Clinical Study Protocol **GE HealthCare**
GE-278-001

Title: An open-label multicenter Phase 2 dose-evaluation study of Altropane (^{123}I) Injection for striatal dopamine transporter visualization using SPECT brain imaging

REVISED TO INCORPORATE AMENDMENT A02

Sponsor

GE HealthCare Ltd. and its Affiliates (hereinafter referred to as the "Sponsor")

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GE HealthCare 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: Altropane (^{123}I) Injection
Name of Active Ingredient: [^{123}I]Altropane
Title of Study: An open-label multicenter Phase 2 dose-evaluation study of Altropane (^{123}I) Injection for striatal dopamine transporter visualization using SPECT brain imaging
Protocol Number: GE-278-001
Investigators and Study Centers: Up to 5 centers in the United States
Phase of Development: 2
Objectives: Note: Altropane (^{123}I) Injection is hereafter referred to as Altropane. **Primary Objective:** • To determine whether a 5-mCi dose of Altropane is acceptable for visualizing the right and left striata. **Secondary Objectives:** • To evaluate the safety of Altropane (using the endpoints adverse event [AE] and serious AE [SAE] frequency, and changes from baseline in vital signs, physical examination, electrocardiogram [ECG], and laboratory parameters).
Study Design: Altropane is a diagnostic radiopharmaceutical under development for striatal dopamine transporter (DAT) visualization using single photon emission computed tomography (SPECT) brain imaging, to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS). Data from a prior clinical study show that an 8-mCi (296-MBq) Altropane dose provides images of diagnostic quality in patients with suspected PS. This open-label Phase 2 dose evaluation study will determine if a 5-mCi (185-MBq) dose would also result in diagnostic-quality images. The study will evaluate a 5-mCi dose in up to 2 groups of subjects, in up to 2 parts. In Part 1, consenting subjects who have a DaTscan image showing normal striatal uptake and who have a consistent clinical diagnosis will be scheduled to undergo striatal SPECT with 5 mCi of Altropane administered intravenously. If the visual interpretation of the striatal images of these subjects is concluded not to be acceptable, then Part 2 will not be conducted, the study will end, and the 8-mCi dose will be selected for further clinical development. However, if the visual interpretation is acceptable, then the study will proceed to Part 2. In Part 2, consenting subjects who have a DaTscan image showing abnormal striatal uptake and who have a consistent clinical diagnosis (degenerative PS [dPS]) will be scheduled to undergo striatal SPECT with 5 mCi of Altropane administered intravenously. If the visual interpretation of the striatal images from the dPS subjects is not acceptable, then the 8-mCi dose will be selected. However, if the visual interpretation is acceptable, then the 5-mCi dose will be selected. At least 10 subjects with normal striatal uptake on DaTscan images will be recruited in Part 1. If Part 2 proceeds (dependent on the results of Part 1), then additionally at least 20 subjects with abnormal striata1 uptake on DaTscan images (dPS subjects) will be recruited. Thus, the total number of subjects will be at least 10, or, if Part 2 is conducted, at least 30. Altropane SPECT images will be acquired for 30 minutes starting 15 to 20 minutes after dosing. Safety will be monitored continuously throughout the study and at a 24-hour follow-up telephone call after Altropane imaging. The anticipated effective radiation dose of Altropane from a 5-mCi dose is 4.09 mSv. Visual interpretation of the Altropane SPECT images will be conducted by 5 independent expert readers who are blinded to each subject's clinical information, and who are not otherwise involved in the study. Their visual image interpretations will be a forced choice between *normal* (caudate and putamen fully visible on left and

Name of Sponsor/Company: GE HealthCare Ltd. and its Affiliates
Name of Finished Product: Altropane (^{123}I) Injection
Name of Active Ingredient: [^{123}I]Altropane
right, or with small insignificant defects) or *abnormal* (unilateral or bilateral reduced) striatal uptake. Readers will also evaluate their confidence in striatal visualization, rating it as *high*, *medium*, or *low*, and will assess image quality (as *excellent*, *good*, *fair*, *poor*, or *unevaluable*). [redacted] The dose selection decision will be based on consideration of all of the available data acquired within the study.
Selection of Subjects: **Inclusion Criteria:** Patients may be included in the study if they meet all of the following criteria: (1) For Part 1: a) the patient has a DaTscan image, obtained within 1 year (preferably within 6 months) before screening, that shows normal striatal uptake and b) the patient has a clinical diagnosis (made by a board-certified neurologist who is qualified by training and experience in the diagnosis of movement disorders) that is consistent with the DaTscan image. For Part 2 (if applicable): a) the patient has a DaTscan image, obtained within 1 year (preferably within 6 months) before screening, that shows abnormal (unilateral or bilateral reduced) striatal uptake and b) the patient also has a confirmed clinical diagnosis of a dPS (such as Parkinson's disease, multiple system atrophy, corticobasal degeneration, progressive supranuclear palsy, etc.) made by a board-certified neurologist who is qualified by training and experience in the diagnosis of movement disorders, and c) the diagnosis is consistent with the DaTscan image. (2) The patient is male or female, ≥18 years of age, of any race and ethnicity. (3) The patient is able and willing to comply with study procedures and signed and dated informed consent is obtained. (4) If the patient is a woman of childbearing potential*, she must use a highly effective method of contraception** from Screening until 30 days after the last administration of Altropane, and the results of a serum or urine human chorionic gonadotropin pregnancy test, performed at Screening and on the day of Altropane administration (with the result known before Altropane administration), must be negative. (5) If the patient is a male*** with a sexual partner who is a woman of childbearing potential*, he and his partner must use adequate contraception** from Screening until 30 days after the last administration of Altropane. * A woman of childbearing potential is neither post-menopausal nor surgically sterile. Post-menopausal means having had no menses for at least 12 months without an alternative medical cause. Surgically sterile means having had a documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy, or any combination of these. ** A highly effective method of contraception is one that has a failure rate of less than 1% per year when used consistently and correctly; such methods include combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device; intrauterine hormone-releasing system; bilateral tubal ligation/occlusion; vasectomized partner (with medical confirmation of success); and abstinence from heterosexual intercourse involving a woman of childbearing potential. *** A male is considered fertile after puberty unless permanently sterile by bilateral orchidectomy, or vasectomized with confirmation of success. **Exclusion Criteria:** Patients must be excluded from participating in this study if they meet any of the following criteria: (1) The patient was previously included in this study. (2) Fewer than 7 disintegration half-lives have elapsed between the patient's last procedure (therapeutic or diagnostic) involving a radioisotope and Visit 2 (altropane SPECT imaging).

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Name of Finished Product:

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Name of Active Ingredient:

[^{123}I]Altropane

(3) Including participation in this study, the patient's total exposure to radiation during medical procedures/tests in the past year would exceed 50 mSv.
(4) The patient has participated in an investigational drug or device clinical trial within 30 days before the date of informed consent.
(5) The patient has any clinically significant or unstable physical or psychological illness, structural brain abnormality, abnormal laboratory results, or abnormal ECG (based on medical history or physical examination at Screening), as determined by the Principal Investigator, that would interfere with study participation.
(6) The patient has any history of drug or alcohol abuse in the 2 years prior to the date of informed consent.
(7) The patient has a positive urine screen for drugs of abuse at Screening.
(8) The patient is a pregnant or breast-feeding female, or is a female of child-bearing potential that is not using appropriate birth control.
(9) The patient is unable to lie supine for 1 hour.
(10) The patient has any thyroid disease other than adequately treated hypothyroidism.
(11) The patient has known or suspected allergy/hypersensitivity to any ingredient in Altropane or to the thyroid blocking medication to be used before imaging.
(12) The patient is currently taking any of the medications/treatments listed in the Concomitant Medication List as disallowed and cannot or will not discontinue use at least 12 hours prior to SPECT exam.
(13) The patient was referred to DaTscan imaging for evaluation of possible cognitive impairment including dementia.

Number of Subjects/Centers Planned: At least 10 subjects with normal striatal uptake on DaTscan images will be recruited in Part 1. If Part 2 proceeds (dependent on the results of Part 1), then additionally at least 20 subjects with abnormal striatal uptake on DaTscan images (dPS subjects) will be recruited. Thus, the total number of subjects will be at least 10, or, if Part 2 is conducted, at least 30. Up to 5 centers in the United States will be utilized for the study.

Treatment of Subjects

Investigational Medicinal Product: Altropane (^{123}I) Injection (referred to as Altropane), 5 mCi, administered intravenously.

Control: None.

Adjunctive Drugs: Thyroid blocking medication will be administered orally at least 1 hour ± 15 minutes before administration of Altropane, unless institutional protocols dictate otherwise.

Duration of Treatment: The study will require 2 visits for each subject. Each subject will attend a screening visit (Visit 1) within 30 days before the SPECT visit (Visit 2). There will be a 24-hour safety follow-up phone call after Visit 2.

Efficacy and Safety Variables

Part 1:

Primary Efficacy Endpoint:

- Striatal visualization, reported as a forced choice of either *normal* (caudate and putamen fully visible on left and right, or with small insignificant defects) or *abnormal* (unilateral or bilateral reduced) striatal uptake.

Secondary Efficacy Endpoints

- Reader confidence in striatal visualization
- Reader assessment of image quality
- Inter-reader agreement

Name of Sponsor/Company:
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Secondary Safety Endpoints:

- Subjects reporting 1 or more AE
- Adverse drug reaction (ADR) frequency
- Changes from baseline in vital signs, physical examination, ECG, or laboratory parameters.

[redacted]

<u>Part 2 (if applicable)</u>:

Primary Efficacy Endpoint:

- Striatal visualization, reported as a forced choice of either *normal* (caudate and putamen fully visible on left and right, or with small insignificant defects) or *abnormal* (unilateral or bilateral reduced) striatal uptake

Secondary Efficacy Endpoints

- Reader confidence in striatal visualization
- Reader assessment of image quality
- Inter-reader agreement
- Intra-reader reproducibility (including the images from Part 1)

Secondary Safety Endpoints:

- Subjects reporting 1 or more AE
- ADR frequency
- Changes from baseline in vital signs, physical examination, ECG, or laboratory parameters

[redacted]

Statistical Methods and Planned Analysis:
Sample Size Calculation:
Based on prior experience with an approved DAT imaging agent (DaTscan), it is expected that the probability of a correct subject classification based on Altropane images will be 92% in Part 1 and 91% in Part 2 (if it is conducted).

In Part 1, 10 subjects with normal striatal uptake will be sufficient to determine whether or not the 5-mCi Altropane dose provides acceptable visualization of normal striatal uptake. Ten subjects with normal striatal uptake can achieve 62% power to detect whether the 5-mCi dose can result in a rate of correct subject classification of 70% or higher by a 1-sided exact test at a target significance level of 0.04. These results assume that the true rate of correct subject classification under the null hypothesis is 92% in Part 1.

If Part 2 proceeds, then 20 subjects with abnormal striatal uptake will be sufficient to determine whether or not to proceed with the 5-mCi dose in Phase 3. Twenty subjects with abnormal striatal uptake will have 76% power to detect whether the 5-mCi dose can result in a rate of correct subject classification of 75% or higher under the assumption that the true rate of correct subject classification is 91%.

Name of Sponsor/Company:

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Name of Finished Product:

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[^{123}I]Altropane

Analysis Populations:

The Safety Analysis Set is defined as all subjects who receive any amount of Altropane.

The Full Analysis Set is defined as all subjects who receive any amount of Altropane and have an Altropane image interpretation.

For Part 1 the dose-evaluation (efficacy) analysis will be based on the Full Analysis Set. For Part 2 (if conducted) the dose-evaluation (efficacy) will also be based on the Full Analysis Set.

Primary Efficacy Analyses:

- Number and percentage of correct classifications of 5-mCi Altropane images from subjects with normal striatal uptake (Part 1)
- Number and percentage of correct classifications of 5-mCi Altropane images from subjects with abnormal striatal uptake (Part 2, if applicable)

The correctness of image classification will be determined from the majority interpretation of the 5 expert blinded readers (at least 3 of 5 readers).

The 5-mCi dose will be considered to show acceptable striatal visualization if the percentage of correct majority classifications is greater than 70% in Part 1 and 75% in Part 2 (if applicable).

Secondary Efficacy Analyses:

Reader Assessment of Image Quality

- Number and percentage of Part 1 subjects with 5-mCi Altropane image quality judged as *excellent* or *good*
- Number and percentage of subjects in Part 2 (if applicable) with 5-mCi Altropane image quality judged as *excellent* or *good*

The quality will be graded as *excellent*, *good*, *fair*, *poor*, or *unevaluable*. The results of this secondary analysis will be considered consistent with the results of the primary analysis if the percentage of images with *excellent* or *good* majority ratings is greater than 70%.

Reader Confidence in Striatal Visualization

- Number and percentage of Part 1 subjects with *high* confidence ratings for their 5-mCi Altropane images
- Number and percentage of Part 2 subjects (if applicable) with *high* confidence ratings for their 5-mCi Altropane images

The confidence level will be graded as *high*, *medium*, or *low*. The results of this secondary analysis will be considered consistent with the results of the primary analysis if the percentage of images with *high* majority ratings of confidence is at least 70%.

Inter-Reader Agreement

- Number and percentage of images for which 5, 4, and 3 readers, respectively, are in agreement on the subject classification for Part 1, and, if applicable, Part 2.

Intra-Reader Reproducibility (Part 2 Only)

- Number and percentage of subjects for whom each reader's second image interpretation agrees with his/her first image interpretation.

If Part 2 is conducted, each reader will read all images (including the images from Part 1) at least twice to determine intra-reader reproducibility.

[redacted]

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Name of Finished Product: Altropane (^{123}I) Injection
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Secondary Safety Analyses: The following applies to Part 1, and, if conducted, to Part 2. Safety analyses will be performed for treatment-emergent AEs, treatment-emergent SAEs, ADRs, serious ADRs, vital signs, physical examination, ECG, and laboratory tests.

2 TABLE OF CONTENTS

2.1 Overall Table of Contents

Page Number

2.2 List of Tables

2.3 List of Figures

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation/Term	Definition
ADR	Adverse Drug Reaction
AE	Adverse event
Altropane (^{123}I) Injection	Drug product; referred to as Altropane in this protocol
BIE	Blinded Image Evaluation
BP	Blood pressure
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case report form
CRO	Contract research organization
DAT	Dopamine transporter
dPS	Degenerative Parkinsonian Syndrome(s)
ECG	Electrocardiogram
eCRF	Electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
hCG	Human chorionic gonadotropin
ICF	Informed consent form
ICH	International Council for Harmonisation (formerly International Conference on Harmonisation)
IMP	Investigational medicinal product
IRB	Institutional/Independent Review Board
IV	Intravenous
PD	Parkinson’s Disease
PS	Parkinsonian syndrome(s)
SAE	Serious adverse event
SBR	Striatal binding ratio
SOP	Standard operating procedure
SPECT	Single photon emission computed tomography
UTI	Urinary tract infection

4 BACKGROUND INFORMATION

Movement disorders are common in elderly adults, yet arriving at a specific diagnosis can be difficult even for movement disorder experts [Abdo et al. 2010]. A subgroup of movement disorders includes the Parkinsonian syndromes (PS; also called Parkinsonism), of which the most common type is Parkinson's disease (PD) [Abdo et al. 2010]. A PS is a clinical syndrome that includes bradykinesia in combination with rest tremor, rigidity, or both [Postuma et al. 2015]. PS are very common in people aged 65 and older, ranging from 15% in the 65-to-74 year age group to 52% in people aged 85 years and older [Bennett et al. 1996].

Some types of PS, such as PD, are neurodegenerative, i.e., they involve nigrostriatal neurodegeneration, an irreversible loss of dopaminergic nigrostriatal neurons, which is responsible for the symptoms and signs in these disorders [Fahn 2003]. In evaluating patients with suspected PS, it is therefore helpful to differentiate between neurodegenerative PS (PD, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, and others) and non-neurodegenerative PS and other movement disorders (drug-induced PS, psychogenic PS, mimics of PS [such as depression, obsessive slowness, spasticity, dystonic tremor, frozen shoulder, slowing due to normal aging, and catatonia], and essential tremor) [Abdo et al. 2010].

In neurodegenerative PS, the reduction in nigrostriatal neurons is accompanied by a reduction in the presynaptic membrane expression of the dopamine transporter (DAT) protein. DAT facilitates dopamine removal from the synapse and its re-uptake into presynaptic nerve endings. Along with the reduction in DAT, there is a decrease in dopamine concentration. Thus, DAT can be considered a surrogate marker for the integrity of the nigrostriatal neuron bundle [Bannon et al. 2005].

Based on evidence from human autopsies and a non-human primate model of PD, it is believed that a loss of at least 30% to 60% of nigrostriatal neurons must occur before symptoms begin [Bezard et al. 2001]. Once symptoms do begin, the degree of DAT loss is directly associated with the severity of symptoms [Ma et al. 1997].

The ability to visualize striatal DAT (or its loss) during life using diagnostic imaging is a valuable adjunct to clinical examination of patients with suspected Parkinsonian symptoms. The development of radiolabeled tropane derivatives with high binding affinity for the DAT, such as [^{123}I]ioflupane (also known as [^{123}I]FP-CIT and marketed as DaTscan® by GE HealthCare), [^{99m}Tc]TRODAT-1, [^{123}I]β-CIT, and [^{123}I]altropane, which act as functional tracers for DAT, make it possible to use single photon emission computed tomography (SPECT) imaging to visualize the distribution and density of nigrostriatal DAT [Brooks 2010] [Kung et al. 2007] [Marshall et al. 2009]. Indeed, DAT loss, as reflected by decreased striatal uptake of the radioligand, has been seen in the earliest clinical presentations of idiopathic PD and increases with the duration and severity of the disease [Chou et al. 2004] [Marshall and Grosset 2003].

Although DAT imaging does not distinguish PD from other neurodegenerative PS, a normal DAT SPECT image does rule out nigrostriatal degeneration as a cause of the patient's movement disorder. Thus, it would suggest an alternate diagnosis (such as essential tremor) that does not involve nigrostriatal neurodegeneration. Accurate diagnosis is important because

it affects disease management decisions. One meta-analysis showed that the use of [^{123}I]ioflupane for SPECT imaging of the DAT in suspected cases of PS led to a change in management for 54% of patients [Bega et al. 2021].

[^{123}I]β-CIT is a SPECT DAT imaging agent commonly used in clinical research. It has slow brain uptake kinetics and must be administered 24 hours before imaging [Bega et al. 2021]. [^{123}I]Ioflupane is the only DAT tracer currently approved for use in the European Union (where it is marketed as DaTSCAN) and in the United States and Canada (where it is marketed as DaTscan®). Its brain uptake kinetics are faster than those of [^{123}I]β-CIT, but it still must be administered 3 to 6 hours before imaging, limiting the timing and number of procedures at an imaging center. A tracer with even faster kinetics would be preferable for patient convenience and improved delivery of care.

One such tracer is Altropane (^{123}I) Injection (hereafter referred to as Altropane). It is being developed by GE HealthCare as a striatal SPECT imaging agent as an alternative to DaTscan. An important potential advantage of Altropane over DaTscan is the rapid uptake of the molecule resulting in significantly decreased time from injection to imaging (15 minutes with Altropane [Seibyl and Marek 2007] [Seibyl et al. 2008] vs. 3 to 6 hours with DaTscan [DaTscan Package Insert]). In addition, Altropane requires only 30 minutes of time in the scanner [Seibyl and Marek 2007] compared to the need to acquire 1.5 million counts for DaTscan (approximately 45 minutes) [DaTscan Package Insert].

To date, 10 clinical investigations of Altropane have been completed. These include 3 Phase 1 studies, 4 Phase 2 studies, and 3 Phase 3 studies (for more details, please refer to the Altropane Investigator's Brochure). These prior studies indicated that an 8-mCi dose of Altropane would be appropriate for clinical use. However, the question arose whether a 5-mCi dose (closer to the approved dose range of 3 to 5 mCi for DaTscan) would also be acceptable.

This is a dose-evaluation study to determine if a 5-mCi Altropane dose would be acceptable for subsequent clinical studies including a Phase 3 study. This study has 2 parts: Part 1, which will definitely be conducted, and Part 2, which will only be conducted if Part 1 shows the 5-mCi dose to be acceptable.

In Part 1, subjects with known normal striatal uptake on DaTscan images obtained within 1 year (preferably within 6 months) before study enrollment and who have a clinical diagnosis (made by a movement disorder expert) that is consistent with the DaTscan images will undergo striatal SPECT imaging following intravenous (IV) administration of 5 mCi of Altropane. In a blinded image evaluation (BIE), 5 trained expert blinded readers will interpret, in random order, the Altropane 5-mCi images collected in this study along with normal and abnormal 8-mCi Altropane images collected in prior studies; the 8-mCi images will be included to reduce the potential for bias if the blinded readers read only normal images. Endpoints that will be evaluated visually in the BIE are striatal visualization, reader confidence in striatal visualization, and image quality. Inter-reader agreement will be determined. The value of quantitative image data (striatal binding ratios [SBRs]) will be explored as well. If the 5-mCi dose of Altropane is found to be acceptable in Part 1, then Part 2 will be initiated; otherwise, the study will end after Part 1 and the 8-mCi dose will be selected for subsequent clinical studies. If Part 2 is conducted, then an additional endpoint will be intra-reader reproducibility.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

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

Primary:

- To determine whether a 5-mCi dose of Altropane is acceptable for visualizing the right and left striata.

The results will be used in deciding whether a 5-mCi or an 8-mCi dose will be recommended for subsequent clinical studies. The decision will be based first on whether a 5-mCi dose of Altropane is acceptable to visualize the striata in subjects with normal striatal uptake. If it is acceptable, then it will be additionally determined whether a 5-mCi dose of Altropane is acceptable to visualize the striata in subjects with abnormal striatal uptake (subjects with confirmed degenerative PS [dPS]).

Secondary:

- To evaluate the safety of Altropane (using the endpoints adverse event [AE] and serious AE [SAE] frequency, and changes from baseline in vital signs, physical examination, electrocardiogram [ECG], and laboratory parameters).

5.2 Study Endpoints

5.2.1 Study Endpoints for Part 1

5.2.1.1 Part 1 Primary Efficacy Endpoint

- Striatal visualization, reported as a forced choice of either *normal* (caudate and putamen fully visible on left and right, or with small insignificant defects) or *abnormal* (unilateral or bilateral reduced) striatal uptake.

5.2.1.2 Part 1 Secondary Efficacy Endpoints

- Reader confidence in striatal visualization
- Reader assessment of image quality
- Inter-reader agreement

5.2.1.3 Part 1 Secondary Safety Endpoints

- Subjects reporting 1 or more AE

- Adverse drug reaction (ADR) frequency
- Changes from baseline in vital signs, physical examination, ECG, or laboratory parameters

5.2.1.4 [redacted]

[redacted]

[redacted]

5.2.2 Study Endpoints for Part 2 (If applicable)

5.2.2.1 Part 2 Primary Efficacy Endpoint

- Striatal visualization, reported as a forced choice of either *normal* (caudate and putamen fully visible on left and right, or with small insignificant defects) or *abnormal* (unilateral or bilateral reduced) striatal uptake.

5.2.2.2 Part 2 Secondary Efficacy Endpoints

- Reader confidence in striatal visualization
- Reader assessment of image quality
- Inter-reader agreement
- Intra-reader reproducibility (including the images from Part 1)

5.2.2.3 Part 2 Secondary Safety Endpoints

- Subjects reporting 1 or more AE
- ADR frequency
- Changes from baseline in vital signs, physical examination, ECG, or laboratory parameters

5.2.2.4 [redacted]

[redacted]

[redacted]

6 STUDY DESIGN

6.1 Overall Study Design and Plan

Altropane is a diagnostic radiopharmaceutical under development for striatal DAT visualization using SPECT brain imaging, to assist in the evaluation of adult patients with suspected PS. Data from a prior clinical study show that an 8-mCi (296-MBq) Altropane dose provides images of diagnostic quality in patients with suspected PS. This open-label Phase 2 dose evaluation study will determine if a 5-mCi (185-MBq) dose would also result in diagnostic-quality images. The study will evaluate a 5-mCi dose in up to 2 groups of subjects, in up to 2 parts.

In Part 1, consenting subjects who have a DaTscan image showing normal striatal uptake and who have a consistent clinical diagnosis will be scheduled to undergo striatal SPECT with 5 mCi of Altropane administered intravenously. If the visual interpretation of the striatal images of these subjects is concluded not to be acceptable, then Part 2 will not be conducted, the study will end, and the 8-mCi dose will be selected for further clinical development. However, if the visual interpretation is acceptable, then the study will proceed to Part 2.

In Part 2, consenting subjects who have a DaTscan image showing abnormal striatal uptake and who have a consistent clinical diagnosis (dPS) will be scheduled to undergo striatal SPECT with 5 mCi of Altropane administered intravenously. If the visual interpretation of the striatal images from the dPS subjects is not acceptable, then the 8-mCi dose will be selected. However, if the visual interpretation is acceptable, then the 5-mCi dose will be selected. Figure 1 presents an overview of the 2-part study design and Figure 2 presents an overview of study procedures.

At least 10 subjects with normal striatal uptake on DaTscan images will be recruited in Part 1. If Part 2 proceeds (dependent on the results of Part 1), then additionally at least 20 subjects with abnormal striatal uptake on DaTscan images (dPS subjects) will be recruited. Thus, the total number of subjects will be at least 10, or, if Part 2 is conducted, at least 30. Up to 5 centers in the United States will be utilized for the study.

Altropane SPECT images will be acquired for 30 minutes starting 15 to 20 minutes after dosing. Safety will be monitored continuously throughout the study and at a 24-hour follow-up telephone call after Altropane imaging. The anticipated effective radiation dose of Altropane from a 5-mCi dose is 4.09 mSv.

Visual interpretation of the Altropane SPECT images will be conducted by 5 independent expert readers who are blinded to each subject's clinical information, and who are not otherwise involved in the study. Their visual image interpretations will be a forced choice between *normal* (caudate and putamen fully visible on left and right, or with small insignificant defects) or *abnormal* (unilateral or bilateral reduced) striatal uptake. Readers will also evaluate their confidence in striatal visualization, rating it as *high*, *medium*, or *low*, and will assess image quality (as *excellent*, *good*, *fair*, *poor*, or *unevaluable*).

[redacted]

The dose selection decision will be based on consideration of all of the available data acquired within the study.

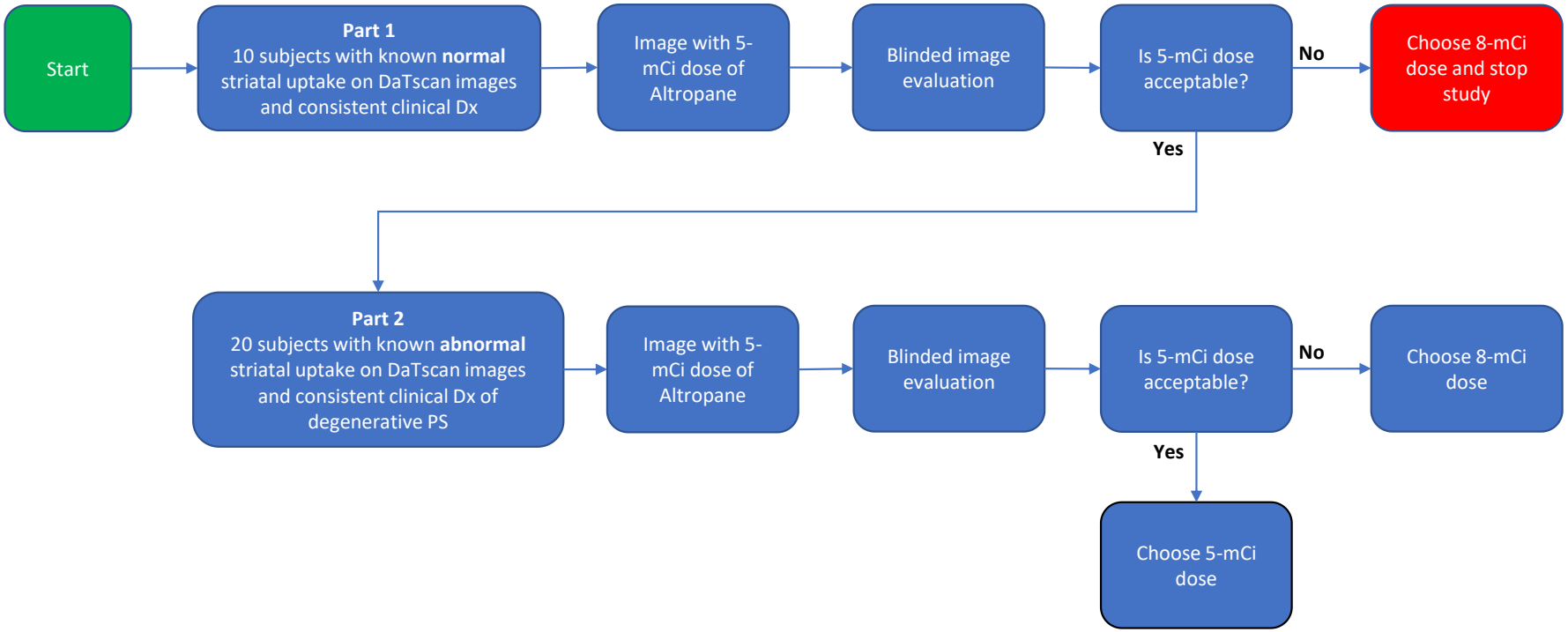

Figure 1 Overall 2-Part Study Diagram

Dx=diagnosis; PS = Parkinsonian syndrome
The conduct of Part 2 is dependent on the results of Part 1.

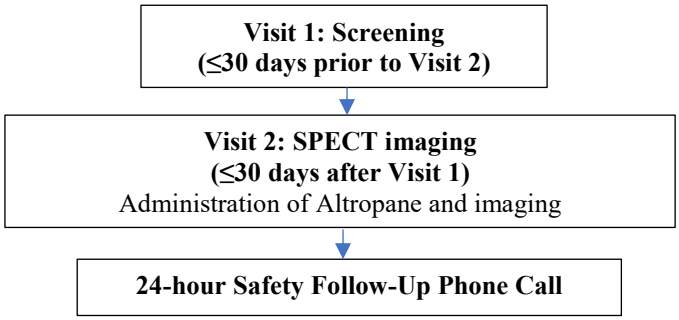

Figure 2 Subject Study Procedures

6.2 Scientific Rationale for Study Design

Altropane is an investigational DAT imaging agent that is under development for striatal DAT visualization using SPECT brain imaging to assist in the evaluation of adult patients with suspected PS. Its mechanism of action is similar to that of the approved agent DaTscan (ioflupane).

DAT imaging agents bind reversibly with high affinity to the DAT protein, which is present on presynaptic dopaminergic nigrostriatal neurons. Radioactive decay of the attached tracer (I 123 in the case of Altropane and ioflupane) releases photons that are suitable for imaging, allowing visualization of the striata.

Figure 3

In transaxial images, normal striatal DAT images are characterized by 2 symmetric comma- or crescent-shaped focal regions of activity mirrored about the median plane. Striatal activity is distinct relative to surrounding brain tissue. An example image, made using the DAT imaging agent DaTscan, is shown in Figure 4.

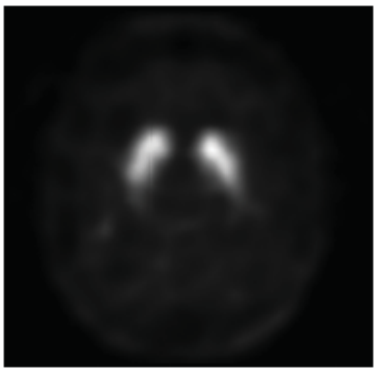

Figure 4 Normal DAT SPECT Image

Ref: [DaTscan Package Insert]

Degenerative forms of PS such as PD result in loss of neurons, and concomitant loss of the DAT, which reduces binding of DAT imaging agents. Therefore, DAT SPECT images show reduced or absent activity where it would normally be expected. Depending on the extent of loss of nigrostriatal neurons, abnormal images may show partial (Figure 5) to complete (Figure 6) loss of activity in the caudate and/or putamen.

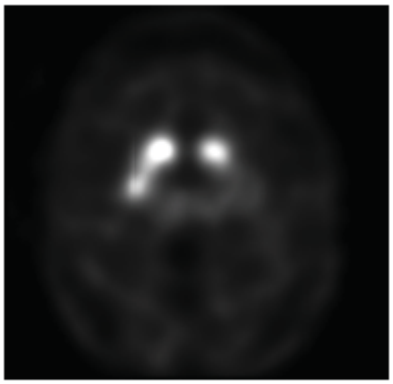

Figure 5 Partial Loss of Activity in Striata, with Greater Loss on the Left Side

Ref: [DaTscan Package Insert]

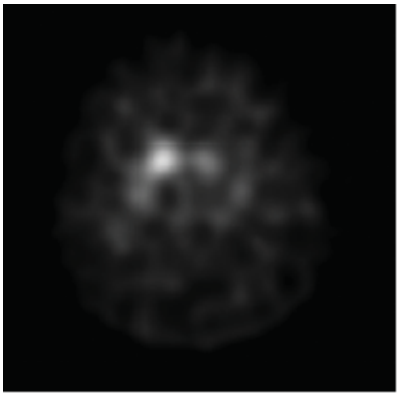

Figure 6 Complete Loss of Striatal Activity on the Left Side and Near Complete Loss on the Right Side

Ref: [DaTscan Package Insert]

From the above discussion, it should be evident that the dose of DAT imaging agent must be sufficient to completely visualize both striata when they are normal. Insufficient doses may result in incomplete visualization of either or both striata, which could result in a false-positive interpretation (i.e., apparent loss of activity in normal striatal uptake). Therefore, the first criterion for dose selection for a DAT imaging agent is acceptable visualization of normal striatal uptake.

The second criterion is that the dose is able to visualize abnormal striatal uptake when there is at least some remaining DAT density. However, disease management depends on the normal/abnormal interpretation and not on the degree of abnormality, so as long as the dose results in the correct image classification (normal or abnormal) it is less important that it be able to categorize degrees of abnormality at this time.

This study will evaluate a 5-mCi dose of Altropane for possible selection for Phase 3 instead of an 8-mCi dose. In accordance with the discussion above, it will first be determined (in Part 1) if a 5-mCi dose of Altropane results in acceptable visualization of normal striatal uptake. If it does not, then it would be unnecessary to test it in subjects with abnormal striatal uptake, in which case unnecessary exposure of subjects to radiation could be avoided.

To avoid potential bias from having readers interpret only (or mostly) normal 5-mCi images in Part 1, some normal and abnormal Altropane images previously collected with 8-mCi doses will be included in random order in the BIE, and will serve as active control data. It should be noted, however, that the 8-mCi images will be from different subjects, so a direct intra-subject comparison of the 5-mCi and 8-mCi images will not be possible in this study.

The design of this Phase 2 study supports the above aims and is consistent with standards typical for the study of a diagnostic imaging agent. The planned safety surveillance in this study is justifiable and adequate in view of the following:

- It permits within-subject comparison of safety variables pre- and post-administration of Altropane.

- It allows a comparison of this study's safety data set with similar data from other studies.
- The 24-hour follow-up for safety monitoring permits detection and evaluation of late-appearing (or late-progressing) AEs.
- The measures used to assess safety are well-defined and reliable, and the proposed safety analyses are adequate to assess the effects of Altropane.

6.3 Study Timeframe

The study is expected to begin enrollment in 2Q 2023. The expected duration of each subject's participation is up to approximately 32 days, with the precise duration dependent on the timing of the screening visit and the scheduling of study visits.

6.4 End of Study Definition

The end of the study is defined as the date of the last visit/follow-up contact of the last subject in the study.

6.5 Risks and Benefits to Subjects

All medical procedures carry some inherent risk. The known risks of Altropane administration include exposure to radiation, site injection effects (such as pain, redness, and or bruising), facial flushing, and headache. Other, as yet unknown, risks may be discovered with additional experience.

Of 573 subjects administered Altropane in previous clinical trials, 206 subjects (36%) experienced at least 1 treatment-emergent AE. AEs considered by the investigator to be related to study drug were reported for 79 subjects (14%). One related AE (blood pressure increased) was considered severe; all others were considered to be mild or moderate in intensity, and most resolved within 24 hours. Headache was the most common ADR and was reported by 14 subjects (2%).

Four SAEs occurred: balance disorder, myocardial infarction, urinary tract infection (UTI), and transient ischemic attack. Of these events, only the UTI (of moderate intensity) was judged by the investigator to be possibly treatment related. GE HealthCare is unaware of a plausible mechanism by which Altropane could cause a UTI. No SAE was fatal.

No clinically significant abnormalities in vital signs, laboratory parameters, ECG parameters, or physical or Mini-Mental State Examinations (MMSE®) were attributed to Altropane administration in previous clinical trials.

Altropane is a radiopharmaceutical product and is therefore radioactive, emitting gamma radiation. Appropriate safety measures should be used when handling Altropane to avoid

unnecessary radiation exposure to the subject, occupational workers, clinical personnel, and other persons. Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclides.

Altropane contains the iodine radioisotope ^{123}I; to prevent accumulation of ^{123}I by the thyroid, thyroid blocking medication should be administered at least 1 hour ± 15 minutes before administration of Altropane, unless institutional practice dictates otherwise.

It is recommended with the use of most radiopharmaceutical products to drink ample amounts of water and void frequently after the procedure and this is also recommended for Altropane.

Altropane is an investigational drug product, meaning that it has not been approved by the Food and Drug Administration (FDA) to treat or diagnose a disease or syndrome. There is no anticipated direct benefit to the study subject from Altropane administration other than the opportunity to assist future patients who may receive the product for diagnostic purposes if it is approved by the FDA.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of Altropane may be found in the Investigator's Brochure.

Nonclinical Safety Studies of Altropane

The nonclinical toxicology program included acute testing in rats and rabbits, single- and repeated-dose toxicity studies in Sprague Dawley rats, and 3 studies (including 2 *in vitro* studies and 1 *in vivo* study) designed to assess mutagenic potential. The non-radioactive form of the active ingredient of Altropane ([^{127}I]-E-IACFT) did not result in any acute effects in rats or rabbits at a dose of 51 ng/kg (a human equivalent dose at least 35-fold higher, based on relative body surface areas, than the highest dosage of [^{123}I]altropane considered for clinical use (9 mCi [approximately 16 ng]). In the 5-day repeated-dose study in rats, daily doses of 6 µg/kg [^{127}I]-E-IACFT for 5 consecutive days were well tolerated. This dosage, which is approximately 4000 times the highest dosage of Altropane considered for clinical use (9 mCi; 16 ng), can be considered a no-observed adverse effect level dose.

7 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Procedures for Enrollment

In Part 1, subjects with normal striatal uptake on prior DaTscan images will be recruited at each study center. Potentially eligible subjects will be asked by study personnel about their willingness to participate in this study.

Sites may identify subjects with abnormal striatal uptake (dPS subjects) for Part 2 but may not enroll them unless the decision is made by GE HealthCare to proceed with Part 2.

7.2 Inclusion Criteria

Patients may be included in the study if they meet all of the following criteria:

(1) For Part 1: a) the patient has a DaTscan image, obtained within 1 year (preferably within 6 months) before screening, that shows normal striatal uptake and b) the patient has a clinical diagnosis (made by a board-certified neurologist who is qualified by training and experience in the diagnosis of movement disorders) that is consistent with the DaTscan image.

For Part 2 (if applicable): a) the patient has a DaTscan image, obtained within 1 year (preferably within 6 months) before screening, that shows abnormal (unilateral or bilateral reduced) striatal uptake and b) the patient also has a confirmed clinical diagnosis of a dPS (such as Parkinson's disease, multiple system atrophy, corticobasal degeneration, progressive supranuclear palsy, etc.) made by a board-certified neurologist who is qualified by training and experience in the diagnosis of movement disorders, and c) the diagnosis is consistent with the DaTscan image.

(2) The patient is male or female, ≥18 years of age, of any race and ethnicity.

(3) The patient is able and willing to comply with study procedures and signed and dated informed consent is obtained.

(4) If the patient is a woman of childbearing potential*, she must use a highly effective method of contraception** from Screening until 30 days after the last administration of Altropane, and the results of a serum or urine human chorionic gonadotropin (hCG) pregnancy test, performed at Screening and on the day of Altropane administration (with the result known before Altropane administration), must be negative.

(5) If the patient is a male*** with a sexual partner who is a woman of childbearing potential*, he and his partner must use adequate contraception** from Screening until 30 days after the last administration of Altropane.

* A woman of childbearing potential is neither post-menopausal nor surgically sterile. Post-menopausal means having had no menses for at least 12 months without an alternative medical cause. Surgically sterile means having had a documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy, or any combination of these.

** A highly effective method of contraception is one that has a failure rate of less than 1% per year when used consistently and correctly; such methods include combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device; intrauterine hormone-releasing system; bilateral tubal ligation/occlusion; vasectomized partner (with medical confirmation of success); and abstinence from heterosexual intercourse involving a woman of childbearing potential.

*** A male is considered fertile after puberty unless permanently sterile by bilateral orchidectomy, or vasectomized with confirmation of success.

7.3 Exclusion Criteria

Patients must be excluded from participating in this study if they meet any of the following criteria:

(1) The patient was previously included in this study.

(2) Fewer than 7 disintegration half-lives have elapsed between the patient's last procedure (therapeutic or diagnostic) involving a radioisotope and Visit 2 (altropane SPECT imaging).

(3) Including participation in this study, the patient's total exposure to radiation during medical procedures/tests in the past year would exceed 50 mSv.

(4) The patient has participated in an investigational drug or device clinical trial within 30 days before the date of informed consent.

(5) The patient has any clinically significant or unstable physical or psychological illness, structural brain abnormality, abnormal laboratory results, or abnormal ECG (based on medical history or physical examination at Screening), as determined by the Principal Investigator, that would interfere with study participation.

(6) The patient has any history of drug or alcohol abuse in the 2 years prior to the date of informed consent.

(7) The patient has a positive urine screen for drugs of abuse at Screening.

(8) The patient is a pregnant or breast-feeding female, or is a female of child-bearing potential that is not using appropriate birth control.

(9) The patient is unable to lie supine for 1 hour.

(10) The patient has any thyroid disease other than adequately treated hypothyroidism.

(11) The patient has known or suspected allergy/hypersensitivity to any ingredient in Altropane or to the thyroid blocking medication to be used before imaging.

(12) The patient is currently taking any of the medications/treatments listed in the Concomitant Medication List (Table 1) as disallowed and cannot or will not discontinue use at least 12 hours prior to SPECT exam.

(13) The patient was referred to DaTscan imaging for evaluation of possible cognitive impairment including dementia.

7.4 Screen Failures

Screen failures are subjects who consent to participate in the clinical study but do not meet all inclusion and exclusion criteria within 30 days before Visit 2. Demographic and other data will be collected for all screen failures (see Section 9.1). Screen failures may be rescreened using their original screening number if there is a reasonable expectation that the reason(s) for the prior screen failure have resolved.

7.5 Withdrawal and Termination Criteria

7.5.1 Subject Withdrawal

There are no formal withdrawal criteria for this study. During the conduct of the study, the Sponsor and Investigator 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 investigational medicinal product (IMP; i.e., Altropane), 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 is being withdrawn from the study.

The reason for withdrawal must be noted in the electronic case report form (eCRF). If the reason for withdrawal is an AE, monitoring will continue until the outcome is evident. The specific event or test result(s) must be recorded in the eCRF.

To meet the study objectives, enrollment will continue to replace subjects who withdraw prior to completing SPECT scanning with Altropane.

7.5.2 Subject Lost to Follow-Up

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit/follow-up as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

- A subject will be considered lost to follow-up if he or she repeatedly fails to participate in scheduled follow-up and cannot be contacted by the study site. Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address [or local equivalent methods]). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

7.5.3 Study or Site Termination

There are no formal termination criteria for this study. The Sponsor reserves the right to terminate the study or any site at any time for any reason.

8 TREATMENT OF SUBJECTS

8.1 Investigational Medicinal Products

8.1.1 Investigational Medicinal Product: Altropane (^{123}I) Injection

Altropane, [^{123}I]-2β-carbomethoxy-3β-(4-fluorophenyl)-N-((E)-3-iodoallyl) nortropane (also known as [^{123}I]E-IACFT), will be provided as a sterile solution in a single-use vial as a formulation suitable for human IV administration. It contains excipients previously approved by the FDA for other IV products. Altropane is a clear, colorless solution. It should be stored at room temperature with appropriate radiation shielding.

The drug substance (Altropane) is made with no carrier added. The molecular formula is $C_{18}H_{21}FINO_2$. The anhydrous formula weight is 425 Da. The chemical mass of drug substance in a 5-mCi (185-MBq) dose is not more than 9 ng. The radioactive isotope of the drug substance, ^{123}I, emits a 159-keV gamma ray which is readily detected by suitable SPECT cameras. The radioisotope has a disintegration half-life of 13.2 hours.

Altropane will be manufactured and handled according to the applicable Good Manufacturing Practice at a qualified production facility. Before release, each batch of Altropane will be assessed by a number of quality control tests according to methods approved by the Sponsor. The batch produced must meet pre-specified criteria for color, clarity, radionuclidic identity and purity, radiochemical identity and purity, chemical purity, radioactive concentration, total vial radioactivity, pH, bacterial endotoxin level, and autoclave requirements. Results from sterility testing will not be available until after administration of Altropane. The final product will be formulated as a sterile solution for IV injection. All manufacturing, quality control testing, and documentation will be controlled and documented by the responsible person at the production site.

Altropane is currently classified as a Schedule II controlled substance. The institution and/or relevant personnel must have a current Drug Enforcement Administration license for handling Schedule II substances. The site must also comply with the relevant FDA regulation (21 CFR 312.69), which states, in part:

> "The investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution."

Additional details of the chemical and pharmaceutical properties and formulation are described in the current Investigator's Brochure. Sites will be provided with the Investigator's Brochure for Altropane.

Administration of Altropane

Altropane is a clear, colorless solution. When possible, the solution should be inspected visually for particulate matter and discoloration and not administered if either are seen.

For administration of Altropane, access into a large peripheral vein (e.g., antecubital vein) should be established using a suitable IV catheter (22 gauge or larger diameter). To avoid extravasation of Altropane, correct localization of the catheter must be ensured by a test injection of normal saline prior to Altropane injection.

Each subject will receive a single IV administration of 5 mCi (185 MBq) Altropane. The exact radioactive dose administered must be determined by calculating the difference between the radioactivity in the syringe and delivery system immediately before and after injection. After the dose is delivered, the syringe will be filled with a volume of saline equal to the administered dose volume and the syringe will be recounted under the same conditions as used to determine the dose; separately, the delivery system will be placed in a suitably sized plastic container and counted in the dose calibrator using the same parameters used for the dose. Measured radioactivity values, times of measurement, and total injected volume will be documented in the source documents and recorded in the eCRF.

8.1.2 Comparator

There is no direct comparator in this study.

8.1.3 Adjunctive Product: Thyroid Blocking Medication

Thyroid blocking medication (e.g., potassium iodide) will be administered orally at least 1 hour ± 15 minutes before administration of Altropane, unless institutional protocols dictate otherwise. This should be recorded on the appropriate eCRF page.

8.1.4 Altropane Accountability

Each investigator is responsible for ensuring that deliveries of Altropane and other study materials from the Sponsor are correctly received, recorded, handled, and stored safely and properly in accordance with all applicable regulatory guidelines (including those pertaining to radioactive products and Schedule II controlled substances), and used in accordance with this protocol.

All Altropane containers (opened, unopened, or empty) must be destroyed on site after the study (following local institutional policies for disposal of hazardous waste), and after overall drug accountability has been completed by the Sponsor or representative. Radioactive containers, syringes, and delivery systems should be allowed to decay to background levels prior to disposal. See the Altropane handling procedures or similar document (e.g., Pharmacy Manual) for further details on receipt, recording, handling and accountability procedures related to Altropane.

A list of Altropane and other materials that were returned, or 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.

8.1.5 Registration of Product Complaints

In the event of an Altropane complaint (e.g., breakage, leakage, particulate matter, discoloration), the investigator or recipient of Altropane is requested to report the problem on the shipping documentation (e.g., 'Delivery Note for Product', Drug Shipping and Receiving Form, or equivalent form). This should be promptly forwarded to the person indicated on the shipping documentation. The Responsible Person at the Sponsor 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.

Lack of Efficacy: Any unusual/unexpected failure in diagnostic efficacy of Altropane should be reported by the investigator to the Sponsor immediately. The Sponsor will report unusual failure in efficacy of Altropane as required by regulatory authorities.

8.2 Method of Numbering Subjects

A unique allocation number will be assigned to each subject at each center in successive order of entering the study after signing the informed consent form (ICF). No subject may be entered into the study more than once. The allocation number will be unique for each subject in the study and will consist of 7 digits in total: 3 digits for the center identification and 4 digits for the subject identification at the center (e.g., 002-0001: first subject in center No. 2).

Once a subject number is assigned, it cannot be reassigned even if the subject is deemed ineligible or withdraws consent. To preserve the scientific integrity of the study, numbers must be assigned in numeric order.

A subject who has given informed consent (or for whom informed consent has been given) but does not fulfil, within 30 days before Visit 2, the criteria to participate in the study will receive a subject number and will be logged as a screening failure. If the screen failure becomes eligible at a later time, the original number assigned for that subject will be used.

The subject will also be documented on the Screening Log by using the subject's initials (where permitted) and subject number.

8.3 Selection of Doses and Timing

This is a dose-evaluation study. Each subject will undergo SPECT imaging with 5 mCi of Altropane. The 5-mCi dose of Altropane was selected for the study because it is similar to the approved dose of DaTscan (3 to 5 mCi).

8.4 Randomization and Blinding

In this study, each subject will receive one 5-mCi dose of Altropane. No blinding of the Altropane will be performed.

In the BIE, images will be presented in randomized order and readers will be blinded to clinical information, the identity of the tracer and tracer doses used to image subjects, and to this protocol. The BIE will be performed as described in Section 10.1 and the study Independent Review Charter.

8.5 Prior and Concomitant Medications or Procedures

Any medications taken by the subject or medical procedures performed at Screening, Altropane administration, and up to the 24-hour safety follow-up after Visit 2 will be recorded in the eCRF along with the indication and dosage. Either the generic or the trade name may be recorded. The Sponsor/contract research organization (CRO) will encode all therapy and medication according to a current well-recognized dictionary of medical codes.

8.5.1 Prohibited Medications

In accordance with Exclusion Criterion #12, subjects are not eligible for the study if they are currently taking any of the disallowed medications/treatments listed in the Concomitant Medication List (Table 1) and cannot or will not discontinue use at least 12 hours prior to the SPECT exam.

Table 1 Concomitant Medication List

Allowed During Imaging:	Disallowed During Imaging:
Adrafinil Amantadine Amisulpride Apomorphine Benserazide Bromocriptine Cabergoline Carbidopa Citalopram Clozapine Deanxit Dihydroergotamine Domperidone Entacapone Escitalopram Haloperidol Levodopa	Alpha methyldopa Amphetamine and its derivatives, including methamphetamine Benztropine Bupropion Ephedrine Methylphenidate Metoclopramide Modafinil Norephedrine Phentermine Reserpine

Table 1 Concomitant Medication List

Allowed During Imaging:	Disallowed During Imaging:
Lisuride Madopar Melperone Munuca pruriens (velvet bean) Olanzapine Paroxetine Pergolide Pramipexole Quetiapine Rasagiline Risperidone Ropinirole Rotigotine Safinamide Selegiline Sertraline Sinemet Stalevo Tiapride Tolcapone Venlafaxine Ziprasidone	

Ref: GE HealthCare Data on File

8.6 Contraception and Pregnancy Avoidance Procedure

Altropane contains ^{123}I, a source of gamma radiation that is potentially harmful to a fetus. Therefore, care should be taken to avoid enrolling women of childbearing potential who may be or plan to become pregnant, and to ensure that women of childbearing potential who enroll in the study do not become pregnant during the study. Therefore, if the subject is a woman of childbearing potential, she must use a highly effective method of contraception from Screening until 30 days after the administration of Altropane, and the results of a serum or urine hCG pregnancy test, performed at Screening and on the day of Altropane administration (with the result known before Altropane administration), must be negative.

A woman of childbearing potential is neither post-menopausal nor surgically sterile. Post-menopausal means having had no menses for at least 12 months without an alternative medical cause [CTFG Guidance 2020]. Surgically sterile means having had a documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy, or any combination of these.

A highly effective method of contraception is one that has a failure rate of less than 1% per year when used consistently and correctly; such methods include combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral,

intravaginal, or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device; intrauterine hormone-releasing system; bilateral tubal ligation/occlusion; vasectomized partner (with medical confirmation of success); and abstinence from heterosexual intercourse involving a woman of childbearing potential.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy, or vasectomized with confirmation of success.

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process. Women of child-bearing potential must have a negative result for a urine or serum hCG pregnancy test at the time points detailed in Table 2.

8.7 Treatment Compliance

Subjects will receive Altropane under direct supervision of study personnel. Each administration volume and the total radioactivity injected will be checked and the vial code and volume per administration will be recorded in each subject's eCRF. Administered doses that are more than 10% outside of the target dose of 5 mCi must be reported as protocol deviations (see Section 13.3).

9 STUDY PROCEDURES

All efficacy and safety measurements obtained during the course of the study are summarized in the Study Schedule of Events (Table 2).

Table 2 Study Schedule of Events

Activity/Action	Visit 1: Screening	Visit 2: Altropane SPECT (≤30 days after Visit 1)			Visit 3: Follow-Up Phone Call (24 ± 6 hours after injection)
		Pre-Imaging	Imaging[2]	Post-Imaging	
Obtain written informed consent[1]	X				
Assess and record inclusion and exclusion criteria	X				
Record demographic information	X				
Record medical/surgical history	X				
Obtain clinical diagnosis provided by referring physician	X				
Obtain most recent prior DaTscan images	X				
Record prior/concomitant medications	← X →				
Measure and record vital signs (temperature, heart rate, respiration rate, BP)[3]	X	X		X	
Perform and record limited physical examination[4]	X	X		X	
Record 12-lead ECG[5]	X	X		X	
Obtain blood samples for clinical laboratory tests (serum biochemistry and hematology)[6]	X	X		X	
Obtain urine drug screen for drugs of abuse	X	X			
Perform serum or urine hCG pregnancy test (women of childbearing potential only)[7]	X	X			
Inspect IV catheter site[8]		X		X	
Administer approved thyroid blocking medication orally at least 1 hour ± 15 minutes before Altropane injection unless institutional protocols dictate otherwise		X			
Insert IV catheter (22 gauge or larger)		X			
Draw Altropane into sterile syringe, measure activity		X			
Administer Altropane via IV catheter		X			
Measure residual activity in syringe and delivery system (immediately after injection); record administered activity		X			
Perform SPECT imaging[2]			X		
Monitor for adverse events/serious adverse events	X	← X →			X

BP = blood pressure; ECG = electrocardiogram; hCG = human chorionic gonadotropin; IV = intravenous; SPECT = single photon emission computed tomography
[1]Must be obtained before any other screening is done.

Table 2 Study Schedule of Events

Activity/Action	Visit 1: Screening	Visit 2: Altropane SPECT (≤30 days after Visit 1)			Visit 3: Follow-Up Phone Call (24 ± 6 hours after injection)
		Pre-Imaging	Imaging[2]	Post-Imaging	

[2]Imaging should start 15 to 20 minutes after injection and last 30 minutes.
[3]Vital signs determined at screening, within 3 hours before injection, and within 60 minutes after imaging.
[4]Limited physical examination (assessment of general appearance, lungs and heart) at screening, within 3 hours before injection and within 60 minutes after imaging.
[5]12-Lead ECG obtained at screening, within 3 hours before injection, and within 60 minutes after imaging.
[6]Blood samples are collected at screening, within 3 hours before injection, and within 60 minutes after imaging.
[7]Women of childbearing potential must have a negative pregnancy test (serum or urine hCG) result at screening and within 3 hours before injection.
[8]Inspect IV catheter site and record findings within 30 minutes before injection and within 60 minutes after imaging.

9.1 Screening Visit (Visit 1)

A Screening visit (Visit 1) will take place up to 30 days before the SPECT imaging visit (Visit 2). Signed and dated informed consent must be obtained from all subjects prior to their entering the study and any screening procedures being performed. All subjects must satisfy all the inclusion criteria and none of the exclusion criteria listed in Sections 7.2 and 7.3.

At the Screening visit, the following data will be obtained and recorded on the relevant pages of the eCRF:

- Inclusion and exclusion criteria
- Demographic information
- Medical/surgical history
- Most recent prior DaTscan images (obtained within 1 year (preferably 6 months) before screening) showing normal striatal uptake (Part 1) or abnormal striatal uptake (Part 2, if applicable)
- Baseline clinical diagnosis provided by the referring physician, which must be consistent with the DaTscan images
- Prior/concomitant medications
- Vital signs (temperature, heart rate, respiration rate, blood pressure [BP]))
- Limited physical examination (general appearance, lungs and heart)
- 12-lead ECG
- Urine sample (for testing for drugs of abuse)
- Blood for laboratory parameters (hematology and serum biochemistry)
- Serum or urine hCG pregnancy test (for women of child-bearing potential)
- AEs/SAEs

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

9.2 SPECT Imaging Visit (Visit 2)

The Altropane SPECT Imaging Visit (Visit 2) will take place within 30 days after the Screening visit. If DaTscan imaging was conducted recently, the Altropane SPECT imaging

should occur at least 4 full days after the DaTscan imaging, to allow for elimination of DaTscan activity.

The subject will be continuously monitored for the occurrence of AEs/SAEs during the visit. In addition, the following procedures will be performed, and the indicated data obtained and recorded, within the specified time windows:

Within 3 hours before Altropane injection

- Limited physical examination (general appearance, lungs and heart)
- Update prior/concomitant medications
- Urine drug screen (for testing for drugs of abuse)
- Vital signs (temperature, heart rate, respiration rate, BP)
- 12-lead ECG
- Insert IV catheter (22 gauge or larger-diameter)
- Serum or urine hCG pregnancy test (for women of child-bearing potential)
- Blood sampling for serum biochemistry, hematology and pregnancy test (if opting for serum test); may be done at the time of IV catheter insertion.

1 hour ± 15 minutes before injection

- Administer an approved thyroid blocking medication orally, unless institutional protocols dictate other methods of thyroid blockade. Record on appropriate eCRF page.

Within 30 minutes before injection

- Inspect IV catheter site and record findings

Subjects will be administered Altropane (5 mCi [185 MBq]) via the IV catheter, followed by a saline flush; the actual administered activity will be determined and recorded. SPECT imaging will be performed as detailed in the GE-278-001 Imaging Manual (Altropane). Imaging should start 15 to 20 minutes after Altropane injection and last for 30 minutes (the total time from injection until the end of imaging will be approximately 45 to 50 minutes).

Within 60 minutes after imaging:

- Inspect IV catheter site and record findings
- Update prior/concomitant medications

- Vital signs (temperature, heart rate, respiration rate, BP)
- Limited physical examination (general appearance, lungs and heart)
- 12-lead ECG
- Blood sampling for serum biochemistry and hematology

9.3 24-hour Follow-Up (Visit 3)

Subjects will be contacted by telephone 24 ± 6 hours after Visit 2 dosing, and AEs/SAEs and any changes in concomitant medications will be recorded.

9.4 Unscheduled Visits

Unscheduled visits can be arranged at the discretion of the investigator. At a minimum, the date and reason for the visit will be captured. Any procedures performed will also be captured in the eCRF.

10 EFFICACY, SAFETY, AND OTHER ASSESSMENTS

10.1 Efficacy Assessments

Primary, secondary, and exploratory endpoints are provided in Section 5.2.

10.1.1 Image Acquisition

Altropane SPECT images will be acquired for 30 minutes starting 15 to 20 minutes after injection. Further details of Altropane SPECT imaging requirements are provided in the GE-278-001 Imaging Manual.

10.1.2 Image Interpretation and Correlation with Standard of Truth

Altropane SPECT images will be visually interpreted by 5 expert blinded readers who are blinded to the Altropane dose as well as to each subject's clinical information. Readers will interpret images independently of each other and will not be allowed to communicate with each other or be aware of any other reader's findings. Caudate and putamen will be assessed individually in the left and right sides. Visual image interpretations will be a forced choice between *normal* (caudate and putamen fully visible on left and right, or with small insignificant defects) or *abnormal* (unilateral or bilateral reduced) striatal uptake.

Readers will also rate their confidence in striatal visualization for the Altropane images as *high*, *medium*, or *low*, and evaluate image quality as *excellent*, *good*, *fair*, *poor*, or *unevaluable*. The BIE will be conducted in accordance with the study Independent Review Charter.

10.2 Safety Assessments

The investigator(s) and the Sponsor/CRO will review the safety data. The following safety data will be collected and evaluated:

- Clinical laboratory parameters: serum biochemistry and hematology (Table 3).
- Vital signs (temperature, heart rate, respiration rate, BP)
- 12-lead ECG (heart rate, PR interval, QRS interval, QT interval, QTc interval, notation of abnormalities such as arrhythmias, infarct, etc.)
- Limited physical examination (general appearance, lungs and heart)
- AEs and SAEs

Pre-specified normal limits for vital signs and ECG intervals are provided in Section 15.2.

10.2.1 Clinical Laboratory Evaluation

Clinical laboratory parameters assessed in this study are displayed in Table 3.

Table 3 Clinical Laboratory Parameters

Serum Biochemistry	Hematology	Urine Screenings
• Alanine aminotransferase (ALAT) • Albumin • Alkaline phosphatase • Amylase • Aspartate aminotransferase (ASAT) • Bicarbonate • Bilirubin (total, direct, indirect) • Calcium • Chloride • Creatine phosphokinase (CPK), total • Creatinine • Gamma-glutamyltransferase (G-GT) • Glucose • Lactate dehydrogenase • Phosphorous • Potassium • Protein (total) • Sodium • Urea nitrogen • Uric acid	• Red blood cell (RBC) count • Platelet count • White blood cell (WBC) count	Drugs of Abuse • Amphetamine • Barbiturate • Benzodiazepine • Buprenorphine • Cocaine • Fentanyl • Tetrahydrocannabinol (THC) • 3,4-methylenedioxymethamphetamine (MDMA; “Molly”) • Methadone • Methamphetamine • Opiates • Oxycodone • Tricyclic Antidepressants Pregnancy • Human chorionic gonadotropin (hCG; unless serum tested)

The signed and interpreted laboratory results will be kept at the site.

Blood samples will be obtained for screening and for pre- and post-Altropane assessments of serum biochemistry and hematology parameters within the time point ranges described in Table 2. It is anticipated that the maximum amount of blood taken will not be more than 20 mL for all the samples taken during the subject’s study participation. Samples will be analyzed at a central clinical laboratory (for parameters, see Table 3).

All blood samples will be processed and handled per standard laboratory procedures. All retained samples will be destroyed following institutional procedures after completion of the study.

A urine screening for drugs of abuse will be performed at the time points described in Table 2; the drugs targeted by the drug screen are listed in Table 3.

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. Also, additional diagnostic tests may be indicated to determine a more precise diagnosis of the subject's condition (e.g., ordering a white blood cell differential to characterize a high or low white blood cell count, or ordering a determination of red cell indices to characterize a low hematocrit).

10.2.2 Vital Signs

Vital signs (temperature, heart rate, respiration rate, BP) will be monitored at screening, and pre- and post-imaging, according to the study Schedule of Events (Table 2). Before vital signs are measured, the subject should rest for at least 5 minutes (if possible). The same position (e.g., seated) will be used each time vital signs are measured for a given subject, and blood pressure will be measured from the arm contralateral to the site of Altropane administration whenever possible.

10.2.3 Electrocardiograms

A standard 12-lead ECG will be obtained at screening and at the pre- and post-imaging time points in Table 2. ECGs can be obtained on any local ECG machine. ECG clocks should be synchronized with imaging equipment. ECGs will be interpreted by the investigator or by a designee who is qualified by the institution to read ECGs and report the data at the investigative site. Subject management decisions may be based on the 12-lead ECG findings.

Each 12-lead ECG at each time point (and any derived data such as intervals and interpretations) must be identified with the subject's initials and the subject's study number, must show the date and time of recording, must be signed by the investigator with the date of his/her interpretation, and must be retained in the investigator's study record for each subject. Any data required to be entered into the eCRF must be entered promptly.

The investigator will not be expected to calculate QTc intervals. Pre-specified normal limits for 12-lead ECG intervals that will be used by the Sponsor in data analysis are provided in Section 15.2.

10.2.4 Limited Physical Examination

A qualified physician or a non-physician medically certified individual who is permitted by State/National law to perform physical examinations will conduct physical examinations according to the Schedule of Events (Table 2). Ideally, 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, lungs, and heart, and inspection of the IV catheter site before and after imaging. Abnormal injection site findings may include, but are not limited to: extravasation, bleeding, hematoma, redness, and infection. Abnormal injection site findings are to be recorded as AEs in the eCRF.

A *new* abnormal physical finding is one that occurs when a subject's normal baseline physical examination becomes abnormal post-baseline. A *worsening* abnormal physical finding is one that was present at baseline (pre-dosing) that later becomes worse. New abnormal physical findings and worsening abnormal physical findings should be reported as AEs.

10.2.5 Adverse Events and Serious Adverse Events

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 at least 30 minutes after tracer dosing. Treatment of SAEs should be primarily supportive of vital functions.

10.2.5.1 Definition of Adverse Event

AE Definition: An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to that product.

<u>Events Meeting the AE Definition</u>

- Any abnormal laboratory test results (hematology, clinical biochemistry, or urinalysis) or other safety assessments (e.g., ECG, vital-sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- A new condition detected or diagnosed after IMP administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of IMP or a concomitant medication. Overdose *per se* will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Treatment-emergent AE: A treatment-emergent AE is an AE that begins or worsens between the start of IMP administration and the end of the follow-up period.

Adverse Drug Reaction (ADR): An AE that is caused by the IMP.

Suspected Adverse Drug Reaction: An AE for which there is a reasonable possibility that the IMP caused the AE. “Suspected” implies a lesser degree of certainty about causality than adverse drug reaction.

Serious Unexpected Suspected Adverse Drug Reaction: Any suspected ADR that is not in agreement with the Reference Safety Information, in nature or severity. In this study the Reference Safety Information will be the Investigator’s Brochure.

10.2.5.2 Definition of Serious Adverse Event

If an event is not an AE per the above definition, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a) Results in death

b) Is life-threatening

- The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person’s ability to conduct normal life functions.

e) Is a congenital anomaly/birth defect

f) Is another medically important event:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Subjects will report all AEs to the investigator and/or qualified designee.

10.2.5.3 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the 24-hour follow-up phone call at the time points specified in the Schedule of Events (Table 2).

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of a subject's study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and the investigator considers the event to be reasonably related to the IMP or study participation, then investigator must promptly notify the Sponsor.

10.2.5.4 Adverse Event and Serious Adverse Event Recording and Evaluation

Adverse Event and Serious Adverse Event Recording:

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the IMP or study procedures, or that cause the subject to discontinue the study.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. 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. Open-ended and non-leading verbal questioning of the subject (e.g., "How do you feel?") is the preferred method to inquire about AE occurrences. Subjects will be instructed to immediately report any symptoms and signs to the study staff (i.e., between formal observations).

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The investigator will then record all relevant AE/SAE information in the eCRF and/or the SAE reporting form.

It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the Sponsor/CRO in lieu of completion of the AE/SAE eCRF page/reporting form. However, there may be instances when copies of medical records for certain cases are requested by the Sponsor/CRO. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Sponsor/CRO.

The investigator will attempt to establish a diagnosis of the AE based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity (Severity):

The investigator will make an assessment of the highest intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. Note that a severe AE is not the same as a Serious AE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

Assessment of Causality:

The investigator is obligated to assess whether there is a reasonable possibility of a causal relationship between the IMP (Altropane) and each occurrence of each AE/SAE. A "reasonable possibility" of a relationship means that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgment to assess the possibility of a causal relationship.

Causality should be assessed as Related or Not related (Unrelated) to Altropane.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration will be considered and investigated. The investigator will also consult the Investigator's Brochure in his/her assessment to determine whether or not the AE was expected.

The causality assessment is 1 of the criteria used when determining regulatory reporting requirements. Therefore, for each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor/CRO. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor/CRO.

The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

10.2.5.5 Follow-Up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.5.2).

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor/CRO to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. New or updated information will be recorded in the originally completed eCRF.

The investigator will submit any updated SAE data to the Sponsor/CRO within 24 hours of receipt of the information.

10.2.5.6 Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of an IMP under clinical investigation are met. **Study centers are instructed to report all SAEs to the Sponsor/CRO within 24 hours.**

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IMP under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional/Independent Review Boards (IRB), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs or a MedWatch/Council for International Organizations of Medical Sciences [CIOMS]) from the sponsor will review and then file it in the site study file along with the Investigator's Brochure and will notify the IRB if appropriate according to local requirements.

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor/CRO will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-

line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor/CRO by telephone.

Contacts for SAE reporting are:

Parties	Email address	Fax Number	Phone Number
GE HealthCare Pharmacovigilance	[redacted]	[redacted]	[redacted]

SAE Reporting via Paper CRF

- Facsimile (fax) transmission or emailing of a scanned copy of the SAE paper case report form (CRF) is the back-up method to transmit this information to the Sponsor/CRO.
- In rare circumstances and in the absence of facsimile/scanning equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- If an SAE is reported via paper CRF, the site will enter the SAE data into the electronic system as soon as it becomes available.

An investigator who receives a safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs or a MedWatch/CIOMS) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB, if appropriate according to local requirements.

Emergency Contact Information

Study sites are encouraged to provide subjects with study personnel contact information on wallet-sized cards informing them what to do in case of an emergency. In case of a clinical-study related emergency, subjects should call 911 or study personnel, as appropriate to the situation.

For any protocol or safety-related questions site personnel may contact:

[redacted]
GE HealthCare Life Sciences
251 Locke Drive, Marlborough, MA 01752
Mobile: [redacted]
Email: [redacted]

10.2.6 Urgent Safety Measures

In accordance with the principles of Good Clinical Practice (GCP) as laid out in International Council for Harmonisation (ICH) E6, the investigator(s) has/have primary responsibility for assuring subject safety throughout the performance of study procedures. An urgent safety measure is any measure which an investigator may need to implement which is a deviation from, or a change in, the protocol to eliminate one or more immediate hazards to study subjects without prior IRB approval.

The investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical study 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 regulatory authority and the relevant IRB of the measures taken and the circumstances giving rise to those measures.

All urgent safety measures must be reported to the Sponsor/CRO 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.

10.2.7 Pregnancy Reporting

This process is aimed at ensuring the appropriate monitoring of the potential risk related to IMP exposure of pregnant women and/or fetuses 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.

10.2.7.1 Female Study Subjects

Each female study subject must be advised by the investigator to inform him/her immediately if she suspects she may have become pregnant during the 30 days after IMP administration.

When a female study subject reports a pregnancy that occurred within 30 days post-IMP administration, the investigator will arrange a confirmatory pregnancy test for her if the pregnancy has not been confirmed by another healthcare provider. The investigator will collect pregnancy information, record it on the appropriate form, and submit it to the sponsor within 24 hours of learning of the subject’s pregnancy.

The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject 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 fetal status (presence or absence of anomalies) or indication for the procedure.

Any female subject who becomes pregnant while participating in the study will cancel/discontinue IMP administration and/or be withdrawn from the study.

10.2.7.2 Male Study Subjects

Each male study subject must be advised by the investigator to inform him/her immediately if he suspects his partner may have become pregnant within 30 days after the subject was administered with the IMP.

When a study subject reports a partner's pregnancy that occurred within 30 days post-IMP administration, the investigator will attempt to obtain the partner's informed consent for reporting the pregnancy, will arrange a pregnancy test for the study subject's partner if the pregnancy has not been confirmed by another healthcare provider, and will attempt to collect and submit pregnancy information to the sponsor (within 24 hours of learning of the pregnancy.

The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.2.7.3 Pregnancy-Related Adverse Events

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any post-study pregnancy-related SAE considered reasonably related to the IMP by the investigator will be reported to the sponsor as described in Section 10.2.7. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

10.3 Other Variables

10.3.1 Demographic Data

Subject demographic data (age, race, ethnicity, gender, weight, and height) will be recorded at Screening. Body mass index will be calculated from height and weight.

10.3.2 Medical and Surgical History

Each subject's relevant medical and surgical history will be recorded at Screening.

10.3.3 Prior and Concomitant Medication

Each subject's prior/concomitant medications will be recorded at Screening, Visit 2, and the 24-hour follow-up call (post-Visit 2). The thyroid blocking agent administered prior to Altropane SPECT should be recorded separately on the appropriate eCRF page.

10.3.4 Drug Screening

A urine drug screen for drugs of abuse will be performed at Screening (Visit 1) and prior to imaging at Visit 2. Please refer to Table 2 for details.

10.4 Appropriateness of Measurements

All assessments and measurements are appropriate and generally regarded as standard medical practice.

11 DATA HANDLING AND QUALITY ASSURANCE

11.1 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. Full details of procedures for data handling will be documented in the Data Management Plan.

11.2 Completing and Signing Case Report Forms

For electronic CRFs, data will be entered by trained site personnel with reasons given for any missing data. 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 and the reason for the correction. The appropriate electronic signature will be provided.

Any data recorded directly in the CRF, for which no other written or electronic record will be maintained in the subject's medical record, will be considered source data and should be signed by the investigator(s) (e.g., results of physical examinations, vital-sign testing, or the IMP administration procedure).

11.3 Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

11.4 Record Retention

All study documentation at the investigator site and Sponsor site will be retained in accordance with ICH E6 GCP and the Sponsor/CRO's quality standards and standard operating procedures (SOPs).

All study records and documentation at the Investigator site and Sponsor site will be retained for a minimum of 15 years following study completion or discontinuation of the study, unless notified otherwise by the Sponsor or a longer period is required by local legislation. The investigator must request written agreement from the Sponsor before destruction of archived study documentation. No records may be transferred to another location or party without written notification to the Sponsor.

12 STATISTICAL METHODS AND PLANNED ANALYSIS

The data will be analyzed 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.

Data from participating centers in this protocol will be combined so that an adequate number of subjects will be available for analysis. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, and safety observations and measurements.

12.1 General Statistical Considerations

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® software (Version 9.4 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 eCRF and entered into the database will be provided in separate data listings showing individual subject values. Summary tables and data listings will be presented overall, separated by clinical diagnosis at baseline and by study part (Part 1 and Part 2 [if applicable]). The planning and reporting of statistical analysis will be carried out as described in the Sponsor/CRO's SOPs governing clinical studies and will be described in further detail in the Statistical Analysis Plan.

12.2 Populations for Analysis

The Safety Analysis Set is defined as all subjects who receive any amount of Altropane.

The Full Analysis Set is defined as all subjects who receive any amount of Altropane and have an Altropane image interpretation.

For Part 1 the dose-evaluation (efficacy) analysis will be based on the Full Analysis Set. For Part 2 (if conducted) the dose-evaluation (efficacy) will also be based on the Full Analysis Set.

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 Full Analysis Set.
- Number of subjects included in the Safety Analysis Set.

- Number of subjects included in the dose-evaluation analysis set.
- Number of subjects withdrawn from the study and the reason for withdrawal.

Demographic information (age, height, weight, and body mass index) will be summarized using descriptive statistics. Gender and race will be summarized by counts and percentages.

Medical and surgical histories will be summarized by counts and percentages. Prior and concomitant medications will be recorded and coded using a standard classification system and grouped by primary and secondary classes, if applicable.

12.4 Study Treatments

Administered doses of Altropane will be summarized by volume and radioactivity administered in Part 1 and, if applicable, in Part 2.

The amount and type of medication used for thyroid blockade for each subject will also be summarized.

12.5 Primary Efficacy Analysis

12.5.1 Primary Efficacy Analyses

- Number and percentage of correct classifications of 5-mCi Altropane images from subjects with normal striatal uptake (Part 1)
- Number and percentage of correct classifications of 5-mCi Altropane images from subjects with abnormal striatal uptake (Part 2, if applicable)

The correctness of image classification will be determined from the majority interpretation of the 5 expert blinded readers (at least 3 of 5 readers).

12.5.2 Statistical Hypothesis and Method of Analysis

The 5-mCi dose will be considered to show acceptable striatal visualization if the percentage of correct majority classifications is greater than 70% in Part 1 and 75% in Part 2 (if applicable).

12.5.3 Handling of Missing Values/Censoring/Discontinuations

The efficacy (dose-evaluation) analysis is based on the Full Analysis Set; all subjects in that analysis set will have an image. Other missing values will not be imputed, and only observed values will be used in data analyses and reports, unless otherwise specified in the Statistical Analysis Plan.

12.5.4 Handling of Uninterpretable Images

Not applicable. During the BIE the determination of striatal visibility will be forced so all images are considered 'interpretable' with respect to the primary objective.

12.6 Secondary Efficacy Analyses

12.6.1 Reader Assessment of Image Quality

- Number and percentage of Part 1 subjects with 5-mCi Altropane image quality judged as *excellent* or *good*

- Number and percentage of subjects in Part 2 (if applicable) with 5-mCi Altropane image quality judged as *excellent* or *good*

The quality will be graded as *excellent*, *good*, *fair*, *poor*, or *unevaluable*. The results of this secondary analysis will be considered consistent with the results of the primary analysis if the percentage of images with *excellent* or *good* majority ratings is greater than 70%.

12.6.2 Reader Confidence in Striatal Visualization

- Number and percentage of Part 1 subjects with *high* confidence ratings for their 5-mCi Altropane images

- Number and percentage of Part 2 subjects (if applicable) with *high* confidence ratings for their 5-mCi Altropane images

The confidence level will be graded as *high*, *medium*, or *low*. The results of this secondary analysis will be considered consistent with the results of the primary analysis if the percentage of images with *high* majority ratings of confidence is at least 70%.

12.6.3 Inter-Reader Agreement

- Number and percentage of images for which 5, 4, and 3 readers, respectively, are in agreement on the subject classification for Part 1, and, if applicable, Part 2.

12.6.4 Intra-Reader Reproducibility (Part 2 Only)

- Number and percentage of subjects for whom each reader's second image interpretation agrees with his/her first image interpretation.

If Part 2 is conducted, each reader will read all images (including the images from Part 1) at least twice to determine intra-reader reproducibility.

12.7 [redacted]

[redacted]

12.7.1 [redacted]

[redacted]

12.8 Secondary Safety Analyses

The following sections apply to Part 1, and, if conducted, to Part 2.

12.8.1 Secondary Safety Variables and Analyses

Safety analyses will be performed for treatment-emergent AEs, treatment-emergent SAEs, ADRs, serious ADRs, vital signs, physical examination, ECG, and laboratory tests.

12.8.2 Adverse Events

AEs and SAEs will be coded using the Medical Dictionary for Regulatory Activities and all reported events will be listed for the Safety Analysis Set. The number and percentage of subjects with 1 or more treatment-emergent AEs will be summarized by system organ class and preferred term by Part 1 (and, if applicable, Part 2) and overall. Summaries will also be presented by AE intensity and judged relationship to IMP. Treatment-emergent SAEs will also be presented by Part 1 (and, if applicable, Part 2) and overall. Similar analyses will be performed for ADRs.

12.8.3 Clinical Laboratory Evaluation

Descriptive statistics will be displayed for the observed values and changes from baseline in lab parameters. In addition, for each clinical laboratory variable and each time point, the following safety endpoints will be summarized by counts and percentages overall and by dose group:

- 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 (Section 15.2) (not applicable to qualitative parameters). Shift tables based on the normal range will be prepared.

12.8.4 Vital Signs

Descriptive statistics will be displayed for the observed values and changes from baseline in vital signs. For each vital-sign variable and each time point, the following safety endpoints will be summarized by counts and percentages overall and by dose group:

- 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 BP, 10 mm Hg for diastolic BP, 10 beats per minute for heart rate, 1.5°C for body temperature, or 10 breaths per minute for respiration rate).

- The occurrence of post-administration values outside the normal limits (Section 15.2). Shift tables based on the normal range will be prepared.

12.8.5 Electrocardiograms

Descriptive statistics will be displayed for the observed values and changes from baseline in ECG data. For each ECG variable and each time-point, the following safety endpoints will be summarized by counts and percentages overall and by dose group:

- 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 15.2). Shift tables based on the normal range will be prepared.

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

QTc correction:

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

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

12.8.6 Limited 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 overall and by dose group. Shift tables will be prepared.

12.9 Subgroup Analyses

Subgroup analyses by race, gender, and age category (e.g., <65 vs. ≥65) may be conducted as appropriate to the data.

12.10 Interim Analysis

Results from Part 1 will be analyzed and based on the results a decision will be made whether or not to proceed to Part 2.

12.11 Sample Size Calculation

Based on prior experience with an approved DAT imaging agent (DaTscan), it is expected that the probability of a correct subject classification based on Altropane images will be 92% in Part 1 and 91% in Part 2 (if it is conducted).

In Part 1, 10 subjects with normal striatal uptake will be sufficient to determine whether or not the 5-mCi Altropane dose provides acceptable visualization of normal striatal uptake. Ten subjects with normal striatal uptake can achieve 62% power to detect whether the 5-mCi dose can result in a rate of correct subject classification of 70% or higher by a 1-sided exact test at a target significance level of 0.04. These results assume that the true rate of correct subject classification under the null hypothesis is 92% in Part 1.

If Part 2 proceeds, then 20 subjects with abnormal striatal uptake will be sufficient to determine whether or not to proceed with the 5-mCi dose in Phase 3. Twenty subjects with abnormal striatal uptake will have 76% power to detect whether the 5-mCi dose can result in a rate of correct subject classification of 75% or higher under the assumption that the true rate of correct subject classification is 91%.

12.12 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.

12.13 Rules for Excluding Subjects from Analysis

Subjects will be included in the analysis sets as indicated in Section 12.2 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 a 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.

12.14 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 and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

Before starting this study, the protocol, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB and reviewed and approved by the IRB. The protocol will also be submitted to regulatory bodies/local health authorities in accordance with local regulations as required. The study will not start before the IRB gives written approval in accordance with ICH E6-GCP and all applicable regulatory bodies/local health authorities give approval as required.

Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects (see Section 10.2.6).

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
- Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, and all other applicable local regulations

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 centers 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. The investigator or his/her representative will explain the nature of the study to the subject and/or his/her legally authorized representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary and 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.

Subjects or their legally authorized representative will be required to sign and date a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB or study center. Each subject's signed ICF must be obtained before any procedures or assessments are done and after the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force are explained.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

The investigator(s) will keep the original consent forms. A copy of the signed ICF(s) must be provided to the subject or the subject's legally authorized representative.

Subjects who are rescreened are required to sign a new ICF.

13.2.3 Source Data/Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The monitor(s), auditor(s), authorized personnel of the Sponsor/CRO, health authority inspector(s) or their agents, and authorized members of 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 eCRFs and other documents or image material (including materials from all examinations, (e.g., SPECT 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 scrutinized for the purpose of verifying data recorded in the eCRF. This may be done by the monitor(s), properly authorized persons on behalf of the Sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

13.2.5 Data Protection

Subjects will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

13.2.6 Dissemination of Clinical Study Data

Clinical study results will be published on *www.ClinicalTrials.gov*. The results of this study may be published or presented at scientific meetings as described in Section 13.8.

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 preventive 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 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 Financial Disclosure

According to 21 CFR, Part 54, the Sponsor is required to completely and accurately disclose or certify to the FDA information concerning the financial interests of a clinical investigator (or investigating institution) who is not a full-time or part-time employee of the Sponsor. Therefore, the investigator(s) (or investigating institution) must provide the Sponsor with sufficient, accurate financial certification that none of the following financial arrangements (further defined in 21CFR Part 54.2) exist with the Sponsor or fully disclose the nature of the arrangement. This financial disclosure also applies to any financial arrangements that exist between the Sponsor and the investigator's spouse(s) or dependent children:

- Compensation for participation in the study is affected by the outcome of the study.
- Significant equity (greater than $50,000) interest in the Sponsor's company.
- Proprietary interest in the tested product.
- Significant payments of other sorts, exceeding a monetary value of $25,000.

13.7 Insurance

This study is covered under the Sponsor's Liability Insurance Policy. A Certificate of Insurance can be provided upon request.

13.8 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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15 APPENDICES

15.1 Information on Investigational and Registered Products

The reference document for Altropane in this study is the Investigator's Brochure for Altropane. The reference document provides up-to-date information on the efficacy and safety of Altropane, 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 Normal Limits for Vital Signs and ECG Intervals

Table 4 Criteria for Normal Limits for Vital Signs

	Normal Limits	
Vital Sign Parameter	**Low**	**High**
Systolic BP (mmHg)	85	139
Diastolic BP (mmHg)	60	89
Heart Rate (bpm)	60	100
Respiration Rate (rpm)	12	22
Body Temperature	36.4°C (97.5°F)	37.7°C (99.5°F)
Oxygen Saturation (%)	93	100

Table 5 Criteria for Normal Limits for ECGs

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

[a] No lower boundary set for QTc.

16 CLINICAL PROTOCOL AMENDMENT SUMMARIES

16.1 Amendment A01

16.1.1 Reasons for Amendment

- Typographical errors where the timing of some safety assessments were based on timing of the Altropane injection were corrected to be based on the timing of the imaging.
- The start of study enrollment was updated to current expectations.
- Minor typographical corrections.
- GE Healthcare has been formatted to GE HealthCare throughout the protocol for consistency with company branding following spin off. This minor formatting change is not detailed further below.

Where appropriate, the changes documented below are also made in the synopsis. Where appropriate the changes are indicated in *italics*.

16.1.2 Description of Changes

Section 6.3, Study Timeframe, first sentence

Previously read:

The study is expected to begin enrollment in 3Q 2022.

Now reads:

The study is expected to begin enrollment in *2Q 2023*.

Section 9, Study Procedures, Table 2 (Study Schedule of Events)

Previously read:

Table 2 Study Schedule of Events

Activity/Action	Visit 1: Screening	Visit 2: Altropane SPECT (≤30 days after Visit 1)			Visit 3: Follow-Up Phone Call (24 ± 6 hours after dosing)
		Pre-Imaging	Imaging[2]	Post-Imaging	
Obtain written informed consent[1]	X				
Assess and record inclusion and exclusion criteria	X				
Record demographic information	X				
Record medical/surgical history	X				
Obtain clinical diagnosis (ET for Part 1; dPS for Part 2) provided by referring physician	X				
Obtain most recent prior DaTscan images	X				
Record prior/concomitant medications	← X →				
Measure and record vital signs (temperature, heart rate, respiration rate, BP)[3]	X	X		X	
Perform and record limited physical examination[4]	X	X		X	
Record 12-lead ECG	X	X		X	
Obtain blood samples for clinical laboratory tests (serum biochemistry and hematology)[5]	X	X		X	
Obtain urine drug screen for drugs of abuse	X	X			
Perform serum or urine hCG pregnancy test (women of childbearing potential only)[6]	X	X			
Inspect IV catheter site[7]		X		X	
Administer approved thyroid blocking medication orally at least 1 hour ± 15 minutes before Altropane injection unless institutional protocols dictate otherwise		X			
Insert IV catheter (22 gauge or larger)		X			
Draw Altropane into sterile syringe, measure activity		X			
Administer Altropane via IV catheter		X			
Measure residual activity in syringe and delivery system (immediately after injection); record administered activity		X			
Perform SPECT imaging[2]			X		
Monitor for adverse events/serious adverse events	X	← X →			X

BP = blood pressure; dPS = Degenerative Parkinsonian Syndrome; ECG = electrocardiogram; ET = essential tremor; hCG = human chorionic gonadotropin; IV = intravenous; SPECT = single photon emission computed tomography

[1]Must be obtained before any other screening is done.

Table 2 Study Schedule of Events

Activity/Action	Visit 1: Screening	Visit 2: Altropane SPECT (≤30 days after Visit 1)			Visit 3: Follow-Up Phone Call (24 ± 6 hours after dosing)
		Pre-Imaging	Imaging[2]	Post-Imaging	

[2]Imaging should start 15 to 20 minutes after injection and last 30 minutes.
[3]Vital signs determined within 3 hours before injection and within 60 minutes after injection.
[4]Limited physical examination (assessment of general appearance, lungs and heart) at screening, within 3 hours before and within 60 minutes after imaging.
[5]Blood samples collected at screening, within 3 hours before Altropane injection, and within 60 minutes after injection.
[6]Women of childbearing potential must have a negative pregnancy test (serum or urine hCG) result at screening and within 3 hours before radiopharmaceutical injection.
[7]Inspect IV catheter site and record findings within 30 minutes before injection and within 60 minutes after imaging.

Now reads:

Table 2 Study Schedule of Events

Activity/Action	Visit 1: Screening	Visit 2: Altropane SPECT (≤30 days after Visit 1)			Visit 3: Follow-Up Phone Call (24 ± 6 hours after *injection*)
		Pre-Imaging	Imaging[2]	Post-Imaging	
Obtain written informed consent[1]	X				
Assess and record inclusion and exclusion criteria	X				
Record demographic information	X				
Record medical/surgical history	X				
Obtain clinical diagnosis (ET for Part 1; dPS for Part 2) provided by referring physician	X				
Obtain most recent prior DaTscan images	X				
Record prior/concomitant medications	◄	———	X	———	►
Measure and record vital signs (temperature, heart rate, respiration rate, BP)[3]	X	X		X	
Perform and record limited physical examination[4]	X	X		X	
Record 12-lead ECG[5]	X	X		X	
Obtain blood samples for clinical laboratory tests (serum biochemistry and hematology)[6]	X	X		X	
Obtain urine drug screen for drugs of abuse	X	X			
Perform serum or urine hCG pregnancy test (women of childbearing potential only)[7]	X	X			
Inspect IV catheter site[8]		X		X	
Administer approved thyroid blocking medication orally at least 1 hour ± 15 minutes before Altropane injection unless institutional protocols dictate otherwise		X			
Insert IV catheter (22 gauge or larger)		X			
Draw Altropane into sterile syringe, measure activity		X			
Administer Altropane via IV catheter		X			
Measure residual activity in syringe and delivery system (immediately after injection); record administered activity		X			
Perform SPECT imaging[2]			X		
Monitor for adverse events/serious adverse events	X	◄	———	X	——— ►	X

BP = blood pressure; dPS = Degenerative Parkinsonian Syndrome; ECG = electrocardiogram; ET = essential tremor; hCG = human chorionic gonadotropin; IV = intravenous; SPECT = single photon emission computed tomography

[1]Must be obtained before any other screening is done.

[2]Imaging should start 15 to 20 minutes after injection and last 30 minutes.

[3]Vital signs determined *at screening*, within 3 hours before injection, and within 60 minutes after *imaging*.

Table 2 Study Schedule of Events

Activity/Action	Visit 1: Screening	Visit 2: Altropane SPECT (≤30 days after Visit 1)			Visit 3: Follow-Up Phone Call (24 ± 6 hours after *injection*)
		Pre-Imaging	Imaging[2]	Post-Imaging	

[4]Limited physical examination (assessment of general appearance, lungs and heart) at screening, within 3 hours before *injection* and within 60 minutes after imaging.
[5]*12-Lead ECG obtained at screening, within 3 hours before injection, and within 60 minutes after imaging.*
[6]Blood samples collected at screening, within 3 hours before injection, and within 60 minutes after *imaging*.
[7]Women of childbearing potential must have a negative pregnancy test (serum or urine hCG) result at screening and within 3 hours before injection.
[8]Inspect IV catheter site and record findings within 30 minutes before injection and within 60 minutes after imaging.

Section 10.2.2, Vital Signs, First sentence

Previously read:

Vital signs (temperature, heart rate, respiration rate, BP) will be monitored at screening, and pre- and post-administration, according to the study Schedule of Events (Table 2).

Now reads:

Vital signs (temperature, heart rate, respiration rate, BP) will be monitored at screening, and pre- and post-*imaging*, according to the study Schedule of Events (Table 2).

Section 10.2.3, Electrocardiograms, First sentence

Previously read:

A standard 12-lead ECG will be obtained at screening and at the pre- and post-administration time points in Table 2.

Now reads:

A standard 12-lead ECG will be obtained at screening and at the pre- and post-*imaging* time points in Table 2.

16.2 Amendment A02

16.2.1 Reasons for Amendment

Feedback from the study sites has indicated that few patients with essential tremor undergo DaTscan imaging, and that, although there is a high proportion of DaTscan images that are negative (about 50% at one site), relatively few of these have essential tremor. As a result, enrollment has been slow in Part 1. Therefore, the protocol is being amended to allow patients with negative DaTscan images to be considered for Part 1 (provided they meet all other inclusion and exclusion criteria).

Where appropriate, the changes documented below are also made in the synopsis. Where appropriate the changes are indicated in *italics*. In addition, minor typographical edits were made for clarity or as a result of these edits.

16.2.2 Description of Changes

Section 4, Background Information, Last Paragraph, First Sentence

Previously read:

In Part 1, subjects with known normal striatal uptake on DaTscan images obtained within 1 year (preferably within 6 months) before study enrollment and who have a clinical diagnosis of ET will undergo striatal SPECT imaging following intravenous (IV) administration of 5 mCi of Altropane.

Now reads:

In Part 1, subjects with known normal striatal uptake on DaTscan images obtained within 1 year (preferably within 6 months) before study enrollment and who have a clinical diagnosis *(made by a movement disorder expert) that is consistent with the DaTscan images will* undergo striatal SPECT imaging following intravenous (IV) administration of 5 mCi of Altropane.

Section 5.1, Objectives, Primary Paragraph

Previously read:

The results will be used in deciding whether a 5-mCi or an 8-mCi dose will be recommended for subsequent clinical studies. The decision will be based first on whether a 5-mCi dose of Altropane is acceptable to visualize the striata in subjects with normal striatal uptake (who have confirmed ET). If it is acceptable, then it will be additionally determined whether a 5-mCi dose of Altropane is acceptable to visualize the striata in subjects with abnormal striatal uptake (subjects with confirmed degenerative PS [dPS]).

Now reads:

The results will be used in deciding whether a 5-mCi or an 8-mCi dose will be recommended for subsequent clinical studies. *The decision will be based first on whether a 5-mCi dose of Altropane is acceptable to visualize the striata in subjects with normal striatal uptake.* If it is acceptable, then it will be additionally determined whether a 5-mCi dose of Altropane is acceptable to visualize the striata in subjects with abnormal striatal uptake (subjects with confirmed degenerative PS [dPS]).

Section 6.1, Overall Study Design and Plan, 2nd and 4th Paragraphs

Previously read:

…

In Part 1, consenting subjects who have a DaTscan image showing normal striatal uptake and who have a consistent clinical diagnosis (ET) will be scheduled to undergo striatal SPECT with 5 mCi of Altropane administered intravenously. If the visual interpretation of the striatal images of these subjects is concluded not to be acceptable, then Part 2 will not be conducted, the study will end, and the 8-mCi dose will be selected for further clinical development. However, if the visual interpretation is acceptable, then the study will proceed to Part 2.

…

At least 10 subjects with normal striatal uptake on DaTscan images (ET subjects) will be recruited in Part 1. If Part 2 proceeds (dependent on the results of Part 1), then additionally at least 20 subjects with abnormal striatal uptake on DaTscan images (dPS subjects) will be recruited. Thus, the total number of subjects will be at least 10, or, if Part 2 is conducted, at least 30. Up to 5 centers in the United States will be utilized for the study.

…

Now reads:

…

In Part 1, consenting subjects who have a DaTscan image showing normal striatal uptake and who have a consistent clinical diagnosis will be scheduled to undergo striatal SPECT with 5 mCi of Altropane administered intravenously. If the visual interpretation of the striatal images of these subjects is concluded not to be acceptable, then Part 2 will not be conducted, the study will end, and the 8-mCi dose will be selected for further clinical development. However, if the visual interpretation is acceptable, then the study will proceed to Part 2.

…

At least 10 subjects with normal striatal uptake on DaTscan images will be recruited in Part 1. If Part 2 proceeds (dependent on the results of Part 1), then additionally at least 20 subjects with abnormal striatal uptake on DaTscan images (dPS subjects) will be recruited. Thus, the total number of subjects will be at least 10, or, if Part 2 is conducted, at least 30. Up to 5 centers in the United States will be utilized for the study.

…

Section 6.1, Overall Study Design and Plan, Figure 1

Previously read:

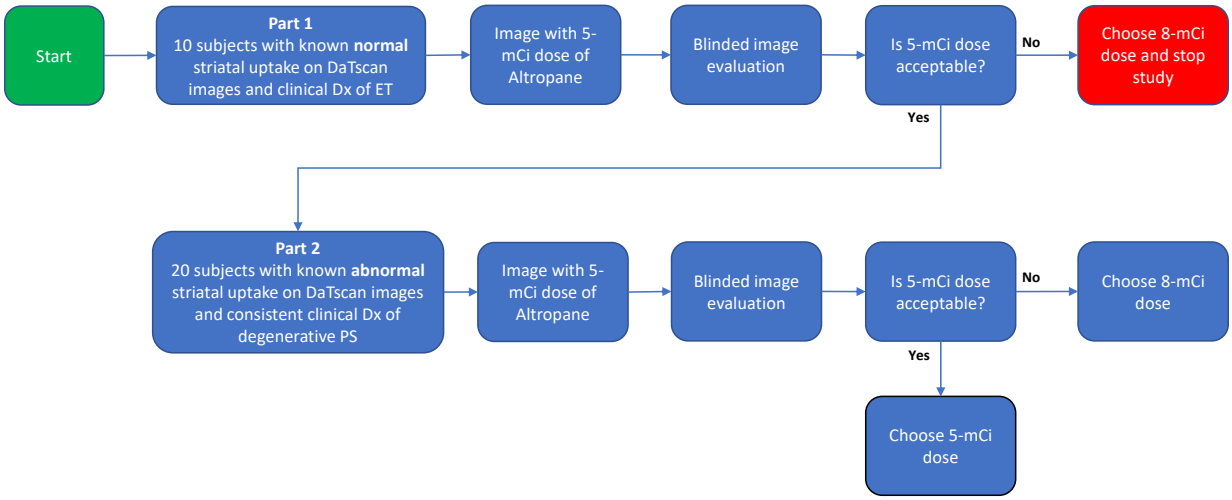

Figure 1 Overall 2-Part Study Diagram

Dx=diagnosis; ET = essential tremor; PS = Parkinsonian syndrome
The conduct of Part 2 is dependent on the results of Part 1.

Now reads:

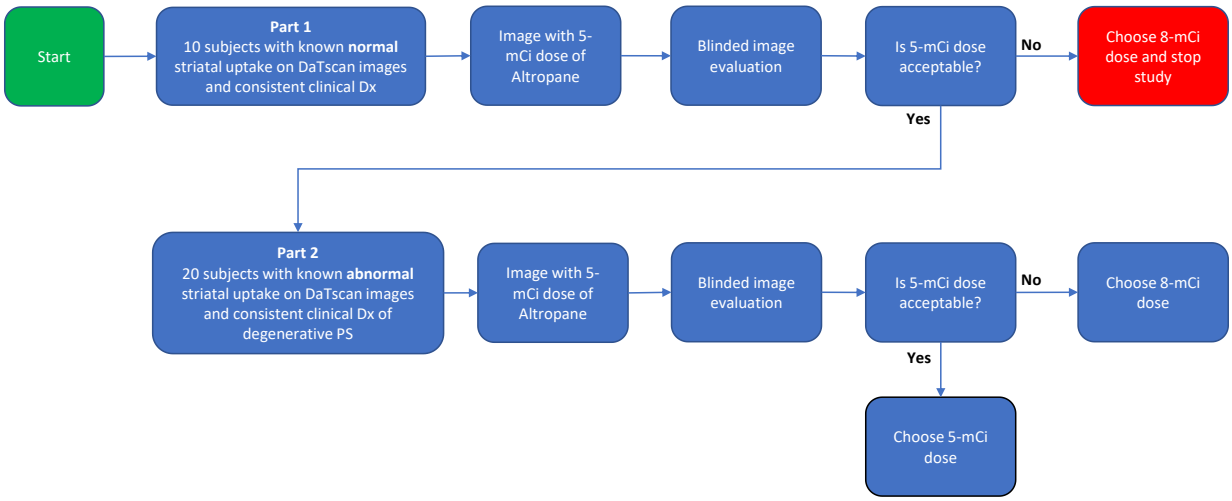

Figure 1 Overall 2-Part Study Diagram

Dx=diagnosis; PS = Parkinsonian syndrome
The conduct of Part 2 is dependent on the results of Part 1.

Section 7.1, Procedures for Enrollment, First Paragraph

Previously read:

In Part 1, subjects with normal striatal uptake (ET subjects) on prior DaTscan images will be recruited at each study center. Potentially eligible subjects will be asked by study personnel about their willingness to participate in this study.

Now reads:

In Part 1, subjects with normal striatal uptake on prior DaTscan images will be recruited at each study center. Potentially eligible subjects will be asked by study personnel about their willingness to participate in this study.

Section 7.2, Inclusion Criteria #1

Previously read:

(1) For Part 1: a) the patient has a DaTscan image, obtained within 1 year (preferably within 6 months) before screening, that shows normal striatal uptake and b) the patient has a clinical diagnosis of ET made by a board-certified neurologist who is qualified by training and experience in the diagnosis of movement disorders, and c) the diagnosis is consistent with the DaTscan image.

For Part 2 (if applicable): a) the patient has a DaTscan image, obtained within 1 year (preferably within 6 months) before screening, that shows abnormal (unilateral or bilateral reduced) striatal uptake and b) the patient also has a confirmed clinical diagnosis of a dPS (such as Parkinson's disease, multiple system atrophy, corticobasal degeneration, progressive supranuclear palsy, etc.) made by a board-certified neurologist who is qualified by training and experience in the diagnosis of movement disorders, and c) the diagnosis is consistent with the DaTscan image.

Now reads:

(1) For Part 1: a) the patient has a DaTscan image, obtained within 1 year (preferably within 6 months) before screening, that shows normal striatal uptake and *b) the patient has a clinical diagnosis (made by a board-certified neurologist who is qualified by training and experience in the diagnosis of movement disorders)that is consistent with the DaTscan image*.

For Part 2 (if applicable): a) the patient has a DaTscan image, obtained within 1 year (preferably within 6 months) before screening, that shows abnormal (unilateral or bilateral reduced) striatal uptake and b) the patient also has a confirmed clinical diagnosis of a dPS (such as Parkinson's disease, multiple system atrophy, corticobasal degeneration, progressive supranuclear palsy, etc.) made by a board-certified

neurologist who is qualified by training and experience in the diagnosis of movement disorders, and c) the diagnosis is consistent with the DaTscan image.

Section 7.3, Exclusion Criteria #2

Previously read:

(2) The patient has had any exposure to radiopharmaceutical products within 30 days before the date of informed consent.

Now reads:

(2) *Fewer than 7 disintegration half-lives have elapsed between the patient's last procedure (therapeutic or diagnostic) involving a radioisotope and Visit 2 (altropane SPECT imaging).*

Section 7.3, Exclusion #13 (New Criteria)

Now reads:

(13) The patient was referred to DaTscan imaging for evaluation of possible cognitive impairment including dementia.

Section 7.4, Screen Failures

Previously read:

Screen failures are subjects who consent to participate in the clinical study but do not meet all inclusion and exclusion criteria. Demographic and other data will be collected for all screen failures (see Section 9.1). Screen failures may be rescreened using their original screening number if there is a reasonable expectation that the reason(s) for the prior screen failure have resolved.

Now reads:

Screen failures are subjects who consent to participate in the clinical study but do not meet all inclusion and exclusion criteria *within 30 days before Visit 2*. Demographic and other data will be collected for all screen failures (see Section 9.1). Screen failures may be rescreened using their original screening number if there is a reasonable expectation that the reason(s) for the prior screen failure have resolved.

Section 8.2, Method of Numbering Subjects, 3rd Paragraph

Previously read:

A subject who has given informed consent (or for whom informed consent has been given) but does not fulfil, the criteria to participate in the study will receive a subject number and will be logged as a screening failure. If the screen failure becomes eligible at a later time, the original number assigned for that subject will be used.

Now reads:

A subject who has given informed consent (or for whom informed consent has been given) but does not fulfil, *within 30 days before Visit 2,* the criteria to participate in the study will receive a subject number and will be logged as a screening failure. If the screen failure becomes eligible at a later time, the original number assigned for that subject will be used.

Section 8.6, Contraception and Pregnancy Avoidance Procedure, First Paragraph

Previously read:

Altropane contains ^{123}I, a source of gamma radiation that is potentially harmful to a fetus. Therefore, care should be taken to avoid enrolling women of childbearing potential who may be or plan to become pregnant, and to ensure that women of childbearing potential who enroll in the study do not become pregnant during the study. Therefore, if the subject is a woman of childbearing potential, she must use a highly effective method of contraception from Screening until 30 days after the last administration of radiopharmaceutical, and the results of a serum or urine hCG pregnancy test, performed at Screening and on the day of radiopharmaceutical administration (with the result known before radiopharmaceutical administration), must be negative.

Now reads:

Altropane contains ^{123}I, a source of gamma radiation that is potentially harmful to a fetus. Therefore, care should be taken to avoid enrolling women of childbearing potential who may be or plan to become pregnant, and to ensure that women of childbearing potential who enroll in the study do not become pregnant during the study. *Therefore, if the subject is a woman of childbearing potential, she must use a highly effective method of contraception from Screening until 30 days after the administration of Altropane, and the results of a serum or urine hCG pregnancy test, performed at Screening and on the day of Altropane administration (with the result known before Altropane administration), must be negative.*

Section 9, Study Procedures, Table 2

Previously read:

Table 2 Study Schedule of Events

Activity/Action	Visit 1: Screening	Visit 2: Altropane SPECT (≤30 days after Visit 1)			Visit 3: Follow-Up Phone Call (24 ± 6 hours after injection)
		Pre-Imaging	Imaging[2]	Post-Imaging	
Obtain written informed consent[1]	X				
Assess and record inclusion and exclusion criteria	X				
Record demographic information	X				
Record medical/surgical history	X				
Obtain clinical diagnosis (ET for Part 1; dPS for Part 2) provided by referring physician	X				
Obtain most recent prior DaTscan images	X				
Record prior/concomitant medications	◄ X ►				
Measure and record vital signs (temperature, heart rate, respiration rate, BP)[3]	X	X		X	
Perform and record limited physical examination[4]	X	X		X	
Record 12-lead ECG[5]	X	X		X	
Obtain blood samples for clinical laboratory tests (serum biochemistry and hematology)[6]	X	X		X	
Obtain urine drug screen for drugs of abuse	X	X			
Perform serum or urine hCG pregnancy test (women of childbearing potential only)[7]	X	X			
Inspect IV catheter site[8]		X		X	
Administer approved thyroid blocking medication orally at least 1 hour ± 15 minutes before Altropane injection unless institutional protocols dictate otherwise		X			
Insert IV catheter (22 gauge or larger)		X			
Draw Altropane into sterile syringe, measure activity		X			
Administer Altropane via IV catheter		X			
Measure residual activity in syringe and delivery system (immediately after injection); record administered activity		X			
Perform SPECT imaging[2]			X		

Table 2 Study Schedule of Events

Activity/Action	Visit 1: Screening	Visit 2: Altropane SPECT (≤30 days after Visit 1)			Visit 3: Follow-Up Phone Call (24 ± 6 hours after injection)
		Pre-Imaging	Imaging[2]	Post-Imaging	
Monitor for adverse events/serious adverse events	X	←	X	→	X

BP = blood pressure; dPS = Degenerative Parkinsonian Syndrome; ECG = electrocardiogram; ET = essential tremor; hCG = human chorionic gonadotropin; IV = intravenous; SPECT = single photon emission computed tomography

[1]Must be obtained before any other screening is done.

[2]Imaging should start 15 to 20 minutes after injection and last 30 minutes.

[3]Vital signs determined at screening, within 3 hours before injection, and within 60 minutes after imaging.

[4]Limited physical examination (assessment of general appearance, lungs and heart) at screening, within 3 hours before injection and within 60 minutes after imaging.

[5]12-Lead ECG obtained at screening, within 3 hours before injection, and within 60 minutes after imaging.

[6]Blood samples collected at screening, within 3 hours before injection, and within 60 minutes after imaging.

[7]Women of childbearing potential must have a negative pregnancy test (serum or urine hCG) result at screening and within 3 hours before injection.

[8]Inspect IV catheter site and record findings within 30 minutes before injection and within 60 minutes after imaging.

Now reads:

Table 2 Study Schedule of Events

Activity/Action	Visit 1: Screening	Visit 2: Altropane SPECT (≤30 days after Visit 1)			Visit 3: Follow-Up Phone Call (24 ± 6 hours after injection)
		Pre-Imaging	Imaging[2]	Post-Imaging	
Obtain written informed consent[1]	X				
Assess and record inclusion and exclusion criteria	X				
Record demographic information	X				
Record medical/surgical history	X				
Obtain clinical diagnosis provided by referring physician	X				
Obtain most recent prior DaTscan images	X				
Record prior/concomitant medications	← X →				
Measure and record vital signs (temperature, heart rate, respiration rate, BP)[3]	X	X		X	
Perform and record limited physical examination[4]	X	X		X	
Record 12-lead ECG[5]	X	X		X	
Obtain blood samples for clinical laboratory tests (serum biochemistry and hematology)[6]	X	X		X	
Obtain urine drug screen for drugs of abuse	X	X			
Perform serum or urine hCG pregnancy test (women of childbearing potential only)[7]	X	X			
Inspect IV catheter site[8]		X		X	
Administer approved thyroid blocking medication orally at least 1 hour ± 15 minutes before Altropane injection unless institutional protocols dictate otherwise		X			
Insert IV catheter (22 gauge or larger)		X			
Draw Altropane into sterile syringe, measure activity		X			
Administer Altropane via IV catheter		X			
Measure residual activity in syringe and delivery system (immediately after injection); record administered activity		X			
Perform SPECT imaging[2]			X		
Monitor for adverse events/serious adverse events	X	← X →			X

BP = blood pressure; ECG = electrocardiogram; hCG = human chorionic gonadotropin; IV = intravenous; SPECT = single photon emission computed tomography

Table 2 Study Schedule of Events

Activity/Action	Visit 1: Screening	Visit 2: Altropane SPECT (≤30 days after Visit 1)			Visit 3: Follow-Up Phone Call (24 ± 6 hours after injection)
		Pre-Imaging	Imaging[2]	Post-Imaging	

[1]Must be obtained before any other screening is done.
[2]Imaging should start 15 to 20 minutes after injection and last 30 minutes.
[3]Vital signs determined at screening, within 3 hours before injection, and within 60 minutes after imaging.
[4]Limited physical examination (assessment of general appearance, lungs and heart) at screening, within 3 hours before injection and within 60 minutes after imaging.
[5]12-Lead ECG obtained at screening, within 3 hours before injection, and within 60 minutes after imaging.
[6]Blood samples *are* collected at screening, within 3 hours before injection, and within 60 minutes after imaging.
[7]Women of childbearing potential must have a negative pregnancy test (serum or urine hCG) result at screening and within 3 hours before injection.
[8]Inspect IV catheter site and record findings within 30 minutes before injection and within 60 minutes after imaging.

Section 9.1, Screening Visit (Visit 1), 5th Bullet

Previously read:

- Baseline clinical diagnosis (ET in Part 1, or dPS in Part 2, if applicable) provided by the referring physician, which must be consistent with the DaTscan images

Now reads:

- *Baseline clinical diagnosis provided by the referring physician, which must be consistent with the DaTscan images*

Section 9.2, SPECT Imaging Visit (Visit 2), First Paragraph

Previously read:

The SPECT Imaging Visit (Visit 2) will take place within 30 days after the Screening visit.

Now reads:

The *Altropane* SPECT Imaging Visit (Visit 2) will take place within 30 days after the Screening visit. *If DaTscan imaging was conducted recently, the Altropane SPECT imaging should occur at least 4 full days after the DaTscan imaging, to allow for elimination of DaTscan activity.*

Section 10.2.1, Clinical Laboratory Evaluation, 2nd Paragraph

Previously read:

Blood samples will be obtained for assessment of serum biochemistry and hematology parameters at the pre- and post-treatment time point ranges described in Table 2. It is anticipated that the maximum amount of blood taken will not be more than 20 mL for all the samples taken during the subject's study participation. Samples will be analyzed at a central laboratory (for parameters, see Table 3). All blood samples will be processed and handled per standard laboratory procedures. All retained samples will be destroyed following institutional procedures after completion of the study.

Now reads:

Blood samples will be obtained for screening and for pre- and post-Altropane assessments of serum biochemistry and hematology parameters within the time point ranges described in Table 2. It is anticipated that the maximum amount of blood taken will not be more than 20 mL for all the samples taken during the subject's study participation. Samples will be analyzed at a central *clinical* laboratory (for parameters, see Table 3).

All blood samples will be processed and handled per standard laboratory procedures. All retained samples will be destroyed following institutional procedures after completion of the study.

Section 12.9, Subgroup Analysis

Previously read:

Subgroup analyses by race, gender, and age category (e.g., <65 vs. >65) may be conducted as appropriate to the data.

Now reads:

Subgroup analyses by race, gender, and age category (e.g., <65 vs. ≥*65*) may be conducted as appropriate to the data.

Section 13.7, Insurance

Previously read:

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.

Now reads:

This study is covered under the Sponsor's Liability Insurance Policy. A Certificate of Insurance can be provided upon request.

SIGNATURE PAGE

Date / Name	Justification / Role
Signed By: [redacted] Date of signature: 12-Oct-2023 04:45:08 GMT+0000	Justification: Approved Role: [redacted]
Signed By: [redacted] Date of signature: 12-Oct-2023 07:28:45 GMT+0000	Justification: Approved Role: [redacted]
Signed By: [redacted] Date of signature: 12-Oct-2023 08:54:53 GMT+0000	Justification: Approved Role: [redacted]

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