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

Clinical Study Protocol: GE-278-001

Statistical Analysis Plan

Version 1.0

05 September 2023

Version History

Version	Version Date	Author/Title/Organization	Summary of Key Changes
1.0	05 September 2023	[redacted] [redacted]Fortrea	Initial Release

Document Approval

Author	
Written By	[redacted]
Signature	SEE ELECTRONIC SIGNATURE
Date	SEE ELECTRONIC SIGNATURE
Role	[redacted] Fortrea

Approval	
Approved By	[redacted]
Signature	SEE ELECTRONIC SIGNATURE
Date	SEE ELECTRONIC SIGNATURE
Role	[redacted] GE HealthCare

Approval	
Approved By	[redacted]
Signature	SEE ELECTRONIC SIGNATURE
Date	SEE ELECTRONIC SIGNATURE
Role	[redacted] GE HealthCare

TABLE OF CONTENTS

List of Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
BIE	Blinded Image Evaluation
BP	Blood Pressure
CRF	Case Report Form
DAT	Dopamine Transporter
dPS	degenerative Parkinsonian Syndrome(s)
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
ET	Essential Tremor
hCG	Human Chorionic Gonadotropin
ICF	Informed Consent Form
ICH	International Council for Harmonisation (formerly International Conference on Harmonisation)
IMP	Investigational medicinal product
IV	Intravenous
PD	Parkinson's Disease
PS	Parkinsonian Syndrome(s)
SADR	Suspected Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBR	Striatal Binding Ratio
SPECT	Single Photon Emission Computed Tomography
TEAE	Treatment-Emergent AE

1 INTRODUCTION

This statistical analysis plan (SAP) describes the planned statistical methods to be used during the reporting and analysis of data collected under the Clinical Study Protocol, "An open-label multicenter Phase 2 dose-evaluation study of Altropane (^{123}I) Injection for striatal dopamine transporter visualization using SPECT brain imaging". This SAP should be read in conjunction with the study protocol and associated case report forms (CRFs). This version of the analysis plan has been developed with respect to the current approved study protocol v2.0. Any revisions to the protocol or CRFs that impact the planned analyses may require updates to the SAP. If there are any discrepancies between the SAP and the protocol, the SAP will prevail. The SAP will be finalized and approved (i.e., signed by all relevant parties) before the study database is locked.

This SAP is written with consideration of the recommendations outlined in the International Council for Harmonisation (ICH) E3 guideline *Structure and Content of Clinical Study Reports*, ICH E8 guideline *General Considerations for Clinical Trials*, and ICH E9 guideline *Statistical Principles for Clinical Trials*.[1,2,3]

2 STUDY DESIGN

2.1 Overview

Movement disorders are common in elderly adults, yet arriving at a specific diagnosis can be difficult even for movement disorder experts. A subgroup of movement disorders includes the Parkinsonian syndromes (PS; also called Parkinsonism), of which the most common type is Parkinson's disease (PD). Some types of PS, such as PD, are neurodegenerative, i.e., they involve nigrostriatal neurodegeneration, an irreversible loss of dopaminergic nigrostriatal neurons. In neurodegenerative PS, the reduction in nigrostriatal neurons is accompanied by a reduction in the presynaptic membrane expression of the dopamine transporter (DAT) protein. Hence, 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, 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 in the living brain.

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 approved DAT imaging agent). 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 vs. 3 to 6 hours with DaTscan). In addition, Altropane requires only 30 minutes of time in the scanner compared to the need to acquire 1.5 million counts DaTscan (approximately 45 minutes).

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. 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 study is a prospective, multicenter, open-label, Phase 2 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 of essential tremor (ET) 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. [redacted]

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.

2.2 Sample Size and Number of Planned Centers

Based on prior experience with 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**, at least 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 at least 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%.

Subjects will be enrolled at up to 5 centers in the United States.

2.3 Enrollment

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. 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.

2.4 Screen Failure

Screen failures are subjects who consent to participate in the clinical study but do not meet all inclusion criteria or meet at least one of the exclusion criteria. The subjects with screen failures will receive a subject number. Demographic and other data will be collected for all screen failures. 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.

2.5 Randomization and Blinding

No blinding of the investigational medicinal product (IMP) 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 the study protocol.

2.6 Study Completion

Subjects will have completed their involvement with the study when their 24-hour follow-up visit has been completed.

2.7 Study Exit

Should a subject decide to withdraw after administration of the 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 adverse event (AE), monitoring will continue until the outcome is evident. The specific event or test result(s) must be recorded in the eCRF.

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

3 STUDY DATA COLLECTION SCHEDULE

The study will require 3 visits for each subject: a screening visit (Visit 1) within 30 days before the SPECT imaging visit (Visit 2), followed by a safety follow-up phone call (Visit 3) 24 hours after Visit 2.

3.1 Screening Visit (Visit 1)

A Screening visit 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.

At the Screening visit, the following data will be obtained and recorded on the relevant pages of the eCRF. Data that are collected through any source of data including Electronic Data Capture (EDC) device are specified below.

- Inclusion and exclusion criteria
- Demographic data
- 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). The conclusions of the assessment will be collected through EDC.
- 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
- Prior/concomitant medications
- Vital signs (temperature, heart rate, respiration rate, blood pressure [BP])
- Limited physical examination (general appearance, lungs, and heart)
- 12-lead electrocardiogram (ECG)
- Urine sample (for testing for drugs of abuse)
- Blood for laboratory parameters (hematology and serum biochemistry)
- Serum or urine human chorionic gonadotropin (hCG) pregnancy test for women of child-bearing potential
- AEs/Serious AEs (SAEs)

3.2 SPECT Imaging Visit (Visit 2)

The SPECT Imaging Visit will take place within 30 days after the Screening visit. The following data will be collected within the specified time windows:

3.2.1 Within 3 hours before the IMP 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
- Serum or urine hCG pregnancy test for women of child-bearing potential
- Blood sampling for serum biochemistry, hematology, and pregnancy (if opting for serum test)

3.2.2 One hour ± 15 minutes before injection

- Administration of an approved thyroid blocking medication

3.2.3 Within 30 minutes before injection

- Findings from the IV catheter site inspection (e.g., bleeding, hematoma, infection)

3.2.4 Altropane administration

- Actual IMP administered activity

3.2.5 SPECT imaging

- SPECT imaging to start 15 to 20 minutes after Altropane injection and last for 30 minutes

3.2.6 Within 60 minutes after imaging

- Findings from the IV catheter site inspection
- 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

3.3 24-hour Follow-Up Visit (Visit 3)

Subjects will be contacted by telephone 24±6 hours after Visit 2 dosing to:

- Update concomitant medications
- Assess for any AEs/SAEs

3.4 Unscheduled Visits

- Date and reason for the visit
- Additional procedures will be captured through the eCRF

4 COLLECTED DATA ELEMENTS

4.1 Clinical Laboratory Parameters

Table 1 presents the clinical laboratory parameters. Blood samples will be obtained for assessment of serum biochemistry and hematology parameters at the pre- and post-treatment time points as specified in Section 3 of this document, and urine screenings will be performed for drugs of abuse. In addition, serum, or urine hCG pregnancy test will be performed for women of childbearing potential. Any abnormal laboratory findings that constitute an AE should be reported as such and should be followed up until the outcome is known. Additional diagnostic tests may be indicated to determine a more precise diagnosis of the subject's condition.

Table 1 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)

4.2 Vital Signs

Vital signs consist of temperature, heart rate, respiration rate, and blood pressure collected at time points as specified in Section 3 of this document. Table 2 presents the vital sign parameters and the normal limits.

Table 2 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)

4.3 Electrocardiograms

A standard 12-lead ECG will be obtained at screening and at the pre- and post-imaging time points as specified in Section 3. 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. The ECG variables and normal limits are presented in Table 3.

Table 3 Criteria for Normal Limits for ECGs

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

[a] No lower boundary set for QTc.

4.4 Limited Physical Examination

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.

4.5 AEs and SAEs

In addition to AEs and SAEs, treatment-emergent AEs (TEAEs), adverse drug reactions (ADRs), suspected adverse drug reactions (SADRs), and suspected unexpected serious adverse drug reactions will be collected. Furthermore, the investigator will make an assessment of the highest intensity for each AE and SAE reported during the study and assign it to one of the following categories: Mild, Moderate, and Severe. The causality of the AE/SAE will be also reported as Related or Unrelated to the IMP.

4.6 Demographic Data

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

4.7 Medical and Surgical History

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

4.8 Prior/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. All therapies and medications will be encoded according to a current well-organized dictionary of medical codes.

4.9 Blinded Image Evaluation

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. The readers will assess:

- Image interpretation (normal or abnormal)
- Confidence in striatal visualization (high medium, or low)
- Image quality (excellent, good, fair, poor, or unevaluable)

5 OBJECTIVES

5.1 Primary Objective

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

5.2 Secondary Objective

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

6 PART 1 ENDPOINTS

6.1 Primary 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.

6.2 Secondary Endpoints

6.2.1 Secondary Efficacy Endpoints

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

6.2.2 Secondary Safety Endpoints

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

6.3 [redacted]

6.3.1 [redacted]

- [redacted]
- [redacted]

7 PART 2 ENDPOINTS

7.1.1 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.

7.1.2 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)

7.1.3 Secondary Safety Endpoints

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

7.1.4 [redacted]

- [redacted]
- [redacted]

8 ANALYSIS CONVENTIONS

8.1 General Considerations

Tables and listings will be prepared in accordance with the current the International Council for Harmonisation (ICH) Guidelines. The information and explanatory notes to be provided in the "footer" or bottom of each table and listing will include the following information:

1. Date and time of output generation

2. SAS® program name, including the path that generates the output
3. Any other output specific details that require further elaboration
4. Source data listing number to identify the data listing(s) that are the source for the table

In general, tables will present results for all subjects within the determined analysis set. Column entries will display findings associated to the topic for all subjects of the analysis set. Row entries in tables are made only if data exists for at least one subject (i.e., a row with all zeros will not appear). Summary tables will clearly indicate the number of subjects to which the data apply and unknown or not performed will be distinguished from missing data.

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]).

8.2 Data Presentation

The following conventions will be applied to all data presentations and analyses.

- Summary statistics for categorical variables will consist of the number and percentage of responses in each level. The number and percentage of responses will be presented in the form XX (XX.X%).
- Unless specified differently, summary statistics for discrete variables will consist of the counts and percentages.
- Unless specified differently, summary statistics for continuous variables will consist of the number of subjects in the analysis (n), mean, median, standard deviation (SD), minimum, and maximum values.
- Unless specified differently, all mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to 2 more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.
- All p-values, if applicable, will be rounded to 4 decimal places. All p-values that round to 0.0000 will be presented as ‘<0.0001’ and p-values that round to 1.0000 will be presented as ‘>0.9999’. Two-sided P-values <0.05 will be considered to be statistically significant unless otherwise specified.
- Study Day 1 is defined as the date at which the patient receives IMP. All study days are determined relative to Day 1.

- Study days prior to Day 1 will be calculated as:

  Study Day = Assessment Date – Injection Date

- Study days after Day 1 will be calculated as:

  Study Day = Assessment Date – Injection Date + 1.

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

- Change from baseline will be calculated as follows:

  Change = post-baseline value - baseline value

  The baseline value is defined as the most recent non-missing measurement prior to or on the IMP injection.

- Date variables will be formatted as DDMMMYYYY for presentation. Unless complete dates are needed for calculation of durations or days between events, incomplete dates will not be imputed, but the available information will be listed (for example, __MAY2022 or _____2022).

  - If complete dates are needed for calculation of durations or days between events, but complete date was not reported/recorded, a clinically meaningful and/or conservative imputation will be applied to missing date parts.

  - Any imputation of incomplete dates will be included as a footnote to applicable tables, listings, or figures.

- Time variables will be displayed as 24-hour clock time HH:MM.

- Tables, figures, and listings will be presented in landscape orientation.

8.3 Analysis Sets

The analysis sets are defined as follows:

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

- Full Analysis Set: 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.

8.4 Statistical Hypothesis and Level of Significance

There are no formal tests of statistical hypotheses conducted in this study. 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).

8.5 Handling of Missing Data

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.

8.6 Handling of Uninterpretable Images

During the BIE the determination of striatal visibility will be forced so all images are considered "interpretable" with respect to the primary objective. Therefore, no images will be categorized as "uninterpretable".

8.7 Rules for Excluding Subjects from Analysis

All dosed subjects will be included in the analysis sets according to the analysis sets defined in Section 8.3 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.

8.8 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.

8.9 Subgroup Analysis

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

8.10 Statistical Software

All statistical analysis, tables, listings, and figures described in this SAP will be produced using SAS® software (Version 9.4 or higher) in SAS Grid Manager Environment.

9 STATISTICAL ANALYSES

9.1 Primary Efficacy Analysis

The following primary efficacy analysis will be performed for Full Analysis Set.

- 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).

9.2 Secondary Efficacy Analyses

The following secondary efficacy analyses will be performed for Full Analysis Set.

9.2.1 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%.

9.2.2 Reader Confidence in Striatal Visualization

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

- Number and percentage of Part 2 subjects (if applicable) with *high* confidence rating 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%.

9.2.3 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.

9.2.4 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.

9.3 [redacted]

[redacted]

- [redacted]

9.3.1 [redacted]

[redacted]

9.4 Secondary Safety Analysis

Safety analyses will be performed for treatment-emergent AEs, treatment-emergent SAEs, ADRs, serious ADRs, vital signs, physical examination, ECG, and laboratory tests. The secondary safety analysis will be performed using the Safety Analysis Set.

9.4.1 Analysis of Adverse Events

AEs and SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) 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

(SOC) and Preferred Term (PT) by Part 1 (and, if applicable, Part 2), and overall. A TEAE will be defined as an AE that begins or worsens between the start of IMP administration and the end of the follow-up period. Summaries will also be presented by AE intensity (severity) and relationship to IMP (Related or Not related [Unrelated]) as assessed by the investigator. Treatment-emergent SAEs will also be presented by Part 1 (and, if applicable, Part 2, and overall). All AEs will be listed. In addition to the data recorded in the database, the listings will include derived onset time and duration. Onset time will be calculated from the time of the start of the injection for TEAEs only. Narratives for deaths, SAEs, AEs leading to discontinuation and other clinically meaningful TEAEs will be included in the CSR. Similar analyses will be performed for ADRs.

9.4.2 Analysis of Clinical Laboratory Data

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 part 1 or part 2:

- The occurrence of 1 or more changes from baseline, at each post-administration time point, greater than 40% and 80% of the span of the normal limits (not applicable to qualitative parameters).
- The occurrence of post-administration values outside the normal limits (not applicable to qualitative parameters). Shift tables based on the normal range will be prepared.

9.4.3 Analysis of 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, 1.5ºC for body temperature, or 10 breaths per minute for respiration rate).
- The occurrence of post-administration values outside the normal limits. Shift tables based on the normal range will be prepared.

9.4.4 Analysis of Electrocardiograms Data

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: <30ms, 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. 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: $QTcB = \frac{QT}{\sqrt{RR}}$

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

9.4.5 Analysis of Limited Physical Examination Data

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 Part 1 or Part 2. Shift tables will be prepared.

9.5 Subject Disposition and Population Assignment

Subject disposition and population assignment will be listed. A summary table will be provided based on the Safety Analysis Set. Screen failure data summary table including the reason for screen failure will be provided separately, based on the screened subjects population.

9.6 Demographic and Baseline Characteristics

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. The demographics and baseline characteristics will be presented for the Safety Analysis Set.

9.7 Protocol Deviations

The protocol deviations will be listed for all screened subjects in accordance with ICH E3-GCP. All protocol deviations will be considered prior to database lock.

9.8 Medical and Surgical History

Medical and surgical histories will be summarized by counts and percentages.

9.9 Prior/Concomitant Medications

Prior and concomitant medications will be recorded and coded using a standard classification system and grouped by primary and secondary classes, if applicable.

9.10 Study Drug Exposure and Compliance

Administered doses of Altropane will be summarized by volume (in mL) and radioactivity administered (in MBq) 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.

10 DEVIATION FROM PLANNED ANALYSES

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.

11 CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSIS

There were no significant changes from the protocol-specified analyses.

12 REFERENCES

1. ICH. ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports (E3). 30 November 1995.

2. ICH. ICH Harmonised Tripartite Guideline: General considerations for clinical trials (E8). 17 July 1997.

3. ICH. ICH Harmonised Tripartite Guideline: Statistical principles for clinical trials (E9). 5 February 1998.

SIGNATURE PAGE

Date / Name	Justification / Role
Signed By: [redacted] Date of signature: 06-Sep-2023 12:47:07 GMT+0000	Justification: Approved Role: [redacted]
Signed By: [redacted] Date of signature: 06-Sep-2023 15:31:59 GMT+0000	Justification: Approved Role: [redacted]
Signed By: [redacted] Date of signature: 06-Sep-2023 21:56:52 GMT+0000	Justification: Approved Role: [redacted]
Signed By: [redacted] Date of signature: 04-Oct-2023 16:30:47 GMT+0000	Justification: I hereby confirm that this Digital Copy matches the Physical Source Document Role: [redacted]

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