments are available for Week 7/8, the latest 2 consecutive values will be considered. The same applies for the assessments in Week 2, Week 3, Week 4, and Week 11: If more than 2 consecutive assessments are available per week, the latest 2 consecutive values will be considered.

Has been changed to:

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

Change from Baseline to Week 2, Week 3, Week 4, Week 7/8, and Week 11 in the motor scores derived from the Kinesia-360 wearable technology by Neupro dose level (mg/24h) for the Experimental Group will be summarized for following scores:

- average daily tremor score
- average daily slowness score
- average daily dyskinesia score
- percent wear-time tremor detected
- percent wear-time dyskinesia detected
- percent wear-time user not moving
- percent wear-time user was walking score
- percent wear-time user active but not walking
- number of steps per hour while wearing device

The average daily scores of tremor, slowness and dyskinesia will be derived from the 2-minutes interval data. Only those 2-minutes interval data records, when the device was not paused, will be considered. For each day, starting at 0:00 until 23:58, the available non-paused 2-minutes interval scores of tremor (and similarly for slowness and dyskinesia) will be selected and the arithmetic mean of these will be calculated which results in the average daily scores.

The percent wear-times and number of steps per hour will be derived from the daily Kinesia-360 data. Multiple records per day will be averaged and weighted by wear-time.

These daily scores will be used to derive the scores per visit week. The **daily** scores will be averaged from 2 consecutive days of wearing in the respective assessment week. Assessments on study day 8 to 14 are eligible for Week 2 scores, assessments on study day 15 to 21 are eligible for Week 3 scores, assessments on study day 22 to 28 are eligible for Week 4 scores, assessments on study day 43 to 56 are eligible for Week 7/8 scores, and assessments on study day 71 to 77 are eligible for Week 11 assessments. The Week 7/8 is an artificially added Week, which considers the data collected on voluntary basis during that time interval, and therefore might have sparse data. If more than 2 consecutive assessments are available for Week 7/8, the latest 2 consecutive values will be considered. The same applies for the assessments in Week 2, Week 3, Week 4, and Week 11: If more than 2 consecutive assessments are available per week, the latest 2 consecutive values will be considered.

In addition, the maximum relative day of Kinesia-360 usage will be listed, and the number of days the subject used the Kinesia-360 device will be calculated by subject and summarized.

Changes in section 8.2.2

The Parkinson's Disease Questionnaire (PDQ-39; Jenkinson, 1997) is a simple questionnaire that assesses health related quality of life in individuals with PD. The answer categories are coded as follows: 0=never, 1=occasionally, 2=sometimes, 3=often, 4=always or cannot do at all. It provides scores in 8 scales: mobility (questions 1-10), activities of daily living (questions 11-16), emotions (questions 17-22), stigma (questions 23-26), social support (questions 27-29), cognition (questions 30-33), communication (questions 24-36), and bodily discomfort (questions 37-39). It is designed for self-completion by subjects and should take only a few minutes for the subject to complete.

For each of the 8 domains a score will be calculated: The coded answer categories of the corresponding domain questions will be added. This domain raw value will be multiplied with 100 and divided by the maximum domain raw value (e.g. 4*10=40 for the 10 questions of mobility domain). This transformation gives domain scores between 0 and 100.

Domain scores will only be calculated if at least 50% of items on the scale have been answered. If this is the case, the missing items, if any, will be replaced with the overall mean of the item, and the corresponding domain score will be calculated based on the replaced questions.

Has been changed to:

The Parkinson's Disease Questionnaire (PDQ-39; Jenkinson, 1997) is a simple questionnaire that assesses health related quality of life in individuals with PD. The answer categories are coded as follows: 0=never, 1=occasionally, 2=sometimes, 3=often, 4=always or cannot do at all. It provides scores in 8 scales: mobility (questions 1-10), activities of daily living (questions 11-16), emotions (questions 17-22), stigma (questions 23-26), social support (questions 27-29), cognition (questions 30-33), communication (questions **34**-36), and bodily discomfort (questions 37-39). It is designed for self-completion by subjects and should take only a few minutes for the subject to complete.

For each of the 8 domains a score will be calculated: The coded answer categories of the corresponding domain questions will be added. This domain raw value will be multiplied with

100 and divided by the maximum domain raw value (e.g. 4*10=40 for the 10 questions of mobility domain). This transformation gives domain scores between 0 and 100.

Domain scores will only be calculated if at least 50% of items on the scale have been answered. If this is the case, the missing items, if any, will be replaced with the overall mean of the item, and the corresponding domain score will be calculated based on the replaced questions.

The social support domain consists of questions 27, 28, and 29. If respondents indicate that they do not have a spouse or partner on question 28 then social support will be calculated as follows: social support = (sum of questions 27 + 29) / (4 * 2) * 100.

13.2 AMENDMENT 2

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.