STATISTICAL ANALYSIS PLAN

A multicentre, phase 3, clinical study to compare the striatal uptake of a dopamine transporter radioligand, DaTSCAN™ ioflupane (^{123}I) injection, after intravenous administration to Chinese patients with a diagnosis of Parkinson's disease, multiple system atrophy, progressive supranuclear palsy, or essential tremor and to healthy controls

STUDY DRUG: DaTSCAN™ ioflupane (^{123}I) injection

PROTOCOL NUMBER: GE-001-024

VERSION/[redacted]: 1.0/[redacted]

Prepared by: PPD Inc., on behalf of

GE Healthcare Ltd. and its Affiliates
Pollards Wood
Nightingales Lane
Chalfont St Giles
HP8 4SP
United Kingdom

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
BIE	blinded image evaluation
CRF	case report form
CT	computed tomography
DSM	Diagnostic and Statistical Manual of Mental Disorders
ET	essential tremor
FAS	full analysis set
FN	false negatives
FP	false positives
HV	healthy volunteer
H&Y	Hoehn and Yahr
IMP	investigational medicinal product
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination
MSA	multiple system atrophy
PD	Parkinson’s disease
PP	per-protocol
PSP	progressive supranuclear palsy
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDD	striatal dopaminergic deficit
SOC	system organ class
SPECT	single photon emission computed tomography
TEAE	treatment-emergent adverse event
TN	true negatives
TP	true positives
UPDRS	United Parkinson's Disease Rating Scale
WHIGET	Washington Heights-Inwood Genetic Study of Essential Tremor
WHO Drug	World Health Organization Drug Directory

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the analyses and data presentations for GE Healthcare's protocol GE-001-024 "A multicentre, phase 3, clinical study to compare the striatal uptake of a dopamine transporter radioligand, DaTSCAN™ ioflupane (^{123}I) injection, after intravenous administration to Chinese patients with a diagnosis of Parkinson's disease (PD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), or essential tremor (ET) and to healthy controls" which was issued and finalized as protocol amendment A03, version 1.0 approved on 25 Nov 2020. It contains definition of analysis populations, derived variables and statistical methods for analysis of safety and efficacy of DaTSCAN™ ioflupane (^{123}I) injection, which will determine the sensitivity and specificity of a measure of striatal uptake of [^{123}I]ioflupane as visualized in single photon emission computed tomography (SPECT) images taken 3 to 6 hours after a single intravenous (IV) administration of DaTSCAN™ ioflupane (^{123}I) injection (111 to 185 MBq [3 to 5 mCi]) for the diagnosis of Parkinsonian syndrome (PS) involving striatal dopaminergic deficit (SDD; specifically, PD, MSA, or PSP) as opposed to ET (no SDD) or no neurologic disease (healthy volunteers [HVs]) in Chinese subjects.

The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data. All statistical analyses detailed in this SAP will be conducted using SAS® version 9.3 or later (SAS Institute Inc., Cary, North Carolina). The SAP will be finalized and signed prior to the clinical database lock for the final analysis.

2. OBJECTIVES

2.1. Primary Objective

- To determine the sensitivity and specificity of a measure of striatal uptake of [^{123}I]ioflupane as visualized in SPECT images taken 3 to 6 hours after a single IV administration of DaTSCAN™ ioflupane (^{123}I) injection (111 to 185 MBq [3 to 5 mCi]) for the diagnosis of PS involving SDD (specifically, PD, MSA, or PSP) as opposed to ET (no SDD) or no neurologic disease (HVs) in Chinese subjects.

2.2. Secondary Objectives

- To assess the striatal uptake of [^{123}I]ioflupane in healthy Chinese volunteers (no SDD).
- To assess safety parameters (haematology, biochemistry and urinalysis, and vital signs) and the adverse event (AE) profile in Chinese patients/HVs after a single IV administration of DaTSCAN™ ioflupane (^{123}I) injection.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This study is a multicentre, open-label, non-controlled, non-randomised clinical study to compare the SPECT findings after a single IV administration of DaTSCAN™ ioflupane (^{123}I) injection for subjects with a clinical diagnosis of PS (SDD; specifically, subjects with PD [SDD], MSA [SDD] or PSP [SDD]) as compared with subjects with a clinical diagnosis of ET (no SDD) and age-matched healthy controls. The study will be conducted at approximately 10 centres in China. The planned sample size for this clinical investigation will be 140 evaluable subjects (60 with movement disorder and SDD, 60 with movement disorder but without SDD, 20 HVs). After adjustment for losses, 150 subjects with movement disorders (with and without SDD) and 22 HVs will need to be enrolled. Each subject will be required to visit the study centre for a screening visit, baseline visit, DaTSCAN™ imaging visit, and 1 follow-up visit.

In order to prevent misinterpretations of the DaTSCAN™ SPECT images by the independent blinded readers (who will not be supplied with clinical data), the absence of structural abnormalities in the basal ganglia must be ruled out by a magnetic resonance imaging scan or cerebral computed tomography (CT) image findings performed within 6 months prior to inclusion. During the baseline visit, safety assessments and an extensive neurologic examination will be performed. At that visit, each subject will receive a clinical diagnosis (e.g., PD or ET or no neurologic disease). The dose of DaTSCAN™ to be used in this study is within the range of 111 to 185 MBq (3 to 5 mCi) per subject in a maximum volume of 5 mL. Subjects should undergo appropriate thyroid blocking treatment prior to and/or after injection according to local practices in order to minimise thyroid uptake of radioactive iodine. During the DaTSCAN™ imaging visit, all subjects will receive a single IV injection of DaTSCAN™ ioflupane (^{123}I) injection. SPECT imaging will be performed between 3 to 6 hours post-injection and will last approximately 20 minutes to 1 hour, depending on type of SPECT camera. The DaTSCAN™ imaging visit may occur as soon as possible after the baseline visit but no later than 28 days after baseline. Each subject will be asked to return for a final follow-up visit at 3 (±1) days after the administration of DaTSCAN™ injection for a safety assessment. Safety will be assessed from the rates of AEs, changes in vital signs, changes in physical examination findings, changes in clinical laboratory findings, changes in injection site monitoring, and changes in neurologic examination. To rule out any metabolic disturbances that may underlie changes in neuropsychiatric state, routine laboratory parameters, including glucose and those reflecting hepatic and renal function, will also be assessed.

3.2. Study Endpoints

3.2.1. Primary Endpoint

- Assessment of DaTSCAN™ SPECT images by 3 independent blinded readers to compare specific striatal uptake with the clinical diagnosis.

3.2.2. Secondary Endpoints

- Central read (by semi-quantitative assessment by use of DaTQUANT™) of DaTSCAN™ SPECT images to compare specific uptake with clinical diagnosis.
- Comparison and assessment of safety parameters and AEs reported by all study participants.

3.3. Treatments

In this open-label study, each subject will receive 1 dose of the investigational medicinal product (IMP), DaTSCAN™ ioflupane (^{123}I) injection, during the imaging visit. Each subject will undergo appropriate thyroid blocking treatment prior to and/or after injection and receive a dose of 111 to 185 MBq DaTSCAN™ in a maximum volume of 5 mL. To minimise pain upon injection, the dose will be delivered by a slow IV injection (not less than 15 to 20 seconds) into an arm vein. SPECT imaging should take place between 3 and 6 hours after injection. Details of IMP and procedures are outlined in the protocol Sections 8 and 9.

3.4. Dose Adjustment/Modification

All subjects will be administered the IMP by study personnel. No dose adjustment/ modification is allowed under normal circumstances. Doses administered outside of specific dose requirements or defined range must be reported as protocol deviations.

4. GENERAL STATISTICAL CONSIDERATIONS

4.1. Reporting Conventions

Continuous data (absolute values and change from baseline values) will be described using descriptive statistics (i.e. n, mean, standard deviation (SD), median, minimum, and maximum). Categorical data will be described using frequency count and percentage in each category. For the summary statistics of all numerical variables, unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. SD/ standard error will be displayed to two levels of precision greater than the data collected. For the summary statistics of categorical variables, all percentages will be rounded to one decimal place. Number and percentage values will be presented as xx (xx.x). If the percentage is 100, no decimal is required. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001." If a p-value is greater than 0.999 it will be reported as ">0.999." All general and safety analysis and summary tables will have the population sample size in the column headers in the form of N=XXX for the single diagnostic category according to subjects' clinical diagnosis (PS (including PD, MSA, PSP), ET, HV, and all subjects) performed at baseline visit, and the efficacy analysis group for sensitivity, specificity and accuracy are specified in section 8. All enrolled subject data recorded on the case report form (CRF) and entered into the database will be provided in separate data listings showing individual subject values. Data will be displayed in all listings sorted by baseline clinical diagnosis, subject number and visit (time point, if applicable).

All laboratory data will be reported using international system of units (SI).

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that clinical diagnosis category within the analysis set of interest, unless otherwise specified.

4.2. Baseline and Standard of Truth Definition

The last observation prior to administration of IMP will be used as the baseline value for calculating changes from baseline after administration of IMP.

The clinical diagnosis as established by the investigator at baseline at the recruiting centres according to internationally accepted diagnostic criteria and based on a standardized and comprehensive clinical and neuropsychiatric assessment will be the standard of truth used for determining sensitivity and specificity.

The study day/time will be calculated as assessment date/time – date/time of injection + 1 if the presented date is on or after the date/time of injection. Otherwise, the study day/time will be calculated as assessment date/time – date/time of injection.

4.3. Sample Size Determination

The null hypothesis tests are given as H_0: $p \leq p_0$ where p_0 is the specified threshold. The alternate hypothesis is given by H_a: $p>p_0$. The parameter p represents the sensitivity/specificity of the blinded independent read of DaTSCAN™ SPECT images in detecting or excluding SDD, using the clinical diagnosis as established by the investigator as the standard of truth.

An exact binomial test with a nominal 0.05 1-sided significance level will have 80% power to detect the difference between the null hypothesis diagnostic sensitivity threshold of 0.85 and the assumed alternative proportion of 0.95 when the sample size is 59 subjects with SDD present.

An exact binomial test with a nominal 0.05 1-sided significance level will have 80% power to detect the difference between the null hypothesis diagnostic specificity threshold of 0.85 and the assumed alternative proportion of 0.95 when the sample size is 59 subjects with SDD absent.

An extensive set of values for the specified threshold, p_0, and the resultant sample size (for either sensitivity or specificity) are as follows: $P_0 = 0.89$: n=128; $P_0 = 0.88$: n=107; $P_0 = 0.87$: n= 89;

$P_0 = 0.86$: n= 73; $P_0 = 0.85$: n= 59; $P_0 = 0.84$: n= 55; $P_0 = 0.83$: n= 44; $P_0 = 0.82$: n= 41; $P_0 = 0.81$: n= 39; $P_0 = 0.80$: n=30.

However, according to regulatory guidelines sample size for a new product with more than 1 indication (which is the case for DaTSCAN™) requires a minimum of 60 pairs of cases. Therefore, the final number of evaluable diseased individuals will be 60 in each group (SDD present and absent).

In addition to the 120 evaluable subjects (subjects with movement disorder), each centre will be requested to recruit 2 to 4 HVs (subjects without movement disorder) for the sole purpose of the creation of a normal database. A total of 20 HVs will be recruited across the centres. These subjects will also be included in the safety analysis.

On the basis of a previous study (DP008-003), it is projected that evaluable results will be obtained for 80% of diseased individuals and 90% of HVs. After adjustment for losses, it is therefore expected that 150 subjects with movement disorders (with or without SDD) and 22 HVs will be needed to provide at least the minimum required number of evaluable subjects.

4.4. Imputation of Incomplete Data

Generally, missing values will not be substituted by estimated values but treated as missing in the statistical evaluation. Available data analysis will be applied to this study. All observed data from all subjects dosed in the study will be included in all listings, plots, summary tables, and statistical analyses when appropriate. Missing and incomplete data for AEs, medical/surgical history, prior and concomitant medication will be specifically imputed according to the following rules for analysis.

Adverse Event

- If onset date is completely missing, then onset date is set to date of IMP injection.
- If onset date's (year is present and month and day are missing) or (year and day are present and month is missing):
    - If year = year of IMP injection, then set onset month and day to month and day of IMP injection
    - If year < year of IMP injection, then set onset month and day to December 31st.
    - If year > year of IMP injection, then set onset month and day to January 1st.
- If onset date's month and year are present and day is missing:
    - If year=year of IMP injection and
        - If month = month of IMP injection then set day to day of IMP injection date
        - If month < month of IMP injection then set day to last day of month
        - If month > month of IMP injection then set day to 1st day of month
    - If year < year of IMP injection then set day to last day of month
    - If year > year of IMP injection then set day to 1st day of month
- For all other cases, set onset date to date of IMP injection
- If relationship to IMP is missing, AE will be reported separately and the relationship will be evaluated based on AE onset date compared with date of study procedures.
- If Intensity is missing, it will be imputed as Severe.

Medical and Surgical History

- If start date is completely missing then start date will not be imputed.
- If (start year is present and start month and start day are missing) or (start year and start day are present and start month is missing) then set start month and start day to January 1.
- If start year and start month are present and start day is missing then set start day to 1st day of month.
- If end date is completely missing then end date will not be imputed.

- If (end year is present and end month and end day are missing) or (end year and end day are present and end month is missing) then set end month and end day to December 31.
- If end year and end month are present and end day is missing then set end day to last day of the month.

Prior and Concomitant Medications

- If start date is completely missing then start date will not be imputed.
- If (start year is present and start month and start day are missing) or (start year and start day are present and start month is missing) then set start month and start day to January 1.
- If start year and start month are present and start day is missing then set start day to 1st day of month.
- If end date is completely missing then end date will not be imputed.
- If (end year is present and end month and end day are missing) or (end year and end day are present and end month is missing) then set end month and end day to December 31.
- If end year and end month are present and end day is missing then set end day to last day of the month.

4.5. Randomization

No randomization will take place in this open-label study.

4.6. Analysis Sets

The Enrolled population for this study includes all subjects enrolled, i.e., who meet the inclusion/exclusion criteria and are dosed with DaTSCAN™ ioflupane (^{123}I).

The following analysis sets will be used in the statistical analyses.

Full-analysis set (FAS): The efficacy analysis will be performed for the FAS, which will consist of all subjects who have both a DaTSCAN™ image set and a clinical diagnosis made by the investigator.

Per-protocol (PP) population: The PP population will include subjects in the FAS who comply with the following conditions:

- Meet the inclusion/exclusion criteria, and did not withdraw informed consent (if applicable)
- Have DaTSCAN™ image sets that are considered evaluable by at least 2 of the 3 blinded readers
- No major protocol violations

Safety population: All subjects who receive an injection of IMP will be included in the safety population.

For this study, efficacy analyses will be performed on both the FAS and PP populations, and safety analyses will be performed on the safety population.

5. SUBJECT DISPOSITION

5.1. Disposition

Subject disposition will be summarized for all screened and enrolled subjects and will include the number and percentage of subjects in the FAS, PP and safety populations, the number and percentage of subjects who have completed or discontinued the study, as well as reasons for withdrawal/ discontinuation.

Reasons for withdrawal/discontinuation will be collected on the CRF and will be summarized for subjects who withdrew/discontinued from study with the following categories:

- Adverse event
- Subject voluntarily withdrew consent
- Technical problems
- Lost to follow-up
- Investigator decision
- Death
- Other

5.2. Protocol Deviations/Violations

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the independent ethics committee and agreed to by the investigator. According to the protocol, doses administered outside of specific dose requirements or defined range must be reported as protocol deviations.

All protocol deviations (significant or not) will be reviewed by the study team and sponsor prior to the database lock, to identify major protocol deviations that would potentially exclude a subject from the PP population.

A by-subject listing of protocol deviations/violations in all subjects will be provided.

6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

6.1. Demographics

Baseline demographics will be summarized for all subjects in the safety population. Subjects' age (years), height (cm), weight (kg), and body mass index (kg/m^2) at screening will be summarized using descriptive statistics; gender, race, ethnicity, and level of education will be summarized by counts and percentages. Subject demographics will be presented in a listing.

6.2. Inclusion/Exclusion Criteria

The criteria number will be listed for screened subjects who did not satisfy the inclusion/exclusion criteria.

6.3. Baseline Characteristics

6.3.1. Medical History and Pregnancy Test

General medical/surgical history and neuropsychiatric history (including dementia history) will be presented in a data listing based on the safety population. A summary table by counts and percentages of medical/surgical history and neuropsychiatric history by system organ class (SOC) and preferred term (PT) will also be provided for all subjects in the safety population using version 22.0 or later of the Medical Dictionary for Regulatory Activities (MedDRA).

Pregnancy test information at the screening and imaging visits will be presented in a data listing for each female subject in the safety population. Descriptive statistics will be applied to summarize observed values for all subjects in the safety population.

6.3.2. DSM-5 Diagnostic and Neuropsychiatric Examination

Information on DSM-5 diagnostic and neuropsychiatric examinations (including Mini-Mental State Examination (MMSE), United Parkinson's Disease Rating Scale (UPDRS) Part III assessment, Hoehn and Yahr (H&Y) Scale for Parkinson's disease, and Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) for ET) will be presented in a data listing.

6.3.3. Clinical Diagnosis

The clinical diagnosis of PS (SDD; specifically, PD, MSA, or PSP) or no SDD (ET or healthy controls) as determined by the investigator at baseline for enrolled subjects will be summarized by counts and percentages in the disposition table and will be presented in a data listing.

7. TREATMENTS AND MEDICATIONS

7.1. Prior and Concomitant Medications

Any prior and concurrent therapy or medication (and the indication for the treatment) given to a subject from 28 days prior to screening visit and throughout the follow-up period after IMP administration will be recorded in EDC. If a medication ended before IMP administration, this medication will be categorized as prior medication; if a medication started or continued to be used after the time of IMP administration, it will be categorized as concomitant medication. All medications will be mapped to PTs according to the World Health Organization (WHO) drug dictionary September 1, 2018 or later. The number and percentage of all subjects in the safety population having prior medications or concomitant medications will be tabulated by Anatomical Therapeutic Chemical Code Level 3 classification system and WHO drug PT. At each level of summarization, a subject is counted only once if she/he reported one or more medication. Prior medications and procedures, concomitant medications, and concomitant procedures will be presented in by-subject listings. If the start or end date of concomitant medications is missing, it will be imputed as shown in Section 4.4.

7.2. Thyroid Blockade

The amount and type of medication used for thyroid blockade for each subject will be summarized for all subjects in the safety population. All thyroid-blocking treatment will be included and presented in prior and concomitant medication listings.

7.3. Study Treatments

Exposure to IMP will be summarized for all subjects in the safety population. The radioactivity (in megabecquerels) of the syringe before and after injection, volume (in millilitres) of IMP administered, total radioactivity (in megabecquerels), duration of injection (seconds), and saline flush volume (in millilitres) administered will be summarized using descriptive statistics. IMP administration information recorded in EDC will be presented in a listing.

7.4. Handling of Uninterpretable Images

The image interpretation by 3 independent readers (including 10% re-read assessments) will be presented in a data listing. The image will be classified as SDD if blinded image evaluation (BIE) readers assess the image as abnormal with typical or atypical SDD, and it will be classified as no SDD if BIE readers assess the image as normal. If BIE readers determine the image is technically not adequate for interpretation or abnormal but cannot be assigned to typical and atypical SDD, the image will be defined as an uninterpretable image. The number and proportion of images that are uninterpretable will be displayed in table for all subjects by reader in FAS.

7.5. Reader Difference

Subjects having DaTSCAN^{TM} assessment as SDD and no SDD will be categorized as SDD positive and negative, respectively. Intra-reader (within-reader) agreement of blinded visual image assessment will be measured by overall percentage agreement, which is calculated as the total number of subjects who have a consistent assessment on the two reads divided by the total number of all re-read subjects. This will be based on a random selection of 10% of the subjects having re-read images. An overall percentage agreement with an exact 95% confidence interval will be determined for each reader comparison and all readers for subjects with re-reads of images.

8. EFFICACY ANALYSIS

Efficacy analyses will be performed on both the FAS and PP populations defined in Section 4.6. Uninterpretable images will be excluded from the efficacy analysis. In cases where images are re-read, the result of the first read will be included in the efficacy analysis.

8.1. Primary Efficacy Analysis

The sensitivity and specificity of the blinded independent read of DaTSCAN™ SPECT images in detecting or excluding SDD, when the clinical diagnosis as established by the investigator is used as the standard of truth, will be summarized with both by-reader and majority-read analyses. Generally, True Positives (TP) include subjects with a clinical diagnosis of PS and having DatSCAN™ assessment as SDD positive. False Negatives (FN) include subjects with a clinical diagnosis of PS but having DatSCAN™ assessment as SDD negative. True negatives (TN) include subjects with a clinical diagnosis of ET or HV and having DatSCAN™ assessment as SDD negative. False Positives (FP) include subjects with a clinical diagnosis of ET or HV but having DatSCAN™ assessment as SDD positive. The efficacy will be measured by the following and presented by timepoint in the following summary tables:

- Sensitivity: Subjects with a clinical diagnosis of PS will be included. It will be defined as positive percentage agreement and calculated as the number of TP / (number of TP + number of FN): TP/(TP + FN), and a 2-sided 95% binomial confidence interval constructed around it.
- Specificity: Only subjects with a clinical diagnosis of ET will be included, which means that the HVs will be excluded from this analysis. It will be defined as negative percentage agreement and calculated as the number of TN / (number of TN + number of FP): TN/(TN + FP), and a 2-sided 95% binomial confidence interval constructed around it.
- Accuracy: Subjects with clinical diagnosis of PS, ET, and HV will be included. It will be calculated as overall percentage agreement and calculated as (TP + TN) / (TP + FN + TN + FP), and a 2-sided 95% binomial confidence interval constructed around it.

The two primary hypotheses and alternative hypotheses are:

- Sensitivity ≤ 85% vs Sensitivity >0.85
- Specificity ≤ 85% vs Specificity >0.85

The sensitivity will be successfully established for **a reader** if the lower bound of the 1-sided 95% confidence interval of the sensitivity for this reader is > 85%. The sensitivity will be successfully established **for the study**, only if the sensitivity is successfully established for at least two readers. The specificity will be similarly analyzed.

Additional sensitivity and specificity analyses will be performed based on the outcome from the majority read as supportive analyses. In these analyses, only data with valid majority outcomes will be included (i.e., records with a three-way tie will not be included in this analysis.).

8.2. Secondary Efficacy Analysis

A semi-quantitative analysis of the striatal uptake ratios in specific regions of interest (ROIs; including left and right striatum, caudate, and putamen) of DaTSCAN™ SPECT images will be performed with DaTQUANT™. To account for nonspecific binding, the DaTSCAN™ uptake in the ROI will be normalised to DaTSCAN™ uptake in the subject's occipital cortex. The normalised DaTSCAN™ uptake values for each ROI will be summarized with descriptive statistics for each category of subjects with SDD, ET, and HV. For all striatal uptake ratios, an analysis of variance (ANOVA) will be carried out to test for differences in the striatal uptake ratios among the clinical diagnosis groups. A by-subject listing of DaTSCAN™ uptake values for each ROI will be provided.

9. SAFETY ANALYSIS

Safety analyses will be performed on the safety population defined in Section 4.6. For each of the safety parameters, a summary statistic will be provided overall and by clinical diagnosis groups and no inferential testing will be performed.

9.1. Adverse Events

An AE is defined as any untoward medical occurrence or an already present event that worsens either in intensity or frequency. A DaTSCAN™-emergent AE, globally defined as treatment-emergent AE (TEAE), is defined as an AE that starts on or after the time of the injection of DaTSCAN™ until the follow-up visit at 3 (±1) days later regardless of its causal relationship to investigational agent, therefore it can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the exposure to the IMP, whether or not considered related to that product. A serious adverse event (SAE) is defined as any event that results in death, is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is another important medical event defined in protocol Section 10.3.5.1. Other significant AEs are defined as laboratory abnormalities that qualify as AEs (other than those meeting the definition for serious) and any events that lead to an intervention (including premature discontinuation of IMP, dose reduction, or significant additional concomitant therapy).

AE terms recorded by the clinical site will be mapped to SOC and PT using MedDRA version 22.0 or later. If the start date, end date, severity, or relationship of AE is missing, it will be imputed as shown in Section 4.4.

The following summaries of AEs by SOC and PT will be provided:

- All AEs
- All TEAEs
- All SAEs
- All treatment-emergent SAEs
- All TEAEs resulting in study treatment discontinuation
- All related TEAEs
- All related treatment-emergent SAEs
- All other significant AEs
- All TEAEs by intensity
- All treatment-emergent SAEs by intensity
- All most common AEs (defined as AEs reported by at least 5% of the subjects).

If a subject experiences the same AE more than once with different intensity (mild, moderate, and severe), then the event with the highest intensity will be tabulated in “by intensity” tables. If a subject experiences multiple TEAEs under the same PT (or SOC), then the subject will be counted only once for that PT (or SOC).

In summary tables, AEs are sorted by alphabetical order of SOC, and then descending frequencies of PT.

Data listings will be provided for all AEs. The incidence of deaths and the primary cause of death will be displayed in a listing.

9.2. Clinical Laboratory Evaluations

Haematology, serum biochemistry, and urinalysis results will be summarized with descriptive statistics at each time point. Numeric haematology and serum biochemistry results will be summarized by actual result and change from baseline. Summaries by timepoint will include data from scheduled assessments only.

The occurrence of 1 or more changes from baseline, at each post-administration time point, greater than 40% and 80% of the span of the normal limits (not applicable to qualitative parameters), will be summarized by counts and percentages for haematology and serum biochemistry tests for the overall safety population and for each diagnostic group subset.

A shift table representing the shift from baseline category (High, Normal, and Low) to each post-baseline visit for haematology and serum biochemistry tests will be provided by counts and percentages for the overall safety population and for each diagnostic group subset.

All laboratory results will be displayed in separate data listings.

9.3. Vital Sign

Vital sign measurements include systolic and diastolic blood pressure, and heart rate. Descriptive statistics of observations and changes from baseline in results for vital signs will be summarized by timepoint. Summaries by timepoint will include data from scheduled assessments only.

The occurrence of 1 or more changes from baseline, at each post-administration time point, greater than a pre-specified magnitude (20 mm Hg for systolic blood pressure, 10 mm Hg for diastolic blood pressure, 10 beats per minute for heart rate) will be summarized by counts and percentages for the overall safety population and for each diagnostic group subset.

Shifts from baseline during the treatment based on below, within, and above the normal ranges will be summarized by visit for the overall safety population and for each diagnostic group subset. Data from both scheduled and unscheduled assessments will be included for analysis of minimum and maximum post-baseline values in the shift table.

Vital Sign Parameter	Normal Range	
	Low	High
Systolic BP (mmHg)	85	139
Diastolic BP (mmHg)	60	89
Heart Rate (beats/minute)	60	100

Vital signs results at all time points will be displayed in a listing.

9.4. Physical Examination

Physical examination will include recording an assessment for the presence of abnormalities of the following: general appearance, lungs, cardiovascular system, and abdomen.

Descriptive statistics will be applied to summarize observed values at each time point. Shift table representing the shift from baseline status (Normal, Abnormal) to each post-administration time point will be prepared for the overall safety population and each diagnostic group subset.

Physical examination results will be displayed in a data listing.

9.5. Neurological Examination

Neurological examination will include recording an assessment for the presence of abnormalities of the following: level of consciousness, cranial nerves (II-XII), motor function, sensory function, proprioception/position sense of extremities, reflexes (biceps, triceps, patellar, ankle), mood and affect, cognitive function, cerebellar, speech, orientation, memory, and gait.

Descriptive statistics will be applied to summarize observed values at each time point. Shift table representing the shift from baseline status (Normal, Abnormal) to each post-administration time point will be prepared for the overall safety population and each diagnostic group subset.

Neurological examination results will be displayed in a data listing.

9.6. Injection Site Monitoring

Injection site findings will be summarized by time point for the overall safety population and each diagnostic group subset. Shift table representing the shift from baseline status (Normal, Abnormal) to each post-administration time point will be prepared as well for the overall safety population and each diagnostic group subset. All injection site monitoring results will be displayed in a data listing.

10. INTERIM ANALYSES

No formal interim analysis is planned in this study.

11. CHANGES TO THE PLANNED ANALYSIS

No changes to the statistical analyses section of the protocol are made in this SAP.

12. REFERENCES

GE Healthcare Ltd. and its Affiliates GE-001-024 Protocol Amendment A03: A multicentre, phase 3, clinical study to compare the striatal uptake of a dopamine transporter radioligand, DaTSCAN™ ioflupane (^{123}I) injection, after intravenous administration to Chinese patients with a diagnosis of Parkinson's disease, multiple system atrophy, progressive supranuclear palsy, or essential tremor and to healthy controls.

13. APPENDICES

13.1. Study Schedule of Events

	Screening Visit [a]	Treatment						
		Baseline Visit [a]	Imaging Visit					Follow-up
			Pre-injection			Post-injection		
	Within 28 days prior to imaging visit	Within 28 days prior to imaging visit	Within 1 to 4 hours prior to injection	Within 30 min prior to injection	0	10 min	3 to 6 hours	3 (±1) days [b]
Informed consent	X							
Subject number assignment	X							
Demographic information	X							
Inclusion/exclusion criteria	X	X	X					
Medical and surgical history	X							
Neuropsychiatric history (including dementia history)	X							
Neurological examination	X	X						X
Pregnancy test (if applicable)	X		X					
Prior and concomitant medication	X----------							----X
Laboratory tests [c]	X							X
Physical examination		X						X
Neuropsychiatric examination [d]	X	X						
Clinical diagnosis		X						
Vital signs (blood pressure, heart rate)	X			X			X	X
Thyroid blocking			X[e]				X[e]	
Injection site monitoring				X	X	X	X	
DaTSCAN™ injection					X			
SPECT imaging							X[f]	
Adverse events	X----------							----X

[a] The screening visit and baseline visit may be combined and conducted on the same day.
[b] Performed at 3 (±1) days after injection of DaTSCAN™
[c] Some tests will only be performed at screening
[d] Mini Mental State Examination, UPDRS-III, United Parkinson's Disease Rating Scale Part III; H&Y, Hoehn and Yahr and WHIGET assessment
[e] The dosage and timing of administration will be based on investigator's discretion according to local practice of each site (e.g., to be administered within 1 to 4 hours prior to and 12 to 24 hours after injection of DaTSCAN™ are just for reference)
[f] Performed 3 to 6 hours after injection of DaTSCAN™

SIGNATURE PAGE

Date / Name	Justification / Role
Signed By: [redacted] Date of signature: 21-Oct-2021 14:39:55 GMT+0000	Justification: Approved Role: Head of Biometrics
Signed By: [redacted] Date of signature: 21-Oct-2021 14:54:45 GMT+0000	Justification: Approved Role: Head of Clinical Development