Clinical Study Protocol **GE Healthcare**

GE-001-023

Title: A phase 1, nonrandomised, noncomparative, open-label study to assess the safety, biodistribution, and internal radiation dosimetry of a single dose of DaTSCAN™ ioflupane (^{123}I) injection in Chinese healthy volunteers

REVISED TO INCORPORATE AMENDMENT A02

Sponsor

GE Healthcare Ltd. and its Affiliates (hereinafter referred to as the "sponsor")

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Confidentiality Statement

Investigator's Signature Page

I have read this protocol and all associated case report forms and agree to conduct this study in full accordance with the stipulations of the protocol described herein.

Signature _____ Date _____

Print Name _____

1 SYNOPSIS

Name of Sponsor/Company: GE Healthcare Ltd. and its Affiliates **Name of Finished Product:** DaTSCAN™ **Name of Active Ingredient:** Ioflupane (^{123}I)	**Individual Study Table Referring to Part of Dossier in Which the Individual Study or Study Table is Presented:** **Volume:** **Reference:**	**(For National Authority Use Only)**

Title of Study: A phase 1, nonrandomised, noncomparative, open-label study to assess the safety, biodistribution, and internal radiation dosimetry of a single dose of DaTSCAN™ ioflupane (^{123}I) injection in Chinese healthy volunteers.

Protocol Number: GE-001-023

Investigators and Study Centre: This study will be conducted in a single study centre in the People's Republic of China

Phase of Development: Phase 1

Objectives:

Primary Objective:

- To evaluate the safety of a single dose of ioflupane (^{123}I) injection in Chinese healthy volunteers (HVs)

Secondary Objectives:

- To determine the biodistribution, internal radiation dosimetry, and effective dose (ED) of ioflupane (^{123}I) injection after intravenous (IV) administration in Chinese HVs.
- To compare biodistribution and dosimetry findings in this Chinese group with those previously established in European HVs.
- To compare brain single photon emission computed tomography (SPECT) imaging results in this Chinese group with those previously established in European HVs.

Study Design:

This is a phase 1, single-centre, single-group, nonrandomised, noncomparative, open-label, single-dose study to evaluate the safety, biodistribution, internal radiation dosimetry, and ED of DaTSCAN™ ioflupane (^{123}I) injection in Chinese HVs. Eight evaluable subjects (4 males and 4 females) will be included in the study.

The study will consist of a minimum of 3 visits for each subject. Each subject will attend a screening visit within 20 days before injection, an imaging visit, and a follow-up visit approximately 2 weeks after injection. During the screening visit, the subjects must satisfy all entry criteria and undergo safety assessments.

During the imaging visit, each subject will receive by bolus IV administration, a single dose of ioflupane (^{123}I) injection with a nominal ^{123}I activity of 111 MBq ± 10% and will undergo simultaneous whole-body (head to mid-thigh) anterior and posterior planar scintigraphy scans at 10 minutes, 1 hour, 2 hours, 4 hours, 5 hours, 24 hours, and 48 hours after administration. Brain SPECT imaging will be performed at 3 and 6 hours after administration. A reference source will be imaged alongside the subject. Time-activity curves will then be generated from ^{123}I activity data from all 8 subjects and integrated to obtain the normalised-cumulated activity in each source region, which will then be used along with the Medical Internal Radiation Dosimetry (MIRD) schema to determine the internal radiation dosimetry. The dosimetry will be evaluated for the Cristy-Eckerman female and hermaphrodite male phantoms.

For evaluation of the biodistribution and radiation dosimetry, blood (up to 5 mL) samples will be collected at 1 hour before administration of ioflupane (^{123}I) injection and at the following times after administration: 5, 15, 30 minutes and 1, 2, 3, 4, 5, 24, and 48 hours. Urine excreted from 1 hour before administration of ioflupane (^{123}I) injection to 48 hours after administration will be collected as voided.

At the follow-up visit, all subjects will undergo specified safety assessments, and all female subjects of childbearing potential will also have a urine pregnancy test.

All subjects' safety will be monitored during the course of the study. The safety analysis will include the following:

- Adverse events (AEs) up to study exit.

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- A tolerability questionnaire to be completed at approximately 1 hour before injection and at approximately 15 minutes, 1, 4, 24, 48 hours after injection.
- Physical examination at prespecified time points.
- Clinical laboratory tests (serum biochemistry, haematology, and urinalysis) at screening visit (which will be considered baseline), and at approximately 3 hours, 48 hours, and 2 weeks after injection.
- Injection site monitoring (at baseline, at approximately 1 hour before injection, and at approximately 4 hours after injection).
- Vital signs and oxygen saturation (at screening visit; at baseline; at approximately 1 hour before injection; and at approximately 10, 20, and 30 minutes; approximately 1, 2, 4, 24, and 48 hours; and approximately 2 weeks after injection).
- 12-lead electrocardiogram (ECG) (at screening visit, at approximately 1 hour before injection, and at approximately 2 and 5 hours after injection).
- Concomitant medications.

Selection of Subjects:
Inclusion Criteria:
To be included in this study, a subject will have to meet all of the following criteria:
(1) Chinese male or female who has agreed to sign and date the written informed consent form
(2) Age 18-70 years
(3) Body mass index (BMI) of 18-30 kg/m^2
(4) General good state of health as judged by a qualified physician after completing physical examination
(5) Fit, co-operative, and able to provide consent

Exclusion Criteria:
Subjects are to be excluded from this study if they meet any of the following criteria:
(1) Sensitivity to DaTSCAN™ ioflupane (^{123}I) injection or any of its ingredients
(2) A history of motor disturbances
(3) A history of pulmonary, cardiovascular, neurological, renal or hepatic, hormonal or coagulation disorders or hyperthyroidism
(4) A history of drug, alcohol, or solvent abuse
(5) The subject has been previously enrolled in this study or participated in a clinical study involving an investigational pharmaceutical product within 30 days prior to screening
(6) Radionuclide injection within a minimum of 5 radioactive half-lives prior to screening
(7) Use of any medication (except paracetamol [acetaminophen] or oral contraceptive), including traditional Chinese medicine, within 2 weeks prior to the imaging visit
(8) Classification as a radiation worker
(9) Women of child-bearing potential not accepting a highly effective method of birth control (A woman is considered of child-bearing potential, i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Postmenopausal is defined as 12 months with no menses without an alternative medical cause, in International Council on Harmonisation (ICH) M3 (R2); A highly effective method of birth control is defined as one which results in a low failure rate (i.e., less than 1 % per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence or vasectomised partner, in ICH M3 (R2).)
(10) Pregnant or lactating women

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Number of Subjects/Centres Planned: A total of 8 adult HVs (4 males and 4 females) at 1 centre

Treatment of Subjects:

- **Investigational Medicinal Product (IMP):** Each subject will receive a single administration of ioflupane (^{123}I) injection by bolus IV injection contralaterally to the sampling catheter. The nominal activity of ^{123}I should be 111 MBq ±10%, in a maximum volume of 5 mL.
- **Standard of Truth:** None.
- **Duration of Treatment:** The administration of ioflupane (^{123}I) injection will last for 15 to 20 seconds via injection into an arm vein, followed by whole body imaging, brain SPECT imaging, etc. The duration of the imaging visit will last approximately 48 hours after injection of IMP.

Safety and Biodistribution/Dosimetry Variables:

Safety Variables:

Primary Outcome Measures:

Safety variables will include monitoring of the following:

- Occurrence of AEs up to study exit
- Results of a tolerability questionnaire to be completed at prespecified time points
- Results of physical examinations at prespecified time points
- Results of clinical laboratory tests at prespecified time points
- Results of injection site monitoring at prespecified time points
- Results of vital signs (blood pressure, heart rate, body temperature, respiratory rate) and oxygen saturation at prespecified time points
- Results of ECG examinations at prespecified time points

Secondary Outcome Measures: Dosimetry estimates and cumulated activity by source region and by entire body (including whole blood, plasma, and excreted urine) at time points up to 48 hours after administration in HVs.

Biodistribution/Dosimetry:

Biodistribution data in HVs will consist of ^{123}I activity in organs and tissues of interest at multiple time points, ^{123}I activity in whole blood and plasma at multiple time points, and ^{123}I activity in voided urine. The ^{123}I activity in voided urine will be calculated as the product of the ^{123}I activity measured in each void multiplied by the volume of that void. The absorbed doses of radiation to organs and tissues will be evaluated for the Cristy-Eckerman female and hermaphrodite male phantoms. Descriptive statistics of absorbed doses to the target organs and tissues specified in the MIRD schema will be tabulated.

Imaging Variables:

Planar whole-body scanning will be performed serially at prespecified time points over a period of approximately 48 hours after administration (n=8 HVs). Brain SPECT imaging will be acquired at 3 and 6 hours after administration (n=8 HVs).

Statistical Methods and Planned Analysis:

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed with SAS® software. No confirmatory hypothesis testing is intended to be performed. *P*-values will be interpreted as a metric of uncertainty. All data will be listed by subject number and time point (if applicable). Confidence intervals, both individual and simultaneous, will be at the 95% confidence level unless otherwise noted. The last pre-administration observation will be used as the baseline value for calculating post-administration changes from baseline. Demographic and other baseline information will be summarised.

An overall summary of AEs will be presented, and they will be coded with Medical Dictionary for Regulatory Activities (MedDRA) and summarised by MedDRA system organ class and preferred term. Results of the following evaluations performed before and after DaTSCAN™ administration will be summarised with

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observed values and changes from baseline: physical examinations, 12-lead ECGs, vital signs (blood pressure, heart rate, respiratory rate, and body temperature) and oxygen saturation, injection site monitoring, and clinical laboratory evaluations (haematology, serum biochemistry, and urinalysis). Concomitant medications will be summarised. In addition, results of the tolerability questionnaire given after DaTSCAN™ administration will be summarised in descriptive statistics and boxplot.

Dosimetry estimates (using MIRD methods) and cumulated activity by source region and by entire body (including whole blood, plasma, and excreted urine) at time points up to 48 hours after administration will be summarised. The ED as calculated by using International Commission on Radiological Protection (ICRP) methods will be summarised. In addition, the following measures will be compared between the Chinese subjects from this study and European subjects: the normalised cumulative activity, absorbed doses, and ED. These measures will be compared by using the 2-sample t-test.

Striatal binding ratios (SBR) will be analysed to determine the stability of striatal uptake relative to a reference region over the proposed imaging window of 3 to 6 hours after administration. The difference between the SBR at 3 and 6 hours calculated for each subject will be tested by Wilcoxon signed-rank test.

Sample Size Estimates: No sample size calculations were performed. The sample size has been chosen to fulfil local regulatory requirements.

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2.1 Overall Table of Contents

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
BMI	Body mass index
CRF	Case report form
CRO	Contract research organisation
DAT	Dopaminergic transporter protein
ECG	Electrocardiogram
ED	Effective dose
EDC	Electronic data capture
GCP	Good Clinical Practice
β-hCG	Beta-human chorionic gonadotropin
HV	Healthy volunteer
IB	Investigator Brochure
ICH	International Council on Harmonisation
ICRP	International Commission on Radiological Protection
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional/Independent Review Board
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MIRD	Medical internal radiation dose
PS	Parkinsonian syndromes
ROI	Region of interest
SAE	Serious adverse event
SBR	Striatal binding ratios
SOP	Standard operating procedure
SPECT	Single photon emission computed tomography
TEAE	Treatment-emergent adverse event
VAS	Visual analogue scales
WBC	White blood cell

4 BACKGROUND INFORMATION

DaTSCAN™ ioflupane (^{123}I) injection—marketed as DaTscan™ (Ioflupane I 123 injection) in the United States—is a radiopharmaceutical for diagnostic use only. The active substance in DaTSCAN™ is ioflupane (^{123}I), which binds with high affinity to the presynaptic dopaminergic transporter protein (DAT, also known as the dopamine reuptake site).

DaTSCAN™ is approved in Europe, the United States, Hong Kong and Canada for detecting loss of functional dopaminergic neuron terminals in the striatum of patients with clinically uncertain Parkinsonian syndromes (PS), including Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. DaTSCAN™ is useful for differentiating PS from essential tremor.

In Europe, Singapore, Japan, and Mexico, DaTSCAN™ is also approved for use in adult patients to help differentiate probable dementia with Lewy bodies from Alzheimer’s disease. DaTSCAN™ is unable to discriminate between dementia with Lewy bodies and Parkinson’s disease dementia.

The current phase 1 study is intended to determine the safety, biodistribution, internal radiation dosimetry, and effective dose (ED) of DaTSCAN™ ioflupane (^{123}I) injection after intravenous (IV) administration in Chinese healthy volunteers (HVs). The results of this study will be compared with corresponding findings from the study of European HVs. The results of this study will be incorporated into a submission to regulatory authorities in the People's Republic of China.

5 STUDY OBJECTIVES AND PURPOSE

The primary and secondary objectives of the study are as follows:

Primary Objective

- To evaluate the safety of a single dose of ioflupane (^{123}I) injection in Chinese HVs.

Secondary Objectives

- To determine the biodistribution, internal radiation dosimetry, and ED of ioflupane (^{123}I) injection after IV administration in Chinese HVs.
- To compare biodistribution and dosimetry findings in this Chinese group with those previously established in European HVs.
- To compare brain single photon emission computed tomography (SPECT) imaging results in this Chinese group with those previously established in European HVs.

6 STUDY DESIGN

6.1 Overall Study Design and Plan

This is a phase 1, single-centre, single-group, nonrandomised, noncomparative, open-label, single-dose study to evaluate the safety, biodistribution, internal radiation dosimetry, and ED of DaTSCAN™ ioflupane (^{123}I) injection in Chinese HVs. Eight evaluable subjects (4 males and 4 females) will be included in the study. The study will be conducted at a single centre in the People's Republic of China.

The study will consist of a minimum of 3 visits for each subject. Each subject will attend a screening visit within 20 days before injection, an imaging visit, and a follow-up visit approximately 2 weeks after injection. During the screening visit, the subjects must satisfy all entry criteria and undergo safety assessments.

During the imaging visit, each subject will receive, by bolus IV administration, a single dose of ioflupane (^{123}I) injection with a nominal iodine (^{123}I) activity of 111 MBq ± 10% and will undergo simultaneous whole-body (head to mid-thigh) anterior and posterior planar scintigraphy scans at 10 minutes, 1 hour, 2 hours, 4 hours, 5 hours, 24 hours, and 48 hours after administration. Brain SPECT imaging will be performed at 3 and 6 hours after administration. A reference source will be imaged alongside the subject. Time-activity curves will then be generated from ^{123}I activity data from all 8 subjects and integrated to obtain the normalised-cumulated activity in each source region, which will then be used along with the Medical Internal Radiation Dosimetry (MIRD) schema to determine the internal radiation dosimetry. The dosimetry will be evaluated for the Cristy-Eckerman female and hermaphrodite male phantoms.

For evaluation of the biodistribution and radiation dosimetry, blood (up to 5 mL) samples will be collected at 1 hour before administration of ioflupane (^{123}I) injection and at the following times after administration of IMP: 5, 15, 30 minutes and 1, 2, 3, 4, 5, 24, and 48 hours. Urine excreted from 1 hour before administration of ioflupane (^{123}I) injection to 48 hours after administration will be collected as voided.

At the follow-up visit, all subjects will undergo specified safety assessments, and all female subjects of childbearing potential will also have a urine pregnancy test.

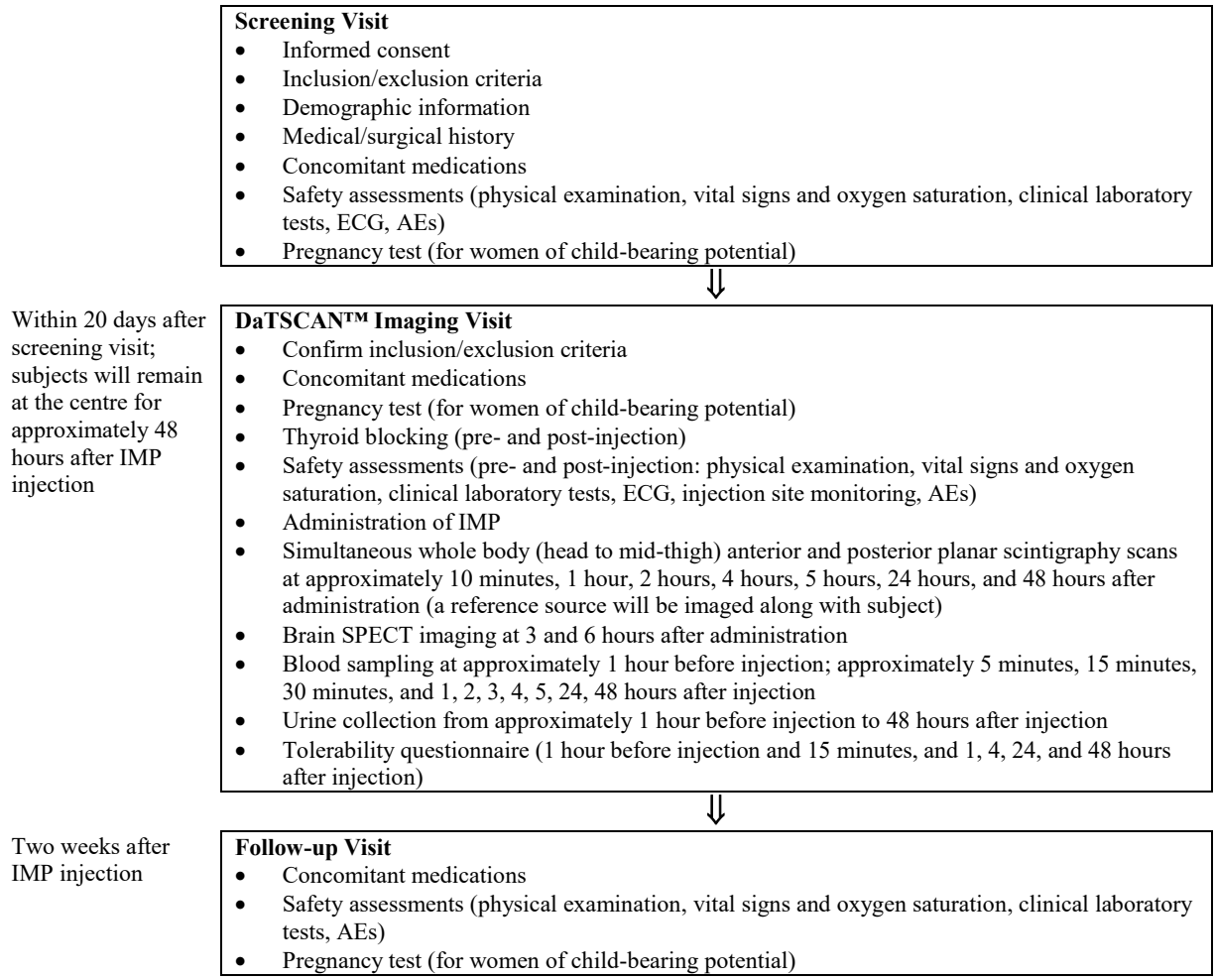
All subjects' safety will be monitored during the course of the study. The safety analysis will include the following:

- AEs up to study exit.
- A tolerability questionnaire to be completed at approximately 1 hour before injection and at approximately 15 minutes, 1, 4, 24, 48 hours after injection.
- Physical examination at prespecified time points.

- Clinical laboratory tests (serum biochemistry, haematology, and urinalysis) at screening visit (which will be considered baseline), and at approximately 3 hours, 48 hours, and 2 weeks after injection.
- Injection site monitoring (at baseline, at approximately 1 hour before injection, and at approximately 4 hours after injection).
- Vital signs and oxygen saturation (at screening visit; at baseline; at approximately 1 hour before injection; and at approximately 10, 20, and 30 minutes; approximately 1, 2, 4, 24, and 48 hours; and approximately 2 weeks after injection).
- 12-lead electrocardiogram (ECG) (at screening visit, at approximately 1 hour before injection, and at approximately 2 and 5 hours after injection).
- Concomitant medications.

An overview of study procedures is presented in Figure 1.

Figure 1 Study Diagram



6.2 Study Rationale

The quantity of ioflupane in the 5 mL formulation of DaTSCAN™ ioflupane (^{123}I) injection is 0.625 µg. The pharmacokinetics of DaTSCAN™ ioflupane (^{123}I) injection has been studied in healthy adults. Because administration is IV, absorption is complete and ioflupane (^{123}I) is completely bioavailable.

The pharmacokinetics of DaTSCAN™ ioflupane (^{123}I) injection were studied by monitoring radioactivity after IV injection. Similar studies have already been done to evaluate the pharmacokinetics of DaTSCAN™ ioflupane (^{123}I) injection in European subjects [Study CY 95.FP.1], [Frear 1998] and Japanese subjects (Study NMA98P1 [Takano et al 1999]). The current study will involve Chinese subjects.

In this study, anterior and posterior whole-body images will be obtained by using a 2-headed gamma camera at 10 minutes, 1 hour, 2 hours, 4 hours, 5 hours, 24 hours, and 48 hours after injection of DaTSCAN™. A dual-head scintillation camera, medium-energy collimator, and standard imaging techniques will be used. An external ^{123}I calibration source will be imaged alongside the subject.

Biodistribution of ^{123}I after administration of DaTSCAN™ will be measured by whole-body imaging in conjunction with serial blood and urine sampling. From regions of interest (ROIs) placed upon conjugate anterior and posterior whole-body images, the activities in the brain, striatum, thyroid, lungs, liver, spleen, stomach, heart, and intestines will be determined. The data will be used to calculate initial organ uptake, normalised cumulative activity, absorbed organ dose and the ED, according to the methodology of MIRD [Siegal et al 1999] and the International Commission on Radiological Protection (ICRP) [ICRP 1991].

6.2.1 Rationale for Administered Radioactivity

It is planned that the administered radioactivity will be 111 MBq ± 10%. This is less than the 111 to 185 MBq recommended for clinical DaTSCAN™ SPECT but is sufficient, according to previous experience, for planar imaging to determine biodistribution and dosimetry while minimising radiation exposure to HVs.

6.2.2 Rationale for Safety Monitoring Plan

Safety assessments will be performed at screening, before and after administration of IMP, and approximately 2 weeks after administration of IMP. The planned safety assessments are designed to ensure subject safety and to identify and minimise unnecessary risks.

This study's safety monitoring plan is justifiable and adequate from a safety standpoint in view of the following:

- The design of the safety plan permits a comparison of the safety variables at baseline (in this study baseline period is defined as "after the screening visit up to 1 hour prior to administration" except clinical laboratory tests, of which baseline value is that taken during

screening visit) and after IV injection of DaTSCAN™ ioflupane (^{123}I) injection in the same subject.

- Safety variables collected in the present study can be compared with safety variables from other related studies.

- The 2-week safety monitoring permits the evaluation of late-appearing adverse events (AEs) that may emerge or progress after the administration of DaTSCAN™ ioflupane (^{123}I) injection.

- Evaluation of the safety database held by the sponsor (which includes clinical study data as well as post marketing data in the United States and Europe) does not show any new safety signals that would require a modification of the safety assessments as planned.

- The measures used to assess safety are well defined and reliable, and the proposed safety analyses are adequate to assess the effects of the administration of ioflupane (^{123}I) injection in HVs.

6.3 Study Timeframe

The study is expected to begin enrolment in 2020. The start of the study is defined as the point at which all necessary regulatory and local approvals are in place, the study centre staff have been adequately trained, and the study centre has sufficient resources available to start enrolling subjects. The end of the study is defined as the date of last subject last visit.

Each subject's participation will consist of 3 study visits. The screening visit may take place up to 20 days before IMP injection. The imaging visit will last approximately 48 hours, followed by a follow-up visit approximately 2 weeks after IMP injection.

6.4 Risks and Benefits to Subjects

As is true for many phase 1 studies, there are no expected direct benefits to HVs who will be subjects in this trial. However, data collected from study participants may help others (especially patients) prospectively by contributing to a knowledge base for further evaluation of the use of DaTSCAN™ ioflupane (^{123}I) injection.

The risks to subjects mainly relate to the IV injection and the radiation emitted by the drug. From previous experience, IV injection is known to carry a small risk of infection and haematoma. This risk is not related to the IMP but to the procedure itself. IV lines will be placed and monitored by qualified personnel in order to minimise risk to the subjects.

DaTSCAN™ is a radiopharmaceutical. As such, it exposes the recipient to ionising radiation. However, previous studies have shown that the effective radiation dose is 21 to 24 µSv/MBq, so the dose for this procedure is approximately 2.7 mSv, which is slightly over the published annual ED equivalent from natural radiation in China [Ziquiang et al 1994]. As the product is a radiopharmaceutical intended for diagnostic use, evaluation of dosimetry estimates is

mandatory for a marketing authorisation. Therefore, administration of a radioactive dose is unavoidable. However, the dose chosen for this study is based on previous experience to ensure that useful images can be obtained while minimising the radiation exposure to the HV. Administration of a radioactive dose that would not yield useful evaluable images would be unethical.

7 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Procedures for Enrolment

The subjects will be recruited by means accepted by the respective regulatory bodies/local health authority (in accordance with local regulations) and the local Independent Ethics Committee (IEC).

A maximum of 8 evaluable subjects (HVs) will be enrolled. A written and dated informed consent form will be obtained from all subjects prior to any protocol specific procedures being performed.

Each potential subject will attend the clinical site for a screening visit within 20 days before IMP administration to ensure that they fulfil the study entry criteria. Each subject will be given a unique identification number. The identification number will be assigned to the subject during the screening visit, after the informed consent document has been signed and dated. Once an identification number has been assigned, it cannot be reassigned, even if the subject is deemed ineligible or withdraws consent. No subject may enter the study more than once.

Subjects withdrawing before IMP administration (i.e., a non-evaluable subject) will be replaced. Additional subjects may be enrolled to reach the required number of evaluable subjects within each step (see Section 6.1). Replacement subjects will be assigned unique subject numbers.

7.2 Inclusion Criteria

To be included in this study, a subject will have to meet all of the following criteria:

(1) Chinese male or female who has agreed to sign and date the written informed consent form

(2) Age 18-70 years

(3) Body mass index (BMI) of 18-30 kg/m^2

(4) General good state of health as judged by a qualified physician after completing physical examination

(5) Fit, co-operative, and able to provide consent

7.3 Exclusion Criteria

Subjects are to be excluded from this study if they meet any of the following criteria:

(1) Sensitivity to DaTSCAN™ ioflupane (^{123}I) injection or any of its ingredients

(2) A history of motor disturbances

(3) A history of pulmonary, cardiovascular, neurological, renal or hepatic, hormonal or coagulation disorders or hyperthyroidism

(4) A history of drug, alcohol, or solvent abuse

(5) The subject has been previously enrolled in this study or participated in a clinical study involving an investigational pharmaceutical product within 30 days prior to screening

(6) Radionuclide injection within a minimum of 5 radioactive half-lives prior to screening

(7) Use of any medication (except paracetamol [acetaminophen] or oral contraceptive), including traditional Chinese medicine, within 2 weeks prior to the imaging visit

(8) Classification as a radiation worker

(9) Women of child-bearing potential not accepting a highly effective method of birth control (A woman is considered of child-bearing potential, i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Postmenopausal is defined as 12 months with no menses without an alternative medical cause, in International Council on Harmonisation (ICH) M3 (R2); A highly effective method of birth control is defined as one which results in a low failure rate (i.e., less than 1 % per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence or vasectomised partner, in ICH M3 (R2).)

(10) Pregnant or lactating women

7.4 Withdrawal and Termination Criteria

7.4.1 Subject Withdrawal

There are no formal withdrawal criteria for this study. During the conduct of the study, the sponsor or its designee will review the safety data for trends and signals that would indicate the need for withdrawal of a subject.

In accordance with the Declaration of Helsinki, each subject is free to withdraw from the study at any time. Investigator(s) also have the right to withdraw subjects from the study in the event of illness, AEs, or other reasons concerning the health or well-being of the subject, or in the case of lack of co-operation.

Should a subject decide to withdraw after administration of the IMP, or should the investigator(s) decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final

evaluation at the time of the subject's withdrawal should be made and an explanation given of why the subject is withdrawing or being withdrawn from the study.

The reason for withdrawal must be noted in the Case Report Form (CRF). If the reason for withdrawal is an AE, the specific event or test result(s) must be recorded in the CRF. If the subject discontinues for a serious AE (SAE), such as hospitalization, the subject data will be collected and monitored until the outcome is evident. If the event has ended, the stop date of the event will be recorded in the CRF. If the event is still ongoing, the outcome of the event must be Ongoing or Not Yet Resolved. An outcome of Unknown is not acceptable, even if the event is ongoing on the date of study discontinuation.

Subjects who withdraw from the study before the study procedures are complete will be replaced.

7.4.2 Study or Site Termination

The sponsor reserves the right to terminate the study at any time.

8 TREATMENT OF SUBJECTS

8.1 Investigational Medicinal Product

8.1.1 DaTSCAN™ Ioflupane (^{123}I) Injection

DaTSCAN™ ioflupane (^{123}I) injection is a clear, colourless ethanolic solution for IV injection. It is provided in a 5-mL vial for our study.

The active ingredient in DaTSCAN™ ioflupane (^{123}I) injection is ioflupane (^{123}I). The 5.0 mL vial contains 370 MBq at reference time in 5.0 mL of solution. The radionuclidic purity is >99%. The radiochemical purity is ⩾96% [^{123}I]ioflupane at release, ⩾94% [^{123}I]ioflupane at expiry; ⩽4% [^{123}I]iodide at release, ⩽6% [^{123}I]iodide at expiry. The expiry time is 20 hours after the activity reference time stated on the label for the 5.0-mL presentation. Inactive ingredients include nonradioactive ioflupane (0.1 µg/mL), acetic acid (5.5 mg/mL), sodium acetate (7.8 mg/mL), ethanol (5% v/v), water for injection, to 5 mL.

Like other radiopharmaceuticals, DaTSCAN™ ioflupane (^{123}I) injection should be used only by qualified personnel with the appropriate government authorisation for the use and manipulation of radionuclides within a designated clinical setting. Appropriate radiation precautions should be observed during the preparation and storage of the agent. The product should be stored at room temperature and should never be frozen.

Handling of the material and spill clean-up and disposal will be performed in accordance with local regulations and local practice in the nuclear medicine department.

In this study, each subject will receive 1 dose of DaTSCAN™ ioflupane (^{123}I) injection. Each subject will receive a dose of 111 MBq ± 10%, 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.

8.1.2 Supply and Packaging

DaTSCAN™ ioflupane (^{123}I) injection is provided in a properly labelled, single-use 5-mL vial.

8.1.3 Stability and Storage

The IMP should be stored at room temperature (<25°C, no freezing). During both storage and dose preparation, appropriate radiation precautions should be observed.

8.1.4 Comparator

No comparator is to be used in this study.

8.1.5 Thyroid Blocking

To minimise thyroid uptake of radioactive iodine, subjects must undergo appropriate thyroid blocking, according to local practice, prior to and after administration of the IMP. For example, potassium iodide tablet (approximately 120 mg) or potassium iodide oral solution/Lugol's solution (equivalent to 100 mg iodide) or potassium perchlorate (400 mg) may be used for blockade of the thyroid gland, to be administered within 1 to 4 hours prior to and 12 to 24 hours after injection of DaTSCAN™.

The thyroid blocking agent will be preferably sourced locally by the hospital. If it is not available in the hospital, then sponsor/contract research organisation (CRO) should provide it. The administered time, date and dose will be captured on the concomitant medication page of CRF.

8.1.6 IMP Accountability

Each investigator is responsible for ensuring that deliveries of IMP(s) and other study materials from the sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with all applicable regulatory guidelines, and used in accordance with this protocol.

All IMP containers (opened, unopened, or empty) must be destroyed on site after IMP administration for each subject; the site has the option to use external destruction services if preferred. The overall drug accountability must be completed by the sponsor or representative. A list of IMP(s) and other materials that were destroyed, must be prepared and signed by the principal investigator or designee. If there are any discrepancies, an explanation for these should also be provided.

The current Investigator's Brochure for the IMP will be supplied to the site.

8.1.7 Registration of Investigational Medicinal Product Complaints

In the event of an IMP complaint (e.g., breakage, leakage, particulate matter, discoloration), the investigator or recipient of the IMP is requested to report the problem on the IMP shipping documentation (e.g., 'Delivery Note for Product', Drug Shipping and Receiving Form, or equivalent form). This report should be promptly forwarded to the person indicated on the shipping documentation. Once the report is received, the Clinical Supplies Manager will register the complaint and determine if the complaint is minor or significant, according to sponsor procedures. All complaints will be followed up, and the appropriate action will be implemented according to sponsor procedures.

8.2 Method of Numbering Subjects and Assigning Subjects to Treatment Groups

This is an open-label noncomparative study. Thus, there will be no randomisation or assignment to treatment groups. However, all subjects will be assigned a unique study number to protect their privacy.

8.3 Selection of Doses and Timing

In this study, each of the subjects will receive 1 dose of DaTSCAN™ ioflupane (^{123}I) injection. The subjects will receive a dose at the lower end of the approved dose range in Europe and the United States. The dose in this study will be 111 MBq ± 10%, in a maximum volume of 5 mL. This dose was used in the phase 1 study (CY95.FP.I) conducted in Europe.

The dose is to be delivered by slow bolus (15 to 20 seconds) IV injection; aseptic technique will be used during the administration.

8.4 Blinding

This is an open-label study. Therefore, there will be no blinding.

8.5 Concomitant Medications

Individuals who have taken any medication other than paracetamol (acetaminophen) or oral contraceptives within 2 weeks prior to the imaging visit are excluded from the study. Subjects will receive thyroid blocking agent according to local practice before and after administration of DaTSCAN™ ioflupane (^{123}I) injection (Section 8.1.5).

Any medications taken by the subject from screening to the end of follow-up visit will be recorded in the CRF along with the indication and dosage. Either the generic or the trade name may be recorded. The sponsor/CRO will encode all therapy and medication according to a current well-recognised dictionary of medical codes.

8.6 Treatment Compliance

The IMP will be administered by study personnel. Each administration volume and the total radioactivity injected will be checked and the vial code, dose, and volume per administration will be recorded in each subject's CRF. A dose administered outside of specific dose requirements or defined range must be reported as protocol deviations (see Section 13.3).

9 STUDY PROCEDURES

All measurements obtained during the course of the study are summarised in the Study Schedule of Events (Table 1).

Table 1 Study Schedule of Events

Variables	Screening Visit (≤20 days before IMP)	Imaging Visit																Follow-up Visit (2 weeks ±2 days)
		Before IMP Administration		IMP	After IMP Administration													
		Baseline (to –1 h)	-1 h (±10 min)	0	5 min (±2 min)	10 min (±5 min)	15 min (±2 min)	20 min (±5 min)	30 min (±5 min)	1 h (±10 min)	2 h (±10 min)	3 h (±10 min)	4 h (±10 min)	5 h (±10 min)	6 h (±10 min)	24 h (±2 h)	48 h (± 3 h)	
Informed consent	X																	
Entry criteria	X	X																
Demographic information	X																	
Medical/surgical history	X																	
Clinical laboratory tests	X											X[a]					X	X
Concomitant medications																		
Pregnancy test (for women of child-bearing potential)	X	X																X
Physical examination	X	X											X[b]					X
Vital signs and oxygen saturation	X	X	X			X		X	X	X	X		X			X	X	X
12-lead ECG	X		X[b]								X[b]			X[b]				
Thyroid blocking		X[f]			X[f]													
Injection site monitoring		X	X										X[b]					
DaTSCAN™ injection				X														
Planar Image acquisition						X[c]				X	X		X[d]	X[d]		X	X	
Brain SPECT imaging												X			X			
Blood sampling (biodistribution/ radiation dosimetry)			X		X		X		X	X	X	X	X	X		X	X	
Tolerability questionnaire			X				X[e]			X			X			X	X	
AE monitoring	All AEs and serious AEs (SAEs) will be recorded																	
Urine collection			Each urine voided approximately 1 hour before IMP administration to 48 hours after IMP administration will be collected															

Table 1 Study Schedule of Events

Variables	Screening Visit (≤20 days before IMP)	Imaging Visit															Follow-up Visit (2 weeks ±2 days)
		Before IMP Administration		IMP	After IMP Administration												
		Baseline (to –1 h)	-1 h (±10 min)	0	5 min (±2 min)	10 min (±5 min)	15 min (±2 min)	20 min (±5 min)	30 min (±5 min)	1 h (±10 min)	2 h (±10 min)	3 h (±10 min)	4 h (±10 min)	5 h (±10 min)	6 h (±10 min)	24 h (±2 h)	48 h (± 3 h)	

AE = adverse event; ECG = electrocardiogram; h = hours; min = minutes; shaded areas indicate continuous measurement or monitoring

[a] Time point window is ±1 hour.
[b] Time point window is ±30 minutes.
[c] Time point window is ±10 minutes.
[d] Time point window is ±20 minutes.
[e] Time point window is ±5 minutes.
[f] The dosage and timing of administration will be based on investigator's discretion according to local practice of the study centre (Section 8.1.5).

9.1 Screening Visit

The screening visit must take place within 20 days before IMP injection. At the screening visit, demographic information and concomitant medications will be recorded; clinical laboratory tests, vital signs and oxygen saturation, and a complete medical and surgical history will be taken; and a physical examination, including 12-lead ECG, will be performed. For women of child-bearing potential, a serum beta-human chorionic gonadotropin (β-hCG) test for pregnancy will be performed.

To be eligible for this study, subjects must satisfy all entry criteria (fulfil all of the inclusion criteria listed in Section 7.2 and none of the exclusion criteria listed in Section 7.3). A signed and dated informed consent form must be obtained from all subjects prior to their entering the study.

Waivers or protocol exceptions will not be granted prospectively by the sponsor under any circumstances. Any exceptions to protocol-specified requirements will be considered to be protocol deviations.

AE will be monitored after signed and dated informed consent is obtained.

9.2 Imaging Visit

The imaging visit must start within 20 days after the screening visit. This visit will last approximately 48 hours.

9.2.1 Before IMP Administration

During the baseline period (defined as “after the screening visit up to 1 hour prior to administration”), the following will be recorded/conducted:

- Confirm inclusion/exclusion criteria
- Concomitant medications recording
- Physical examination and injection site monitoring
- Vital signs and oxygen saturation
- Thyroid blocking (see Section 8.1.5)
- Urine β-hCG test for pregnancy (for women of child-bearing potential)
- AE monitoring

Subjects will avoid all food and drink (except water) for 2 hours before and 2.5 hours after injection of DaTSCAN™. Then, light meals and unlimited decaffeinated/noncarbonated drinks are permitted out to 6 hours after injection. After that, there are no food restrictions, but caffeinated/carbonated drinks are limited to 4 cups per 24-hour period.

For subject comfort and prior to IMP administration, subjects will be advised to empty their bladder, and if necessary, have a bowel movement prior to positioning on the scanner and the initial scan commencing.

For women of child-bearing potential, the urine β-hCG test for pregnancy will be performed. These subjects cannot participate in the study until the result of the urine β-hCG test is found to be negative.

At approximately 1 hour before injection of IMP, 12-lead ECG, and vital signs and oxygen saturation will be recorded, and a tolerability questionnaire filled out. Collection of urine will begin. A blood sample for biodistribution and radiation dosimetry will be collected. Two cannulas (or indwelling catheters) will be placed, one is in left/right arm/antecubital vein for blood sampling, the other is in contralateral side for IMP administration. The injection site will be examined for any abnormal findings prior to IMP administration.

9.2.2 IMP Administration

The IMP will be administered by bolus IV injection, injected slowly (15 to 20 seconds) into an arm vein under aseptic technique, contralaterally to the sampling catheter.

9.2.3 After IMP Administration

The following will be performed after IMP administration:

- 12-lead ECG will be performed at 2 hours (± 30 minutes) and 5 hours (± 30 minutes) after IMP administration.

- Blood (up to 5 mL) samples for biodistribution and radiation dosimetry will be collected at 5 minutes (± 2 minutes), 15 minutes (± 2 minutes), and 30 minutes (± 5 minutes) and at 1 hour (±10 minutes), 2 hours (± 10 minutes), 3 hours (± 10 minutes), 4 hours (± 10 minutes), 5 hours (± 10 minutes), 24 hours (± 2 hours), and 48 hours (± 3 hours) after IMP administration.

- Each urine excreted from approximately 1 hour before ioflupane (^{123}I) injection to 48 hours after ioflupane (^{123}I) injection will be collected as voided.

- Subjects will undergo simultaneous whole body (head to mid-thigh) anterior and posterior planar scintigraphy scans at 10 minutes (+ 10 minutes), 1 hour (± 10 minutes), 2 hours (± 10 minutes), 4 hours (± 20 minutes), 5 hours (± 20 minutes), 24 hours (± 2 hours), and 48 hours (± 3 hours) after IMP administration. A reference source will be imaged alongside the subject.

- Brain SPECT imaging will be performed at 3 hours (± 10 minutes) and 6 hours (± 10 minutes) after IMP administration.
- Physical examination and injection site monitoring will be performed at 4 hours (± 30 minutes) after IMP administration.
- Clinical laboratory test (blood and urine) samples will be obtained at 3 hours (±1 hour) and 48 hours (±3 hours) after IMP administration.
- Vital signs and oxygen saturation will be recorded at 10 minutes (± 5 minutes), 20 minutes (± 5 minutes), and 30 minutes (± 5 minutes) and at 1 hour (± 10 minutes), 2 hours (± 10 minutes), 4 hours (± 10 minutes), 24 hours (± 2 hours), and 48 hours (± 3 hours) hours after IMP administration.
- A tolerability questionnaire will be completed at 15 minutes (± 5 minutes) and 1 hour (± 10 minutes), 4 hour (± 10 minutes), 24 hours (± 2 hours), and 48 hours (± 3 hours) after IMP administration.
- Thyroid blocking (see Section 8.1.5)
- AE monitoring.
- Concomitant medications recording

See Study Schedule of Events (Table 1) for further details. Full details of the image protocol are presented in the GE-001-023 Imaging Manual.

9.3 Follow-up Visit

The follow-up visit will be conducted 2 weeks (± 2 days) after IMP administration. The following will be performed during this visit:

- Concomitant medications recording
- Physical examination
- Vital signs and oxygen saturation
- Clinical laboratory test (blood and urine)
- Urine β-hCG test for pregnancy (for women of child-bearing potential)
- AE monitoring

10 OUTCOME MEASURES

10.1 Primary Outcome Measures (Safety Variables)

The primary objective of this study is to evaluate the safety of a single dose of ioflupane (^{123}I) injection in Chinese HVs.

Safety variables will include monitoring of the following:

- Occurrence of AEs up to study exit
- Results of a tolerability questionnaire to be completed at prespecified time points
- Results of physical examinations at prespecified time points
- Results of clinical laboratory tests at prespecified time points
- Results of injection site monitoring at prespecified time points
- Results of vital signs (blood pressure, heart rate, body temperature, respiratory rate) and oxygen saturation at prespecified time points
- Results of ECG examinations at prespecified time points

Prespecified normal limits for vital signs, oxygen saturation and ECG intervals are provided in Section 15.3.

10.1.1 Clinical Laboratory Evaluation

Clinical laboratory parameters assessed in this study are displayed in Table 2.

Table 2 Clinical Laboratory Parameters

Serum Biochemistry	Haematology	Urinalysis
Alanine aminotransferase (ALAT)	C-reactive protein	Bilirubin
Albumin	Haematocrit	Glucose
Alkaline phosphatase	Haemoglobin	Ketone
Amylase	Red blood cell count	Occult blood
Aspartate aminotransferase (ASAT)	White blood cell count	pH
Bicarbonate	Platelet count	Protein
Bilirubin (total, direct, indirect)	Prothrombin time (PT)	Specific gravity
Calcium	Activated partial thromboplastin time (APTT)	Urobilinogen
Chloride	Thrombin time (TT)	
Creatine phosphokinase (total) (CPK)	Fibrinogen (FIB)	
Creatinine		
Gamma-glutamyltransferase (G-GT)		
Glucose		
Lactate dehydrogenase		
Phosphorous		
Potassium		
Protein (total)		
Sodium		
Urea nitrogen		
Uric acid		
Thyroid function (at screening and 48 hours after IMP administration)		

The signed and interpreted laboratory results will be kept together with the subject's CRF as supplemental pages, both centrally and at the site.

All blood samples will be processed and handled per standard laboratory procedures. All retained samples will be destroyed according to local practice at site.

Urine will be collected from approximately 1 hour before IMP administration to 48 hours after IMP administration, as described in Table 1. The time of void will be documented on the CRF. Urinalysis will be performed as described in Table 2. Urine voided will also be analysed for radioactivity.

Any abnormal laboratory findings that constitute an AE (e.g., any abnormal findings leading to an intervention other than repeating the laboratory test) should be reported as such and should be followed up until the outcome is known.

Additional diagnostic tests may be indicated to determine a more precise diagnosis of the subject's condition (e.g., ordering a white blood cell [WBC] differential to help characterise a high or low WBC count, or ordering a determination of red cell indices to help characterise a low haematocrit).

10.1.2 Vital Signs and Oxygen Saturation

Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) and oxygen saturation will be monitored before and after administration of IMP, according to the Study Schedule of Events, Table 1. Before vital signs and oxygen saturation are measured, the subject should rest for at least 5 minutes (if possible). The same position will be used each time vital signs and oxygen saturation are measured for a given subject.

10.1.3 Electrocardiograms

A standard 12-lead ECG will be performed at the various pre- and post-injection time points described in Table 1. All ECG recordings will be read at the investigational site.

Each 12-lead ECG examination will be evaluated by a licensed physician. A physician reading ECGs may make clinical management decisions as needed.

Reference range limits for 12-lead ECG intervals are provided in Section 15.3. Each 12-lead ECG tracing must be signed and dated.

Interpretation and follow-up of interval data outside of reference ranges and abnormal waveforms should be conducted in conjunction with the clinical situation of the subject.

Each 12-lead ECG examination result at each time point (all intervals, heart rate and interpretation, and identified with the subject's initials, subject's study number, and date and time of recording), will be retained in the investigator's study record for each subject. The investigator will not be expected to calculate QTc intervals.

10.1.4 Physical Examination

A qualified physician will conduct physical examinations at the time points indicated in Table 1. Where possible the same individual should conduct the physical examination at all required time points. The physical examination will include recording an assessment for the presence of abnormalities of the following: general appearance, skin, lungs, cardiovascular system, back and spine, abdomen, extremities, lymph nodes, and neurological exam.

In the event that *new* abnormal physical findings and *worsening* abnormal physical findings are encountered during the study, these terms are defined as follows: a new abnormal physical finding is defined as one that occurs when a subject's normal baseline physical examination becomes abnormal post baseline. A worsening abnormal physical finding is defined as one that occurs when a subject's abnormal baseline physical examination becomes worse post baseline.

10.1.5 Injection Site Monitoring

The injection site will be monitored at the times indicated in the Study Schedule of Events (Table 1).

Abnormal injection-site findings include, but are not limited to, radiopharmaceutical extravasation, bleeding, haematoma, redness, and infection. Abnormal injection site findings will be recorded as AEs in the CRF.

10.1.6 Tolerability Questionnaire Interview

Each subject is required to complete a tolerability questionnaire (see Appendix 15.4) at approximately 1 hour before injection and at approximately 15 minutes and 1, 4, 24, 48 hours after injection. The questionnaire evaluates subject mood, pain at injection site, itchiness of injection site, loss of function at injection site and quality of sleep using 100 mm visual analogue scales (VAS)* anchored by the following descriptors:

Mood	Bad – 0mm	Good – 100mm
Pain at Injection Site	Normal – 0mm	Painful – 100mm
Itchiness of Injection Site	Normal – 0mm	Itchy – 100mm
Loss of Function at Injection Site	Normal – 0mm	Loss of Function – 100mm
Quality of Sleep	Bad – 0mm	Good – 100mm

*Visual Analog Scale (VAS) is a continuous scale comprised of a horizontal line, usually 10 centimetres (100 mm) in length, anchored by 2 verbal descriptors: “0” stands for normal, and 100 mm stands for each symptom extreme, or “0” stands for bad, and 100 mm stands for good.

10.1.7 Adverse Events

All AEs/SAEs that occur after informed consent shall be recorded in the AE/SAE report form (see the Study Schedule of Events, Table 1).

Study personnel must remain vigilant for the occurrence of AEs, particularly those that may be life threatening. Personnel who are trained in the acute management of anaphylaxis and other emergencies and who have access to appropriate clinical supplies must be immediately available for no less than 60 minutes to observe for possible anaphylactoid reactions after dosing. Treatment of SAEs should be primarily supportive of vital functions.

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject which does not necessarily have to have a causal relationship with the IMP. AEs will be asked for from time of informed consent through the follow up visit at 2 weeks (± 2 days) after IMP administration.

A treatment-emergent AE (TEAE) is any unfavourable and unintended sign, symptom, or disease temporally associated with the use of DaTSCAN™, whether or not considered related to that product. Only symptoms/signs that begin or worsen in severity and/or frequency after DaTSCAN™-administration/use will be recorded as TEAEs in the CRF.

The subjects will be closely observed and questioned for any kind of AE during the study procedures and at follow-up appointments throughout the study period with non-leading questioning (e.g., "How do you feel?"). The subjects will be instructed to immediately report any symptoms and signs to the study staff.

Both the investigator(s) and sponsor/CRO will perform a causality assessment on any AE, to assess whether or not there is a reasonable possibility (evidence to suggest) that the IMP caused the event.

Causal relationship

Both the investigator(s) and sponsor/CRO will perform a causality assessment on any AE, to assess whether or not there is a reasonable possibility (evidence to suggest) that the IMP caused the event.

The relationship of an AE with DaTSCAN™ will be assessed and reported by the investigator as:

- Reasonably related to study drug ("Reasonable cause"): - A causal relationship between DaTSCAN™ and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
- Not reasonably related to study drug ("Not reasonable cause"): - A causal relationship between DaTSCAN™ and an AE is not a reasonable possibility.

Expectedness

All DaTSCAN™-emergent AEs will be assessed, by the sponsor (or CRO on behalf of the sponsor), as to whether they were expected to occur or unexpected, meaning not anticipated based on current knowledge found in the applicable safety information included in the reference safety information in the Investigator Brochure (IB) for DaTSCAN™.

Unexpected: An unexpected DaTSCAN™-emergent AE is a reaction, for which the nature, seriousness, severity or outcome is not consistent with the applicable safety information included in the IB.

Expected: An expected DaTSCAN™-emergent AE is a reaction which is consistent with the applicable safety information included in the IB.

Adverse Reaction: An AE that is caused by the IMP.

Suspected Adverse Reaction: A suspected adverse reaction is an AE where reasonable possibility exists for causality between DaTSCAN™ and the AE.

10.1.8 Serious Adverse Events

An SAE is defined as any AE that:

- Results in death.
- Is life threatening.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is another important medical event.*

(*Other important medical events are those that may not result in death, be life threatening, or require hospitalisation, but may be considered an SAE when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical intervention to prevent one of the outcomes listed above.)

10.1.9 Other Significant Adverse Events

Clinically notable results from vital signs, clinical laboratory, and injection site findings should be reported as AEs, where applicable.

10.1.10 Adverse Event and Serious Adverse Event Reporting

All AEs should be recorded by using acceptable diagnoses, if possible. If an AE has already been reported, it is not necessary to report each individual sign and symptom of that AE as a separate AE. For example, if myocardial infarction is reported as an AE, there is no need to report elevated creatine kinase and abnormal ECG or other related signs, symptoms, or laboratory values as separate AEs. However, if both occurred in isolation and myocardial infarction was not diagnosed, then each event would be reported as an AE.

The intensity of all AEs will be graded as mild, moderate, or severe by using the following definitions:

Mild:	Tolerable.
Moderate:	Interferes with normal activity.
Severe:	Incapacitating (causes inability to perform usual activity or work).

The investigator will be instructed to closely monitor each subject who experiences an AE (whether ascribed to the IMP or not) until the outcome of the AE has been determined.

In addition to the investigator's own description of the AEs, each AE will be encoded by the sponsor/CRO according to a well-recognised dictionary of medical codes.

SAEs will be recorded in the CRF if they occur as follows:

- After a subject first signed informed consent and throughout the subject's follow-up period*, whether or not considered related to the IMP, and
- After the subject's follow-up period, and for which a causal relationship to the IMP cannot be ruled out.

(*Follow-up period is defined as the protocol-stipulated period or, for subjects prematurely withdrawn from a study, the duration of a subject's participation.)

All serious and non-serious AEs must be followed for a final outcome until the end of the follow-up period. An outcome of "unknown" is not considered to be an acceptable final outcome. An outcome of "not yet resolved" is an acceptable final outcome for non-serious AEs at the end of a subject's participation in a study, and for SAEs at database lock.

The investigator will report all SAEs to local authorities, sponsor, and IECs/ Institutional/Independent Review Boards (IRBs) as required by local regulations, sponsor standard operating procedures (SOPs), and site-specific IECs/IRBs. The CRO (on behalf of the sponsor) will report all SAEs to local health authorities, IECs/IRBs and investigators as required by local regulations and sponsor/CRO SOPs.

Study centres are instructed to report all SAEs (including DaTSCAN™-emergent SAEs), together with a causality assessment, to the sponsor (or a service provider/CRO acting on behalf of the sponsor) within 24 hours.

All AEs and SAEs are reported in the AE form of the CRF. Detailed information about management of AE information will be provided, e.g., in a Safety Management Plan or equivalent document.

SAE information will be captured in electronic data capture (EDC). If the EDC system is unavailable, the Investigators must complete an SAE form in English and forward it by fax to PPD Pharmacovigilance via at SAE Fax: +44 1223 374 102, immediately (within 24 hours) of becoming aware of the event.

Refer to the current SAE Form and Guidelines for completing and submitting the SAE form.

Requests for additional information will be made via the CRO personnel at the site.

Suspected unexpected serious adverse (drug) reactions will be reported to regulatory authorities, investigators, and IECs/IRBs in accordance with applicable legal requirements and applicable sponsor SOPs.

10.1.11 Urgent Safety Measures

In accordance with the principles of Good Clinical Practice (GCP) as laid out in ICH E6, the investigator(s) has/have primary responsibility for assuring subject safety throughout the performance of study procedures. An urgent safety measure is defined as any measure which

an investigator may need to implement which is a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IEC/IRB approval/favourable opinion.

The investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical trial against any immediate hazards to their health or safety. However, the investigator must inform the sponsor/CRO within 24 hours of having taken such measures.

The sponsor in turn shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the licensing authority and the relevant IEC/IRB of the measures taken and the circumstances giving rise to those measures.

All urgent safety measures must be reported to the sponsor/CRO by using the SAE contact numbers listed in Section 10.1.1 within 24 hours of having to take such a measure(s). Such reports can be initiated by telephone but must be officially documented by the investigator (by email or fax) and must include details of what measures were taken and the circumstances giving rise to those measures.

10.1.12 Pregnancy Reporting

This process is aimed at ensuring the appropriate monitoring of the potential risk related to IMP exposure of pregnant women and/or foetuses as well as the risks associated with exposure of a father, regarding congenital abnormalities or birth defects in their offspring. It also ensures compliance with applicable international and local regulations.

The requirements are applicable to all subjects following exposure to IMP.

Female trial subjects: The trial subject must be advised by the investigator to inform him/her immediately if she suspects she may be pregnant believes that conception occurred within 30 days after IMP administration.

Male trial subjects: The trial subject must be advised by the investigator to inform him/her immediately if he suspects his partner became pregnant within 30 days after IMP administration.

When a trial subject reports a pregnancy (post-IMP administration) to the investigator, a pregnancy test should be arranged for the trial subject (or their partner) by the investigator within 7 days of the pregnancy being reported.

The investigator must inform the sponsor/CRO within 24 hours of receiving positive pregnancy test results using a copy of the relevant CRF page (demography or AE). The investigator should include an estimated date of conception when communicating with the sponsor/CRO, as follow-up after end of pregnancy is required.

A reported pregnancy will be followed to determine the outcome. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond

the estimated delivery date. Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for the procedure.

10.2 Secondary Outcome Measures

Dosimetry estimates and cumulated activity by source region and by entire body (including whole blood, plasma, and excreted urine) at time points up to 48 hours after administration in HVs.

10.2.1 Biodistribution

One of the secondary objectives of this study is to determine the biodistribution of ioflupane (^{123}I) injection after IV administration to Chinese HVs. Biodistribution data in HVs will consist of ^{123}I activity in organs and tissues of interest at multiple time points, ^{123}I activity in whole blood and plasma at multiple time points, and ^{123}I activity in voided urine. The ^{123}I activity in voided urine will be calculated as the product of the ^{123}I activity measured in each void multiplied by the volume of that void. The absorbed doses of radiation to organs and tissues will be evaluated for the Cristy-Eckerman female and hermaphrodite male phantoms [Cristy and Eckerman 1987]. Descriptive statistics of absorbed doses to the target organs and tissues specified in the MIRD schema will be tabulated.

Evaluation of radiation dosimetry outcome measures includes assessing the counts in ROIs from whole-body images, and the assay of radioactivity in whole blood, plasma, and urine.

This will enable the following:

- Estimation of whole-body retention of ^{123}I at each imaging time point post-injection
- Estimation of individual organ uptake, washout and retention of ^{123}I at each imaging time point post-injection
- Estimated clearance of administered ^{123}I in whole blood and plasma
- Estimation of elimination of ^{123}I in blood and urine
- Calculation of the absorbed radiation dose in target organs and tissues
- Calculation of ED

10.2.1.1 Image Acquisition

Whenever possible, images will be acquired at prespecified time points and without any interference in appropriate medical care; the latter will take priority. The sponsor will provide a detailed Imaging Manual to the site which contains a full description of planar and SPECT imaging procedures.

10.2.1.2 Radioactive Counts in Region of Interest and Biodistribution Measurements

In HVs, quantitative measurements of ^{123}I activity in ROIs (including, but not limited to, lungs, heart, liver, gallbladder, spleen, kidneys, gastrointestinal tract and urinary bladder) will be made at several time points post-injection. Time-activity curves will be generated and integrated to obtain the cumulated activity in each region, and these values will be used to determine the internal radiation dosimetry by using the MIRD schema [Siegal et al 1999].

The temporal variations of ^{123}I activity concentrations in whole blood and plasma and the rate and amount of ^{123}I activity excreted through the urinary pathway will be measured.

10.2.1.3 Counting of ^{123}I in Blood, Plasma, and Urine

Ioflupane ^{123}I activity in whole blood, plasma, and urine will be measured by using a gamma counter according to the working instructions at the site. Sample volumes will be adjusted to avoid counter saturation. For time points of blood and urine sampling, see Table 1. A full description of blood and urine collection procedures will be given in Imaging Manual.

(a) Whole Blood and Plasma Assays

For HVs, up to 5 mL venous blood samples will be taken at multiple time points to allow measurement of ^{123}I content in whole blood and plasma over time.

The maximum amount of blood taken for activity counting will be 55 mL for HVs.

The up to 5 mL sample is withdrawn from the subject to a labelled collection tube, and the time of sampling is noted. The times at which samples will be assayed after collection will be specified in the Imaging Manual provided by the sponsor. The time at which the blood sample is taken and the time at which the ^{123}I counting is started will be recorded in the radioactivity counting system, as will be the number of counts per specified time interval. The beginning of injection will be considered time zero.

Following removal of an aliquot of blood for whole-blood activity counting, the remaining blood will be centrifuged to obtain plasma. Immediately thereafter, an aliquot of the resulting supernatant (i.e., plasma) will be transferred with a fresh disposable pipette to a pre-labelled tube for activity counting. The time at which the blood sample is taken and the time of ^{123}I counting will be recorded in the CRF, as will be the number of counts per specified time interval in 0.5 mL plasma. The beginning of injection will be considered time zero.

(b) Urine Assays

Subjects will be asked to void from approximately 1 hour before IMP administration. Urine will be collected whenever voided up to a period of 48 hours post-administration. The total volume of the sample and the time of collection will be accurately recorded in the CRF.

Radioactivity in each urine sample should be recorded in the CRF together with the volume measured, the total urine volume, and the time of measurement. The beginning of injection will be considered time zero.

10.2.2 Assessment of Striatal Binding Ratio

Left and right striatal binding ratios (SBR) will be determined from brain SPECT images acquired at 3 and 6 hours after administration.

10.2.3 Standard of Truth, Comparator, or Reference Imaging

No standard of truth, comparator, or reference imaging will be used in this study.

10.2.4 Image Interpretation and Correlation with Standard of Truth

Images obtained will be analysed by using ROIs in order to quantify counts in the organs of interest at prespecified time points. There will be no standard of truth in this trial as it is not a trial to assess diagnostic efficacy.

10.2.5 Radiation Dosimetry

The calculation of radiation dosimetry will be done in accordance with the sponsor's SOP for radiation dosimetry studies, unless otherwise specified. For HV data, the absorbed doses per unit administered activity to organs and tissues will be estimated using the cumulated activities [Stabin et al 2005]. The ED per unit administered activity will be evaluated from this ensemble of absorbed dose data. A summary of the biodistribution and radiation dosimetry data will be presented in the clinical study report, and a full report produced by the sponsor.

10.2.6 Effective Dose

A secondary objective of this study is to determine the ED of ioflupane (^{123}I) injection after IV administration to Chinese HVs. The cumulative activities will be used to calculate the absorbed doses to organs and tissues per unit of administered activity [Stabin et al 2005]. The ED per unit of administered activity will be evaluated from this ensemble of absorbed dose data.

10.3 Other Variables

Demographic data (age/date of birth, weight, height, BMI, sex and race) will be collected during the screening visit. Data on the subject's medical and surgical history will be collected at the screening visit. Data on the subject's concomitant medications will be collected from the screening visit to follow-up visit.

11 DATA HANDLING AND QUALITY ASSURANCE

11.1 Completing and Signing Case Report Forms

For electronic CRFs, data will be entered by trained site personnel, Any errors should be corrected within the electronic system. The audit trail will record all changes made, the date and time of the correction, and the person correcting the error. The appropriate electronic signature will be provided.

11.2 Clinical Data Management

The sponsor or CRO will be responsible for the processing and quality control of the data. Data management will be carried out by the sponsor or CRO. The handling of data, including data quality control, will comply with all applicable regulatory guidelines.

11.3 Archiving

All study documentation at the investigator site and sponsor site will be archived in accordance with ICH E6-GCP and the sponsor/CRO's quality standards and SOPs.

12 STATISTICAL METHODS AND PLANNED ANALYSIS

The data will be analysed by the sponsor and/or designated CRO. Any data analysis carried out independently by the investigator should be submitted to the sponsor before publication or presentation.

The data will be summarised with respect to demographic and baseline characteristics, safety observations and measurements, biodistribution, and radiation dosimetry.

12.1 General Statistical Considerations

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed with SAS® software, Version 9.2 or higher. Descriptive statistics for continuous data in summary tables will include the number of subjects in the analysis (n), mean, standard deviation, median, and range (minimum, maximum). Descriptive statistics for categorical data in summary tables will include counts and percentages. The last observation prior to administration of IMP will be used as the baseline value for calculating changes from baseline after administration of IMP. All data obtained on the CRF and entered into the database will be provided in separate data listings showing individual subject values. The planning and reporting of statistical analysis will be carried out as described in the sponsor/CRO's SOPs governing clinical studies.

12.2 Populations for Analysis

All subjects who receive ioflupane (^{123}I) injection will be included in the safety analysis set.

Subjects who receive ioflupane (^{123}I) injection, undergo planar scintigraphy, have a complete set of images and complete blood sampling at prespecified timepoints will be included in the pharmacokinetic analysis set. Subjects who do not meet all of these criteria may be replaced.

12.3 Subject Demographics/Other Baseline Characteristics

A table will be provided with the following information:

- Number of subjects enrolled.
- Number of subjects included in the safety analysis.
- Number of subjects included in the pharmacokinetic analysis.
- Number of subjects withdrawn from the study and the reason for withdrawal.

Demographic information: Age, height, weight, and BMI will be summarised by using descriptive statistics. Sex and race will be summarised by counts and percentages.

Medical history will be summarised by counts and percentages.

12.4 Study Treatments

IMP information, including the duration of the injection, saline flush volume, radioactivity and volume in syringe prior to administration, and total radioactivity administered, will be summarised.

Any concomitant medication, including indication, given to a subject from 14 days prior to IMP administration throughout the follow-up visit at 2 weeks (± 2 days) after IMP administration, will be tabulated by counts and percentages using the World Health Organisation Drug Directory (WHO Drug), Version June 1, 2015 or later, and summarised by Anatomic Therapeutic Chemical Code Level 3 and preferred name.

12.5 Primary Analysis (Safety)

All safety data will be listed by subject number and time point (if applicable). No confirmatory hypothesis testing is intended to be performed. *P*-values will be interpreted as a metric of uncertainty. All data will be listed by subject number and time point (if applicable). Confidence intervals, both individual and simultaneous, will be at the 95% confidence level unless otherwise noted. The last pre-administration observation will be used as the baseline value for calculating post-administration changes from baseline.

An overall summary of AEs will be presented, and they will be coded with Medical Dictionary for Regulatory Activities (MedDRA) and summarised by MedDRA system organ class and preferred term.

Observations and changes from baseline in the results of the physical examination, vital signs and oxygen saturation, 12-lead ECG, and clinical laboratory evaluation (haematology, serum biochemistry, and urinalysis) will be summarised (see Table 1). Other safety measures that will be summarised including results of tolerability questionnaire and injection site monitoring, and concomitant medications.

12.5.1 Clinical Laboratory Evaluation

Descriptive statistics will be displayed for the observed values and changes from baseline. In addition, for each clinical laboratory variable and each time point, the following safety outcome measures will be summarised by counts and percentages:

- 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).

- The occurrence of post-administration values outside the normal limits (not applicable to qualitative parameters). Shift tables based on the normal range will be prepared.

12.5.2 Vital Signs and Oxygen Saturation

Descriptive statistics will be displayed for the observed values and changes from baseline. For each vital sign and oxygen saturation variable and each time point, the following safety outcome measures will be summarised by counts and percentages:

- 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/min for heart rate, 1.5°C for body temperature, 10 breaths/min for respiration rate, and 5% for oxygen saturation).

- The occurrence of post-administration values outside the normal limits (Section 15.3). Shift tables based on the normal range will be prepared.

12.5.3 Electrocardiograms

Descriptive statistics will be displayed for the observed values and changes from baseline. For each ECG variable and each time-point, the following safety outcome measures will be summarised by counts and percentages:

- The occurrence of 1 or more changes from baseline in the PR interval, at each post-administration time point, within pre-specified increments of 4 ms (<4, 4 to 8, >8 to 12, and >12 ms), 10 ms (<10, 10 to 20, and >20 ms) and 25 ms (<25, 25 to 50, and >50 ms).

- The occurrence of 1 or more changes from baseline in the QTc, QRS and RR interval at each post-administration time point within the following pre-specified increments: <30 ms, 30 to 60 ms, and >60 ms increments for QTc interval; <50 ms, 50 to 100 ms, and >100 ms increments for QRS interval; <250 ms, 250 to 500 ms, and >500 ms increments for RR interval.

- The occurrence of post-administration values outside the normal limits in the PR, QTc, QRS or RR interval (Section 15.3). Shift tables based on the normal range will be prepared.

Two correction formulae will be employed in analysing QTc data in an attempt to reduce the bias resulting from over- or under-correction:

- Bazett's: $QTcB = QT/\sqrt{RR}$

- Fridericia's: $QTcF = QT/\sqrt[3]{RR}$

ECGs for which the overall interpretation was abnormal will be summarised by counts and percentages at each post-administration time point.

12.5.4 Physical Examination

The number and percentage of subjects with changes in physical examination status from normal at baseline to abnormal at each post-administration time point (and vice versa) will be presented. Shift tables based on the normal range will be prepared.

12.5.5 Adverse Events

The number and percentage of subjects with 1 or more AEs will be summarised. Summaries will also be presented by AE intensity and judged relationship to IMP.

SAEs will be presented separately. TEAE will be presented separately.

Other significant AEs, will also be summarised.

12.5.6 Tolerability Questionnaire

The results of the tolerability questionnaire performed pre- and post-injection will be summarised. The boxplot of values over time will be plotted for each tolerability parameter.

12.5.7 Injection Site Monitoring

The findings of injection site monitoring pre- and post-injection will be summarised.

12.6 Secondary Analysis

12.6.1 Biodistribution

By using activity data from ROIs, data from the whole-body images, as well as activity data from serial blood and urine samples, descriptive statistics will be generated for biodistribution data (decay-corrected percentage administered activity per organ) at each time point for each organ and tissue of interest in HVs. Time-activity curves will then be generated from ^{123}I activity data from all 8 subjects and integrated to obtain the normalised-cumulated activity in each source region, which will be summarised with descriptive statistics. The amount of ^{123}I activity in plasma and excreted in urine will be calculated from the product of concentration of ^{123}I activity measured in each sample and the volume of each sample.

The cumulative amount of ^{123}I activity excreted in urine will be tabulated for each subject and summarised. In addition, the normalised cumulative activity in each source region will be compared between the Chinese subjects from this study and European subjects by using the 2-sample t-test.

SBR will be analysed to determine the stability of striatal uptake relative to a reference region over the proposed imaging window of 3 to 6 hours after administration. The difference

between the SBR at 3 and 6 hours calculated for each subject will be tested by Wilcoxon signed-rank test.

12.6.2 Radiation Dosimetry

Descriptive statistics of absorbed doses to the target organs and tissues specified in the MIRD schema will be tabulated. In addition, the absorbed doses to these target organs and tissues will be compared between the Chinese subjects from this study and European subjects by using the 2-sample t-test.

12.6.3 Effective Dose

ED will be calculated according to ICRP methodology of ICRP publication 60 [ICRP 1991]. In addition, the ED will be compared between the Chinese subjects from this study and European subjects by using the 2-sample t-test.

12.6.4 Statistical Hypothesis, Model, and Method of Analysis

No confirmatory hypothesis testing is intended to be performed in this study.

12.6.5 Handling of Missing Values/Censoring/Discontinuations

Missing values will not be substituted by estimated values but treated as missing in the statistical evaluation. All data from all subjects dosed in the study will be included in all listings, plots, summary tables, and statistical analyses when appropriate.

12.6.6 Supportive Analyses

No sensitivity analyses are currently planned in this study.

12.6.7 Handling of Uninterpretable Images

The number of images that are uninterpretable will be displayed in tables.

12.7 Interim Analysis

No interim analysis will be performed in this study.

12.8 Sample Size Calculation

No sample size calculations were performed. The number of subjects in this study was determined to fulfil local regulatory requirements.

12.9 Power for Analysis of Critical Secondary Variables

No power calculations were made on any secondary variables.

12.10 Procedures for Missing, Unused and Spurious Data

Missing values will not be substituted by estimated values but treated as missing in the statistical evaluation. All data from all subjects dosed in the study will be included in all listings, plots, summary tables, and statistical analyses when appropriate.

12.11 Rules for Excluding Subjects from Analysis

All dosed subjects with a complete set of images will be included in the analyses unless otherwise specified. The sponsor will make any decisions regarding whether any subjects or any individual values belonging to a subject will be excluded from the evaluations when the protocol violation is considered to have a negative impact on the scientific aspects and interpretation of the study results. Such judgments should be made in a blinded fashion before database lock and before any analyses have been performed. If the subject has received any IMP, all available safety data will be used. The reason(s) for any exclusion will be described in the report.

12.12 Procedures for Reporting Deviations from Original Statistical Plan

Any deviations from the statistical analysis outlined in this protocol will be described, and reasons for the deviations listed, in the final Clinical Study Report.

13 SPECIAL REQUIREMENTS AND PROCEDURES

13.1 Regulatory, Institutional and Ethical Review

Before starting this study, the protocol (authorised by the sponsor) will be submitted to the regulatory bodies/local health authorities (in accordance with local regulations) and to the IEC/IRB for evaluation. The protocol will also be signed by the principal investigator before submission to the IEC/IRB. The study will not start before the IEC/IRB gives written approval or a favourable opinion in accordance with ICH E6-GCP and all applicable regulatory bodies/local health authorities give approval or a favourable opinion as required.

No changes from the final approved (authorised) protocol will be initiated without the IEC's/IRB's prior written approval or favourable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the change involves only logistics or administration. The sponsor will authorise and the principal investigator(s) will sign the protocol amendment prior to submission to the IEC/IRB. Protocol amendments should be submitted to the IEC/IRB without delay. Any significant deviation from the protocol when no approved amendment exists will be regarded as a protocol violation and will be addressed as such during the reporting of the study.

13.2 Investigator's Responsibilities

13.2.1 Overall Responsibilities

The investigator(s) is/are responsible for conducting the study in full accordance with the Protocol and the Declaration of Helsinki, the *Good Clinical Practice: Consolidated Guideline*, approved by the ICH, and any applicable national and local laws and regulations. Information regarding any investigational centres participating in this study that cannot comply with these standards will be documented.

13.2.2 Subject Informed Consent

Written and oral information about the study in a language understandable by the subject will be given to all subjects. Each subject's willingness to participate in the study will be documented in a signed and dated informed consent form before any procedures or assessments are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained. It will also be explained to the subjects that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. The informed consent process will be documented in the subject's medical record and the investigator will sign, date, and time the informed consent form after the subject has signed, dated, and recorded the time. The investigator(s) will keep the original consent forms, and copies will be given to the subjects.

13.2.3 Direct Access to Source Data/Documents

The monitor(s), auditor(s), authorised personnel of the sponsor/CRO, health authority inspector(s) or their agents, and authorised members of IECs/IRBs will be given direct access to source data and documentation (e.g., medical charts/records, laboratory results, printouts, videotapes, etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements.

13.2.4 Confidentiality Regarding Study Subjects

The investigator(s) must assure that the privacy of the subjects, including their personal identity and all other personal medical information, will be maintained at all times. In CRFs and other documents or image material (including materials from all examinations) submitted to the sponsor/CRO, subjects will not be identified by their names, but by an identification code (e.g., study subject number).

Personal medical information may be scrutinised for the purpose of verifying data recorded in the CRF. This may be done by the monitor(s), properly authorised persons on behalf of the sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

13.3 Protocol Deviations

Any deviation from the protocol when no approved amendment exists must be documented as a protocol deviation and reported according to local requirements. If appropriate, corrective and preventative action must be implemented to avoid repetition. Protocol deviations and any potential impact on the study results will be discussed during the reporting of the study.

Waivers or protocol exceptions will not be granted prospectively by the sponsor under any circumstances.

13.4 Study Monitoring

Study monitoring will be performed in accordance with ICH E6-GCP, the sponsor/CRO SOPs, the protocol, and applicable local regulations.

13.5 Audit and Inspection

According to ICH E6-GCP, the sponsor or regulatory authorities may audit the investigational site. The sponsor’s Quality Assurance Unit, independent of the Clinical Research and Development Department, is responsible for auditing the study.

The investigator(s) must accept that regulatory authorities may conduct an inspection to verify compliance of the study with GCP.

13.6 Insurance

This study is covered under the sponsor's Liability Insurance Policy (under General Electric Insurance Company and/or a company designated by the study sponsor). A Certificate of Insurance and/or an information leaflet containing essential information about the insurance coverage can be provided upon request.

13.7 Publication Policy

The investigator and/or Institution shall have the right to publish the results of their work conducted under this protocol, subject to providing the sponsor with the opportunity to review the contents of any proposed abstract or publication concerning the work, including any results of the study, in advance of publication and if necessary to delay publication for a limited time not to exceed 60 days in order to protect the confidentiality or proprietary nature of any information contained therein. The sponsor will make every reasonable effort to consider and release each proposed publication within 30 days, or proposed abstract within 15 days, of submission.

14 REFERENCES

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Ziquiang P, Zhenyum H, Yin Y, Mingquiang G. Natural background radiation and population dose in China. Radioprotection 1994;29(1):69-80.

15 APPENDICES

15.1 Information on Investigational and Registered Products

The reference document for this study is the current version of the European Union Summary of Product Characteristics approved by the European Medicines Agency. The reference document provides up-to-date information on the efficacy and safety of the IMP and is used for assessing expectedness of Serious Adverse Drug Reactions, in order to determine regulatory reportability. An unexpected adverse drug reaction is a reaction for which the nature, seriousness, severity, or outcome is not consistent with the applicable product information.

15.2 Equipment Parameters

Please refer to the **Imaging Manual**.

15.3 Normal Limits for Vital Signs, Oxygen Saturation and ECG Intervals

Table 3 Criteria for Normal Limits for Vital Signs and Oxygen Saturation

	Normal Limits	
Vital Signs Parameter	**Low**	**High**
Systolic BP (mm Hg)	85	139
Diastolic BP (mm Hg)	60	89
Heart rate (beats/minute)	60	100
Respiration rate (breaths/minute)	12	22
Body Temperature	36.4°C 97.5°F	37.7°C 99.5°F
Oxygen saturation (%)	93	100

[a] Changes in body weight are evaluated by the investigator (without taking height into account) since BMI is not collected on the CRF.
[b] BMI is calculated and analysed retrospectively by the sponsor, at which time height is taken into account.

Table 4 Criteria for Normal Limits for ECGs

ECG Variable	Normal Limits (ms) Low	High
PR interval	120	200
QRS interval	50	100
RR interval	600	1000
QT interval (Sex not specified)	—	≤440
QTc interval[a] (Sex not specified)	—	≤440

[a] No lower boundary set for QTc.

15.4 Tolerability Questionnaire

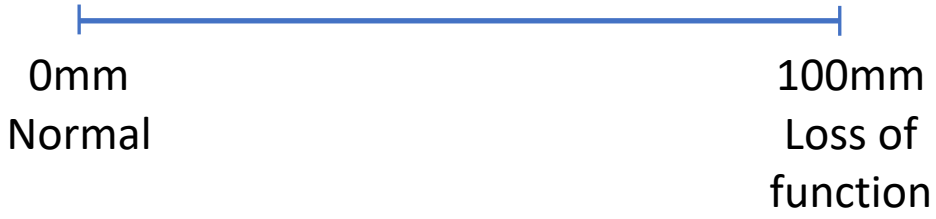
Before and after the administration of DaTSCAN™ Injection, please ask the subject to mark on the line below how he/she is feeling with a single line (not a cross), to record the status of mood, pain at injection site, itchiness of injection site, loss of function at injection site, and quality of sleep, using Visual Analog Scale (VAS) method*.

Mood:

Pain at Injection Site:

Itchiness of Injection Site:

Loss of Function at Injection Site



Quality of Sleep[#]:

*Visual Analog Scale (VAS) is a continuous scale comprised of a horizontal line, usually 10 centimetres (100 mm) in length, anchored by 2 verbal descriptors: "0" stands for normal, and 100 mm stands for each symptom extreme, or "0" stands for bad, and 100 mm stands for good.

[#] At -1h (± 10 min), assessment is based on how subject feels during past 2 weeks' sleep quality; At 15mins (± 5 min), 1h (± 10 min), 4h (± 10 min), assessments seem to be not applicable; At 24h (± 2 h), assessment is based on quality of first sleep after IMP injection; At 48h (± 3 h), assessment is based on quality of second sleep after IMP injection.

Tolerability Questionnaire Scoring Table

	Tolerability Questionnaire Timepoint[&]					
	-1h (± 10 min)	15min (± 5 min)	1h (± 10 min)	4h (± 10 min)	24h (± 2 h)	48h (± 3 h)
Mood						
Pain at Injection Site						
Itchiness of Injection Site						
Loss of Function at Injection Site						
Quality of Sleep						

h = hours, min = minutes
[&]15mins, 1h, 4h, 24h, 48h mean various timepoints post administration of IMP. -1h means 1 hour before the administration of IMP.

Scoring Implication

Mood	Bad – 0mm	Good – 100mm
Pain at Injection Site	Normal – 0mm	Painful – 100mm
Itchiness of Injection Site	Normal – 0mm	Itchy – 100mm
Loss of Function at Injection Site	Normal – 0mm	Loss of Function – 100mm
Quality of Sleep	Bad – 0mm	Good – 100mm

16 CLINICAL PROTOCOL AMENDMENT SUMMARIES

16.1 Amendment A01

16.1.1 Reasons for Amendment

The China Center for Drug Evaluation requested that GE Healthcare evaluate the Study GE-001-023 protocol according to the ICH E5 requirement. As a result, changes have been incorporated to provide better characterisation of DaTSCAN™ in the Chinese population. Furthermore, available data from the Takano study will be used for comparison between Chinese and Japanese subjects.

16.1.2 Summary of Key Changes

Addition:

- Results from SPECT imaging performed at 3 and 6 hours to support label wording of imaging at 3 to 6 hours after DaTSCAN™ administration.
- Exclusion criteria for radionucleotide injection within 2 weeks prior to the imaging visit.
- Exit visit 2 weeks (± 2 days) after DaTSCAN™ injection – Compliance of M3 (requirement for adequate follow-up for women of childbearing potential) and longer safety follow-up for all subjects.

Changed:

- Minimum age for subjects enrolled in the study changed from 40 to 50 years.

Deletion:

- Planar imaging at 3 hours to make way for SPECT imaging at 3 hours.
- Electroencephalogram, since this is not the first-in-man study, no abnormalities have been detected in the past, and there is no safety concern of epilepsy in European Union Summary of Product Characteristics.

16.2 Amendment A02

16.2.1 Reasons for Amendment

This Protocol Amendment is to provide further explanation and clarification to certain items in the protocol and to avoid potential ambiguity of interpretation. Meanwhile, some content was revised according to idiomatic expression.

16.2.2 Summary of Key Changes

Addition:

- Added content regarding the Tolerability Questionnaire Interview.
- Added serum biochemistry and haematology parameters.
- Added that TEAEs will be presented separately.

Changed:

- The GE Healthcare UK address and Medical Director details were updated.
- Updated the dose of “111 MBq” and “range from 100 to 122 MBq” to “111 MBq ± 10%”. The maximum volume was changed from 3 mL to 5 mL.
- Clarification of study visits included in the study and timing of events was provided throughout.
- Revised “abnormalities” with “tests” instead for clinical laboratory test; Remove “abnormalities” for physical examination and ECG, and added “results” for "physical examination", "clinical lab test", "Injection site monitoring", "vital signs" and "ECG".
- Revised “all urine” to “each urine” at the sentence of “All urine excreted from 1 hour before administration of ioflupane (^{123}I) injection to 48 hours after administration will be collected as voided.”
- Updated with information from the DaTSCAN™ IB and the study Imaging Manual, including removal of 2.5 mL DaTSCAN™ vials.
- Updated the enrolment start date from 2018 to 2020.
- Updated exclusion criteria to keep consistence with Study GE-001-024 and align with current standards.
- Updated handling of withdrawals for AEs.
- Updated thyroid blocking procedures.

- AE monitoring and reporting of AEs were updated.

Deletion:

- Removed inclusion of Japanese healthy volunteer data for comparison.
- Removed 5 mL of plasma samples.
- Removed prior medications and pre-treatment AEs.
- Removed age requirement that half of the subjects would be in the 50-70 years category.
- Removed the maximum blood volume for sample collection; removed “central laboratory”.

SIGNATURE PAGE

Date / Name	Justification / Role
Signed By: Shamsul Mohammed Alam Date of signature: 03-Feb-2020 21:18:57 GMT+0000	Justification: Approved Role: Head of Biometrics
Signed By: Francois Tranquart Date of signature: 04-Feb-2020 07:24:28 GMT+0000	Justification: Approved Role: Head of Clinical Development

This is a representation of an electronic record that was signed electronically in accordance with GxP guidelines and controls. The information above is a valid manifestation of the electronic signature(s) and is legally binding