PROTOCOL

TITLE:	**TAU PET LONGITUDINAL SUBSTUDY ASSOCIATED WITH: A DOUBLE-BLIND, PLACEBO-CONTROLLED PARALLEL-GROUP STUDY IN PRECLINICAL *PSEN1 E280A* MUTATION CARRIERS RANDOMIZED TO CRENEZUMAB OR PLACEBO, AND IN NON-RANDOMIZED, PLACEBO-TREATED NON-CARRIERS FROM THE SAME KINDRED, TO EVALUATE THE EFFICACY AND SAFETY OF CRENEZUMAB IN THE TREATMENT OF AUTOSOMAL-DOMINANT ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	*BN40199* (Tau PET Longitudinal Substudy)
VERSION NUMBER:	3
EUDRACT NUMBER:	NA
IND NUMBER:	NA
NCT NUMBER:	NCT03977584
TEST PRODUCT:	[^{18}F]GTP1 (RO6880276)
MEDICAL MONITOR:	[redacted], M.D., *M.A.S.*
SPONSOR:	*F. Hoffmann–La Roche Ltd*
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
11-Jun-2020 23:21:01	Company Signatory	[redacted]

PROTOCOL HISTORY

Version	Date Final	Protocol Number
2	4 October 2017	GN28352-1
1	5 January 2017	GN28352-1

PROTOCOL AMENDMENT, VERSION 3: RATIONALE

Protocol BN40199 (originally GN28352−1, see below) has been amended to adjust the timing between [^{18}F] Genentech Tau Probe 1 (GTP1)−tau positron emission tomography (PET) scans. Changes to the protocol, along with a rationale for each change, are summarized below.

- The study number has been changed. The Tau PET substudy associated with main Study GN28352 was originally assigned study number GN28352−1. However, extending the main study number for the substudy proved to be incompatible with internal Sponsor information technology platforms that report into ClinicalTrials.gov. Therefore, a new study number, BN40199, has been issued for the Tau PET substudy associated with the main Study GN28352.
- The Sponsor of Protocol BN40199 has been changed from Genentech to F. Hoffmann-La Roche Ltd (hereafter referred to as Roche) as a global change. Genentech is a member of the Roche group.
- Updated safety information from clinical studies with [^{18}F]GTP1 has been included (Section 1.2). These studies demonstrate that [^{18}F]GTP1 exposure and imaging procedures are generally well tolerated.
- The timing of [^{18}F]GTP1−tau PET scans has been adjusted (Section 3.1 and Appendix 1) in order to standardize the interval between the first and second scans, and to clarify the timing of the final scan. The second [^{18}F]GTP1−tau PET scan, which was previously performed between Weeks 248 and 260, is now scheduled 52 [±2] weeks from the first [^{18}F]GTP1−tau PET scan. In addition, timing of the third [^{18}F]GTP1−tau PET scan has been specified in greater detail to clarify how this scan should be integrated with either the ET (early termination) or final visit.
- Re-consent language for participants who lose capacity to consent during the trial has been added to harmonize with the main study protocol (Section 4.3.1).
- Language has been revised to account for the fact that some sites may not allow follow-up on partner pregnancies (Section 5.3.1.2).
- Language has been added to indicate that the study will comply with applicable local, regional, and national laws (Section 8.1).
- The process for reviewing and handling protocol deviations has been updated per internal standard operating procedures (Section 9.2).
- Language has been revised to clarify that study data may be shared with others who are not participating in this study and that redacted Clinical Study Reports and other summary reports will be made available upon request (Section 9.5).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**TAU PET LONGITUDINAL SUBSTUDY ASSOCIATED WITH: A DOUBLE-BLIND, PLACEBO-CONTROLLED PARALLEL-GROUP STUDY IN PRECLINICAL *PSEN1 E280A* MUTATION CARRIERS RANDOMIZED TO CRENEZUMAB OR PLACEBO, AND IN NON-RANDOMIZED, PLACEBO-TREATED NON-CARRIERS FROM THE SAME KINDRED, TO EVALUATE THE EFFICACY AND SAFETY OF CRENEZUMAB IN THE TREATMENT OF AUTOSOMAL-DOMINANT ALZHEIMER'S DISEASE**
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MEDICAL MONITOR:	[redacted], M.D., *M.A.S.*
SPONSOR:	*F. Hoffmann–La Roche Ltd*

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return the signed original of this form as instructed by your local study monitor. Please retain a copy for your study files.

PROTOCOL SYNOPSIS

TITLE:	**TAU PET LONGITUDINAL SUBSTUDY ASSOCIATED WITH: A DOUBLE-BLIND, PLACEBO-CONTROLLED PARALLEL-GROUP STUDY IN PRECLINICAL *PSEN1 E280A* MUTATION CARRIERS RANDOMIZED TO CRENEZUMAB OR PLACEBO, AND IN NON-RANDOMIZED, PLACEBO-TREATED NON-CARRIERS FROM THE SAME KINDRED, TO EVALUATE THE EFFICACY AND SAFETY OF CRENEZUMAB IN THE TREATMENT OF AUTOSOMAL-DOMINANT ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	*BN40199* (Tau PET Longitudinal Substudy)
VERSION NUMBER:	3
EUDRACT NUMBER:	NA
IND NUMBER:	NA
NCT NUMBER:	NCT03977584
TEST PRODUCT:	[^{18}F]GTP1 (RO6880276)
INDICATION:	Alzheimer's Disease
SPONSOR:	*F. Hoffmann–La Roche Ltd*

Objective

The objective of this substudy is to assess changes in tau burden over time in participants enrolled in Study GN28352 who are treated with crenezumab or placebo.

Study Design

Description of Study

Participants enrolled in the main Study GN28352 will have the option to participate in this substudy. Participants must sign a separate Informed Consent Form and fulfill entry criteria. Enrollment in this substudy does not preclude enrollment in other substudies of the main study unless radiation exposure limits are expected to be exceeded.

Only participants from the Medellin and Yarumal sites will be eligible for enrollment into this substudy. There are approximately 150 participants expected to enroll in this substudy, which may include up to the entire enrolled participant pool at the Medellin and Yarumal sites. Approximately 50 participants per treatment arm in the main study are expected to enroll in the substudy. Participants enrolled in the substudy will be allocated to the main study treatment (crenezumab or placebo) as described in the main study protocol.

Participants enrolled in this substudy will receive up to three intravenous (IV) injections of [^{18}F] Genentech Tau Probe 1 (GTP1) and will undergo a tau positron emission tomography (PET) scan after each IV injection of [^{18}F]GTP1. Because this substudy is being introduced after the main study has started, the schedule for [^{18}F]GTP1 injections and PET scans has been made flexible to maximize the number of participants who may be enrolled in the substudy. Participants should only be enrolled into this substudy if it is reasonably expected that at least two [18F]GTP1-tau PET scans can be obtained, per the schedule provided below.

As with the [^{18}F]fluorodeoxyglucose (FDG) and [^{18}F]florbetapir PET scans described in the main study, [18F]GTP1–tau PET scans should only be performed if the investigator has determined that the total annual radiation exposure from all PET and CT scans (and including any other scans involving radiation that may have been acquired outside of this study) does not exceed

local safety guidelines. Radiation exposure for [^{18}F]GTP1 doses can be found in the [^{18}F]GTP1 Investigator's Brochure. Radiation exposure for [^{18}F]florbetapir doses can be found in the Amyvid U.S. Package Insert (0.019 mSv/MBq whole-body Effective Dose). Radiation exposure for [^{18}F]FDG can be found in Quinn et al. (2016) (7.4 mSv whole-body Effective Dose for a 10 mCi [^{18}F]FDG dose).

There will be up to three [^{18}F]GTP1-tau PET scans for each participant in this substudy (see the schedule of activities). The first two [^{18}F]GTP1-tau PET scans will be 52 [± 2] weeks apart. To maximize the ability to detect changes in tau burden, the third scan should be at the early termination (ET) or final visit, whichever is later, under the timing constraints described below.

The first [^{18}F]GTP1–tau PET scan may occur on any visit that occurs in the main protocol (GN28352), from the Week 130 visit to the Week 224 visit. The timing of this first scan visit may be different for each participant. For each participant, this first scan should occur as early as possible within the Week 130 to Week 224 visit period. The flexibility in the timing of this first scan is intended to allow the maximum number of participants to receive this scan, since participants may join this substudy at different timepoints relative to their enrollment in the main study.

The second scan may occur at any visit that occurs in the main protocol (GN28352) that is approximately 52 [± 2] weeks after the first scan. The timing of this second scan visit may be different for each participant.

The third [^{18}F]GTP1 tau PET scan is intended to maximize the interval in which tau pathology might develop between the first and last scan, with the goal of maximizing the ability to detect potential treatment effects of crenezumab. Thus, the third [^{18}F]GTP1 tau PET scan would take place at the ET or final visit if at least 6 months elapsed since the previous [^{18}F]GTP1–tau PET scan. The timing of this third scan will take into consideration the total annual radiation exposure and will not exceed local safety guidelines for each participant.

Number of Participants

There are approximately 150 participants expected to enroll in this substudy, which may include up to all participants enrolled at the Medellin and Yarumal sites. Per the randomization schedule in the main Study Protocol GN28352, approximately 50 participants in each of the main study's three treatment arms are expected to be enrolled into the substudy.

Target Population

Inclusion Criteria

Participants must meet all the criteria listed in the main Study Protocol GN28352 and the following criteria for substudy entry:

- Enrolled in main Study GN28352
- Signed separate consent for participation in the Tau PET Longitudinal Substudy *BN40199* (co-signed by the participant's next of kin or study partner, if required by the local regulations, guidelines, and Ethics Committee [EC])
- Ability to comply with the substudy protocol, in the investigator's judgment

Exclusion Criteria

Participants will be excluded from this substudy if they meet the following criterion:

- Contraindication to PET scan procedures, possibly including, but not limited to, the following:

  Current, past, or planned participation in studies involving radioactive agents, including the main Study GN28352 and this Tau PET substudy, such that the total research-related radiation dose to the participant in any given year would exceed the limits set forth in the U.S. Code of Federal Regulations (CFR) Title 21 Section 361.1 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=361.1)

For further information on crenezumab, please refer to the main Study Protocol GN28352, the pharmacy manual, and the crenezumab Investigator's Brochure.

End of Study

The end of this substudy is defined as the date when all participants enrolled in the substudy have completed their final tau PET scan or discontinued from the main study.

Investigational Medicinal Products

The selective tau PET radioligand, [^{18}F]GTP1, will be used in this substudy. It is intended that participants will receive [^{18}F]GTP1 on up to three occasions.

Statistical Methods

Analysis

The absolute change from the first [^{18}F]GTP1 scan in several measures of tau burden (including but not limited to SUVR and tau distribution metrics) will be analyzed using a mixed-effects model for repeated measures similar to that described for the primary efficacy endpoint in the main study. Additional descriptive summaries that describe the relationship between tau PET and other endpoints will be generated.

The specific tau distribution metrics used will be further defined after key data, external to this study (for example study GN30009), become available. Such details (as well as details of hypothesis testing) will be specified in the Statistical Analysis Plan, prior to unblinding of study treatment (crenezumab or placebo) in the main protocol.

Other exploratory analyses may also be conducted that may not be pre-specified prior to database unblinding.

Determination of Sample Size

The sample size was determined based on the maximum number of participants from the main Study GN28352 who can still undergo two tau PET scans with at least one year in between.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AD	Alzheimer's disease
CRO	contract research organization
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
FDG	fluorodeoxyglucose
GTP1	Genentech Tau Probe 1
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IV	intravenous
PET	positron emission tomography
SUVR	standardized uptake value ratio

1. BACKGROUND

1.1 BACKGROUND ON TAU POSITRON EMISSION TOMOGRAPHY

Tau protein has been identified as one of the key pathological features of Alzheimer's disease (AD) (Grundke-Iqbal et al. 1986; Kosik et al. 1986; Wood et al. 1986). Tau is the primary protein composing neurofibrillary tangles, and 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). Given the role of tau protein in the pathology of AD, expanding neuroimaging biomarkers to include a tau radioligand offers the potential to improve understanding of the pathological process in AD. Thus, a positron emission tomography (PET) imaging agent that binds to aggregated tau has the potential to serve as a biomarker for monitoring disease progression and for monitoring efficacy of therapeutics that influence AD progression.

Until recently, post-mortem examination of brain tissues was the only means available for directly evaluating the changes occurring in the brain in AD. 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 disease process over time in a living individual. Briefly, these techniques involve intravenous (IV) administration of radioactively-labeled compounds that bind to selective target sites in the 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 target in different brain regions. Using these PET techniques, β-amyloid aggregates have been successfully imaged in several studies in AD patients using high affinity 11-C and 18-F–labeled PET radioligands (PIB and florbetapir, AV-1) (Klunk et al. 2004, 2005; Clark et al. 2011; Hyman et al. 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 (Leinonen et al. 2008; Sojkova et al. 2011; Ni et al. 2013; Quiroz et al. 2016).

[^{18}F] Genentech Tau Probe 1 (GTP1) (also known as [^{18}F]RO6880276) has been developed as a positron emitting radiopharmaceutical for *in vivo* imaging of tau protein aggregates. [^{18}F]GTP1 has been previously evaluated in three completed studies in humans and is currently being evaluated in a longitudinal, observational study in humans (Study GN30009). Refer to the [^{18}F]GTP1 Investigator's Brochure for more details on these studies.

1.2 HUMAN SAFETY AND TOLERABILITY OF [^{18}F]GTP1

Available safety data from the initial clinical studies with [^{18}F]GTP1 show that exposure to [^{18}F]GTP1 and imaging procedures are generally well tolerated. There have been no deaths, no adverse events of special interest, and no hypersensitivity reactions. *Currently there are no adverse drug reactions identified for [^{18}F]GTP1.* Refer to the

[^{18}F]GTP1 Investigator's Brochure for more details of these studies and for a full non-clinical evaluation of the tracer and the clinical experience to date.

1.3 SUBSTUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

This is a substudy associated with the main Study GN28352, which is a Phase II study to evaluate the safety and efficacy of crenezumab in preclinical *PSEN1 E280A* mutation carriers and non-carriers from the same kindred. This substudy will evaluate the effect of crenezumab on tau burden as measured by [^{18}F]GTP1–tau PET in this study population. The results of this substudy are expected to help understand the effects of crenezumab on the longitudinal progression of tau burden as well as the relationship between changes in [^{18}F]GTP1–tau PET and changes in other endpoints in the main study.

Participants in this substudy must be enrolled in the main Study GN28352. In order to blind substudy participants to their mutation carrier status, similar to the main study, carriers and non-carriers of the *PSEN1 E280A* mutation will be enrolled in this substudy.

There is no expected therapeutic benefit of [^{18}F]GTP1 to trial participants. However, participation in this substudy will enhance the understanding of disease progression in the preclinical stage of familial AD and will enhance the understanding of the effect of crenezumab on familial AD progression. Participation in this substudy may also enhance the understanding of the progression of sporadic AD, as current and future investigations delineate the overlap in the pathophysiology of familial and sporadic disease. The emerging safety profile of [^{18}F]GTP1 indicates that there is no measurable added risk of participation in this substudy, aside from potential risks from radiation exposure. Please see Section 3.1 and 4.1.2 for instruction on limiting radiation exposure to that permitted by local safety guidelines to minimize this risk.

2. OBJECTIVE

The objective of this substudy is to assess changes in tau burden over time in participants enrolled in Study GN28352 who are treated with crenezumab or placebo.

3. SUBSTUDY DESIGN

3.1 DESCRIPTION OF THE SUBSTUDY

Participants enrolled in the main Study GN28352 will have the option to participate in this substudy. Participants must sign a separate Informed Consent Form and fulfill entry criteria as detailed in Section 4.1. Enrollment in this substudy does not preclude enrollment in other substudies of the main study unless radiation exposure limits are expected to be exceeded.

Only participants from the Medellin and Yarumal sites will be eligible for enrollment into this substudy. There are approximately 150 participants expected to enroll in this substudy, which may include up to the entire enrolled participant pool at the Medellin

and Yarumal sites. Approximately 50 participants per treatment arm in the main study are expected to enroll in the substudy. Participants enrolled in the substudy will be allocated to the main study treatment (crenezumab or placebo) as described in the main study protocol.

Participants enrolled in this substudy will receive up to three IV injections of [^{18}F]GTP1 and will undergo a tau PET scan after each IV injection of [^{18}F]GTP1. Because this substudy is being introduced after the main study has started, the schedule for [^{18}F]GTP1 injections and PET scans has been made flexible to maximize the number of participants who may be enrolled in the substudy. Participants should only be enrolled into this substudy if it is reasonably expected that at least two [^{18}F]GTP1-tau PET scans can be obtained, per the schedule provided below.

As with the [^{18}F]fluorodeoxyglucose (FDG) and [^{18}F]florbetapir PET scans described in the main study, [^{18}F]GTP1–tau PET scans should only be performed if the investigator has determined that the total annual radiation exposure from all PET and CT scans (and including any other scans involving radiation that may have been acquired outside of this study) does not exceed local safety guidelines. Radiation exposure for [^{18}F]GTP1 doses can be found in the [^{18}F]GTP1 Investigator's Brochure. Radiation exposure for [^{18}F]florbetapir doses can be found in the Amyvid U.S. Package Insert (0.019 mSv/MBq whole-body Effective Dose). Radiation exposure for [^{18}F]FDG can be found in Quinn et al. (2016) (7.4 mSv whole-body Effective Dose for a 10 mCi [^{18}F]FDG dose).

There will be up to three [^{18}F]GTP1-tau PET scans for each participant in this substudy (see the schedule of activities in Appendix 1). The first two [^{18}F]GTP1-tau PET scans will be 52 [± 2] weeks apart. To maximize the ability to detect changes in tau burden, the third scan should be at the early termination (ET) or final visit, whichever is later, under the timing constraints described below.

The first [^{18}F]GTP1–tau PET scan may occur on any visit that occurs in the main protocol (GN28352), from the Week 130 visit to the Week 224 visit. The timing of this first scan visit may be different for each participant. For each participant, this first scan should occur as early as possible within the Week 130 to Week 224 visit period. The flexibility in the timing of this first scan is intended to allow the maximum number of participants to receive this scan, since participants may join this substudy at different timepoints relative to their enrollment in the main study.

The second scan may occur at any visit that occurs in the main protocol (GN28352) that is approximately 52 [± 2] weeks after the first scan. The timing of this second scan visit may be different for each participant.

The third [^{18}F]GTP1–tau PET scan is intended to maximize the interval in which tau pathology might develop between the first and last scan, with the goal of maximizing the ability to detect potential treatment effects of crenezumab. Thus, the third

[18F]GTP1–tau PET scan would take place at the ET or final visit if at least 6 months elapsed since the previous [18F]GTP1–tau PET scan. The timing of this third scan will take into consideration the total annual radiation exposure and will not exceed local safety guidelines for each participant.

If a participant discontinues the study prior to the end of the GN28352 study, a [18F]GTP1–tau PET scan should occur at the time of ET unless any of the following conditions are met:

- *The participant discontinued for safety reasons that would contraindicate PET scans*
- *The interval between the most recent [18F]GTP1–tau PET scan and the ET scan would be less than 6 months*
- *The annual radiation exposure including the ET scan would exceed locally permitted limits*

3.2 END OF SUBSTUDY

The end of this substudy is defined as the date when all participants enrolled in the substudy have completed their final tau PET scan or discontinued from the main study.

4. STUDY POPULATION

4.1 PARTICIPANTS

There are approximately 150 participants expected to enroll in this substudy, but it may include up to all participants enrolled at the Medellin and Yarumal sites. Per the randomization schedule in the main study protocol (GN28352), approximately 50 participants in each of the main study's three treatment arms are expected to be enrolled into the substudy. Participants will be eligible for this substudy if they are eligible for the main study and satisfy the following additional inclusion and exclusion criteria.

4.1.1 Inclusion Criteria

Participants must meet all the criteria listed in the main study protocol (GN28352) and the following criteria for substudy entry:

- Enrolled in main Study GN28352
- Signed separate consent for participation in the Tau PET Longitudinal Substudy *BN40199* (co-signed by the participant's next of kin or study partner, if required by the local regulations, guidelines, and Ethics Committee [EC])
- Ability to comply with the substudy protocol, in the investigator's judgment

4.1.2 Exclusion Criterion

Participants will be excluded from this substudy if they meet the following criterion:

- Contraindication to PET scan procedures, possibly including, but not limited to, the following:

  Current, past, or planned participation in studies involving radioactive agents, including the main Study GN28352 and this Tau PET substudy, such that the total research-related radiation dose to the participant in any given year would exceed the limits set forth in the U.S. Code of Federal Regulations (CFR) Title 21 Section 361.1

  (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=361.1)

For further information on [^{18}F]GTP1 please refer to the [^{18}F]GTP1 Investigator's Brochure.

4.2 STUDY TREATMENT

4.2.1 Investigational Agent [^{18}F]GTP1

[^{18}F]GTP1 is a clear solution formulated for IV injection. [^{18}F]GTP1 is formulated in 0.9% sodium chloride injection containing ethanol and ascorbic acid. 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 identification, 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 unit dose solution in a sterile syringe. The syringe is contained within an outer lead or tungsten shield ("pig") to protect from gamma radiation. For more detail, please refer to the GTP1 Investigator Brochure and the [^{18}F]GTP1–Tau PET Technical Operations Manual.

[^{18}F]GTP1 will be considered an investigational product because [^{18}F]GTP1 is not approved for marketing in Colombia.

4.2.2 Source of Production of [^{18}F]GTP1

[^{18}F]GTP1 will be provided by Ciclotron SAS (Medellin, Colombia) in accordance with the locally approved prescribing information and in accordance with approved national and/or local standards.

4.3 STUDY ASSESSMENTS

See Appendix 1 for the schedule of activities performed during the study.

4.3.1 Informed Consent Forms

All participants or their authorized representatives must review, sign, and date the most current Institutional Review Board/Ethics Committee (IRB/EC) –approved written Informed Consent Form for participation in the Tau PET Longitudinal Substudy *BN40199* before any substudy-specific evaluations are performed. Informed Consent Forms for

enrolled participants and for those who are not subsequently enrolled will be maintained at the study site.

If, during the course of the trial, a participant develops dementia and loses his/her capacity to consent, the most recently signed consent form prior to loss of capacity will remain active. Any revisions to the consent form will require re-consent by the participant's authorized representative (consisting of either a legally authorized representative or a temporary representative if a legally authorized representative is unavailable) as well as assent from the participant as per site standard operating procedure TR-Pr-058.

For further details on the main study, please see the protocol and Informed Consent Forms for Study GN28352.

4.3.2 Tau Positron Emission Tomography

Up to three [^{18}F]GTP1–tau PET scans are included in this substudy. For details of scan timing, please refer to Section 3.1.

If occurring in the same visit, [^{18}F]GTP1–tau PET scans will be performed after neurocognitive testing but prior to dosing of crenezumab or placebo. [^{18}F]GTP1–tau PET scans should be performed a minimum of 12 hours apart from other PET scans and a maximum of 14 days apart from any accompanying fibrillar amyloid-PET or FDG-PET scan.

The selective tau PET radioligand, [^{18}F]GTP1, will be used in this substudy. It is intended that each participant will receive [^{18}F]GTP1 on up to three occasions.

Detailed methodology, including scanning procedures, is included in the [^{18}F]GTP1–Tau PET Technical Operations Manual.

4.3.2.1 Positron Emission Tomography Imaging Procedures

The Sponsor in conjunction with the imaging contract research organization (CRO) will prepare and distribute a detailed [^{18}F]GTP1–Tau PET Technical Operations Manual for image acquisition and reconstruction procedures and parameters for the PET imaging center prior to the start of the study. All imaging data will be transferred to the imaging CRO for quality control, qualitative image assessment, and quantitative image analysis as documented in the [^{18}F]GTP1–Tau PET Technical Operations Manual.

4.3.2.2 Tau PET Imaging Metrics

Imaging metrics for [^{18}F]GTP1 Tau PET imaging will assess tau pathology burden and longitudinal change; potential examples include:

- Standardized uptake value ratio (SUVR) for multiple cortical brain regions of interest (e.g., middle or inferior temporal gyrus) using cerebellar gray matter as a reference region

- Tau distribution measured by SUVR and/or extent of tau positive voxels
- Other potential measurements reflecting tau distribution, including use of other potential reference regions, will be identified based on data generated outside of the current substudy protocol

4.4 PARTICIPANT, TREATMENT, AND SUBSTUDY DISCONTINUATION

4.4.1 Blinding and Unblinding

In this Tau PET Longitudinal Substudy ($BN40199$), all enrolled participants will receive the unblinded [^{18}F]GTP1 radioligand but will stay blinded with regard to their study treatment assigned in the main study (crenezumab or placebo).

4.4.2 Participant Discontinuation

Participants have the right to voluntarily withdraw from this substudy at any time for any reason. In addition, the investigator has the right to withdraw a participant from the substudy at any time. Reasons for withdrawal from the substudy may include, but are not limited to, the following:

- Participant withdrawal of consent to participate in the substudy at any time without withdrawing from the main Study GN28352
- Participant withdrawal of consent to participate in the main Study GN28352
- Investigator or Sponsor determines it is in the best interest of the participant

Every effort should be made to obtain information on participants who withdraw from the substudy. The primary reason for withdrawal from the substudy should be documented on the appropriate electronic Case Report Form (eCRF). However, participants will not be followed for any reason after consent has been withdrawn.

4.4.3 Substudy Discontinuation

The Sponsor has the right to terminate this substudy at any time. Reasons for terminating the substudy may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to participants
- Participant enrollment is unsatisfactory

5. ASSESSMENT OF SAFETY

Crenezumab is not approved by any health authority, and clinical development is ongoing. The safety plan for participants in this study is based on clinical experience with crenezumab in completed and ongoing studies and is detailed in the main Study Protocol GN28352. Several measures will be taken to ensure the safety of participants who participate in this substudy. Please refer to Section 5 of the main protocol for details of the safety plan.

Please refer to the main protocol and the Crenezumab Investigator's Brochure for a complete summary of safety information related to crenezumab.

[^{18}F]GTP1 is not approved by any health authority, and clinical development is ongoing. The safety plan for participants in this substudy is based on clinical experience with [^{18}F]GTP1 in completed and ongoing studies and is detailed in the [^{18}F]GTP1 Investigator's Brochure, in Section 5 of the main study protocol, and in Section 1.2 in this protocol. More details are provided in the [^{18}F]GTP1 Investigator's Brochure.

5.1 SAFETY PARAMETERS AND DEFINITIONS

Refer to Section 5.1 and sub-sections of Section 5.1 of the main study protocol (GN28352) for an overview of safety assessments and relevant definitions.

In addition to crenezumab and florbetapir being considered investigational products (as stated in Section 5.1.1 of the main study protocol), [^{18}F]GTP1 is also considered an investigational product for participants enrolled in this substudy.

5.2 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

Refer to Section 5.2 and sub-sections of Section 5.2 of the main study protocol (GN28352) for the methods and timing for capturing and assessing safety parameters.

5.2.1 Adverse Events Reporting Period

For participants in this substudy, the adverse event reporting period is the same as that described in Section 5.2.1 of the main study protocol. This section has been included here solely to be explicit that [^{18}F]GTP1 is considered to be an investigational product.

All adverse events and serious adverse events, regardless of attribution, will be collected until 16 weeks following the last administration of any investigational product (crenezumab/placebo, florbetapir, or [^{18}F]GTP1) or discontinuation/termination of either the main study or this substudy, whichever is later. After this 16-week follow-up period, investigators should report only serious adverse events that are felt to be related to prior administration of investigational product (see Section 5.6 of the main study protocol).

5.3 PROCEDURES FOR RECORDING ADVERSE EVENTS

Refer to Section 5.3 and sub-sections of Section 5.3 of the main study protocol (GN28352) for procedures for recording adverse events.

5.3.1 Recording Adverse Events on the eCRF

For participants in this substudy, reporting of pregnancies in participants, or in female partners of male participants, will be the same as that described in the main study protocol. The two subsections included below have been added to be explicit about the adverse event reporting periods, and to be explicit that [^{18}F]GTP1 is considered to be an investigational product.

5.3.1.1 Pregnancies in Female Participants

If a female participant becomes pregnant while receiving investigational therapy or within 16 weeks after the last dose of investigational product (crenezumab/placebo, florbetapir, or [^{18}F]GTP1), a Pregnancy Report eCRF should be completed within 24 hours of learning of the pregnancy. A pregnancy report will automatically be generated and sent to *Roche* Drug Safety by the electronic data capture (EDC) system. Pregnancy should not be recorded on the Adverse Event eCRF. In the event the EDC system is unavailable, a paper Pregnancy Report form and Pregnancy Fax Coversheet should be completed and faxed to *Roche's* Drug Safety Department, or its designee, at the fax numbers listed in Section 5.4.2 of the main study protocol (GN28352).

5.3.1.2 Pregnancies in Female Partners of Male Participants

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant after the first dose of either crenezumab/placebo, florbetapir, or [^{18}F]GTP1 has been administered or within 8 weeks after the last dose of crenezumab/placebo, florbetapir, or [^{18}F]GTP1 has been administered. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to investigational product. *When permitted by the site,* the pregnant partner *would* need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. *If* the authorization has been signed, the investigator *should* update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician. In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.3.1.i of the main study protocol (GN28352).

5.4 EXPEDITED REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (AND PROTOCOL-DEFINED EVENTS OF SPECIAL INTEREST)

Refer to Section 5.4 and sub-sections of Section 5.4 of the main study protocol (GN28352) for expedited reporting requirements for serious adverse events and protocol-defined events of special interest.

5.5 TYPE AND DURATION OF FOLLOW-UP OF PARTICIPANTS AFTER ADVERSE EVENTS

Refer to Section 5.5 of the main study protocol (GN28352) for type and duration of follow-up of participants after adverse events.

5.6 POST-STUDY ADVERSE EVENTS

Refer to Section 5.6 of the main study protocol (GN28352) for reporting of post-study adverse events.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the GTP1 IB.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The absolute change from the first [^{18}F]GTP1 scan in several measures of tau burden (including but not limited to SUVR and tau distribution metrics) will be analyzed using a mixed-effects model for repeated measures similar to that described for the primary efficacy endpoint in the main study. Additional descriptive summaries that describe the relationship between tau PET and other endpoints will be generated.

The specific tau distribution metrics used (see Section 4.3.2.2) will be further defined after key data, external to this study (for example study GN30009), become available. Such details (as well as details of hypothesis testing) will be specified in the Statistical Analysis Plan, prior to unblinding of study treatment (crenezumab or placebo) in the main protocol.

Other exploratory analyses may also be conducted that may not be pre-specified prior to database unblinding.

6.1 DETERMINATION OF SAMPLE SIZE

The sample size was determined based on the maximum number of participants from the main Study GN28352 who can still undergo two tau PET scans with at least one year in between.

6.2 SUMMARIES OF CONDUCT OF SUBSTUDY

Enrollment, participant disposition, and incidence of protocol deviations will be summarized for the intent-to-treat population according to the randomly assigned treatment arms. The number of participants who enroll, discontinue, or complete the substudy will be summarized. Reasons for premature substudy withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of substudy results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age and sex) of the participants who participate in this substudy will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate.

6.4 SAFETY ANALYSES

The safety analyses for [^{18}F]GTP1 will include all participants who participate in the substudy and receive at least one dose of [^{18}F]GTP1.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

Refer to Sections 6.5 and 6.6 of the main study protocol (GN28352) for requirements for study monitoring and use of eCRFs in the substudy.

7.2 SOURCE DATA DOCUMENTATION

Refer to Section 6.7 of the main study protocol (GN28352) for requirements for source data documentation in the substudy.

7.3 USE OF COMPUTERIZED SYSTEMS

Refer to Section 6.8 of the main study protocol (GN28352) for requirements of computerized systems used in the substudy.

7.4 RETENTION OF RECORDS

Refer to Section 6.11 of the main study protocol (GN28352) for requirements for retention of records in the substudy.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This substudy will be conducted in full conformance with the International Council for Harmonisation (ICH) E6 Guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the *applicable* laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The

substudy will comply with the requirements of the ICH E2A Guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) *and applicable local, regional, and national laws.*

8.2 INFORMED CONSENT

The Sponsor's Tau PET Longitudinal Substudy (*BN40199*) sample Informed Consent Form will be provided to participating sites. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Informed Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each participant the objectives, methods, and potential risks associated with each optional procedure. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a participant's agreement to participate in optional procedures. Participants who decline to participate will not provide a separate signature.

The Informed Consent Forms must be signed and dated by the participant or the participant’s authorized representative before his or her participation in the substudy. The case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained prior to participation in the substudy.

The Informed Consent Forms should be revised whenever there are changes to substudy procedures or when new information becomes available that may affect the willingness of the participant to participate. The final revised IRB/EC-approved Informed Consent Forms must be provided to the Sponsor for health authority submission purposes.

Participants must be re-consented to the most current version of the Informed Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the substudy. For any updated or revised Informed Consent Forms, the case history or clinical records for each participant shall document the informed consent process and that written informed consent by the participant or the participant’s authorized representative was obtained

using the updated/revised Informed Consent Forms for continued participation in the substudy (Section 4.3.1).

A copy of each signed Informed Consent Form must be provided to the participant or the participant's authorized representative. All signed and dated Informed Consent Forms must remain in each participant's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the participant, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the substudy is initiated. In addition, any participant recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the substudy to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each participant enrolled in the substudy and the main study through assignment of a unique participant identification number. This means that participant names are not included in data sets that are transmitted to any Sponsor location.

Participant medical information obtained by this substudy is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Medical information may be given to a participant's personal physician or other appropriate medical personnel responsible for the participant's welfare, for treatment purposes.

Data generated by this substudy must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

9. SUBSTUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 SUBSTUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the participant data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. *The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.*

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, participants' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

The overall procedures for quality assurance of clinical study data are described in the Roche standard operating procedures. This study will be sponsored by F. Hoffmann-La Roche Ltd. Roche will provide clinical operations oversight, site monitoring and management, data management support, and medical monitoring Central facilities will be used for study assessments (i.e., PET assessments).

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all

requirements for publication of study results. *Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request.* For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in participants involving an investigational medicinal product (IMP) for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in participants involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to

eliminate an immediate hazard to participants or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

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Appendix 1
Schedule of Activities

	First [^{18}F]GTP1 Scan [a]	*Second* [^{18}F]GTP1 Scan [b]	*Third* [^{18}F]GTP1 Scan[c]/ET [d]
Informed consent for substudy protocol	x		
Review of inclusion and exclusion criteria	x		
Adverse Events	x	x	x
Concomitant Medications	x	x	x
Urine pregnancy test [e]	x	x	x
Vital signs [f]	x	x	x
[^{18}F]GTP1–tau PET scan [g]	x	x	x

ET = early termination; FDG = fluorodeoxyglucose; GTP1 = Genentech Tau Probe 1; PET = positron emission tomography.

[a] The first [^{18}F]GTP1–tau PET scan, and other activities in the table above, may occur on any visit that occurs in the main protocol (GN28352), from the Week 130 visit to the Week 224 visit. This first scan visit may be different for each participant, and only one [^{18}F]GTP1 scan should be obtained per participant for this first scan. For each participant, this first scan should occur as early as possible within the Week 130 to Week 224 visit period. The [^{18}F]GTP1–tau PET scan may be obtained in a ±14-day window for visits in the Week 130 to Week 224 visit period. See Section 3.1 for details.

[b] *The second [^{18}F]GTP1–tau PET scan, and other activities in the table above, may occur on any visit that occurs in the main protocol (GN28352), 52 [± 2] weeks after the first scan. This second scan visit may be different for each participant, and only one [^{18}F]GTP1 scan should be obtained per participant for this second scan.*

[c] *The third [^{18}F]GTP1–tau PET scan should be obtained for each participant at the GN28352 ET or final visit if at least 6 months has elapsed since the previous [^{18}F]GTP1–tau PET scan. See Section 3.1 for details.*

[d] In the event a participant terminates Study GN28352 early, a [^{18}F]GTP1–tau PET scan should only be collected if informed consent has been obtained and at least 6 months has elapsed since any previous [^{18}F]GTP1–tau PET scan and if local annual radiation limits are not exceeded. Refer to Study GN28352 schedule for other ET procedures.

[e] Urine pregnancy test must be administered and have a negative result before any [^{18}F]GTP1–tau PET scan, unless a negative urine pregnancy test was already obtained on the same calendar day as per the schedule of activities in the main study. If the participant has discontinued the study drug but is continuing with study assessments, the urine pregnancy test must be administered for visits during which [^{18}F]GTP1 is administered. Pregnancy testing will apply to all women unless documented (by medical records or physician's note) to be surgically sterile or postmenopausal as defined in Section 3.4.4.3 of the main study protocol (GN28352). It is recommended, but not required, to use effective contraception during sexual intercourse occurring within 24 hours following a male or female participant receiving a [^{18}F]GTP1–tau PET scan.

[f] Vital signs will include measurements of heart rate, and systolic and diastolic blood pressure while the participant has been supine for ≥ 3 minutes. Vital signs should be measured prior to the administration of [18F]GTP1.

[g] If occurring in the same visit, [18F]GTP1–tau PET scans will be performed after neurocognitive testing but prior to dosing of crenezumab or placebo. The [18F]GTP1–tau PET scan should be performed a minimum of 12 hours apart from any other amyloid or FDG PET scan that might be performed *and a maximum of 14 days apart from any accompanying fibrillar amyloid-PET or FDG-PET scan.*