Official Title: Assessment of the Biodistribution and Safety of [^{18}F]GTP1 in Healthy Japanese Subjects

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PROTOCOL FOR RESEARCH INVOLVING HUMAN SUBJECTS

Title of Project:	Assessment of the Biodistribution and Safety of [^{18}F]GTP1 in Healthy Japanese Subjects
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SPONSOR APPROVAL

CLINICAL PROTOCOL TITLE: Assessment of the Biodistribution and Safety of [^{18}F]GTP1 in Healthy Japanese Subjects

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Sponsor Signature [redacted]11190A9CEF8F53F225A Date

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[redacted]
Genentech, Inc.

INVESTIGATOR SIGNATURE

I have read the clinical protocol, and I agree to conduct this study in accordance with the protocol, Good Clinical Practice (GCP) and the current rules and regulations set forth by the applicable health authorities.

CLINICAL PROTOCOL TITLE: Assessment of the Biodistribution and Safety of [^{18}F]GTP1 in Healthy Japanese Subjects

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LIST OF ABBREVIATIONS

Abbreviation	Definition
Aβ	Amyloid beta
AD	Alzheimer's disease
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
AST	Aspartate aminotransferase
BP	Blood pressure
CRF	Case report form
CT	Computed tomography
CN	Cognitive normal
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HAT	Human alimentary tract
HPLC	High-performance liquid chromatography
ICH	International Conference on Harmonization
ICRP	International Commission on Radiological Protection
IHC	Immunohistochemistry
IRB	Institutional Review Board
IV	Intravenous
MBq	Megabequerels
mCi	Milicuries
MIRD	Medical Internal Radiation Dose
NDOB	Name date of birth
OLINDA	Organ Level Internal Dose Assessment
OTC	Over the counter
PET	Positron emission tomography
PMOD	Software for biomedical image quantification
PSP	Progressive supranuclear palsy
QA	Quality assurance
ROI	Region of interest
RR	Respiratory rate
SAE	Serious adverse event
SUV	Standard uptake value
TAC	Time-activity curve
VOI	Volume of interest
ULN	Upper limits of normal

WHO	World Health Organization

PROTOCOL SYNOPSIS

TITLE	Assessment of the Biodistribution and Safety of [^{18}F]GTP1 in Healthy Japanese Subjects
TEST PRODUCT	[^{18}F]GTP1
CLINICAL PHASE	1
INDICATION	Alzheimer's Disease
TRIAL OBJECTIVES	The overall goal of this protocol is to evaluate the biodistribution of [^{18}F]GTP1 as a tau targeted radiopharmaceutical. The specific objectives are: ● To determine the radiation dosimetry of [^{18}F]GTP1 in Japanese subjects ● To assess the safety and tolerability of a single dose of [^{18}F]GTP1 in Japanese subjects
STUDY DESIGN	Up to 6 healthy Japanese subjects (with at least 1 male and 1 female) will be recruited from the healthy controlpopulation by advertising and community outreach. This study will be performed in healthy control research participants. All study procedures will be conducted at Invicro in New Haven, CT. All subjects will undergo written informed consent and a screening evaluation including baseline clinical laboratory testing and baseline physicalevaluation. On the day prior to imaging subjects will be admitted for overnight confinement. On the day of imaging, subjects will be asked to undergo a single bolus injection of [^{18}F]GTP1 followed by serial whole-body positron emission tomography (PET) imaging scans of up to 6 hours. Immediately following the [^{18}F]GTP1 administration a series of approximately nine whole-body PET images from the vertex of the head to the thighs will be obtained. The subject would have at least two breaks during the scanningsession. An isotope transmission scan will be performed each time the subject lies on the camera. Commencingwith radiotracer injection, urine collection will be initiated. Standard Medical Internal Radiation Dose (MIRD) assumptions will be incorporated in dosimetry models for determination of radiation absorbed doses to target organs and whole-body. Urine samples collected over the imaging period will be evaluated to measure the excretion of [^{18}F]GTP1 through the urinary tract. A follow-up phone call to the subject will be conducted within 4 days (± 2 days) post-injection of [^{18}F]GTP1 to confirm subject well-being and to collect information about any new adverse events (AEs).
INCLUSION/EXCLUSION CRITERIA	Healthy volunteer subjects who are medically stable and meet the inclusion criteria and do not meet any of the exclusion criteria will be eligible for enrollment into the study. **Inclusion Criteria** ● Understand the study procedures and agree to participate by providing written informed consent. ● Are willing and able to comply with all study procedures and restrictions.

- Are males or females > 18 years of age.
- Are in good health as determined by the Investigator based on clinical evaluations including past medical history, physical examination, vitalsigns, electrocardiogram (ECG), and laboratory tests at screening and prior to radiopharmaceutical administration.
- For women of childbearing potential, agreement to remain abstinent (refrain from heterosexualintercourse) or use contraception, and agreement to refrain from donatingeggs, as defined below:
    - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausalstate (12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (ie, removalof ovaries, fallopian tubes, and/or uterus) or another cause as determined by the Investigator (eg, Müllerian agenesis). The definition of childbearing potentialmay be adapted for alignment with local guidelines or regulations.
    - Women of childbearing potentialmust remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for 30 days after the final dose of [^{18}F]GTP1. Women must refrain from donatingeggs during this same period.
    - Examples of contraceptive methods with a failure rate of <1% per year include bilateral tuballigation, male sterilization, hormonalcontraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
    - The reliability of sexualabstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usuallifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods) and withdrawalare not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local informed consent form
- Male subjects with partners of childbearing potentialmust commit to the use of two methods of contraception, one of which is a barrier method (ie, condom), for the study duration and 90 days after the last dose.
- Male subjects must not donate sperm for the duration of the study and 90 days after the last dose.
- Subjects must have both Japanese parents and all Japanese grandparents (self-reported).

Exclusion Criteria

- The subject has a clinically significant abnormallaboratory value and/or clinically significant unstable medical or psychiatric illness.

	• The subject is currently exposed to nicotine products or had regular nicotine exposure within a six-month period, to be verified by urine cotinine screening. • History of drug or alcohol abuse within 12 months prior to screening, or evidence of such abuse as indicated by the laboratory assays conducted duringthe screening visit. • The subject has evidence of clinically significant gastrointestinal (GI), cardiovascular, hepatic, renal, hematological, neoplastic, endocrine, neurological, immunodeficiency, pulmonary, or other disorder or disease. • Prior participation in other research protocols or clinical care in the last year in addition to the radiation exposure expected from participation in this clinical study, such that radiation exposure exceeds the effective dose of 50 mSv, which would be above the acceptable annuallimit established by the US Federal Guidelines. • Use of any prescription drugs (except approved forms of birth control noted in Section 5.2.3), herbal supplements, within four weeks prior to initial dosing. • Use of over the counter (OTC) medication (except acetaminophen), dietary supplements, or vitamins, within two weeks prior to initial dosing. • Has a known hypersensitivity to any component of the formulation of [^{18}F]GTP1 or related compounds. • Major surgery, or donation or loss of 400 mL or more of blood within four (4) weeks prior to initial dosing, or longer if required by local regulation. • Have a history or presence of any significant cardiovascular, respiratory, hepatic, renal, GI, endocrine, or neurological disorders which, in the opinion of the Investigator, are capable of altering the absorption, metabolism, or elimination of drugs or posing a health risk to participate in the study. • History of immunodeficiency diseases, including a positive HIV test result. • A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C antibody test result. • Positive pregnancy test result, if female. Women without documentation of non-childbearing potentialwill also receive pregnancy testing. • Women who are lactating and breastfeeding. • Unsuitable veins for repeated venipuncture. • Subject is, in the opinion of the Investigator, unsuitable in any other way to participate in this study.
LENGTH OF STUDY	For each subject participating, the duration of study participation will be up to 36 days. The completion of this study protocol requires each subject to complete three visits: Screening Visit, a single [^{18}F]GTP1 Whole-body PET Imaging Visit and a Follow-up Phone Call. The screening visit will include vital signs, ECG and a physical exam. In addition, each subject will complete clinical assessments and clinical safety labs to ensure the subject is medically stable to complete the study protocol. The screening procedures will occur

	within 30 days of the imaging visit. After subjects have met all study entry criteria, subjects will participate in a single [^{18}F]GTP1 PET whole-body imaging session. The Follow-up Phone Call for AE assessment will occur within approximately 4 days (± 2 days) following the [^{18}F]GTP1 PET imaging.
OUTCOMES	
WHOLE-BODY BIODISTRIBUTION OUTCOME MEASURES	The following parameters will be evaluated: ● Totalsource organ counts based on individualized organ volumes of interest (VOIs) ● Source organ uptake and washout with calculation of the total number of disintegrations (or residence time) using the area under the time-activity curve divided by the injected dose of radiopharmaceutical Radiation absorbed dose estimates based on the MIRD methodology utilizing urine data and International Commission on Radiological Protection (ICRP) GI tract kinetics
SAFETY OUTCOME MEASURES	Safety will be evaluated by review of AEs, clinical laboratory tests, vital signs, physical findings, and ECG findings at screening and intervals throughout the imaging visit. A safety Follow-up Phone Call within 4 days (± 2 days) after imaging will assess for AEs and concomitant medications.
INVESTIGATIONAL AGENT	All subjects will receive a single injection of [^{18}F]GTP1, a PET radioligand selective for tau, once during the course of study participation. (See Section 5.2.2 for full details on [^{18}F]GTP1 administration.)
PROCEDURES	SCREENING: Subject eligibility will be evaluated during screening. The Whole-body [^{18}F]GTP1 PET Imaging Visit will occur within 30 days of screening. Screening will include informed consent, medical history and demography collection, review of medications, review of inclusion and exclusion criteria, urine drug and alcoholtesting, vital signs, ECG, physical exam, and clinical labs to ensure the subject is medically stable to complete the study. All women of childbearing potentialmust have a negative serum pregnancy test. WHOLE-BODY [^{18}F]GTP1 PET IMAGING VISIT: [^{18}F]GTP1 will be synthesized in Invicro's Good Manufacturing Practice (GMP) chemistry laboratory under an approved IND. All women of childbearing potentia lwill have a urine pregnancy test determined to be negative within 24 h before PET tracer injection. Whole-body PET imaging will be performed, acquiring an emission scan for each bed position and an isotope transmission scan or computed tomography (CT) scan each time the subject lies on the camera. Subjects will first receive an isotope transmission scan or CT scan. Then subjects will receive a bolus intravenous (IV) administration of [^{18}F]GTP1. Immediately following the [^{18}F]GTP1 administration, a series of whole-body PET images from the vertex of the head to the thighs will be obtained over a period of up to 6 hours. The subject will have at least two breaks over a six-hour scanning session. Commencingwith radiotracer injection, urine collection will be initiated. Standard MIRD assumptions will be

	incorporated in dosimetry models for determination of radiation absorbed doses to target organs and whole-body. Urine samples collected over the imaging period will be evaluated to measure the excretion of [^{18}F]GTP1 through the urinary tract. During the imaging, safety assessments will be performed, including ECGs, clinical labs, and vitalsign measurements. If a PET scan is cancelled due to synthesis failure of [^{18}F]GTP1 or camera problems, injection of [^{18}F]GTP1 will not occur, and the scanning procedures listed above will be performed on another day in the same subject. FOLLOW-UP PHONE CALL: A follow-up phone call for AE assessment will occur within 4 days (± 2 days) post-injection following the [^{18}F]GTP1 PET scan imaging.
STATISTICAL METHODS	
DEMOGRAPHICS	All data for background and demographic variables will be listed. For these parameters, summary statistics will be provided by subject. Relevant medicalhistory, current medical conditions, results of laboratory screens, and any other relevant information will be listed by subject.
SAFETY	Analysis of safety parameters will include all vital signs, ECG, clinical laboratory tests, physical findings, and AE data listed by subject and visit/time. Summary statistics will be provided by visit/time.
IMAGING	Descriptive statistics will be applied to describe biodistribution of [^{18}F]GTP1 by organ.
SAMPLE SIZE JUSTIFICATION	The sample size for this study was determined by practical considerations and is not based on statistical power calculations. Up to 6 evaluable subjects (with at least 1 male and 1 female) will complete this study. While the sample size is small, this should be adequate to determine biodistribution and dosimetry calculations of [^{18}F]GTP1 in Japanese subjects.

Table 1: Schedule of Assessments

	Screening Visit	[18F]GTP1 Whole-body PET Imaging Visit				Follow-up Phone Call
Day	**Within 30 days of Imaging visit**	**Check-in**	**Within 30 days of screening**			**4 days (± 2 days) post-injection**
Time in relation to radioligand injection		**Day prior to PET Imaging**	**Pre-injection**	**Imaging period**	**Post scan**	
Inclusion/Exclusion Criteria	X		X			
Informed Consent	X					
Medical History	X					
Demography	X					
Physical Examination	X	X[1]				
Height and Weight Measurement[2]	X		X			
Vital Signs[3]	X		X	X	X	
ECG[4]	X		X	X	X	
Hematology, Blood Chemistry, Serology & Urinalysis[5]	X		X		X	
Serum Pregnancy Test (if applicable)[6]	X					
Urine Pregnancy Test (if applicable)[6]			X			
Urine Drug, Alcohol, and Cotinine Screen	X	X				
[18F]GTP1 Injection[7]			X			
Whole-body PET Imaging				X		
Urine Collection[8]				X	X	
Adverse Events	X	X	X	X	X	X
Concomitant Medications	X	X	X			X

[1] The physicalwill be symptom-directed.

[2] Height will only be measured during screening.

[3] Vital signs (systolic and diastolic blood pressure [BP], respiratory rate, and pulse rate) will be obtained after at least 5 minutes of rest in the supine position during screening and at the Whole-body [^{18}F]GTP1 PET Imaging Visit at the following timepoints: pre-injection and approximately 20, 50, 80, and 120 minutes following injection. Oral body temperature will be obtained during screening and at the Whole-body [^{18}F]GTP1 PET Imaging Visit at the following timepoints: pre-injection and at the completion of imaging.

[4] Electrocardiogram (ECG) will be obtained during screening and at the Whole-body [^{18}F]GTP1 PET Imaging Visit at the following timepoints: pre-injection, approximately 25 and 45 minutes following injection, and at the completion of the imaging session.

[5] Safety labs (hematology, blood chemistry and urinalysis) will be obtained during screening and at the Whole-body [^{18}F]GTP1 PET Imaging Visit at the following timepoints: pre-injection and at the completion of imaging. Serology (HIV and Hepatitis B & C testing) will be performed at screening only. Hematology will include hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (absolute count and percentage), and platelet count. Blood chemistry assessments will include albumin, albumin/globulin ratio (calculated), alkaline phosphatase, alanine transaminase (ALT), aspartate aminotransferase (AST), bun/creatinine ratio (calculated), calcium, carbon dioxide, chloride, creatinine with glomerular filtration rate (GFR) estimated, globulin (calculated), glucose, potassium, sodium, totalbilirubin, totalprotein, urea nitrogen. Urinalysis will include leukocytes, nitrites, urobilinogen, protein, pH, blood (erythrocytes), specific gravity, ketone, bilirubin and glucose

[6] For women of childbearing potential, a serum pregnancy test will be performed during screening. Urine pregnancy test will be done at the Whole-body [^{18}F]GTP1 PET Imaging Visit. The test will occur within 24 hours prior to the injection of [^{18}F]GTP1 injection. Women without documentation of non-childbearingpotentialwill also receive pregnancy testing.

[7] Approximately, but not exceeding, 370 MBq (10 mCi) of [^{18}F]GTP1 will be injected IV by bolus injection.

[8] Urine samples will be collected over the imaging period and at scan completion to measure the excretion of [^{18}F]GTP1 through the urinary tract.

1. INTRODUCTION

1.1. Background

Molecular imaging biomarkers have the potential to play a key diagnostic role in tauopathies. Tau protein has been identified as one of the key pathological features of Alzheimer's disease (AD) (Wood et al., 1986; Grundke et al., 1986; Kosik et al., 1986). Given the role of tau protein in the pathology of AD and other non-AD tauopathies, expanding neuroimaging biomarkers to include a tau radiotracer is a logical next target offering the potential to improve our understanding of the pathological process in AD and other tauopathies. Tau is the primary protein composing neurofibrillary tangles and unlike amyloid β (Aβ) deposition, post-mortem studies have shown that neurofibrillary tangle density correlates with neurodegeneration and cognitive impairment (Duyckaerts et al., 1987, 1990; Delaere et al., 1989; Arriagada et al., 1992; McLean et al., 1999). Thus, a positron emission tomography (PET) imaging agent that binds to aggregated tau has the potential to serve as a biomarker for disease severity or neurodegeneration and may be useful for monitoring disease progression in therapeutic trials.

Development of a tau radiotracer would provide a useful tool to evaluate tau specific therapeutics for both AD and non-AD tauopathies. Tau hyperphosphorylation occurs as a result of an imbalance of the kinase and phosphatase activities, which normally tightly regulate its phosphorylation. In addition to this pathogenic hyperphosphorylation, tau dissociates from microtubules and self-aggregates to form insoluble oligomers ultimately progressing to the macroscopic tangles evident in AD and non-AD tauopathies. Potential interventions for tauopathies might include the inhibition of kinases responsible for hyperphosphorylation and many candidate kinases are currently under investigation (Churcher, 2006). The search for these treatments is paralleled by a pursuit for a means to identify those patients best suited for the therapy and methods to non-invasively determine the efficacy of treatments with the potential to reduce tau.

Until recently, post-mortem examination of brain tissues was the only means available for directly evaluating the changes occurring in the brain in AD and non-AD tauopathies. In the last decade, the development of highly specific techniques for imaging the brain in AD and other dementias has expanded our ability to measure the process of the disease over time in a living individual. Briefly, these techniques involve intravenous (IV) administration of radioactively-labeled compounds which bind to selective target sites in brain. PET is able to detect the spatial distribution of the radioactive compound in the brain and can be used as an objective, sensitive, and accurate method to quantify the concentration of the targets site in different brain regions. Using these PET techniques, Aβ aggregates have been successfully imaged in several studies in AD patients using high affinity C-11 and ^{18}F-labeled PET tracers (PIB and florbetapir, AV-1) (Klunk et al., 2004ab; Clark et al, 2011; Hyman 2012). Now there are multiple studies comparing amyloid PET scans to histopathologic assessment that support the relationship between PET amyloid imaging results and cortical neuritic plaque density (Stephens 2014; Ruiqig N 2013; Leinonen, 2008; Sojkova, 2011).

The ability to image brain amyloid has offered an important advance for the diagnosis of neurodegenerative conditions. In contrast to Aβ neuritic plaques, the density and distribution of

phosphorylated tau, aggregated in neurofibrillary tangles, increases with AD-related cognitive impairment and correlates with neurodegeneration (Dickson et al., 1997; Duyckaerts et al., 1987). Thus, the development of PET imaging agent that binds to aggregated tau offers the potential to improve our understanding of the molecular mechanism of neurofibrillary degeneration and is critical to developing a rational therapeutic treatment of AD and related tauopathies.

[^{18}F]GTP1 (also known as [^{18}F]G02941054, and referred to as [^{18}F]MNI-798 in some previous clinical studies) has been developed as a positron emitting radiopharmaceutical for *in vivo* imaging of tau protein aggregates. In a cross-sectional study of cognitively normal and prodromal to moderate AD patients, [^{18}F]GTP1 exhibited good brain penetration and rapid washout, excellent test-retest reproducibility, and favorable radiation dosimetry profile. In general, SUVR values increased with disease severity and differentiated between AD and cognitive normal (CN) cohorts and between brain regions predicted to contain high versus low tau burden, supporting the use of [^{18}F]GTP1 PET imaging as a biomarker of tau pathology in AD (Bohórquez et al.). The study drug is referred to as [^{18}F]GTP1 throughout the protocol and informed consent documents given that the radiopharmaceutical bears the label of [^{18}F]GTP1 and that the names are synonymous.

1.2. Human Safety and Tolerability of [^{18}F]GTP1

As of 1 February 2019, [^{18}F]GTP1 has been evaluated in three completed clinical studies (e0040, e0048, and e0049) and is being evaluated in five ongoing studies: Study GN30009, Substudy WN29922/WN39658, Study GN39763, Substudy BN29552/BN29553, and Study GN40040. All studies in the clinical development program have been conducted in accordance with the principles of Good Clinical Practice. A total of 23 healthy volunteers, 470 patients with AD, and 3 patients with progressive supranuclear palsy (PSP) have been exposed to at least one dose of [^{18}F]GTP1, and there have been a total of 702 doses in total across all studies. Two of the 470 patients with AD were enrolled in more than one study (in Study e0048 and in Study GN30009).

[^{18}F]GTP1 was found to be generally well tolerated. As of 1 February 2019, no deaths or adverse events (AEs) of special interest were reported. One serious adverse event (SAE) was reported in Study GN30009: a Grade 3 urinary tract infection, reported in a [redacted]-year-old [redacted] patient with moderate AD; the SAE was assessed as not related to study drug. One [redacted]-year-old [redacted] patient with prodromal AD discontinued the study due to a non-serious moderate headache and non-serious cervical neck pain 4 days after a baseline [^{18}F]GTP1 PET scan; both events were assessed as not related to study drug.

2. Study Objectives and Endpoints

The overall goal of this protocol is to evaluate the biodistribution of [^{18}F]GTP1 as a tau targeted radiopharmaceutical.

Objectives	Endpoints
To determine the radiation dosimetry of [^{18}F]GTP1 in Japanese subjects	• Total source organ counts based on individualized organ volumes of interest (VOIs) • Source organ uptake and washout with calculation of total number of disintegrations (or residence time, or kinetic values) using the area under the time-activity curve divided by the injected dose of radiopharmaceutical • Radiation absorbed dose estimates based on the MIRD methodology utilizing urine data and International Commission on Radiological Protection (ICRP) gastrointestinal (GI) tract kinetics
To assess the safety and tolerability of a single dose of [^{18}F]GTP1 in healthy Japanese subjects	Safety will be evaluated by review of: • AEs • Clinical laboratory tests • Vital signs • Physical findings • ECG findings

3. INVESTIGATIONAL PLAN

3.1. Study Design

This is an open-label study to evaluate the whole-body biodistribution of [^{18}F]GTP1 in up to 6 evaluable healthy Japanese subjects (with at least 1 male and 1 female) to determine dosimetry for future studies. Subjects will be recruited by Invicro from the healthy population by advertising and community outreach. This study protocol requires each subject to complete the following visits: Screening Visit, Whole-body [^{18}F]GTP1 PET Imaging Visit, and a Follow-up Phone Call. Screening evaluations will occur within 30 days of the Whole-body [^{18}F]GTP1 PET Imaging Visit and may occur over multiple days. Screening procedures will include signing of the informed consent form, review of inclusion and exclusion criteria, collection of medical history and medication information, collection of demography information, physical examination, height and weight measurement, vital signs (respiratory rate, pulse rate, blood pressure [BP] and oral body temperature), laboratory tests (hematology, blood chemistry, and urinalysis), ECG, serum pregnancy test (if applicable), and drug and alcohol screening. Assessments will determine if the subject is medically stable to complete the study protocol and meets the eligibility criteria.

Subjects will be confined on the day prior to [^{18}F]GTP1 imaging in the overnight confinement unit. On the day of check-in, the subjects will receive a symptom-directed physical assessment, drug and alcohol screening, and review of concomitant medications.

The following day, there will be a review of inclusion and exclusion criteria, a weight measurement, a review of concomitant medications, and a urine pregnancy test (if applicable) to assess if the subject still meets the eligibility criteria. For the [^{18}F]GTP1 imaging session, a catheter will be placed for IV administration of [^{18}F]GTP1. Subjects will receive an IV bolus injection of [^{18}F]GTP1 (see Section 5.2.2 for full details on [^{18}F]GTP1 administration). Immediately following the [^{18}F]GTP1 administration, a series of whole-body PET images from the vertex of the head to the thighs will be obtained over a period of up to 6 hours. The subject will have at least two breaks over a six-hour scanning session. An isotope transmission scan or computed tomography (CT) scan will be performed each time the subject lies on the camera. Commencing with radiotracer injection, urine collection will be initiated. Standard MIRD assumptions will be incorporated in dosimetry models for determination of radiation absorbed doses to target organs and whole-body. Urine samples collected over the imaging period and at the completion of imaging will be evaluated to measure the excretion of [^{18}F]GTP1 through the urinary tract. Safety assessments (ie, vital signs, clinical laboratory assessments, and ECGs) will be performed during the imaging visit. The subjects will be discharged after all assessments are complete.

AEs will be assessed from screening until the subject discontinues study participation. An Investigator or designee will evaluate the subject for AEs prior to discharge from the imaging center on the day of the Whole-body [^{18}F]GTP1 PET Imaging Visit. Subjects who experience an AE will not be discharged from the imaging center until the event has resolved or stabilized.

A Follow-up Phone Call to the subject will be conducted within 4 days (± 2 days) post-injection of [^{18}F]GTP1, to confirm subject well-being and to collect information about any new AEs.

3.2. Study Rationale

This is an open-label study to evaluate the reliability of using microdoses (less than 10 µg) of radiotracer [^{18}F]GTP1 for the evaluation of the whole-body biodistribution of the tracer in 6 healthy Japanese subjects (with at least 1 male and 1 female). Evaluating a small number of healthy subjects is standard to develop dosimetry calculations and to evaluate safety and tolerability. While [^{18}F]GTP1 dosimetry studies and safety studies have been performed in healthy subject populations, the dosimetry and safety of [^{18}F]GTP1 have not been specifically studied in Japanese subjects.

The development of a PET tracer for tau offers the possibility to utilize such an agent toward the development of investigational therapies and the further understanding of the pathophysiology of AD and other tauopathies and could therefore provide a societal benefit by accelerating the development of new treatments for AD and other tauopathies.

There is no direct benefit to subjects who participate in this protocol.

3.3. Risk/Benefit for this Study

There may be unknown risks to [^{18}F]GTP1, but given that the investigational agent will be administered as a single microdose, the risk for a pharmacological effect is considered to be minimal. The potential benefit of the agent is the availability of a radiotracer targeting tau protein offering the possibility of improvement in diagnostic accuracy of AD and for measuring changes in tau with novel AD therapies. The primary risk associated with this study involves radiation exposure. The tracer doses used in this study and the experience of the Investigators in the execution of PET studies in humans in addition to the potential benefit of the [^{18}F]GTP1 ligand for diagnostic uses make the relative risk/benefit ratio quite favorable.

4. POPULATION

The Investigator will ensure that all subjects being considered for the study meet the eligibility criteria. Subject selection is to be established by checking through all inclusion/exclusion criteria at screening and at the imaging visit. A relevant record (eg, checklist) will be stored with the source documentation at the study site.

The study population will be composed of healthy Japanese subjects (with at least 1 male and 1 female). Subjects will be enrolled until up to 6 evaluable subjects complete the study.

4.1. Inclusion Criteria

Subjects eligible for inclusion in this study only if they meet **all** the following criteria:

- Understand the study procedures and agree to participate by providing written informed consent.
- Are willing and able to comply with all study procedures and restrictions.
- Are males or females $\geq$ 18 years of age.
- Are in good health as determined by the Investigator based on clinical evaluations including past medical history, physical examination, vital signs, ECG, and laboratory tests at screening and prior to radiopharmaceutical administration.
- For women of childbearing potential, agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:
    - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (ie, removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the Investigator (eg, Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.
    - Women of childbearing potential must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for 30 days after the

final dose of [^{18}F]GTP1. Women must refrain from donating eggs during this same period.

- Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local informed consent form.

- Male subjects with partners of childbearing potential must commit to the use of two methods of contraception, one of which is a barrier method (ie, condom), for the study duration and 90 days after the last dose.
- Male subjects must not donate sperm for the duration of the study and for 90 days after the last dose.
- Subjects must have both Japanese parents and all Japanese grandparents (self-reported).

4.2. Exclusion Criteria

Subjects fulfilling **any** of the following criteria are not eligible for inclusion in this study:

- The subject has a clinically significant abnormal laboratory value and/or clinically significant unstable medical or psychiatric illness.
- The subject is currently exposed to nicotine products or had regular nicotine exposure within a six-month period, to be verified by urine cotinine screening.
- History of drug or alcohol abuse within 12 months prior to screening, or evidence of such abuse as indicated by the laboratory assays conducted during the screening visit.
- The subject has evidence of clinically significant GI, cardiovascular, hepatic, renal, hematological, neoplastic, endocrine, neurological, immunodeficiency, pulmonary, or other disorder or disease.
- Prior participation in other research protocols or clinical care in the last year in addition to the radiation exposure expected from participation in this clinical study, such that radiation exposure exceeds the effective dose of 50 mSv, which would be above the acceptable annual limit established by the US Federal Guidelines.
- Use of any prescription drugs (except approved forms of birth control noted in Section 5.2.3), herbal supplements, within four weeks prior to initial dosing.
- Use of over the counter (OTC) medication (except acetaminophen), dietary supplements, or vitamins, within two weeks prior to initial dosing.
- Has a known hypersensitivity to any component of the formulation of [^{18}F]GTP1 or related compounds.

- Major surgery, or donation or loss of 400 mL or more of blood within four (4) weeks prior to initial dosing, or longer if required by local regulation.
- Have a history or presence of any significant cardiovascular, respiratory, hepatic, renal, GI, endocrine, or neurological disorders which, in the opinion of the Investigator, are capable of altering the absorption, metabolism, or elimination of drugs or posing a health risk to participate in the study.
- History of immunodeficiency diseases, including a positive HIV test result.
- A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C antibody test result.
- Positive pregnancy test result, if female. Women without documentation of non-childbearing potential will also receive pregnancy testing.
- Women who are lactating and breastfeeding.
- Unsuitable veins for repeated venipuncture.
- Subject is, in the opinion of the Investigator, unsuitable in any other way to participate in this study.

5. TREATMENT

5.1. Investigational Agent

[^{18}F]GTP1is a clear solution formulated for IV injection. [^{18}F]GTP1 is formulated in 0.9% sodium chloride injection containing ethanol and sodium ascorbate. The final product bears a label with the following items: total activity (mCi), volume (mL), strength (mCi/mL), calibration date and time, batch number, study ID and shelf life. [^{18}F]GTP1 will be stored at ambient temperature in its original container.

[^{18}F]GTP1 is supplied as a sterile non-pyrogenic solution in sterile borosilicate glass vials with gray butyl septa and aluminum ring seals. The vial is contained within an outer lead or tungsten shield ("pig") to protect from γ radiation.

5.2. Treating the Subject

5.2.1. Study Drug Supply and Storage

The investigational agent, the radiopharmaceutical [^{18}F]GTP1, will be produced in the Invicro radiochemistry facility at 60 Temple Street, New Haven, CT. Quality control testing includes strength by gamma assay, radiochemical purity and identity (HPLC), drug mass and total impurity quantification, pH, visual inspection, pyrogenicity and sterility by compendial tests. The final drug product is provided as a clear, sterile solution in a 30 mL glass vial. The vial is contained within a secondary lead or tungsten radiation shield and may be stored upright at ambient temperature and humidity until administration. The investigational agent must be used within the expiration time (10 hours).

5.2.2. Administration of Investigational Agent

Study center personnel will administer [^{18}F]GTP1 IV as a bolus injection. Prior to PET imaging, subjects will have an IV catheter (for radiotracer administration) inserted according to standard clinical practice. Each subject will receive a single injection of [^{18}F]GTP1. The radioligand, [^{18}F]GTP1, will be injected IV at a dose of not more than 370 MBq (≤10 mCi), with a maximum drug mass dose of 10 µg and maximum volume of 10 mL. The injection will occur as a bolus followed by a 10 mL saline flush. Qualified study staff will accompany subjects during PET imaging procedures.

5.2.3. Concomitant Treatment

Use of any prescription drugs, herbal supplements, within four (4) weeks prior to initial dosing, and/or OTC medication, dietary supplements (vitamins included) within two (2) weeks prior to initial dosing is prohibited. Approved forms of prescription birth control (hormonal contraceptives, hormone-releasing intrauterine devices, and copper intrauterine devices) are not prohibited and will be documented as a concomitant medication. If needed (ie, an incidental and limited need), acetaminophen is acceptable, but must be documented as a concomitant medication/significant non-drug therapy.

5.2.4. Discontinuation of Study Treatment and Premature Subject Withdrawal

The study will be stopped, and no further dosing will occur, pending a full safety review if one or more study drug related SAEs are reported. If a subject withdraws or discontinues the study for any reason, the subject will be replaced until there are up to (with at least 1 male and 1 female) evaluable subjects.

Subjects may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature withdrawal occurs for any reason, the Investigator must make every effort to determine the primary reason for a subject's premature withdrawal from the study and document this information in the study source.

Subjects may develop AEs or abnormalities in vital signs, ECG, physical examination, or laboratory determinations during their participation in the study. If these occur, the Investigator may discontinue a subject from the study if, in his/her clinical judgment, continued participation would result in undue risk or further worsening of the condition.

For subjects who are lost to follow-up (ie, those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the Investigator should show due diligence by documenting attempts to contact the subject, eg, dates of telephone calls, registered letters, or other attempts to communicate.

5.2.5. Study Completion and Post-Study Treatment

The study will be complete when the last subject (including replacement subjects) completes the final phone visit.

The Investigator must provide follow-up evaluation by phone or by clinic visit for all subjects who are prematurely withdrawn from the study or must refer them for appropriate ongoing care.

6. VISIT SCHEDULE AND ASSESSMENTS

The full assessment schedule is presented just before Section 1 (Introduction) of this protocol.

6.1. Study Schedule

Study procedures will be performed at three visits: the Screening Visit (may be performed on more than one day), Whole-body [^{18}F]GTP1 PET Imaging Visit (including check-in procedures), and a Follow-up Phone Call.

6.1.1. Screening Visit

Screening evaluations will occur within 30 days prior to the imaging visit. Before any of the screening evaluations are performed for the specific purpose of this study, the subject must provide informed consent for this study in compliance with Good Clinical Practice (GCP) and IRB requirements. Collection of AE data will begin after the informed consent is signed and will continue until the subject discontinues study participation. The screening procedures listed below will be performed and documented to assess whether a subject meets inclusion/exclusion criteria:

- Inclusion and exclusion criteria will be reviewed.
- A medical history will be taken, and demographics will be recorded.
- Concomitant medication information will be obtained.
- Vital signs will be taken after at least 5 minutes of rest in the sitting position, including systolic and diastolic BP, pulse rate, respiratory rate (RR), and oral temperature.
- A complete physical examination will be performed, including height and weight. Rectal, breast and genital examinations are not required as part of this examination.
- A 12-lead ECG will be performed.
- Blood samples will be collected for clinical chemistry, hematology, HIV, and Hepatitis B and C evaluations.
- Urine sample will be collected for urinalysis, drugs of abuse, alcohol, and cotinine screen.
- Serum pregnancy test, if female of childbearing potential.

6.1.2. Whole-body [^{18}F]GTP1 PET Imaging Visit

AEs will be continuously monitored during the Whole-body [^{18}F]GTP1 PET Imaging Visit. All eligible subjects will be admitted to the overnight confinement unit on the day prior to the Whole-body [^{18}F]GTP1 PET Imaging Visit, which will occur within 30 days of screening. Upon check-in, the following procedures will be performed:

- Urine drug, alcohol, and cotinine screening will be performed.
- A symptom-directed physical will be performed.

- Concomitant medications will be recorded.

On the day of imaging, procedures will be performed to ensure that the subject still meets the eligibility criteria. Prior to imaging the following procedures will be performed:

- Review of inclusion and exclusion criteria.
- Subject weight measurement will be obtained.
- Concomitant medications will be recorded.
- Vital signs will be taken just prior to imaging (after at least 5 minutes of rest in the sitting position), including systolic and diastolic BP, pulse rate, RR, and oral temperature.
- A 12-lead ECG will be performed.
- Blood samples will be collected for clinical chemistry and hematology, and a urine sample will be collected for urinalysis.
- Urine pregnancy test, if female of childbearing potential (which must be confirmed as negative within 24 hours prior to [^{18}F]GTP1 injection).

The subject will have a venous catheter placed in the forearm for administration of [^{18}F]GTP1, and the subject will lie supine on the camera in preparation for [^{18}F]GTP1 administration. [^{18}F]GTP1 will be administered as a bolus IV injection (See Section 5.2.2 for full details on [^{18}F]GTP1 administration.). Immediately following [^{18}F]GTP1 administration, PET acquisition will begin. PET scans will be acquired over approximately 6 hours, and the subject may have two breaks during the scanning period. A CT scan will be performed each time the subject lies on the camera. The following procedures will be performed during PET imaging:

- Vital signs will be taken, including systolic and diastolic BP, pulse rate, and RR (taken after at least 5 minutes of rest in the sitting position), approximately 20, 50, 80, and 120 minutes post-injection of [^{18}F]GTP1.
- ECG will be taken approximately 25 and 45 minutes post-injection of [^{18}F]GTP1, and at completion of PET imaging.
- The subject will be asked to void during scheduled breaks in the imaging session. Urine will be collected over a period of up to 6 hours throughout the imaging visit for dosimetry analysis.

At the completion of imaging the following procedures will be performed:

- Vital signs will be taken, including systolic and diastolic BP, pulse rate, RR, and oral body temperature (taken after at least 5 minutes of rest in the sitting position).
- ECG will be taken.
- Blood samples will be collected for clinical chemistry and hematology, and a urine sample will be collected for urinalysis.
- Urine will be collected for dosimetry analysis.

The subject will be discharged after all assessments are complete and the subject has been evaluated for AEs. Subjects who experience an AE will not be discharged until the event has resolved or stabilized.

6.1.3. Safety Follow-up Phone Visit

Subjects will be contacted by phone approximately 4 days (± 2 days) after the imaging visit, for evaluation of AEs and concomitant medications. The subject will be interviewed to determine if any new AEs occurred or if there have been any new concomitant medications administered. If new medical symptoms have occurred that require further assessment the subject will be asked to return to the research clinic for further evaluation.

6.2. Whole-body [^{18}F]GTP1 PET Imaging Procedures

Whole-body PET imaging will be performed on a Biograph 6 PET/CT camera acquiring an emission scan for each bed position and a CT scan will be performed each time the subject lies on the camera. Subjects will then receive a bolus IV administration of [^{18}F]GTP1 (See Section 5.2.2 for full details on [^{18}F]GTP1 administration.). Immediately following the [^{18}F]GTP1 administration a series of whole-body PET images from the vertex of the head to the thighs will be obtained over a period of up to 6 hours. The subject will have at least two breaks over a six-hour scanning session.

6.3. Urine Collection for Dosimetry Analysis

Commencing with radiotracer injection, urine collection will be initiated. Standard MIRD assumptions will be incorporated in dosimetry models for determination of radiation absorbed doses to target organs and whole-body. Urine samples collected over the imaging period will be evaluated to measure the excretion of [^{18}F]GTP1 through the urinary tract.

6.4. Safety Evaluations

The Investigators will be responsible for monitoring the safety of the subjects that enter this trial. Safety will be evaluated by assessment of AEs, clinical safety laboratory tests, ECG, and vital signs as outlined in the Schedule of Assessments.

6.4.1. Physical Examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, extremities, musculoskeletal, and neurological. Rectal, breast and genital examinations are not required as part of this examination. A symptom-directed exam will be completed upon admission for the Whole-body [^{18}F]GTP1 Imaging Visit; if the subject has new symptoms, only the systems relevant to the symptoms will be examined.

Information for all physical examinations must be included in the source documentation at the study site and will be recorded. Significant findings that are present prior to injection of [^{18}F]GTP1 will be included in the medical history in the subject's source documents. Significant findings made after injection of [^{18}F]GTP1, which meet the definition of an AE must be recorded as an AE.

6.4.2. Vital Signs

Vital signs include systolic and diastolic BP, RR, oral temperature and pulse rate. Vital signs will be obtained during screening and at the Whole-body [^{18}F]GTP1 PET Imaging Visit, as outlined in the Schedule of Assessments. Temperature will not be taken while the subject is actively undergoing imaging, to avoid any head movement.

6.4.3. Height and Weight

Height and body weight (in indoor clothing) will be measured at screening, and weight will be recorded again at the Whole-body [^{18}F]GTP1 PET Imaging Visit.

6.4.4. Laboratory Evaluations

In the case where a laboratory value is outside the reference range at screening, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once (for the purpose of inclusion) and in any case, prior to enrollment/randomization, to rule out laboratory error.

In all cases, the Investigator will document the clinical considerations (ie, result was/was not clinically significant and/or medically relevant) in allowing or disallowing the subject to continue in the study.

Clinically relevant deviations of laboratory test results will be reported as an AE, if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant.

6.4.4.1. Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (absolute count and percentage), and platelet count will be measured.

6.4.4.2. Clinical chemistry

A standard chemistry panel will be obtained including electrolytes, liver function tests and analytes to measure renal function, including albumin, albumin/globulin ratio (calculated), alkaline phosphatase, ALT, AST, bun/creatinine ratio (calculated), calcium, carbon dioxide, chloride, creatinine with GFR estimated, globulin (calculated), glucose, potassium, sodium, total bilirubin, total protein, urea nitrogen.

6.4.4.3. Urinalysis

A midstream urine sample will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments, and a standard, semi-quantitative dipstick performed to evaluate for common urinary tract conditions. Urine dipstick will include leukocytes, nitrites, urobilinogen, protein, pH, blood (erythrocytes), specific gravity, ketone, bilirubin and glucose.

6.4.4.4. Serology

Subjects will be assessed for HIV, Hepatitis B surface antigen, and Hepatitis C antibody results during screening.

6.4.4.5. Pregnancy testing

A serum beta-hCG pregnancy test will be performed at screening for females of childbearing potential. Urine pregnancy testing will be performed for women of childbearing potential within 24 hours prior to the administration of a radioligand using a standard kit.

6.4.5. Electrocardiogram (ECG)

A standard 12 lead ECG will be performed. Interpretation of the tracing must be made by a qualified physician and documented on the ECG section of the case report form (CRF). Each ECG tracing should be labeled with:

Study number

Subject NDOB (Name Date of Birth) code

Subject number

Date

Time

All ECG tracings will be kept in the source documents at the study site. Only clinically significant abnormalities will be reported on this page. Clinically significant abnormalities should also be recorded as relevant medical history/current medical condition.

The ECG parameters to be reported in the database will include:

Date and time of ECG

Heart rate

PR interval

QT interval

QTc interval

QTcF interval

QRS duration

The overall interpretation will be collected with a Yes/No statement to confirm if any clinically significant abnormalities are present which need to be specified further.

Original ECG tracings, appropriately signed, will be archived at study site.

7. SAFETY MONITORING

7.1. Adverse Events

Collection of AEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject discontinues study participation (eg, screen failure, study withdrawal, or study completion [ie, Follow-up Phone Call]).

7.1.1. AE Definition

An AE is the appearance or worsening of any undesirable sign, symptom, or medical condition, even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation during any phase of the study. Medical conditions/diseases present before starting study drug are only considered AEs if they worsen after starting study drug. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of AEs should be sought by non-directive questioning of the subject at each visit during the study. AEs also may be detected when they are volunteered by the subject during or between visits or through physical examination, laboratory test, or other assessments. All AEs must be recorded on the Adverse Event Form with information regarding the intensity, relationship to study drug (imaging ligand), relationship to study procedures, duration and whether it meets the criteria as a SAE.

The World Health Organization (WHO) toxicity grading scale (see Section 12) will be used for assessing AE severity. Table 2 will be used for assessing severity for AEs that are not specifically listed in the WHO toxicity grading scale.

Table 2: Grading of AEs

Grade	Intensity
1	An AE that is mild and transient (<48 hours). No treatment or therapeutic intervention is required.
2	An AE that is moderate. There is a mild to moderate limitation in activity. Some assistance may be needed. No or minimal therapeutic intervention is required.
3	An AE that is severe. There is a marked limitation in activity, and some assistance is usually required. Medical intervention and/or therapy is required. Hospitalization is possible.
4	An AE that is life-threatening. There is an extreme limitation in activity, and significant assistance is required. Significant medical intervention and/or therapy is required, and hospitalization or hospice care is probable.

7.1.2. SAE Definition

An SAE is defined as an event which:

- is fatal or life-threatening
- constitutes a congenital anomaly/birth defect

- results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- is medically significant, ie, defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above
- requires in-patient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a preexisting condition that is unrelated to the indication under study and has not worsened since the start of study drug

7.1.3. Adverse Events of Special Interest Definition

Adverse events of special interest (AESI) are required to be reported by the investigator to the Sponsor immediately (ie, no more than 24 hours after learning of the event; see Section 7.2 for reporting instructions). AESI for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law

  The finding of an elevated ALT or AST (> 3 ULN) in combination with either an elevated total bilirubin (2 ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an AE the occurrence of either of the following:

  - Treatment-emergent ALT or AST > 3x ULN in combination with total bilirubin >2 x ULN
  - Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice

  The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event), either as a SAE or an AESI.

- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a subject exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

7.1.4. Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug
    - In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves AEs but may result in adverse events. Each AE associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event; see Section 7.2). For [^{18}F]GTP1, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with [^{18}F]GTP1, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (eg, wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

7.1.5. Treatment of AEs

All AEs should be treated appropriately. Treatment may include one or more of the following: no action taken (ie, further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this AE; concomitant medication given; non-drug

therapy given; subject hospitalized/subject's hospitalization prolonged. The action taken to treat the AE should be recorded on the Adverse Event Form.

Once an AE is detected, it should be followed until its resolution to baseline grade or better, or until it is judged to be stable or permanent by the investigator, or the participant withdraws consent. Assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about potential risks of the investigational drug will be included in the subject's informed consent and should be discussed with the subject as part of the informed consent signing and during the study as needed.

7.1.6. Relationship of AEs to the Study Drug

The Investigator will document his/her opinion of the relationship of the AE to treatment with the study drug (Table 3).

Table 3: Relationship of AEs to Study Drug

Relationship	Description
Yes	A reaction that follows a reasonable temporal sequence from administration of the drug or in which the drug level has been established in body fluids or tissue; that follows a known or expected response pattern to the suspected drug; and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure.
No	An AE will be considered related, unless it fulfills the criteria specified below: Evidence exists that the AE has a cause other than [^{18}F]GTP1 (eg, preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication). AND/OR The AE does not have a plausible temporal relationship with [^{18}F]GTP1 administration.

7.2. Serious Adverse Event and Adverse Event of Special Interest Reporting

To ensure subject safety, every SAE and AESI, regardless of suspected causality, occurring after the subject has provided informed consent and until the subject has completed the study must be reported to the study sponsor within 24 hours of learning of its occurrence.

SAEs that occur later than the Follow-up Phone Call will not require reporting unless the Investigator believes the event(s) were related to either the investigational study drug or study procedures.

Recurrent episodes, complications, or progression of the initial SAE/AESI must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the Investigator receiving the follow-up information. An SAE/AESI that is considered completely unrelated to a previously reported one should be reported separately as a new event. New signs or symptoms or a change in the diagnosis, significant new diagnostic test results, change in the event's outcome, including recovery, additional information on the clinical course of the event should also be submitted immediately.

All SAE/AESIs, regardless of causality, will be reviewed by the study sponsor.

7.3. Methods for Capturing and Assessing Safety Parameters

The investigator is responsible for ensuring that all adverse events (see Section 7.1.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 7.2 and 7.4. For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 7.1.2 for seriousness criteria), severity (see Section 7.1.1), and causality (see Section 7.1.6).

7.4. Procedures for Recording Adverse Events

7.4.1. Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (eg, record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

7.4.2. Adverse Events That are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF.

7.4.3. Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 7.2), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF.

7.5. Post-Study Adverse Events:

If the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as within 4 days (± 2 days) post-injection of [^{18}F]GTP1), if the event is believed to be related to prior study drug treatment. The investigator should report these events directly to the Sponsor or its designee, by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form using the email address provided below:

Email address: welwyn.pds-pc@roche.com

8. DATA REVIEW AND DATABASE MANAGEMENT

8.1. Site Monitoring

During the study, a contracted clinical research associate (monitor) will visit the site regularly to check the completeness of subject records, the accuracy of data, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the contracted monitor during these visits.

The Investigator will maintain source documents for each subject in the study, consisting of case and visit notes containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information in the database must be traceable to these source documents in the subject's file. The Investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The Investigator will give the monitor access to all relevant source documents to confirm their consistency with the database entries. Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the database are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

8.2. Database Management and Quality Control

Designated Investigator staff must enter the information required by the protocol into the study-specific database.

Subsequently, the entered data are systematically checked by Quality Assurance (QA) and data management staff, including 100% verification with source documentation. Errors or omissions are reconciled with the investigational site for resolution. Quality checking audits of all key safety and efficacy data in the database are made prior to locking the database.

9. DATA ANALYSIS

9.1. Subject Demographics and Other Baseline Characteristics

All data for background and demographic variables will be listed. Summary statistics will be provided for these parameters by subject. Relevant medical history, current medical conditions, results of laboratory screens, drug tests, and any other relevant information will be listed by subject.

9.2. Imaging Analysis and Statistics

Whole-body tomographic PET images created on the PET camera will be transferred to a dedicated PMOD (software for biomedical image quantification) workstation and reviewed visually for assessment of body organ distribution of radioactivity. Manually delineated dynamic

VOIs will be placed on the visually identified source organs and subsequently used for all the study PET frames. Activity within these VOIs is expressed in unit of total radioactivity. Radioactivity will be corrected for body attenuation, but not for decay, and time-activity curves (TACs) will be generated for each source organ. Following the last imaging time point residual radioactivity will be assumed to undergo physical decay only. Total number of disintegrations (ie, kinetic values or residence times) will be determined for each source organ either directly as the area under the curve of each TAC, or from modeling of acquired TACs in certain source organs (eg, gallbladder emptying, urinary bladder voiding, and GI tract modeling). These data will be utilized in the MIRD calculations of target organ specific radiation absorbed dose with correction from urine assays and standard GI kinetic models (ICRP 2006) in Organ Level Internal Dose Assessment (OLINDA) (Stabin et al., 2005). Standard MIRD assumptions will be incorporated in dosimetry models for determination of radiation absorbed doses in target organs and whole-body (Harrison et al. 2015, ICRP 2007).

For whole-body biodistribution, the following parameters will be evaluated:

- Total source organ counts based on an individualized VOI template
- Source organ uptake and washout with calculation of the total number of disintegrations (or residence time) using the area under the time-activity curve divided by the injected dose of radiopharmaceutical
- Radiation absorbed dose estimates based on the MIRD methodology utilizing urine data in the model for increased accuracy of urinary bladder wall dose
- The ICRP 100 human alimentary tract (HAT) model will be applied to compute residence times in the small intestine, lower and upper large intestine

Descriptive statistics will be applied to describe biodistribution of [^{18}F]GTP1 by organ.

9.3. Safety Analysis and Statistics

Safety will be evaluated by the following:

- Incidence and severity of AEs
- Results from measurements of vital signs
- Results from measurements of ECGs
- Physical evaluation
- Results from measurements for parameters of clinical laboratory tests (hematology, clinical chemistry, and urinalysis)

All vital signs, ECG, laboratory and AE data will be listed by subject and visit/time and, if ranges are available, abnormalities will be flagged and brought to the Investigator's attention for review. Summary statistics will be provided by visit/time.

9.4. Sample Size

The sample size for this study was determined by practical considerations and is not based on statistical power calculations. Up to 6 evaluable subjects (with at least 1 male and 1 female) will complete this study.

While the sample size is small, this should be adequate to determine biodistribution and dosimetry calculations of [^{18}F]GTP1 in Japanese subjects.

10. REGULATORY AND ETHICAL CONSIDERATIONS

10.1. Regulatory and Ethical Compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH E6Guidelines for GCP, with applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki.

10.2. Informed Consent Procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB approved informed consent. Informed consent must be obtained before conducting any study-specific procedures (ie, all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents.

10.3. Confidentiality

Participants will be identified by a unique number assigned during screening and participant names will be known only to the Investigators and designated study staff. Representatives from the FDA will have access to the medical records connected to this study. Study records will be kept confidential to the extent provided by law. Name or other identifying data will not be used in any report or publication of this study. The data from this study will be maintained for a minimum of ten years.

10.4. Responsibilities of the Investigator and IRB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB must be present before study initiation. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to the contracted monitor, auditors, IRB, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform the study sponsor immediately that this request has been made.

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12. APPENDIX 1 – WORLD HEALTH ORGANIZATION TOXICITY GRADING SCALE

WHO Toxicity Grading Scale for determining the severity of AEs

ITEM	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
HEMATOLOGY				
Hemoglobin	9.5 - 10.5 gm/Dl	8.0 - 9.4 gm/DI	6.5 - 7.9 gm/DI	<6.5 gm/DI
Absolute Neutrophil Count	1000-1500/mm^3	750-999/mm^3	500-749/mm^3	<500/mm^3
Platelets	75000-99000/mm^3	50000-74999/mm^3	20000-49000/mm^3	<20000/mm^3
Prothrombin Time (PT)	1.01 - 1.25 x ULN	1.26-1.5 x ULN	1.51 -3.0 x ULN	>3 x ULN
Activated Partial Thromboplastin (APPT)	1.01 - 1.66 x ULN	1.67 - 2.33 x ULN	2.34-3 x ULN	>3 x ULN
Fibrinogen	0.75 - 0.99 x LLN	0.50 - 0.74 x LLN	0.25 - 0.49 x LLN	<0.25xLLN
Fibrin Split Product	20-40 mcg/ml	41-50 mcg/ml	51-60 mcg/ml	> 60 mcg/ml
Methemoglobin	5-9.9%	10.0 - 14.9 %	15.0- 19.9%	>20%
LIVER ENZYMES				
AST (SGOT)	1.25-2.5 x ULN	2.6-5 x ULN	5.1-10 x ULN	> 10 x ULN
ALT (SGPT)	1.25-2.5 x ULN	2.6-5 x ULN	5.1-10 x ULN	> 10 x ULN
GGT	1.25 -2.5 x ULN	1.6- 5 x ULN	5.1-10 x ULN	> 10 x ULN
Alkaline Phosphatase	1.25-2. 5 x ULN	1.6- 5 x ULN	5.1-10 x ULN	> 10 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1-5.0 x ULN	>5.1 x ULN
CHEMISTRIES				
Hyponatremia	130-135 mEq/L	123-129 mEq/L	116-122 mEq/L	< 116 or mental status changes or seizures
Hypernatremia	146-150 mEq/L	151-157 mEq/L	158-165 mEq/L	> 165 mEq/L or mental status changes or seizures
Hypokalemia	3.0 - 3.4 mEq/L	2.5 - 2.9 mEq/L	2.0 - 2.4 mEq/L or intensive replacement Rx required or hospitalization required.	<2.0mEq/L or paresis or ileus or life-threatening arrhythmia
Hyperkalemia	5.6 - 6.0 mEq/L	6.1 - 6.5 mEq/L	6.6 - 7.0 mEq/1	> 7.0mEq/L or life-threatening arrhythmia
Hypoglycemia	55-64 mg/dL	40-54 mg/dL	30-39mg/dL	<30 mg/dL or mental status changes or coma

WHO Toxicity Grading Scale for determining the severity of AEs, continued

ITEM	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
CHEMISTRIES (continued)				
Hyperglycemia (note if fasting)	116 - 160 mg/dL	161- 250 mg/dL	251 - 500 mg/dL	> 500 mg/dL or ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 - 7.8 mg/dL	7.7 - 7.0 mg/dL	6.9 - 6.1 mg/dL	< 6.1 mg/dL or life-threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6 - 11.5 mg/dL	11.6 - 12.5 mg/dL	12.6 - 13.5 mg/dL	> 13.5 mg/dL life-threatening arrhythmia
Hypomagnesemia	l.4- l.2mEq/L	1.1 - 0.9 mEq/L	0.8 - 0.6 mEq/L	< 0.6 mEq/L or life-threatening arrhythmia
Hypophosphatemia	2.0 - 2.4 mg/dL	1.5 -1.9 mg/dL or replacement Rx required	1.0-1.4 mg/dL intensive Rx or hospitalization required	< 1.0 mg/dL or life-threatening arrhythmia
Hyperbilirubinemia	1.1 -1.5 x ULN	1.6-2.5 x ULN	2.6-5 x ULN	>5 x ULN
BUN	l.25-2.5 x ULN	2.6-5 x ULN	5.1- l0 x ULN	> l0 x ULN
Creatinine	1.1-l.5 x ULN	1.6-3.0 x ULN	3.l-6 x ULN	> 6 x ULN or required dialysis
URINALYSIS				
Proteinuria	1+or< 0.3% or <3g/L or 200 mg - 1 gm loss/day	2 -3 + or 0.3 - 1.0% or 3-10 g/L 1- 2 gm loss/day	4+or> 1.0% or> 10 g/L 2-3 5 gm loss/day	nephrotic syndrome or > 3 5 gm loss/day
Hematuria	microscopic only	gross, no clots	gross+ clots	obstructive or required transfusion
CARDIAC DYSFUNCTION				
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent; No Rx required	requires treatment
Hypertension	transient inc. >20mm; no Rx	recurrent, chronic, > 20 mm, Rx required	requires acute Rx; No hospitalization	requires hospitalization
Hypotension	transient orthostatic hypotension, No Rx	symptoms correctable with oral fluids Rx	requires IV fluids; no hospitalization required	requires hospitalization
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no Rx	symptomatic effusion; pain; ECG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused

WHO Toxicity Grading Scale for determining the severity of AEs, continued

ITEM	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
RESPIRATORY				
Cough	transient- no Rx	treatment associated cough local Rx	uncontrolled	
Bronchospasm, Acute	transient; no Rx < 80% - 70% FEV_1 (or peak flow)	requires Rx normalizes with bronchodilator; FEV_1 50% - 70% (or peak flow)	no normalization with bronchodilator; FEV_1 25% - 50% (or peak flow retractions)	cyanosis: FEV_1 < 25% (or peak flow) or intubated
GASTROINTESTINAL				
Stomatitis	mild discomfort; no limits on activity	some limits on eating/drinking	eating/talking very limited	requires IV fluids
Nausea	mild discomfort; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity lin1ited	severe discomfort; no significant intake; activities limited	minimal fluid intake
Vomiting	transient emesis	occasional/mode rate vomiting	orthostatic hypotension or IV fluids required	hypotensive shock or hospitalization required for IV fluid therapy
Constipation	Mild	moderate	severe	distensions w/vomiting
Diarrhea	transient 3-4 loose stools/day	5-7 loose stools/day	orthostatic hypotension or > 7 loose stools/ day or required IV fluids	hypotensive shock or hospitalization for IV fluid therapy required
NEURO & NEUROMUSCULAR				
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Mood	mild anxiety or depression	moderate anxiety or depression and therapy required	severe anxiety or depression or mania; needs assistance	acute psychosis; incapacitated, requires hospitalization
Neuro Control (ADL activities of daily living)	mild difficulty concentrating; no Rx; mild confusion/agitation; ADL unaffected	moderate confusion/agitation some limitation of ADL; minima l Rx	severe confusion/agitation needs assistance for ADL; therapy required	toxic psychosis; hospitalization
Muscle Strength	subjective weakness no objective symptoms/signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis

WHO Toxicity Grading Scale for determining the severity of AEs, continued

ITEM	Grade 1 Toxicity	Grade 2 Toxicity	Grade 3 Toxicity	Grade 4 Toxicity
OTHER PARAMETERS				
FEVER: oral, >12 hours	37.7-38.5 C or 100.0-101.5 F	38.6-39.5 C or 101.6-102.9 F	39.6-40.5 C or 103-105 F	>40 C or >105 F
Headache	mild, no Rx therapy	transient, moderate, Rx required	severe, responds to initial narcotic therapy	intractable; required repeated narcotic therapy
Fatigue	no decrease in ADL	normal activity decreased 25-50%	normal activity decreased >50% can't work	unable to care for self
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Local Reaction	tenderness or erythema	induration < 10 cm or phlebitis or inflammation	induration > 10 cm or ulceration	necrosis
Mucocutaneous	erythema; pruritus	diffuse, maculopopular rash, dry desquamation	vesiculation, moist desquamation, or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery

13. APPENDIX 2 – PROTOCOL SUMMARY OF CHANGES, AMENDMENT 1

Rationale:
Updates were included to clarify that approved forms of birth control are not prohibited prescription medications.

The following amendments were incorporated:

Page	Section	17-Jan-2020, v1.0 WAS	21-Jan-2020, v2.0 IS
1	Title Page, Header	V1.0, 17-Jan-2020	V2.0, 21-Jan-2020
9,19	Synopsis, Exclusion Criteria	Use of any prescription drugs, herbal supplements, within four weeks prior to initial dosing.	Use of any prescription drugs (except approved forms of birth control noted in Section 5.2.3), herbal supplements, within four weeks prior to initial dosing.
21	Concomitant Treatment	Use of any prescription drugs, herbal supplements, within four (4) weeks prior to initial dosing, and/or OTC medication, dietary supplements (vitamins included) within two (2) weeks prior to initial dosing is prohibited. If needed (ie, an incidental and limited need), acetaminophen is acceptable, but must be documented as a concomitant medication/significant non-drug therapy.	Use of any prescription drugs, herbal supplements, within four (4) weeks prior to initial dosing, and/or OTC medication, dietary supplements (vitamins included) within two (2) weeks prior to initial dosing is prohibited. Approved forms of prescription birth control (hormonal contraceptives, hormone-releasing intrauterine devices, and copper intrauterine devices) are not prohibited and will be documented as a concomitant medication. If needed (ie, an incidental and limited need), acetaminophen is acceptable, but must be documented as a concomitant medication/significant non-drug therapy.

14. APPENDIX 3 – PROTOCOL SUMMARY OF CHANGES, AMENDMENT 2

Rationale:
Updates were included to add information on adverse events of special interest, special situations (accidental overdose or medication error), and methods for capturing and assessing safety.

The following amendments were incorporated:

Page	Section	21-Jan-2020, v2.0 WAS	09-July-2020, v3.0 IS
1	Title Page, Header	V2.0, 21-Jan-2020	V3.0, 09-Jul-2020
29	Section 7.1.3	N/A	Added section to define adverse events of special interest. (see inserted text below)
29	Section 7.1.4	N/A	Added section to define special situations, cases of accidental overdose or medication error. (see inserted text below)
30	Section 7.1.5	Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome. Information about common side effects already known about the investigational drug will be included in the subject's informed consent and should be discussed with the subject during the study as needed.	Once an AE is detected, it should be followed until its resolution to baseline grade or better, or until it is judged to be stable or permanent by the investigator, or the participant withdraws consent~~.~~ ~~and a~~Assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome. Information about potential risks ~~common side effects already known about~~ of the investigational drug will be included in the subject's informed consent and should be discussed with the subject as part of the informed consent signing and during the study as needed.

31	Section 7.2	**7.2 Serious Adverse Event Reporting** To ensure subject safety, every SAE, regardless of suspected causality, … Recurrent episodes, complications, or progression of the initial SAE must be reported … An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event. All SAEs, regardless of causality, will be reviewed by the study sponsor.	**7.2 Serious Adverse Event <u>and Adverse Event of Special Interest</u> Reporting** To ensure subject safety, every SAE <u>and AESI</u>, regardless of suspected causality, … Recurrent episodes, complications, or progression of the initial SAE<u>/AESI</u> must be reported … An SAE<u>/AESI</u> that is considered completely unrelated to a previously reported one should be reported separately as a new event. <u>New signs or symptoms or a change in the diagnosis, significant new diagnostic test results, change in the event's outcome, including recovery, additional information on the clinical course of the event should also be submitted immediately.</u> All SAE<u>/AESI</u>s, regardless of causality, will be reviewed by the study sponsor.
32	Section 7.3	N/A	Added section to define methods for capturing and assessing safety parameters. (see inserted text below)
32	Section 7.4	N/A	Added section to define the procedures for adverse event reporting. (see inserted text below)
32	Section 7.5	N/A	Added section to define the procedures for post-study adverse events. (see inserted text below)

<u>Sections inserted for Protocol Amendment 2:</u>

<u>Section 7.1.3. - Definition of adverse events of special interest</u>

Adverse events of special interest (AESI) are required to be reported by the investigator to the Sponsor immediately (ie, no more than 24 hours after learning of the event; see Section 7.3 for reporting instructions). AESI for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law
- The finding of an elevated ALT or AST (> 3 ULN) in combination with either an elevated total bilirubin (2 ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an AE the occurrence of either of the following:
- Treatment-emergent ALT or AST > 3x ULN in combination with total bilirubin >2 x ULN
- Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice
- The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event), either as a SAE or an AESI.
- Suspected transmission of an infectious agent by the study drug, as defined below
- Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a subject exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

Section 7.1.4. - Definition of cases of accidental overdose or medication error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug
    - In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves AEs but may result in adverse events. Each AE associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event; see Section 7.2). For [^{18}F]GTP1, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.

- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with [^{18}F]GTP1, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (eg, wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

Section 7.3. – Definition of methods for capturing and assessing safety parameters

The investigator is responsible for ensuring that all adverse events (see Section 7.1.1for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 7.2 and 7.4. For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 7.1.2 for seriousness criteria), severity (see Section 7.1.1), and causality (see Section 7.1.6).

Section 7.4. – Defining procedures for recording adverse events

7.4.1. Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (eg, record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

7.4.2. Adverse Events That are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF.

7.4.3. Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 7.2), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF.

Section 7.5. – Defining procedures for post-study adverse events

If the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as within 4 (± 2 days) post-injection of [^{18}F]GTP1), if the event is believed to be related to prior study drug treatment. The investigator should report these events directly to the Sponsor or its designee, by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form using the email address provided below:

Email address: welwyn.pds-pc@roche.com