A Phase I Study to Determine the Relative Bioavailability of Various Formulations of GDC-0134 in Healthy Female Subjects of Non-Childbearing Potential

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for

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by

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ABBREVIATIONS

A_{eu}	amount excreted in urine over a sampling interval
AE	adverse event
AESI	adverse event of special interest
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransferase
anti-HCV	hepatitis C virus antibody
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-t}	area under the concentration-time curve from Hour 0 to the last measurable concentration
$AUC_{0-\infty}$	area under the concentration-time curve extrapolated to infinity
BMI	body mass index
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed concentration
CL/F	apparent systemic clearance
CL_R	renal clearance
CPET	Clinical Pharmacology Protocol Execution Team
CRU	Clinical Research Unit
C_t	last measurable concentration
C_{trough}	concentration at the end of a dosing interval at steady state
DLK	dual leucine zipper kinase
ECG	electrocardiogram
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ERG	electroretinography
ET	Early Termination
FDA	Food and Drug Administration
$\%F_{eu}$	percentage of dose excreted in urine over a sampling interval
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HBsAg	hepatitis B surface antigen

HDYF?	How do you feel?
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation/International Council for Harmonisation
IND	Investigational New Drug
IOP	intraocular pressure
IRB	Institutional Review Board
JNK	c-jun N-terminal kinase
OSE	open-label safety expansion
PD	pharmacodynamic(s)
PI	Principal Investigator
PK	pharmacokinetic(s)
PPD	purified protein derivative
PPI	proton pump inhibitor
PPS	peripapillary swelling
QD	once daily
QTcF	QT interval corrected through use of Fridericia's formula
RBC	red blood cell
RBR	Research Biosample Repository
RNFL	retinal nerve fiber layer
SAE	serious adverse event
SAP	Statistical Analysis Plan
TB	tuberculosis
TEM	transmission electron microscopy
$t_{1/2}$	apparent terminal elimination half-life
t_{max}	time to maximum observed concentration
UA	urinalysis
ULN	upper limit of normal
V_z/F	apparent volume of distribution during the terminal phase
WBC	white blood cell
WGS	whole genome sequencing
λ_z	apparent terminal elimination rate constant

1 SYNOPSIS

<table>
<tr><td>Title of Study:</td><td>A Phase I Study to Determine the Relative Bioavailability of Various Formulations GDC-0134 in Healthy Female Subjects of Non-Childbearing Potential</td></tr>
<tr><td>Objectives:</td><td>The primary objectives of this study are:
To determine the relative bioavailability of GDC-0134 F16 capsules (newly developed capsule formulation with GDC-0134 malate drug substance) with respect to the current clinical material, GDC-0134 F09 capsules, with a standard meal.
To determine the relative bioavailability of GDC-0134 F15 capsules (newly developed capsule formulation with GDC-0134 freebase) with respect to the current clinical material, GDC-0134 F09 capsules, under fasted conditions.
A description of test products is provided below.

The secondary objectives of this study are:
To determine the safety and tolerability of a single oral dose of GDC-0134 in healthy subjects.
To characterize the pharmacokinetics (PK) of GDC-0134 after oral administration in healthy subjects.
The exploratory objective of this study is:
To determine the urinary elimination of GDC-0134</td></tr>
<tr><td>Methodology/Study Design:</td><td>This will be an open-label, randomized, 2-period crossover study consisting of two parts to determine:
Part 1 – the relative bioavailability of GDC-0134 F16 capsules (Ro 704-0814/F16) and GDC-0134 F09 capsules (Ro 704-0814/F09) with a standard meal
Part 2 – the relative bioavailability of GDC-0134 F15 capsules (Ro 704-0814/F15) and GDC-0134 F09 capsules (Ro 704-0814/F09) under fasted conditions
In each part of the study, plasma PK samples will be collected through 21 days postdose and urine samples will be collected through 48 hours postdose. The following safety assessments will be conducted at specific times during the study: physical examination, 12-lead electrocardiogram (EGC), vital signs, “How do you feel” inquiries (to assess adverse events [AEs]), ophthalmology, and clinical laboratory evaluations.</td></tr>
<tr><td>Number and General Description of Subjects:</td><td>Twenty-two healthy female subjects of non-childbearing potential will be enrolled in each part of the study, in order for at least 18 subjects (9 per treatment sequence) to complete each part (Part 1 and Part 2). If the two parts of the study are run sequentially, subjects will be encouraged to participate in both parts. The maximum number of subjects enrolled into the study will be approximately 44.</td></tr>
<tr><td>Diagnosis and Main Criteria for Inclusion:</td><td>Female subjects of non-childbearing potential between 18 and 65 years of age, inclusive, and within body mass index range of 18.5 to 35 kg/m^2, inclusive.</td></tr>
<tr><td>Test Product(s), Dose, and Mode of Administration:</td><td><table>
<tr><th>Study Drug Product</th><th>Description</th><th>Study Designation</th></tr>
<tr><td>GDC-0134 F09 capsule, 200 mg (aka GDC-0134 capsules, 200 mg in Investigational New Drug CMC dossier)</td><td>Reference drug, current clinical material</td><td>GDC-0134 F09 capsule</td></tr>
<tr><td>GDC-0134 F15 capsule, 200 mg</td><td>Test drug, newly developed capsule formulation with GDC-0134 freebase</td><td>GDC-0134 F15 capsule</td></tr>
</table></td></tr>
</table>

	<table><tr><td>GDC-0134 F16 capsule, 200 mg</td><td>Test drug, newly developed capsule formulation with GDC-0134 malate drug substance</td><td>GDC-0134 F16 capsule</td></tr></table> Subjects will receive the following treatments, according to a randomization schedule generated by a Covance biostatistician: **Part 1:** • GDC-0134 F16 capsules (Ro 704-0814/F16) - 800 mg, oral, with a standard meal • GDC-0134 F09 capsules (Ro 704-0814/F09) - 800 mg, oral, with a standard meal **Part 2:** • GDC-0134 F15 capsules (Ro 704-0814/F15) - 800 mg, oral, fasted • GDC-0134 F09 capsules (Ro 704-0814/F09) - 800 mg, oral, fasted
Duration of Treatment:	Planned Enrollment/Screening Duration: approximately 4 weeks Length of Each Confinement: approximately 1 day predose until approximately 2 days postdose. Planned Individual Study Part Duration: approximately 11 weeks
Criteria for Evaluation: Safety	Safety assessments will include clinical laboratory evaluations, physical examinations, ECGs, ophthalmology, and vital signs. In addition, the nature, frequency and severity of treatment-emergent AEs will be collected and summarized.
Criteria for Evaluation: Pharmacokinetics	The following PK parameters will be derived from the plasma concentrations of GDC-0134 using the model independent approach: Maximum observed concentration (C_{max}), time to maximum observed concentration (t_{max}), area under the concentration-time curve (AUC) from Hour 0 to the last measurable concentration (AUC_{0-t}), AUC extrapolated to infinity ($AUC_{0-\infty}$), apparent terminal elimination rate constant (λ_z), terminal elimination half-life ($t_{1/2}$), apparent systemic clearance (CL/F), and apparent volume of distribution during the terminal phase (V_z/F). The following PK parameters will be derived from the urine concentrations of GDC-0134: amount excreted in urine over a sampling interval (A_{eu}), cumulative amount excreted in urine (Total A_{eu}), percentage of dose excreted in urine over a sampling interval ($\%F_{eu}$), cumulative percentage of dose excreted in urine (Total $\%F_{eu}$), and renal clearance (CL_R).
Statistical Methods:	The primary parameters for analysis will be $AUC_{0-\infty}$, and C_{max} of GDC-0134. A linear mixed model will be applied to analyze the log-transformed primary PK parameters. The model assumes fixed effects for formulation, period, and sequence, and a random effect for subject within sequence. Estimates of geometric mean ratios on the original scale, together with the corresponding 90% CIs, will be derived for the comparisons between Test and Reference treatments. Descriptive statistics will be calculated on the PK data. No formal statistical analyses are planned for safety data.

2 INTRODUCTION

2.1 BACKGROUND

GDC-0134 (also known as G02792134 and RO7040814) is a potent, selective, orally available and brain-penetrant small molecule inhibitor of dual leucine zipper kinase (DLK) being developed as a therapeutic for amyotrophic lateral sclerosis (ALS). Dual leucine zipper kinase has been identified as a central regulator of neuronal degeneration in a variety of settings, and regulates pathways active in chronic neurodegenerative diseases. Both in vitro and nonclinical in vivo studies support the hypothesis that GDC-0134-mediated inhibition of DLK may benefit patients with both familial and sporadic ALS.

ALS is a devastating, incurable neurodegenerative disease of upper and lower motor neurons that affects approximately three in every 100,000 adults in the United States, most commonly people between the ages of 40 and 70 years (1). Degeneration of motor neurons leads to loss of motor control and strength (which affects the limbs, speech, swallowing, and respiration), resulting in the need for permanent respiratory support and ultimately death. Although significant heterogeneity does exist in the rate of disease progression, the majority of patients with ALS die within 3 to 5 years after disease diagnosis (1).

The mechanisms of motor neuron loss are currently unknown and a common pathophysiological mechanism has yet to be identified. Despite numerous clinical trials exploring multiple interventions (2), there have been limited successes, with riluzole and edaravone being the only medications approved in the United States for treatment of ALS. Riluzole, a tetrodotoxin-sensitive sodium channel antagonist confers only a modest (2-3 months) survival benefit and has not consistently demonstrated functional benefit (3). Edaravone, a free radical scavenger, was approved for the treatment of ALS in 2017 in the United States and in Canada in 2018. A survival benefit has not been established (Radicava® U.S. Package Insert). While this recent approval brings one more treatment option to ALS patients, there remains a high unmet medical need for novel therapeutic approaches that could improve function and prolong survival.

Dual leucine zipper kinase is a member of the mixed-lineage kinase family that is an upstream regulator of the c-jun N-terminal kinase (JNK) pathway. This pathway has been shown to contribute to axon degeneration and neuronal apoptosis following nerve injury and excitotoxic insult and in models of chronic neurodegenerative disease (4-6). Motor neurons in particular appear to require DLK in order to degenerate, and loss of DLK signaling is potently neuroprotective in this cell type (4, 8). Stress-induced activation of the DLK/JNK pathway is evident in motor neurons of a mouse model of ALS, and genetic reduction of DLK protects

motor neurons from degeneration, preserves motor function, and extends survival in the SOD1 G93A mouse (9).

Expression of DLK is limited largely to neurons of the central and peripheral nervous systems (7), and does not have an impact on normal physiological JNK activity (4, 5). Inhibition of DLK by GDC-0134, therefore, provides a highly specific approach to preventing neurodegeneration.

2.2 OVERVIEW OF GDC-0134 CLINICAL DEVELOPMENT

There have been two recent clinical studies evaluating GDC-0134. A randomized, double-blind Phase I study (Study GN29823) is ongoing in patients with ALS to evaluate the safety, tolerability and pharmacokinetics (PK) of GDC-0134. An open-label, cross over clinical pharmacology study (Study GP39778) is completed and was conducted in healthy female subjects of non-childbearing potential to investigate the relative bioavailability of two formulations of GDC-0134 and to evaluate the effect of food, a proton pump inhibitor (PPI), and applesauce preparation on GDC-0134 absorption and disposition.

As of 22 October 2018, Study GN29823 has enrolled 43 male and female patients with ALS who have received GDC-0134 or placebo. GDC-0134 has had a favorable safety profile in all single dose, multiple-dose, and open-label safety expansion (OSE) cohorts evaluated in Study GN29823. There have been no reported deaths; one serious adverse event (SAE) in the OSE stage at 400 mg once daily (QD) (life-threatening thrombocytopenia confounded by concomitant medications including cephalexin and ibuprofen), one dose-limiting AE (DLAE) in multiple ascending dose (MAD) stage at 800 mg (non-serious AE of blurred vision with no objective findings), and four withdrawals due to AEs have been observed (two in the single ascending dose [SAD] stage [one asymptomatic non-serious increase in intraocular pressure (IOP); and one non-serious asymptomatic increase in blood bilirubin 161 days after last dose], one in the MAD [the DLAE described previously] and one in the OSE [the SAE described previously]) (see the Investigator Brochure [IB] for full details [10]).

In the completed Study GP39778, a total of 18 healthy female subjects each have received four single doses (200 mg each) of GDC-0134, separated by approximately 3 weeks. Overall, single doses of GDC-0134 were well tolerated. There were no deaths, no SAEs, and no withdrawals due to AEs. There was one severe AE of asymptomatic increased transaminases approximately 2 days after dosing with formulated GDC-0134 with high-fat meal in combination with 20 mg rabeprazole following prior administration of rabeprazole for 3 days (see the IB for full details [10]).

2.3 CLINICAL PHARMACOKINETICS OF GDC-0134

The clinical pharmacokinetics of GDC-0134 has been investigated in ongoing and completed clinical studies. As of 15 September 2018, preliminary PK data from Study GN29823 are available from 17 patients receiving escalating single oral doses of GDC-0134 and from 24 patients administered 100-1200 mg GDC-0134 QD for a planned treatment period of 28 consecutive days in the MAD stage. The PK data from completed Study GP39778 are available from 18 healthy volunteers who received 200 mg single oral doses of GDC-0134.

In Study GN29823, following a single dose, GDC-0134 was rapidly absorbed with peak concentrations achieved at around 1.5 hours (median time to maximum observed concentration [t_{max}]) after dosing. Biphasic elimination with a relatively rapid decline in drug concentration was observed right after t_{max} of up to 6–12 hours, followed by a slower decline of up to 168 hours. Mean apparent terminal elimination half-life ($t_{1/2}$) of GDC-0134 following a single dose was approximately 89 hours. GDC-0134 exposure in the fasted state increased with dose in an approximately dose-proportional manner across the dose range tested to date (20-640 mg).

Following multiple doses (100-1200 mg QD) of GDC-0134 in the MAD stage of Study GN29823, plasma concentrations of GDC-0134 increased with dose after a single dose and at steady state in MAD (100-1200 mg); however, the increase was less than dose proportional within the MAD dose range tested. Consistent with the long terminal elimination half-life, median accumulation following QD dosing was approximately 2 to 3-fold relative to single dose C_{max} and area under the concentration-time curve from 0 to 6 hours (AUC_{0-6}).

In Study GP39778, following analysis of the plasma concentrations of GDC-0134 to determine the effect of formulation, food, and PPI use in healthy volunteers, no significant difference in GDC-0134 exposures between powder-in-capsule and formulated capsule were observed at 200 mg. Statistically significant increases in systemic exposure (C_{max} and AUC) to GDC-0134 were observed with a high-fat meal (1.1 to 1.4 fold) or applesauce preparation (1.4 – 2.8 fold) compared to fasted condition. Systemic exposure (C_{max} and AUC) to GDC-0134 significantly decreased (26%-60% of control) in the presence of a PPI, rabeprazole (administered to subjects after an overnight fast). However, this effect was partially attenuated by the consumption of a high-fat meal (46%–99% of control). In addition, a reduction in inter-subject exposure variability was observed when GDC-0134 was administered with a high-fat meal, as an applesauce preparation, or with a PPI compared with when it was administered alone in the fasted condition.

2.4 STUDY RATIONALE

GDC-0134 is a novel molecule being developed by Genentech as a therapeutic for the treatment of patients with ALS. GDC-0134 is intended for oral administration, and the current formulation of the drug has been investigated in its free base form.

In this study, the systemic exposure to GDC-0134 following oral administration of the current GDC-0134 formulation (GDC-0134 F09 capsule, Ro 704-0814/F09) and the newly developed capsule formulation with GDC-0134 malate drug substance (GDC-0134 F16 capsule) will be investigated to determine the relative bioavailability. A newly developed capsule formulation with GDC-0134 free base (GDC-0134 F15 capsules) will also be compared against the current clinical material GDC-0134 F09 capsules.

2.5 DOSE RATIONALE

A maximum of 800 mg single dose is proposed for this study; this dose is considered safe based on clinical safety data. In the ongoing Phase I GN29823 study in patients with ALS, single doses of 20 mg through 640 mg and multiple doses of 100 mg through 1200 mg QD have been well tolerated to date (see Section 2.2).

The highest dose tested in the Phase I study, 1200 mg QD dose, is expected to provide an exposure margin of >5-fold compared to 800 mg single dose of the current clinical material, GDC-0134 F09 capsules, in fasted condition (1200 mg once daily dosing in patients with ALS resulted in a steady state C_{max} and AUC_{0-6} of 13.6 µM and 60.1 µM*hr, respectively compared to a single dose of 800 mg which resulted in a C_{max} and AUC_{0-6} of 2.62 µM and 8.58 µM*hr, respectively). The PK of single doses of GDC-0134 (200 mg) were shown to be comparable between healthy volunteers (study GP39778) and patients with ALS (study GN29823).

In this study, the exposures with the GDC-0134 F16 and F15 are expected to be comparable with that of the current clinical material GDC-0134 F09 capsules. Systemic exposure to GDC-0134 administered with a meal is expected to be within 2-fold of the systemic exposure observed with current clinical material GDC-0134 F09 capsules in fasted condition. This is based on the food effect observed in study GP39778 (1.1-1.4 fold; see Section 2.3), taking into account that the standard meal planned in this study is expected to have less of an effect than the high-fat meal in study GP39778.

Doses between 600 mg per day and 1200 mg per day, administered QD or divided into two doses, are predicted to be clinically efficacious based on the preclinical PK/PD model and the

population PK model. Therefore, an 800 mg single dose of GDC-0134 is proposed to understand the effects of formulation and food at a clinically meaningful dose.

3 STUDY OBJECTIVES AND CORRESPONDING ENDPOINTS

3.1 PRIMARY OBJECTIVE

The primary objectives of this study are:

- To determine the relative bioavailability of GDC-0134 F16 capsules (newly developed capsule formulation with GDC-0134 malate drug substance) with respect to the current clinical material, GDC-0134 F09 capsules, with a standard meal.
- To determine the relative bioavailability of GDC-0134 F15 capsules (newly developed capsule formulation with GDC-0134 freebase) with respect to the current clinical material, GDC-0134 F09 capsules, under fasted conditions.

A full description of study products is provided in Table 7-4.

3.2 SECONDARY OBJECTIVES

The secondary objectives of this study are:

- To determine the safety and tolerability of a single oral dose of GDC-0134 in healthy subjects.
- To characterize the PK of GDC-0134 after oral administration in healthy subjects.

3.3 EXPLORATORY OBJECTIVES

The exploratory objective of this study is:

- To determine urinary elimination of GDC-0134

3.4 ENDPOINTS

3.4.1 PHARMACOKINETIC ENDPOINTS

The primary PK endpoints of this study are:

- maximum observed concentration (C_{max});
- AUC extrapolated to infinity ($AUC_{0-\infty}$).

The secondary PK endpoints of this study are:

- time to maximum observed concentration (t_{max});
- AUC from Hour 0 to the last measurable concentration (AUC_{0-t});
- apparent terminal elimination rate constant (λ_Z);
- apparent terminal elimination half-life ($t_{1/2}$);
- apparent systemic clearance (CL/F);
- apparent volume of distribution during the terminal phase (V_z/F).

The exploratory PK endpoints of this study are:

- amount excreted in urine over a sampling interval (A_{eu});
- cumulative amount excreted in urine (Total A_{eu});
- percentage of dose excreted in urine over a sampling interval ($\%F_{eu}$);
- cumulative percentage of dose excreted in urine (Total $\%F_{eu}$);
- renal clearance (CL_R).

3.4.2 SAFETY ENDPOINTS

The Safety endpoints of this study are:

- Incidence, nature, and severity of AEs (assessed and graded according to the grading criteria in Section 8.2.3);
- Changes in vital signs, electrocardiograms (ECGs), physical examination findings, ophthalmology assessment findings, and clinical laboratory results during and following GDC-0134 administration.

4 STUDY DESIGN

4.1 DESCRIPTION OF THE STUDY

This will be an open-label, randomized, 2-period crossover study consisting of two parts to determine:

- Part 1 – the relative bioavailability of GDC-0134 F16 capsules and the current clinical material, GDC-0134 F09 capsules;
- Part 2 – the relative bioavailability of GDC-0134 F15 capsules and the current clinical material, GDC-0134 F09 capsules.

Part 1 and Part 2 may occur in parallel or consecutively in either order (Part 1 followed by Part 2, or Part 2 followed by Part 1).

Approximately 22 female subjects of non-childbearing potential (11 per treatment sequence) between 18 and 65 years of age, inclusive, will be enrolled into each part of the study across two clinical research sites. In each part, subjects will be randomized into one of two treatment sequences following a randomization schedule generated by Covance. If the two parts are run sequentially subjects will be encouraged to enroll into more than one part of the study, and there will be a minimum of 22 days between dosing in different parts. A washout period of 21 days is considered to be sufficient based on the mean terminal elimination half-life of GDC-0134 in patients and healthy volunteers being <100 hours, and based on a negligible residual drug concentration of GDC-0134 on Day 21 in healthy volunteers (mean C_{max}/ concentration at the end of a dosing interval at steady state [C_{trough}] ratio >300-fold). A maximum of approximately 44 subjects will be enrolled into this study. The crossover design is presented in Figure 1 and Figure 2.

In each part of the study, potential subjects will be screened to assess their eligibility to enter the study within 27 days prior to Check-in (Day -1) for their first treatment period. Replacement subjects may be enrolled, only if deemed necessary by the Sponsor, to ensure that 18 subjects complete each part of the study (9 subjects per treatment sequence). For all subjects, routine screening procedures, as outlined in Section 5.1, will be performed.

In both parts of the study, eligible subjects will be admitted to the Clinical Research Units (CRUs) on the day prior to dosing for each period (Check-in; Day -1) to collect baseline data and to familiarize the subjects with study procedures that will be used during the rest of the study. Randomization will occur on Day 1 of Period 1.

Part 1

In Part 1, Periods 1 and 2, eligible subjects will receive 800 mg of either GDC-0134 F16 capsules or the current clinical material, GDC-0134 F09 capsules (Ro 704-0814/F09), orally with a standard meal on Day 1 according to the randomization schedule. Subjects will be confined to the CRU from Check-in (Day -1) until Discharge on Day 3. Subjects will be required to return to the CRU for outpatient visits on Days 5, 7, and 15 (or at Early Termination [ET]). Check-in (Day -1) for Period 2 will occur 20 days after dosing in Period 1.

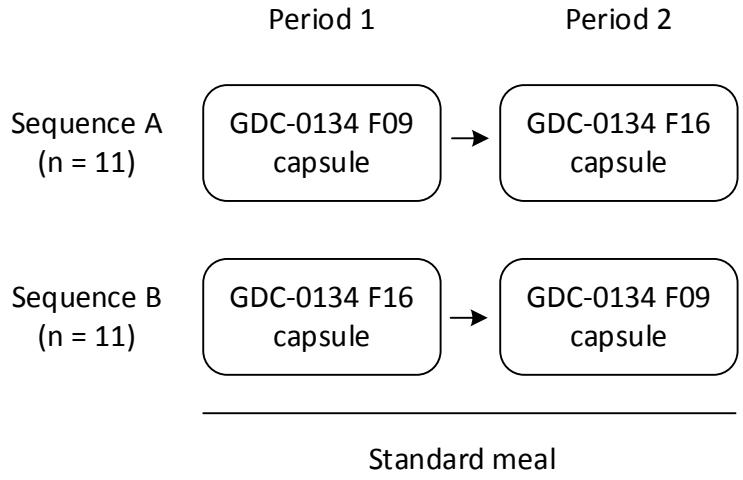
Part 2

In Part 2, Periods 1 and 2, subjects will receive 800 mg of GDC-0134 F15 or the current clinical material, GDC-0134 F09 capsules, after an overnight fast according to the randomization schedule on Day 1. Subjects will not receive food for 4 hours postdose. Part 2 may occur before, after, or in parallel with Part 1.

Subjects will be confined to the CRU from Check-in (Day -1) until Discharge on Day 3 during each period. Subjects will be required to return to the CRU for outpatient visits on Days 5, 7, and 15 (or at ET). Check-in (Day -1) for Period 2 will occur 20 days after dosing in Period 1.

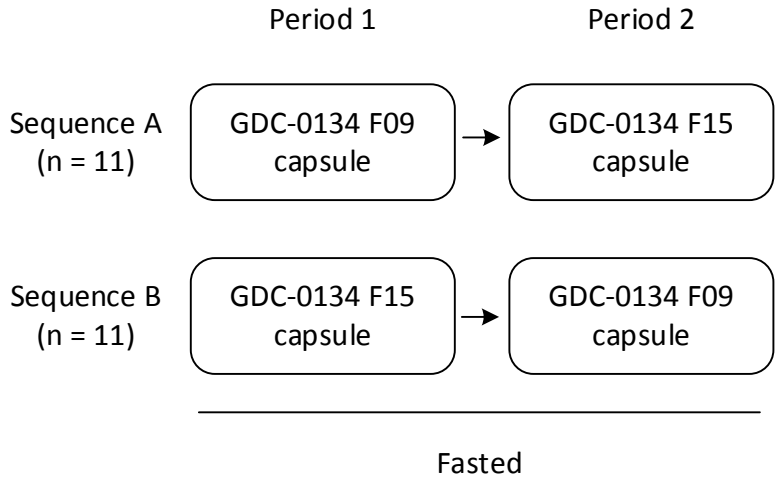
A detailed list of assessments is included in Table 7-1 and Table 7-2.

Figure 1 Study Schematic of Crossover Design – Part 1



Note: F09 capsules = current clinical material of GDC-0134; F16 capsules = newly developed capsule formulation with GDC-0134 malate drug substance

Figure 2 Study Schematic of Crossover Design – Part 2



Note: F09 capsules = current clinical material of GDC-0134; F15 capsules = newly developed capsule formulation with GDC-0134 free base

In this study design, physical examinations, 12-lead ECGs, vital signs, "How do you feel?" (HDYF?) inquiries, ophthalmology assessments, and clinical laboratory evaluations (Appendix A) will be performed at Screening, at specified times during the study, and/or at Study Completion (for specific timepoints and details on each study variable, refer to Section 7). After informed consent has been obtained but prior to initiation of study drug administration (Day 1), only SAEs caused by protocol-mandated interventions will be reported. After initiation of study drug administration on Day 1 of each study part, all AEs, whether volunteered, elicited, or noted upon physical examination, will be recorded throughout the study until 28 days after the last dose of the study (i.e., from Day 1 until Study Completion/ET). Following administration of each treatment in each study part, plasma PK samples will be collected through 21 days postdose and urine PK samples will be collected through 48 hours postdose. A Schedule of Activities is presented in Table 7-1 and Table 7-2.

4.2 RATIONALE FOR STUDY DESIGN

This study will assess the relative bioavailability of newly developed formulations of GDC-0134 compared to the current clinical material in healthy females of non-childbearing potential. A single dose, randomized, 2 part, 2-period crossover study design was considered acceptable to achieve the study objectives. This study will not be blinded as the primary endpoints (GDC-0134 PK) are not subjective or able to be biased by knowledge of study sequence.

4.3 RATIONALE FOR SUBJECT POPULATION

The study will exclude women of childbearing potential and will be limited to healthy female subjects of non-childbearing potential based on findings of maternal toxicity and significant fetal malformations in nonclinical studies in pregnant rats and rabbits (see Section 2.1 and the IB [10] for further details). Males are excluded based on findings of testicular toxicity observed in male rats (see Sections 6.1.4.10). Clinical experience in humans is still limited to assess the translatability of these nonclinical findings to humans.

4.4 RATIONALE FOR EXPLORATORY ASSESSMENTS

Urine samples will be collected to determine urinary elimination of GDC-0134.

4.5 RATIONALE FOR PHARMACOKINETIC SAMPLING SCHEDULE

The frequent sampling schedule is designed to capture data at a sufficient number of timepoints to provide a detailed profile of the concentration-time curve, including maximum observed concentration (C_{max}), time to maximum observed concentration (t_{max}), and apparent terminal elimination half-life ($t_{1/2}$).

4.6 RATIONALE FOR WHOLE GENOME SEQUENCING

A whole blood sample will be collected from all subjects for DNA extraction to enable whole genome sequencing (WGS). Genomics is increasingly informing researcher's understanding of disease pathobiology. Whole genome sequencing provides a comprehensive characterization of the genome and, through the generation of control data from healthy subjects along with clinical data collected in this study, may increase our understanding of PK, response, human diseases, and the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents. Given the complexity and exploratory nature of these analyses, WGS data and analyses will not be shared with the Principal Investigators (PIs) or study subjects unless required by law.

5 SUBJECT SELECTION

Twenty-two healthy volunteer female subjects of non-childbearing potential who meet all the protocol inclusion criteria and none of the exclusion criteria will be enrolled into each part of the study. If the two parts of the study are run sequentially, subjects will be encouraged to participate in multiple parts of the study as long as they continue to meet the eligibility criteria. If the parts are conducted sequentially, any subjects discontinued may be replaced with new subjects prior to the start of each part. The maximum possible number of subjects enrolled into the study will be approximately 44.

5.1 SCREENING PROCEDURES

Refer to Table 7-1 and Table 7-2 for procedures performed for all potential subjects at the Screening visit.

If subjects are participating in multiple parts of the study, they will not be required to re-screen for the second part of the study as long as there are ≤28 days between Clinic Discharge in the first part and Check-in for the second part of the study.

5.2 CHECK-IN PROCEDURES

Refer to Table 7-1 and Table 7-2 for procedures performed at Check-in for Periods 1 and 2 when subjects will report to the study site.

For subjects to continue their participation in the study, the drug screen and pregnancy test must be negative and the clinical laboratory evaluations must be within the normal laboratory range

(unless deemed not clinically significant by the PIs). In addition, continued compliance with concomitant medication and other restrictions will be verified.

5.3 INCLUSION CRITERIA

Subjects who meet the following criteria may be included in the study:

1. Females, between 18 and 65 years of age, inclusive;
   within body mass index (BMI) range 18.5 to 35 kg/m^2, inclusive;
2. In good health, determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, and vital signs;
3. Clinical laboratory evaluations (including chemistry panel [fasted at least 8 hours], complete blood count [CBC], and urinalysis [UA] with complete microscopic analysis (if indicated) within the reference range for the test laboratory, unless deemed not clinically significant by the PIs [Gilberts syndrome is acceptable]);
4. A normal ophthalmology assessment; minor abnormalities or age-related changes are acceptable, if not considered clinically significant, as per the judgment of the ophthalmologist;
5. Negative test for selected drugs of abuse at Screening (does not include alcohol) and at Check-in for each study period (does include alcohol; Appendix A);
6. Negative for cannabinoids (tetrahydrocannabinol) at Screening and at Check-in for both study periods (Appendix A);
7. Negative hepatitis panel (hepatitis B virus core antibody, hepatitis B surface antigen [HBsAg] and hepatitis C virus antibody [anti-HCV]) and negative HIV antibody screens (Appendix A);
8. Females of non-childbearing potential only, defined as:
   - females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks prior to Screening
   - Females of at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels of ≥40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators. Women aged > 60 years old whose

FSH values are not ≥40 mIU/L may be included at the discretion of the PIs and in consultation with the Sponsor

9. Negative screening test for latent mycobacterium tuberculosis (TB) infection by QuantiFERON® TB Gold (Appendix A). Indeterminate results may be confirmed By repeat or by a purified protein derivative (PPD) skin test;
10. Receive an explanation of the mandatory WGS component of the study;
11. Able to comprehend and willing to sign an Informed Consent Form (ICF).

5.4 EXCLUSION CRITERIA

The following will exclude potential subjects from the study:

1. Significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular (including left ventricular hypertension), gastrointestinal (GI), neurological, ophthalmologic, or psychiatric disorder, as determined by the PI (or designee);
2. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the PI (or designee);
3. History of stomach or intestinal surgery or resection (including cholecystectomy) that would potentially alter absorption and/or excretion of orally administered drugs except that appendectomy and hernia repair will be allowed;
4. History or presence of an abnormal ECG at Screening or Check-in (Day -1) for Period 1, which in the PIs opinion, is clinically significant (QTc interval >470 msec, PR interval >210 msec, or QRS complex >120 msec; abnormal ECG findings will be confirmed by calculating the mean of the original value and 2 repeats);
5. History of alcoholism or drug addiction within 1 year prior to Check-in (Day -1) for their first treatment period;
6. Participation in any other investigational study drug trial in which receipt of an investigational study drug occurred within five half-lives (if known) or 30 days (small molecule) or 90 days (biologic) for Check-in (Day -1) of their first treatment period, whichever is longer;
7. Use of any prescription medications/products within 14 days prior to Check-in (Day -1) for their first treatment period and during the entire study duration, unless deemed acceptable by the PI (use of hormone replacement therapy [HRT], thyroid replacement therapy, ophthalmic drops, or other ophthalmic procedures as part of the fundoscopic exam is acceptable);
8. Use of oral antibiotics within 4 weeks or intravenous antibiotics within 8 weeks prior to the Screening evaluation and during the entire study duration;

9. Use of any over-the-counter, non-prescription preparations (including vitamins; minerals; and phytotherapeutic-, herbal-, and plant-derived preparations) within 14 days prior to Check-in (Day -1) for their first treatment period and during the entire study duration, unless deemed acceptable by the PI (acetaminophen [paracetamol] is acceptable [see Section 7.5]);
10. Use of acid reducing medications (PPIs, H2 receptor antagonists, etc.) within 14 days prior to Check-in (Day -1) for their first treatment period and during the entire study duration. As an alternative, antacids may be allowed at least 4 hours before or after dose;
11. Use of strong inhibitors and inducers of CYP3A4/5 and UGT enzymes within 14 days prior to Check-in (Day -1) for their first treatment period until the Study Completion/ET is prohibited, and alternate medications should be considered where possible;
12. Use of any vaccines (including seasonal flu and H1N1 vaccines) within 14 days prior to Check-in (Day -1) for their first treatment period;
13. Use of tobacco- or nicotine-containing products (including, but not limited to, cigarettes, e-cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum) within 6 months prior to Check-in (Day -1) for their first treatment period and during the entire study;
14. Use of alcohol- or caffeine-containing foods or beverages within 72 hours prior to Check-in (Day -1) for their first treatment period until Study Completion/ET;
15. Consumption of grapefruit, grapefruit-containing products, and pomegranate, pomelo, and star fruit juice/products within 7 days prior to Check-in (Day -1) for their first treatment period and during the entire study duration;
16. strenuous exercise within 48 hours prior to Check-in (Day -1) for their first treatment period or during the period of confinement at the study site (e.g., subjects will not begin a new exercise program or participate in any unusually strenuous physical exertion);
17. Poor peripheral venous access;
18. History of malignancy, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer;
19. Donation of blood from 30 days prior to Screening through Study Completion, Clinic Discharge, or ET, inclusive, or of plasma from 2 weeks prior to Screening through Study Completion, Clinic Discharge, or ET, inclusive;
20. Receipt of blood products within 2 months prior to Check-in (Day -1) for their first treatment period;

21. Subjects with best-corrected visual acuity worse than 20/40 in either eye, history of optic neuropathy, history of optic disc swelling or atrophy, and/or history of chronic eye disease (e.g., glaucoma, uveitis, diabetic retinopathy);
22. Any acute or chronic condition or any other reason that, in the opinion of the PI, would limit the subject's ability to complete and/or participate in this clinical study;
23. Any condition that would preclude participants from receiving a lumbar puncture during the study.

Subjects participating in multiple parts of the study:

24. Subjects that have received GDC-0134 within <28 days prior to Day 1
25. Subjects that have an ongoing AE which, in the opinion of the PI, prohibits them from further participation in the study

5.5 REMOVAL OF SUBJECTS FROM STUDY PARTICIPATION

Subjects will be informed that they are free to withdraw from the study at any time and for any reason. The PI may remove a subject from the study if, in the PIs opinion, it is not in the best interest of the subject to continue the study. Subjects may be discontinued due to the following: change in compliance with inclusion/exclusion criterion that is clinically relevant and affects subject safety, occurrence of AEs, occurrence of pregnancy, intake of non-permitted concomitant medication that might affect subject safety or study assessments/objectives, etc. Notification of discontinuation will immediately be made to the Sponsor's Study Monitor. In case of premature discontinuation of study participation, efforts will be made to perform all final study day assessments (see Section 7.16). The date the subject is withdrawn from the study and the reason for discontinuation will be recorded on the subject's electronic Case Report Form (eCRF). All dropouts will be followed until resolution of all their AEs or until the unresolved AEs are judged by the PI to have stabilized or returned to baseline.

For subjects who are discontinued by the PI or who voluntarily withdraw prematurely from the study, replacement subjects may be enrolled only if deemed necessary by the Sponsor. Except for replacements, the subjects will be assigned a number by study site staff. Assignment of numbers will be in ascending order and no numbers will be omitted. Subject numbers will be used on all study documentation. Replacement subjects will be assigned a subject number by adding 100 or 1000 to the number of the subject they are replacing (e.g., Subject No. 105 replaces Subject No. 005).

The entire study may be discontinued at the discretion of the PI, Sponsor, or Sponsor's Medical Monitor based on the occurrence of, but not limited to, the following:

- AEs unknown to date with respect to their nature, severity, and duration;
- Increased frequency, and/or severity, and/or duration of known AEs;
- Medical or ethical reasons affecting the continued performance of the study;
- Difficulties in the recruitment of subjects;*
- Cancellation of drug development.*

* For reasons that are not related to subject safety, the PI will discuss discontinuation of the entire study with the Sponsor prior to making any decisions.

6 ASSESSMENT OF SAFETY

6.1 SAFETY PLAN

GDC-0134 is not approved, and clinical development is ongoing. The safety plan for subjects in this study is based on clinical experience with GDC-0134 in completed and ongoing studies. The anticipated important safety risks for GDC-0134 are outlined below. Please refer to the IB (10) for more details on nonclinical studies in rats and cynomolgus monkeys, and preliminary clinical data

Several measures will be taken to ensure the safety of subjects participating in this study. Eligibility criteria have been designed to exclude subjects at higher risk for toxicities. Subjects will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of AEs.

6.1.1 RISKS ASSOCIATED WITH GDC-0134

There are no identified risks for GDC-0134.

6.1.2 CONTRAINDICATIONS WITH GDC-0134

There are no known contraindications for GDC-0134.

6.1.3 SERIOUS ADVERSE DRUG REACTIONS

No serious adverse drug reactions have been identified for GDC-0134.

6.1.4 POTENTIAL RISKS

6.1.4.1 Phototoxicity

A 3-day, multiple-dose phototoxicity study in rats showed no direct dermal effects, but ocular findings were observed in UVR-exposed rats and included inflammation and edema in the cornea and hyperplasia of the anterior lens epithelium. These findings were considered consistent with phototoxicity.

To prevent potential phototoxicity, subjects will be advised to avoid exposure to direct sunlight with the use of protective clothing, hats, sunglasses, and repeated application of sunscreen for 19 days after last dosing.

6.1.4.2 Skin Lesions

Skin lesions (erosions/ulcerations/scabs/sores/red discharge/alopecia) were observed in rats and monkeys with a dose-related effect. The tail was the most commonly affected area in monkeys, requiring amputation of the tail tip in some animals. Therefore, complete physical examinations, including a complete examination of the skin, will be conducted throughout the study to monitor for skin ulcerations or discolorations that may be indicative of study drug-induced toxicity. Limited, symptom-directed physical examinations may also be performed. In addition, subjects will be asked to do self-examinations on a daily basis.

6.1.4.3 Hypothermia

In repeat-dose toxicity studies in rats, mild reversible body temperature decreases of approximately 0.5ºC were observed. In single- and repeat-dose toxicity studies of GDC-0134 in monkeys, dose-dependent decrease in oral body temperature was noted at higher doses in the 4-week study, but was not observed in the 39-week study. Body temperature will be monitored at baseline and during the study.

6.1.4.4 Retinal Toxicity

Nonclinical toxicology studies with DLK inhibitors have identified reversible peripapillary swelling (PPS) or optic disc edema by ocular examination and retinal nerve fiber layer (RNFL) thickening by optical coherence tomography in cynomolgus monkeys after multiple days of dosing that returns to near baseline after continued drug exposure in the majority of animals. However, in two instances a moderate decrease in RNFL thickness was observed after the transient thickening, and in one instance a continued RNFL thinning was observed 8 weeks after the end of drug exposure. The RNFL thickening was largely correlated with increased axon size.

In the two animals with thinning RNFL, increases in axon size were also noted by transmission electron microscopy (TEM) with one animal also observed to have minimally increased glial cell processes. There was no evidence of axonal loss or degeneration by TEM. On ophthalmic exams, no optic nerve head cupping was observed that would suggest elevated IOP as a factor for the RNFL thinning, and no GDC-0134-related effects were noted on IOP measurements, nor were any visual deficits detected in an animal, as assessed by electroretinography (full field and multi-focal ERGs) or visual evoked cortical potentials. No GDC-0134-related ophthalmic abnormalities, IOP effects, fundus photographic observations, or effects on rod- and cone-driven retinal function, as assessed by scotopic and photopic ERGs, have been observed. The functional consequences of this retinal change are unknown. Patients with best-corrected visual acuity worse than 20/40 in either eye, history of optic neuropathy, history of optic disc swelling or atrophy, and/or history of chronic eye disease (e.g. glaucoma, uveitis, diabetic retinopathy) are excluded from the GDC-0134 studies. Potential ocular toxicities will be evaluated at baseline and throughout GDC-0134 studies as shown in the Schedule of Activities (Table 7-1 and Table 7-2).

6.1.4.5 Increased Intracranial Pressure

As stated above, 4-week and 39-week nonclinical toxicology studies have identified reversible bilateral PPS or optic disc edema in cynomolgus monkeys. One potential mechanism of PPS or optic disc edema is increased intracranial pressure.

Any patient on active drug who experiences clinically significant optic disc edema on funduscopic examination, clinically significant functional visual change from baseline, or clinically significant RNFL thickening by SD-OCT that is deemed study drug related will undergo a lumbar puncture to rule out increased intracranial pressure and will be prohibited from receiving further doses of study medication.

In addition, if clinical signs or symptoms (such as severe headache, dizziness, lethargy, vomiting, seizures, pulsatile tinnitus) raise the suspicion of increased intracranial pressure, a lumbar puncture will be performed. Lumbar punctures should include measurement of opening pressure in the lateral decubitus position. For all patients who undergo lumbar puncture, cerebrospinal fluid will be collected for analysis of glucose, protein, red blood cells (RBCs), white blood cells (WBCs), and differential and potentially cryptococcal antigen and bacterial culture.

6.1.4.6 Cardiac hypertrophy

Increased heart weights were observed in rats with a corresponding slight to moderate increase in thickness (hypertrophy) of the left ventricular wall and interventricular septum of the heart in a 26-week study. In a 4-week study, increased heart weight without microscopic findings of hypertrophy were observed. There were no changes in heart weight or findings of cardiac hypertrophy or other abnormal microscopic changes observed in the hearts of monkeys. However, transient non-adverse increases in heart rate were observed after single doses, with no observed effects on other hemodynamic parameters, blood pressures, or ECG assessments.

6.1.4.7 Gastrointestinal Ulcerations

Gastrointestinal toxicities characterized by the presence of bloody feces or vomit and microscopic findings of gastric erosions or ulcerations were observed in the 4-week toxicity study in monkeys but generally resolved during the 4-week recovery period. GI toxicity was the cause of moribundity and early euthanasia in two animals. In the 39-week study in monkeys, no GI toxicity was observed. Potential GI toxicities will be evaluated regularly by assessing for adverse effects that may indicate intolerability, such as nausea, vomiting, or diarrhea.

6.1.4.8 Glycemic Dysregulation

In nonclinical studies, effects on glucose regulation (rat and monkey) and brown adipose tissue macrovesicular vacuolation (monkey) were consistent with GDC-0134 potentially interfering with glycemic regulation. Serum blood glucose and body temperature will be monitored.

6.1.4.9 Hepatotoxicity

Nonclinical studies with GDC-0134 showed an increase of unconjugated bilirubin (2-4x) in rats, in the absence of elevated liver enzymes. No increases of unconjugated bilirubin or liver enzymes were observed in cynomolgus monkeys. Patients with abnormal baseline clinical laboratory test results will be excluded from GDC-0134 study protocol(s), as will patients positive for anti-HCV or HBsAg.

Liver function tests, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and total and fractionated bilirubin, will be monitored closely. 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, must be reported to Sponsor as an AE of special interest (AESI) within 24 hours (see Section 8.1.3).

6.1.4.10 Reproductive Toxicity

Nonclinical findings showed decreased weights of male and female reproductive organs (rat and monkey), and vacuolation of some cells of the anterior pituitary gland in males (rats) were seen. Men will be excluded from this GDC-0134 study.

Maternal toxicity (e.g. excessive mortality, body weight loss, decreased activity) and multiple fetal malformations (e.g. malrotated hindlimbs, whole body subcutaneous edema, cleft snout, short tails, small mandible, absent tongue) were observed in nonclinical studies in rats and rabbits (see IB for further details). Therefore, GDC-0134 should not be administered to pregnant women. Women of child bearing potential are excluded from this study.

7 STUDY PROCEDURES

7.1 SCHEDULE OF STUDY ACTIVITIES

Table 7-1 Schedule of Activities – Part 1

			Period 1							Cross over	Period 2							
		Screening[a]	Day														Study Completion/ ET	Safety Follow-Up
	Part 1 Study Days	Days -28 to -2	-1	1	2	3	5	7	15	21	22	23	24	26	28	36	Day 43	Day 49
	Period 1 Days		-1	1	2	3	5	7	15	21	22	-	-	-	-	-		
Study Procedures	Period 2 Days		-	-	-	-	-	-	-	-1	1	2	3	5	7	15	22	28
Check-in to CRU			X							X								
Confined to the Study Site			X	X	X	X				X	X	X	X					
Discharge from CRU						X							X					
Outpatient Visit		X					X	X	X					X	X	X	X	
Informed Consent		X																
Demographics		X																
Previous Medication and Compliance with Inclusion/Exclusion Criteria		X	X															
Concomitant Medication				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History		X	X[b]															
Height, Weight, and BMI[c]		X	X														X	
Physical Examination[d]			X			X				X			X				X	
12-Lead ECG		X	X							X							X	
Vital Signs[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Fundoscopic Examination		X																
Visual acuity Assessments			X	X	X	X				X	X	X	X					
Visual Field Examination			X							X								

			Period 1							Cross over	Period 2							
Study Procedures	Part 1 Study Days	Screening[a] Days -28 to -2	Day -1	1	2	3	5	7	15	21	22	23	24	26	28	36	Study Completion/ ET Day 43	Safety Follow-Up Day 49
	Period 1 Days		-1	1	2	3	5	7	15	21	22	-	-	-	-	-		
	Period 2 Days		-	-	-	-	-	-	-	-1	1	2	3	5	7	15	22	28
AE Evaluations (HDYF? Inquiry)				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
GDC-0134 Dose[f]				X							X							
PK Blood Samples[g]				X	X	X	X	X	X		X	X	X	X	X	X	X	
PK Urine Samples[h]				X	X	X					X	X	X					
Chemistry Panel, CBC, and UA[i]		X	X							X						X	X	
Coagulation profile		X	X							X								
Hepatitis B, C, and HIV Screen[i]		X																
Tuberculosis Testing[j]		X																
Drug Screen (including cotinine)[k]		X	X							X								
Serum Pregnancy Test		X	X														X	
FSH[l]		X																
Blood Sample for WGS[m]				X														

AE = adverse event; BMI = body mass index; CBC = complete blood count; ECG = electrocardiogram; ET = Early Termination; FSH = follicle-stimulating hormone; HDYF? = how do you feel?; HIV = human immunodeficiency virus; PK = pharmacokinetic; TB = tuberculosis; UA = urinalysis; WGS = whole genome sequencing.

[a] In the event of a subject agreeing to participate in both parts of the study and there being ≤28 days between Clinic Discharge for the first part that they participate in and Check-in for the second part that they participate in, subjects will not undergo re-screening for the second part. Inclusion/exclusion criteria

will be checked prior to completion of the first part. If there is > 28 days between Clinic Discharge for the first part the subject participates in and Check-in for the second part that they participate in, the subject will undergo re-screening and will sign a new ICF for the second part.

[b] Interim medical history only.

[c] Body weight recorded at Screening, Check-in (Day -1) for Period 1, and Study Completion, and height and BMI recorded at Screening only.

[d] Routine physical examination (Section 7.13) to occur at scheduled timepoints. Unscheduled abbreviated physical examinations may occur at the discretion of the PI (or designee).

[e] Vital signs include: oral temperature, respiratory rate, and supine blood pressure and pulse.

[f] GDC-0134 F09 or F16 capsules will be administered 30 minutes after starting a standard meal according to the randomization schedule.

[g] For PK blood samples collected during the study, refer to Table 7-3. The predose blood sample for Period 2 (study Day 22) will also be used as the Day 22 sample for Period 1.

[h] Urine PK samples collected during the study will include: predose (single sample voided within 1 hour prior to dosing), and pooled samples voided over the following time periods: 0-12 hours, 12-24 hours, 24-36 hours, and 36-48 hours postdose.

[i] Refer to Appendix A for a list of evaluations.

[j] QuantiFERON® TB Gold test. If positive, subject will be excluded. Indeterminate results may be confirmed by repeat or by a PPD skin test. If a negative TB screening test has been documented within 3 months of Screening, no new test is needed.

[k] Includes alcohol testing at Check-in (Day -1) for each period only.

[l] Follicle-stimulating hormone testing performed on postmenopausal females only.

[m] Sample collected prior to the GDC-0134 dose on Day 1 of Period 1. If the subject participates in Part 1 and Part 2, a sample for WGS will only be taken during the first part of the study that the subject participates in.

Table 7-2 Schedule of Activities – Part 2

			Period 1							Cross over	Period 2							
		Screening[a]	Day														Study Completion/ ET	Safety Follow-Up
	Part 2 Study Days	Days -28 to -2	-1	1	2	3	5	7	15	21	22	23	24	26	28	36	Day 43	Day 49
	Period 1 Days		-1	1	2	3	5	7	15	21	22	-	-	-	-	-		
Study Procedures	Period 2 Days		-	-	-	-	-	-	-	-1	1	2	3	5	7	15	22	28
Check-in to CRU			X							X								
Confined to the Study Site			X	X	X	X				X	X	X	X					
Discharge from CRU						X							X					
Outpatient Visit		X					X	X	X					X	X	X	X	
Informed Consent		X																
Demographics		X																
Previous Medication and Compliance with Inclusion/Exclusion Criteria		X	X															
Concomitant Medication				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History		X	X[b]															
Height, Weight, and BMI[c]		X	X														X	
Physical Examination[d]			X			X				X			X				X	
12-Lead ECG		X	X							X							X	
Vital Signs[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Fundoscopic Examination		X																
Visual acuity Assessments			X	X	X	X				X	X	X	X					
Visual Field Examination			X							X								

			Period 1							Cross over	Period 2							
Study Procedures	Part 2 Study Days	Screening[a] Days -28 to -2	Day -1	1	2	3	5	7	15	21	22	23	24	26	28	36	Study Completion/ ET Day 43	Safety Follow-Up Day 49
	Period 1 Days		-1	1	2	3	5	7	15	21	22	-	-	-	-	-		
	Period 2 Days		-	-	-	-	-	-	-	-1	1	2	3	5	7	15	22	28
AE Evaluations (HDYF? Inquiry)				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
GDC-0134 Dose[f]				X							X							
PK Blood Samples [g]				X	X	X	X	X	X		X	X	X	X	X	X	X	
PK Urine Samples[h]				X	X	X					X	X	X					
Chemistry Panel, CBC, and UA [i]		X	X							X						X	X	
Coagulation profile		X	X							X								
Hepatitis B, C, and HIV Screen [i]		X																
Tuberculosis Testing [j]		X																
Drug Screen (including cotinine) [k]		X	X							X								
Serum Pregnancy Test		X	X														X	
FSH [l]		X																
Blood Sample for WGS[m]				X														

AE = adverse event; BMI = body mass index; CBC = complete blood count; ECG = electrocardiogram; ET = Early Termination; FSH = follicle-stimulating hormone; HDYF? = how do you feel?; HIV = human immunodeficiency virus; PK = pharmacokinetic; PPD = purified protein derivative; TB = tuberculosis; UA = urinalysis; WGS = whole genome sequencing.

[a.] In the event of a subject agreeing to participate in both parts of the study and there being ≤28 days between Clinic Discharge for the first part that they participate in and Check-in for the second part that they participate in, subjects will not undergo re-screening for the second part. Inclusion/exclusion criteria

will be checked prior to completion of the first part. If there is > 28 days between Clinic Discharge for the first part the subject participates in and Check-in for the second part that they participate in, the subject will undergo re-screening and will sign a new ICF for the second part.

[b] Interim medical history only.

[c] Body weight recorded at Screening, Check-in (Day -1) for Period 1, and Study Completion, and height and BMI recorded at Screening only.

[d] Routine physical examination (Section 7.13) to occur at scheduled timepoints. Unscheduled abbreviated physical examinations may occur at the discretion of the PI (or designee).

[e] Vital signs include: oral temperature, respiratory rate, and supine blood pressure and pulse.

[f] GDC-0134 F09 or F15 capsules will be administered after an overnight fast according to the randomization schedule.

[g] For PK blood samples collected during the study, refer to Table 7-3. The predose blood sample for Period 2 (study Day 22) will also be used as the Day 22 sample for Period 1.

[h] Urine PK samples collected during the study will include: predose (single sample voided within 1 hour prior to dosing), and pooled samples voided over the following time periods: 0-12 hours, 12-24 hours, 24-36 hours, and 36-48 hours postdose.

[i] Refer to Appendix A for a list of evaluations.

[j] QuantiFERON® TB Gold test. If positive, subject will be excluded. Indeterminate results may be confirmed by repeat or by a PPD skin test. If a negative TB screening test has been documented within 3 months of Screening, no new test is needed.

[k] Includes alcohol testing at Check-in (Day -1) for both periods only.

[l] Follicle-stimulating hormone testing performed on postmenopausal females only.

[m] Sample collected prior to the GDC-0134 dose on Day 1 of Period 1. If the subject participates in Part 1 and Part 2, a sample for WGS will only be taken during the first part of the study that the subject participates in.

Table 7-3 Plasma Pharmacokinetic Sampling Scheme (All Study Periods)

Period Day	PK Sampling Timepoints (Hours Postdose)	Window (+/-)	Analyte (*Matrix*)
Day 1	Predose (0 Hour) any time prior to study drug administration	NA	GDC-0134 (*Plasma*)
	0.5	3 minutes	GDC-0134 (*Plasma*)
	1	5 minutes	GDC-0134 (*Plasma*)
	1.5	5 minutes	GDC-0134 (*Plasma*)
	2	10 minutes	GDC-0134 (*Plasma*)
	3	10 minutes	GDC-0134 (*Plasma*)
	4	10 minutes	GDC-0134 (*Plasma*)
	6	10 minutes	GDC-0134 (*Plasma*)
	8	10 minutes	GDC-0134 (*Plasma*)
	12	10 minutes	GDC-0134 (*Plasma*)
Day 2	24	10 minutes	GDC-0134 (*Plasma*)
Day 3	48	30 minutes	GDC-0134 (*Plasma*)
Day 5	96	6 hours	GDC-0134 (*Plasma*)
Day 7	144	6 hours	GDC-0134 (*Plasma*)
Day 15	336	6 hours	GDC-0134 (*Plasma*)
Day 22 [1]	504	6 hours	GDC-0134 (*Plasma*)

NA = not applicable; PK = pharmacokinetic.

[1.] The predose sample in the second period in each part (Period 2) will be used as the Day 22 PK sample for the first period in each part (Period 1).

7.2 STUDY TREATMENT

The Investigational Medicinal Product for this study is GDC-0134. For details on the drug products used in the study, refer to related Investigational New Drug (IND) quality information amendment.

7.2.1 DRUG SUPPLIES AND ACCOUNTABILITY

The Sponsor or designee will provide the PI with adequate quantities of the study drug (see Table 7-4).

Table 7-4 Study Drug

Study Drug	GDC-0134 hemimalate	GDC-0134	GDC-0134
Study Designation	GDC-0134 F16 capsule	GDC-0134 F15 capsule	GDC-0134 F09 capsule
Description	Test drug, newly developed capsule formulation with GDC-0134 malate drug substance	Test drug, newly developed capsule formulation with GDC-0134 freebase	Reference drug, current clinical material
Formulation [a]	GDC-0134 Capsule, 200 mg (freebase equivalent), Ro 704-0814/F16 form	GDC-0134 Capsule, 200 mg, Ro 704-0814/F15	GDC-0134 Capsule, 200 mg, Ro 704-0814/F09
Strength	200 mg	200 mg	200 mg
Manufacturer	Shanghai STA Pharmaceutical Product Co. Ltd	Roche Basel	Patheon Inc.

[a] Specific ingredients/purity will be identified on the Certificate of Analysis (or equivalent) that is supplied with the study drug(s).

The lot numbers for the study drug will be provided to the study site by the supplier/manufacturer as soon as available.

Study drug will be stored at temperatures below 25°C. The study drug will be transferred from the bulk supplies into the subject's dose container by qualified study site employees. Each unit dose container will be appropriately labeled.

The PI or designee will maintain an accurate record of the receipt of the test materials as shipped by the Sponsor or designee, including the date received. One copy of this receipt will be returned to the Sponsor when the contents of the test material shipment have been verified. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensation. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

If deemed appropriate by the Sponsor, sufficient samples will be randomly selected from the supply provided by the Sponsor or designee and retained by the study site to meet the retention requirements described in U.S. Title 21 Code of Federal Regulations (CFR) 320.38 and 320.63.

At the completion of the study, all unused drug supplies (except for retention supplies, if appropriate) will be returned to the Sponsor or designee or disposed of by the study site, per the Sponsor's or designee's written instructions.

7.2.2 DOSE PREPARATION AND ADMINISTRATION

Each unit dose will be prepared by qualified clinical staff based on the study randomization that will be provided by a Covance biostatistician.

Appropriate unit doses, as described above, will be administered to subjects in ascending order based on the subjects' number. Although the timing of events requires that each subject will be consistently administered the appropriate dose at specific times, the exact dose time of consecutive subjects may be staggered to obviate the need to have all subjects on precisely the same study schedule. For each dose, the subject's actual time will be recorded in the source documents and transcribed into the eCRFs.

Except as part of dose administration or as part of a scheduled meal, subjects will restrict their consumption of water for 1 hour prior to dose and for 2 hours postdose; at all other times during the study, subjects may consume water ad libitum.

7.2.2.1 Part 1 and Part 2

In both parts of the study, each dose will be administered orally with approximately 240 mL room temperature water. A hand and mouth check will be performed to verify that the dose administered was swallowed.

In Part 1, subjects will receive a standard meal starting 30 minutes prior to dosing which must have been entirely consumed within 25 minutes. In Part 2, doses will be preceded by an overnight fast (i.e., at least 8 hours) from food (not including water) and will be followed by a fast from food (not including water) for at least 4 hours postdose.

Cases of GDC-0134 accidental overdose or medication error, along with any associated AEs, should be reported as described in Section 8.4.3.

Details regarding standard meal administration in Part 1 (including, but not limited to, meal start date/time, meal completion date/time, and estimated percentage of meal consumed [if not entirely consumed]) will be recorded.

7.3 REMOVAL OF STUDY BLIND

Not applicable; this is an open-label study and will not be blinded.

7.4 DIET, FLUID, AND ACTIVITY CONTROL

Subjects will refrain from use of tobacco- or nicotine-containing products (including, but not limited to, cigarettes, e-cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, and nicotine gum) within 6 months prior to Check-in (Day -1) for their first treatment period and during the entire study.

Subjects will abstain from consuming alcohol- or caffeine-containing foods and beverages for 72 hours prior to their Check-in (Day -1) to their first study period until Study Completion/ET, unless deemed acceptable by the PI.

Subjects will abstain from consuming grapefruit, grapefruit-containing products, and pomegranate, pomelo, and star fruit juice/products from 7 days prior to Check-in (Day -1) for their first treatment period and during the entire study duration.

Subjects will refrain from strenuous exercise from 48 hours prior to Check-in (Day -1) for their first treatment period and during the period of confinement at the study site and will otherwise maintain their normal level of physical activity throughout the entire study (i.e., will not begin a new exercise program or participate in any unusually strenuous physical exertion).

With the exception of dosing, as applicable, while confined at the study site, subjects will receive a standardized diet at scheduled times that do not conflict with other study-related activities.

Doses will be preceded by an overnight fast (i.e., at least 8 hours) from food (not including water) and will be followed by a fast from food (not including water) for at least 4 hours postdose, or will be preceded by a standard meal prior to dosing, according to the randomization scheme and as detailed in Section 7.2.2.1. Except as part of dose administration, subjects will restrict their consumption of water for 1 hour prior to dose and for 2 hours postdose; at all other times during the study, subjects may consume water ad libitum.

Subjects will remain seated/standing upright for 1 hour following each dose administered, except as necessitated by the occurrence of an AE(s) and/or study procedures.

7.5 CONCOMITANT MEDICATIONS

Concomitant therapy consists of any prescription medications, herbal, vaccines, topical medications, or over-the-counter preparations, including herbal or dietary supplements taken by a subject in addition to protocol-mandated treatment at any time from Check-in (Day -1) for their first treatment period through Study Completion.

Subjects will not have received any investigational study drug within 5 half-lives (if known), or 30 days (small molecule) or 90 days (biologic), whichever is longer, prior to their first treatment period.

Subjects will refrain from the use of any prescription medications during the interval from 14 days prior to Check-in (Day -1) for their first treatment period and for the entire study duration, unless deemed acceptable by the PI (use of HRT or thyroid replacement is acceptable). Subjects will refrain from the use of strong inhibitors and inducers of CYP3A4/5 and UGT enzymes within 14 days prior to Period 1 Check-in (Day -1) for their first treatment period until Study Completion, and alternate medications should be considered where possible.

In addition, subjects will refrain from the use of any over-the-counter non-prescription medications (including vitamins; minerals; and phytotherapeutic-, herbal-, and plant-derived preparations) from 14 days prior to Check-in (Day -1) for their first treatment period and for the entire study duration, unless deemed acceptable by the PI (acetaminophen [paracetamol] is acceptable and may be administered as needed up to 0.5 to 1 g every 4 to 6 hours [maximum 3 g/day] but should be avoided from Check-in [Day -1] for their first treatment period to the end of the study). Use of thyroid medication or ophthalmic drops or other ophthalmic procedures (as part of the fundoscopic exam) is acceptable. Subjects will not use acid reducing medications (PPIs, H2 receptor anatagonists, etc) within 14 days prior to Check-in (Day -1) for their first treatment period and during the entire study duration. As an alternative, antacids may be allowed at least 4 hours before or after dose.

Subjects will not have had any vaccines (including seasonal flu and H1N1 vaccines) within 14 days prior to the Check-in (Day -1) for their first treatment period.

Subjects will not take oral antibiotics within 4 weeks or intravenous antibiotics within 8 weeks prior to the Screening evaluation.

Subjects who have taken drugs of abuse (including opioids) within 4 weeks of Screening or during the entire study will be excluded from this study.

The administration of any other concomitant medications during the study is prohibited without prior approval of the PI, unless its use is deemed necessary in a medical emergency. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source documents and the eCRF.

7.6 PHARMACOKINETIC BLOOD AND URINE SAMPLE COLLECTION AND PROCESSING

Blood samples for PK analysis of GDC-0134 levels will be collected via an indwelling catheter and/or via direct venipuncture using Vacutainer® evacuated collection tubes. Blood samples will be collected at the timepoints listed in Table 7-1, Table 7-2, and Table 7-3.

Processing, storage, and shipping instructions for these PK blood samples are presented in a separate Laboratory Manual.

After the plasma and urine samples collected in the study are analyzed for GDC-0134 concentrations, any residual samples may be used for analysis such as metabolite profiling and identification, interacting drug concentration measurements, ex vivo protein binding, or development of PK or PD assays. Left over PK samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed. When a subject withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the subject specifically requests in writing that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Urine samples for PK analysis will be collected at the time intervals indicated in Table 7-1 and Table 7-2.

The weight of the pooled urine collected during each sampling interval will be recorded. Further details will be provided in the Laboratory Manual.

7.7 ANALYTICAL METHODOLOGY

Plasma and urine concentrations of GDC-0134 will be determined by Covance Laboratories using a validated (plasma) and qualified (urine) analytical procedure.

7.8 CLINICAL LABORATORY EVALUATIONS

Clinical laboratory evaluations (including chemistry panel fasted at least 8 hours, CBC, UA, and coagulation profile) will be collected at the timepoints listed in Table 7-1 and Table 7-2.

Screens for a hepatitis panel and HIV antibody will be performed at Screening. A drug screen for selected drugs of abuse (not including alcohol) will be performed at Screening and repeated

(but including an alcohol breath or urine test) at Check-in (Day -1) for each study period. A serum qualitative pregnancy test (females only) and FSH test (postmenopausal females only) will be performed at the timepoints specified in Table 7-1 and Table 7-2.

Tuberculosis testing will be performed for all subjects at Screening using the following criteria:

- QuantiFERON TB Gold is an acceptable screening assay for latent *mycobacterium tuberculosis* infection;
- An indeterminate QuantiFERON TB Gold test should be repeated. Indeterminate results may also be confirmed by a PPD skin test;
    - A positive PPD tuberculin skin test reaction is considered ≥10 mm (or ≥5 mm in subjects receiving the equivalent of >15 mg/day of prednisone);
- A positive QuantiFERON TB Gold test should be considered a positive diagnostic TB test;
- An indeterminate QuantiFERON TB Gold test followed by a negative QuantiFERON TB Gold test should be considered a negative diagnostic TB test;
- If a negative TB screening test has been documented within 3 months of Screening, no new test is needed.

7.9 SAMPLES FOR THE RESEARCH BIOSAMPLE REPOSITORY

7.9.1 OVERVIEW OF THE RESEARCH BIOSAMPLE REPOSITORY

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, and/or peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for subjects in the future.

Specimens for the RBR will be collected from subjects who give specific consent to participate in this research. The RBR specimen will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, AEs, or disease progression;
- To increase knowledge and understanding of disease biology;
- To study drug response, including drug effects and the processes of drug absorption and disposition;
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays.

7.9.2 APPROVAL BY THE INSTITUTIONAL REVIEW BOARD

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the ICF by each site's Institutional Review Board (IRB) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, Sections 7.9 through 7.9.7 of this protocol will not be applicable at that site.

7.9.3 MANDATORY SAMPLES FOR WHOLE GENOME SEQUENCING SAMPLE COLLECTION

A mandatory whole blood sample will be collected for DNA extraction to enable WGS and may be sent to one or more laboratories for analysis. The WGS sample is considered an RBR sample.

For sampling procedures, storage conditions, and shipment instructions, see the Laboratory Manual.

The RBR specimens will be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved ICF and applicable laws (e.g., health authority requirements). When a subject withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the subject specifically requests in writing that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

7.9.4 CONFIDENTIALITY

Specimens and associated data will be labeled with a unique subject identification number.

Subject medical information associated with RBR specimens is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the subject, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses, data derived from RBR specimens will generally not be provided to study PIs or subjects unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

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

7.9.5 CONSENT TO PARTICIPATE IN THE RESEARCH BIOSAMPLE REPOSITORY

The ICF will contain a separate section that addresses participation in the RBR. The PI or authorized designee will explain to each subject the objectives, methods, and potential hazards of participation in the RBR. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period (the withdrawal of their RBR specimen will coincide with withdrawal from the study). A separate, specific signature will be required to document a subject's agreement to provide RBR specimens for WGS.

The PI (or designee) should document whether or not the subject has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

7.9.6 WITHDRAWAL FROM THE RESEARCH BIOSAMPLE REPOSITORY

Subjects who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time and for any reason. If a subject wishes to withdraw consent to the testing of their specimens, the PI must inform the Medical Monitor in writing of the subject's wishes using the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The subject will be provided with instructions on how to withdraw consent after the trial is closed. A subject's withdrawal from this study does not, by itself, constitute withdrawal of specimens from the RBR.

7.9.7 MONITORING AND OVERSIGHT

The RBR specimens will be tracked in a manner consistent with Good Clinical Practice (GCP) by a quality-controlled, auditable, and appropriately-validated laboratory information management system to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the ICF. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to subject participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

7.10 12-LEAD ELECTROCARDIOGRAMS

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the times Table 7-1 and Table 7-2.

Single 12-lead ECGs will be repeated twice, and an average taken of the three readings, if any of the following criteria apply:

- QT interval corrected through use of Fridericia's formula (QTcF) value >470 msec
- PR interval >210 msec
- QRS complex >120 msec
- QTcF change from the baseline (predose) is > 60 msec.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The PI (or designee) will perform a clinical assessment of each 12-lead ECG.

To minimize variability in autonomic tone and heart rate, subjects will rest quietly and in a supine position for at least 5 minutes prior to recording the ECG. Blood draws, other procedures, activity, and environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and between ECG recordings, to minimize variability due to the effects of activity and stress on cardiac electrophysiology. Whenever possible, ECG tracings for each subject should be obtained from the same type of machine throughout the study.

When 12-lead ECGs are scheduled at the same time as blood draws and vital signs, the blood draws will be obtained at the scheduled timepoint, and the 12-lead ECGs and vital signs will be obtained as close to the scheduled blood draw as possible, but prior to the blood draw (order of assessments = ECGs, vital signs, blood samples).

7.11 VITAL SIGNS

Vital signs (including oral temperature, respiratory rate, and supine blood pressure and pulse) will be obtained at the timepoints specified in Table 7-1 and Table 7-2.

Supine blood pressure and pulse will be obtained after the subject has been supine for at least 5 minutes. When vital signs are scheduled at the same time as blood draws, the blood draws will be obtained at the scheduled timepoint, and the vitals will be obtained as close to the scheduled blood draw as possible, but prior to the blood draw.

7.12 HOW DO YOU FEEL? INQUIRY

Subjects will be asked a non-leading HDYF? question such as "Have there been any changes in your health status since Screening/since you were last asked?" once daily on the days specified in Table 7-1 and Table 7-2. Subjects will also be encouraged to voluntarily report AEs occurring at any other time during the study. See Section 8.3 and Section 8.4 for reporting requirements for AEs and SAEs, respectively.

7.13 PHYSICAL EXAMINATIONS

A routine physical examination will be performed at the timepoints specified in Table 7-1 and Table 7-2.

A routine physical examination will consist of an assessment of general appearance, skin, thorax/lungs, abdomen, lymph nodes, head, ears, eyes, nose, throat, neck (including thyroid); and cardiovascular, musculoskeletal, and neurological systems. The PI or designee may conduct unscheduled abbreviated physical examinations if required.

7.14 OPHTHALMOLOGY ASSESSMENTS

During the screening period, a fundoscopic examination will be performed by a qualified optician/ophthalmologist as per the local standard of care.

The following assessments will be conducted at the times indicated in Table 7-1 and Table 7-2:

- Best-corrected visual acuity at a distance of 4 meters
- Near visual acuity using a card
- Visual field examination

Subjects are allowed to use their own glasses for visual acuity and visual field assessments. If a subject has a 2-line decrease in visual acuity, they will be referred for an ophthalmology assessment. Additional ophthalmology assessments may be conducted during the study at the discretion of the PI.

7.15 CLINIC DISCHARGE PROCEDURES

Refer to Table 7-1 and Table 7-2 for procedures performed on the days of Discharge.

7.16 STUDY COMPLETION/EARLY TERMINATION PROCEDURES

Refer to Table 7-1 and Table 7-2 for procedures performed at Study Completion or at ET.

8 ADVERSE EXPERIENCES

8.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including SAEs and AESIs, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study. The Sponsor or its designee is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating PIs, in accordance with International Conference on Harmonisation/International Council for Harmonisation (ICH) guidelines, Food and Drug Administration (FDA) regulations, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 8.4.

8.1.1 ADVERSE EVENTS

According to the ICH Guideline for GCP, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product;
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition);
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline;

- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug;
- AE that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

8.1.2 SERIOUS ADVERSE EVENTS (IMMEDIATELY REPORTABLE TO THE SPONSOR)

An SAE is any AE that meets any of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death);
- Is life-threatening (i.e., the AE, in the view of the PI, places the subject at immediate risk of death); this does not include any AE that had it occurred in a more severe form or was allowed to continue might have caused death;
- Requires or prolongs inpatient hospitalization;
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug;
- Is a significant medical event in the PIs judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

All AEs that do not meet any of the criteria for serious should be regarded as non-serious AEs.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, according to National Cancer Institute Common Terminology Criteria for Adverse Events); the event itself may be of relatively minor medical significance (such as severe headache) without any further findings. An event should be considered "serious" only if it meets the regulatory criteria outlined in the above-mentioned paragraph outlining seriousness criteria.

Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness need to be independently assessed for each AEs recorded on the eCRF.

Serious AEs are required to be reported by the PI to the Sponsor via the Covance project manager immediately (i.e., no more than 24 hours after learning of the event; see Section 8.4.2 for reporting instructions).

8.1.3 ADVERSE EVENTS OF SPECIAL INTEREST (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the PI to the Sponsor via the Covance project manager immediately (i.e., no more than 24 hours after learning of the event; see Section 8.4.2 for reporting instructions). The AESI for this study are as follows:

- Clinically significant peripapillary or optic disc swelling on funduscopic examination, as determined by the local site PI/ophthalmologist
- Clinically significant functional visual change from baseline, as determined by the local site PI/ophthalmologist

- Cases of potential drug-induced liver injury that include an elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 8.3.1.6);
- Suspected transmission of an infectious agent by the study drug as defined below:
  - Any organism, virus, or infectious particle (e.g., 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. The term applies only when a contamination of the study drug is suspected.

8.2 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The PI is responsible for ensuring that all AEs (as defined in Section 8.1) are recorded on the AE eCRF and reported to the Sponsor via the Covance project manager in accordance with protocol instructions (see Section 8.4.2).

For each AE recorded on the AE eCRF, the PI will make an assessment of seriousness (see Section 8.1.2 for seriousness criteria), severity, and causality (see Section 8.2.3).

8.2.1 ADVERSE EVENT REPORTING PERIOD

Principal Investigators will seek information on AEs at each subject contact. All AEs, whether reported by the subject or noted by study personnel, will be recorded in the subject's medical record and on the AE eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only SAEs caused by a protocol-mandated intervention (e.g., discontinuation of medications) will be reported (see Section 8.4.2 for instructions for reporting SAEs). After initiation of study drug administration, all AEs will be reported until 28 days after the final dose.

Instructions for reporting AEs that occur after the AE reporting period are provided in Section 8.5.

The PI is not required to actively monitor subjects after the study has ended or for AEs after the end of the AE reporting period (defined as 28 days after the final dose of study drug, whichever is longer). However, the Sponsor should be notified if the PI becomes aware of any death, other SAEs, or AESIs occurring after the end of the AE reporting period that are believed to be related to prior study drug treatment. The Sponsor should also be notified if the PI becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a female subject exposed to study drug.

8.2.2 ELICITING ADVERSE EVENT INFORMATION

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all subject evaluation timepoints. Examples of non-directive questions include the following:

- "How have you felt since your last clinic visit?"
- "Have you had any new or changed health problems since you were last here?"

8.2.3 ASSESSMENT OF SEVERITY OF ADVERSE EVENTS

The World Health Organization (WHO) toxicity grading scale will be used for assessing AE severity. Table 8-1 will be used for assessing severity for AEs that are not specifically listed in the WHO toxicity grading scale.

Table 8-1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in WHO Toxicity Grading Scale

Grade	Severity
1	Mild; transient or mild discomfort (<48 hours); no medical intervention or therapy required
2	Moderate; mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	Severe; marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	Life-threatening; extreme limitation in activity; significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

Notes: Developed by the Division of Microbiology and Infectious Diseases.
Regardless of severity, some events may also meet seriousness criteria. Refer to definition of an SAE (see Section 8.1.2).

8.2.4 ASSESSMENT OF CAUSALITY OF ADVERSE EVENTS

Principal Investigators should use their knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an AE is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 8-2):

- Temporal relationship of event onset to the initiation of study drug;
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable);
- Known association of the event with the study drug or with similar treatments;
- Known association of the event with the disease under study;
- Presence of risk factors in the subject or use of concomitant medications known to increase the occurrence of the event;
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

Table 8-2 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug based on facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge. **Principal Investigators should apply facts, evidence, or rationales based on scientific principles and clinical judgment to support a causal/contributory association with a study drug.**
NO	**AE will be considered related, unless they fulfill the criteria as specified below.** Evidence exists that the adverse event has an etiology other than the study drug (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug). Note: The PIs assessment of causality for individual adverse event reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual adverse event reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to PIs and applicable regulatory authorities. **Attribution of SAEs will be reviewed on an ongoing basis, and may be changed as additional clinical data emerges (e.g., reversibility of adverse event, new clinical findings in subject with adverse event, effects of re-treatment, and AE in other subjects)**.

8.3 PROCEDURES FOR RECORDING ADVERSE EVENTS

8.3.1 RECORDING ADVERSE EVENTS ON THE CASE REPORT FORM

Principal Investigators should use correct medical terminology/concepts when recording AEs on the AE eCRF. Colloquialisms and abbreviations should be avoided.

All AEs should be recorded on the AE eCRF page. If the AE qualifies as an SAE or non-serious AESI, the PI should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on a paper Clinical Trial SAE/AESI Reporting Form. The completed paper Clinical Trial SAE/AESI Reporting Form and safety fax coversheet should be emailed to Roche Safety Risk Management via the Covance project manager within 24 hours of learning of the event (see Section 8.4.2). The AE and SAE eCRF should also be completed within this timeframe. It is important that the information on the SAE Reporting Form and AE and SAE eCRF is consistent and identical.

Only one AE term should be recorded in the event field on the AE eCRF.

8.3.1.1 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

If known, a diagnosis should be recorded on the AE eCRF rather than individual signs and symptoms (e.g., 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 AE eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

8.3.1.2 ADVERSE EVENTS THAT ARE SECONDARY TO OTHER EVENTS

In general, AEs 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 AE that is separated in time from the initiating event should be recorded as an independent event on the AE eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF;
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF;
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF;
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF;
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately on the AE eCRF if it is unclear as to whether the events are associated.

8.3.1.3 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent AE is one that extends continuously, without resolution between subject evaluation timepoints. Such events should only be recorded once in the AE eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent AE becomes more severe, the most extreme severity should also be recorded on the AE eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 8.4.2 for

reporting instructions). The AE eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.

A recurrent AE is one that resolves between subject evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded as a separate event on the AE eCRF.

8.3.1.4 ABNORMAL LABORATORY VALUES

Not every laboratory abnormality qualifies as an AE. A laboratory test result should be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms;
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation);
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy;
- Is clinically significant in the PIs judgment.

It is the responsibility of the PI to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin five times the upper limit of normal (ULN) associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the AE eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the AE eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the AE eCRF (see Section 8.3.1.3 for details on recording persistent AEs).

8.3.1.5 ABNORMAL VITAL SIGN VALUES

Not every vital sign abnormality qualifies as an AE. A vital sign result should be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms;
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation);
- Results in a medical intervention or a change in concomitant therapy;
- Is clinically significant in the judgment of the PI.

It is the responsibility of the PI to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the AE eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the AE eCRF (see Section 8.3.1.3 for details on recording persistent AEs).

8.3.1.6 ABNORMAL LIVER FUNCTION TESTS

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, PIs must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST >3 × ULN in combination with total bilirubin >2 × ULN;
- Treatment-emergent ALT or AST >3 × 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 AE eCRF (see Section 8.3.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as an SAE or an AESI (see Section 8.4.2).

8.3.1.7 DEATHS

All deaths that occur during the protocol-specified AE reporting period (see Section 8.2.1), regardless of relationship to study drug, will be recorded on the AE eCRF as well as on the paper Clinical Trial SAE Reporting Form and immediately reported to the Sponsor via the Covance project manager (see Section 8.4.2 for reporting instructions).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the AE eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the AE eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g. "sudden cardiac death").

Deaths that occur after the AE reporting period should be reported as described in Section 8.5.

8.3.1.8 PRE-EXISTING MEDICAL CONDITIONS

A pre-existing medical condition is one that is present at the Screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF page.

A pre-existing medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an AE eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "accelerated worsening of headaches").

8.3.1.9 HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any AE that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 8.1.2) except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an AE or SAE:

- Hospitalization for respite care;

- Hospitalization for a pre-existing condition, provided that all of the following criteria are met:
    - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease;
    - The subject has not experienced an AE.

An event that leads to hospitalization under the following circumstances is not considered to be an SAE but should be reported as an AE instead:

- Hospitalization that was necessary because of the subject's requirement for outpatient care outside of normal outpatient clinic operation hours.

8.4 IMMEDIATE REPORTING REQUIREMENTS FROM PRINCIPAL INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The PI must report such events to the Sponsor immediately via the Covance project manager; under no circumstances should reporting take place more than 24 hours after the PI learns of the event. The following is a list of events that the PI must report to the Sponsor within 24 hours (see Section 8.4.2) after learning of the event, regardless of relationship to study drug:

- SAEs (see Section 8.4.2 for further details);
- AESIs (see Section 8.1.3 for further details);
- Pregnancies (see Section 8.4.2.3 for further details);
- Accidental overdoses or medication errors (see Section 8.4.3 for details on reporting requirements);

The PI must report new significant follow-up information for these events to the Sponsor immediately via the Covance project manager (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis;
- Significant new diagnostic test results;
- Change in causality based on new information;
- Change in the event's outcome, including recovery;
- Additional narrative information on the clinical course of the event.

Principal Investigators must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

8.4.1 REPORTING REQUIREMENTS FOR FATAL OR LIFE-THREATENING SERIOUS ADVERSE EVENTS

Any life-threatening (e.g., imminent risk of death) or fatal AE that is attributed by the PI to study drug will be telephoned to the Medical Monitor immediately, followed by completion of the paper Clinical Trial SAE Reporting Form within 24 hours of learning of the event as described in Section 8.4.2.

Medical Monitor: William Cho, M.D., Ph.D.
Genentech, Inc.
(650) 225-4087 (Office Telephone No.)
((650) 302-3027 (Mobile Telephone No.)

8.4.2 REPORTING REQUIREMENTS FOR ALL SERIOUS ADVERSE EVENTS

8.4.2.1 EVENTS THAT OCCUR PRIOR TO STUDY DRUG INITIATION

After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by protocol-mandated intervention should be reported. The completed paper Clinical Trial SAE/AESI Reporting Form provided to the PI should be completed and submitted to the Sponsor via the Covance project manager immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided below.

The Covance project manager to receive the PI-generated SAE reports:
Name: Jaclyn Lowe
Email Address: Jaclyn.lowe@covance.com
608-210-5359 (Office Telephone No.)
214-502-8547 (Mobile Telephone No.)

8.4.2.2 EVENTS THAT OCCUR AFTER STUDY DRUG INITIATION

After initiation of study drug, SAEs and AESIs will be reported until 28 days after the final dose of study drug. Principal Investigators should record all case details that can be gathered immediately on a paper Clinical Trial SAE/AESI Reporting Form. The completed paper Clinical Trial SAE/AESI Reporting Form should be completed and submitted to the Sponsor (via the Covance project manager) immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided in Section 8.4.2.1. All information will also need to be entered into the AE eCRF.

Relevant follow-up information should be submitted to Roche Safety Risk Management via the Covance project manager on an updated paper Clinical Trial SAE/AESI Reporting Form as soon as it becomes available and/or upon request. Any updates to the paper Clinical Trial SAE/AESI Reporting Form must also be updated in electronic data capture (EDC) on the AE eCRF.

Relevant follow-up information should be submitted to Roche Safety Risk Management via the Covance project manager on an updated paper Clinical Trial SAE/AESI Reporting Form as soon as it becomes available and/or upon request. Any updates to the paper Clinical Trial SAE/AESI Reporting Form must also be updated in EDC on the AE eCRF.

8.4.2.3 REPORTING REQUIREMENTS FOR PREGNANCIES

8.4.2.3.1 PREGNANCIES IN FEMALE SUBJECTS

Subjects should be females of non-childbearing potential in order to be eligible to enter this study. However, the subject will be instructed to immediately inform the PI if they become pregnant during the study or within 28 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed by the PI immediately (i.e., no more than 24 hours after learning of the pregnancy) and emailed to Roche Safety Risk Management via the Covance project manager (see Section 8.4.2 for reporting instructions). Pregnancy should not be recorded on the AE eCRF. The PI should discontinue study drug and counsel the subject, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the AE eCRF. In addition, the PI will submit a paper Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

8.4.2.3.2 CONGENITAL ANOMALIES/BIRTH DEFECTS AND ABORTIONS

Any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be classified as an SAE, recorded on the AE eCRF, and reported to the Sponsor immediately via the Covance project manager (see Section 8.4.2 for reporting instructions) (i.e., no more than 24 hours after learning of the event; see Section 8.4.2). Any abortion should be reported in the same fashion (as the Sponsor considers abortions to be medically significant events).

8.4.3 REPORTING REQUIREMENTS FOR 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 AEs. Each AE associated with a special situation should be recorded separately on the AE eCRF. If the associated AE fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 8.4.2). For GDC-0134, AEs associated with special situations should be recorded as described below for each situation:

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

In addition, all special situations associated with GDC-0134, regardless of whether they result in an AE, should be recorded on the AE eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded 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 (e.g., 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 the completion of two AE eCRF pages, one to report the accidental overdose and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

8.4.4 FOLLOW-UP OF SUBJECTS AFTER ADVERSE EVENTS

8.4.4.1 PRINCIPAL INVESTIGATOR FOLLOW-UP

The PI should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the PI, the subject is lost to follow-up, or the subject withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported. During the study period, resolution of AEs (with dates) should be documented on the AE eCRF and in the subject's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

8.4.4.2 SPONSOR FOLLOW-UP

For SAEs, AESI, and pregnancies, the Sponsor or a designee may follow-up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

8.5 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

At the Study Completion/ET visit or at Clinic Discharge, the PI should instruct each subject to report to the PI any subsequent AEs that the subject's personal physician believes could be related to prior study drug treatment or study procedures. The Sponsor should be notified if the PI becomes aware of any SAE that occurs after the end of the AE reporting period (defined as 28 days after the final dose of study drug) if the event is believed to be related to prior study drug treatment.

These events should be reported through the use of the AE eCRF. However, if the EDC system is not available, the PI should report these events directly to the Sponsor or its designee, by faxing or by scanning and emailing the paper Clinical Trial SAE/AESI Reporting Form using the below fax number or email address provided to PIs.

Genentech US Drug Safety
Email Address: us_drug.safety@gene.com
Fax No.: (650) 225-4682

8.5.1 EXPEDITED REPORTING TO HEALTH AUTHORITIES, PRINCIPAL INVESTIGATORS, AND INSTITUTIONAL REVIEW BOARDS

The Sponsor will promptly evaluate all SAEs and AESIs against cumulative product experience to identify and expeditiously communicate possible new safety findings to PIs, IRBs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events using the following reference document(s):

- GDC-0134 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 PIs assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

The IRB will be notified by the investigative site in writing (e.g., email) within the timeframe required per local IRB regulations for when a reportable AE is first recognized or reported. In addition, a copy of the written confirmation or summary of the AE, as submitted to the Sponsor, will also be submitted to the IRB within that same timeframe from when the AE is first recognized or reported. The IRB Serious and Unexpected AE Submission Form will be completed and submitted with the copy of the written confirmation or summary of the AE.

9 STATISTICAL ANALYSES

The Safety Population will consist of all subjects who received the study drug and have at least one postdose safety assessment.

The PK Population will consist of all subjects who received the study drug and have at least one evaluable postdose PK sample. A subject will be excluded from the PK summary statistics and statistical analysis (where applicable) if the subject has an AE of vomiting that occurs at or before 2 times median t_{max}.

Baseline is defined as the last result prior to the study drug administration on Day 1. As necessary, baseline will be further defined in the Statistical Analysis Plan (SAP).

9.1 SAFETY AND TOLERABILITY ANALYSIS

Safety will be assessed by a review of AEs, physical examinations, vital signs, clinical laboratory assessments, ophthalmologic assessments, and ECGs. Clinical laboratory assessments, vital signs (including oral temperature, respiratory rate, and supine blood pressure and pulse), weight data, ophthalmologic assessments, and ECGs will be listed by subject number and scheduled time. Changes from baseline will be summarized.

Verbatim descriptions of AEs will be coded according to current Medical Dictionary for Regulatory Activities version 20.0 (or higher) guidelines. Adverse events will be summarized. Adverse events of special interest that could indicate hypersensitivity reactions will be summarized separately. Enrollment and discontinuations from the study will be summarized overall. Demographics and baseline characteristics such as age, sex, and BMI will be summarized overall.

9.2 PHARMACOKINETIC ANALYSIS

The following PK parameters will be derived from the plasma concentrations of GDC-0134 using the model independent approach:

C_{max}	maximum observed concentration
t_{max}	time to maximum observed concentration
AUC_{0-t}	area under the concentration-time curve from Hour 0 to the last measurable concentration, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations
$AUC_{0-\infty}$	area under the concentration-time curve extrapolated to infinity, calculated using the formula: $AUC_{0-\infty} = AUC_{0-t} + \frac{C_t}{\lambda_z}$

	where C_t is the last measurable concentration and λ_z is the apparent terminal elimination rate constant
λ_z	apparent terminal elimination rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase
$t_{1/2}$	apparent terminal elimination half-life (whenever possible), where $t_{1/2}$ = natural log (ln)2/λ_z
CL/F	apparent systemic clearance, calculated as dose/ $AUC_{0-\infty}$
V_z/F	apparent volume of distribution during the terminal phase, calculated as CL/F/λ_z

The following PK parameters will be derived from urine concentrations of GDC-0134:

A_{eu}	amount excreted in urine over a sampling interval
Total A_{eu}	cumulative amount excreted in urine
$\%F_{eu}$	percentage of dose excreted in urine over a sampling interval
Total $\%F_{eu}$	cumulative percentage of dose excreted in urine
CL_R	renal clearance

Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as Phoenix WinNonlin (Certara Inc., Version 6.4 or higher).

Other parameters may be added as appropriate. Final PK parameters reported will be detailed in the SAP.

Pharmacokinetic analysis will use actual times as recorded on the eCRF. Other data handling procedures will be detailed in the SAP.

9.3 WHOLE GENOME SEQUENCING ANALYSIS

The WGS data will be analyzed in the context of this study and explored in aggregate with data from other studies to increase researcher's understanding of disease pathobiology and guide the development of new therapeutic approaches.

9.4 INTERIM ANALYSIS

No interim analyses are planned for this study.

9.4.1 OPTIONAL INTERIM ANALYSIS

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct interim analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel.

9.5 STATISTICAL ANALYSIS OF PHARMACOKINETIC DATA

Descriptive statistics (mean, median, minimum, maximum, standard deviation, geometric mean, and geometric coefficient of variation) will be calculated for all PK parameters and PK concentration data.

The primary parameters for analysis will be $AUC_{0-\infty}$ and C_{max} of GDC-0134. A linear mixed model will be applied to analyze the log-transformed primary PK parameters. The model assumes fixed effects for formulation, period, and sequence, and a random effect for subject within sequence. Estimates of geometric mean ratios on the original scale, together with the corresponding 90% CIs, will be derived for the comparisons between Test and Reference treatments.

Time to maximum observed concentration will be analyzed by using Wilcoxon signed-rank test, and Hodges-Lehmann estimate to generate the difference in medians between treatments (Test-Reference) and 90% CI of the median difference.

All calculations will be performed using SAS® version 9.4 or greater.

Specification of PK parameters for analysis; statistical level of significance to be used; criteria for study termination; procedures for accounting for missing, unused, or spurious data; procedures for reporting deviations from the original statistical plan; and selection of subjects to be included in the analyses population(s) will be presented in the Clinical Study Report and/or SAP as appropriate.

Statistical analyses details will be included in the SAP.

9.6 STATISTICAL ANALYSES OF SAFETY DATA

Descriptive statistics will be used for the safety parameters. No formal statistical analyses are planned.

9.7 SAMPLE SIZE

The sample size chosen for this study was based upon precedent set by other PK studies of similar nature and was not based on power calculations.

9.8 QUALITY CONTROL AND QUALITY ASSURANCE

Quality control and quality assurance will be performed according to Covance Standard Operating Procedures or per client request and as applicable according to the contract between Covance and the Sponsor.

10 ADMINISTRATIVE ASPECTS

10.1 CHANGE IN PROTOCOL

There will be no alterations in the protocol without agreement between the Sponsor and the PI.

There will be no alterations in the protocol affecting subject safety without the express written approval of the Sponsor, PI, and the IRB (see Form FDA 1572).

10.2 PRINCIPAL INVESTIGATOR MEETING; SITE INITIATION

Prior to the start of the clinical study, the representative(s) of the Sponsor will meet with the PI(s) and appropriate clinical staff to familiarize the PI and clinical staff with the materials necessary for conducting the clinical study.

10.3 DISCLOSURE

All information provided regarding the study, as well as all information collected and documented during the course of the study, will be regarded as confidential. The PI agrees not to disclose such information in any way without prior written permission from the Sponsor.

Any publication of the results, either in part or in total (e.g., articles in journals or newspapers, oral presentations, abstracts) by the PI(s) or their representative(s), shall require prior notification and review, within a reasonable timeframe, by the Sponsor, and cannot be made in violation of the Sponsor's confidentiality restrictions or to the detriment of the Sponsor's intellectual property rights.

10.4 MONITORING (CLINICAL RESEARCH ASSOCIATE)

The Sponsor will designate a Sponsor's Study Monitor who will be responsible for monitoring this clinical trial. The Sponsor's Study Monitor will monitor the study conduct, proper eCRF and source documentation completion and retention, and accurate study drug accountability. To this end, the Sponsor's Study Monitor will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. It is essential that the Sponsor's Study Monitor have access to all documents, including study data, subject medical records, and eCRFs, at any time these are requested. In turn, the Sponsor's Study Monitor will adhere to all requirements for subject confidentiality as outlined in the ICF. The PI and PIs staff will be expected to cooperate with the Sponsor's Study Monitor, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

10.5 INSTITUTIONAL REVIEW BOARD

In accordance with 21CFR 56, the protocol, advertisement, and ICF will be reviewed and approved by the IRB. The Sponsor will supply relevant material for the PI to submit to the IRB for the protocol's review and approval. Verification of the IRB unconditional approval of the protocol and the written ICF statement will be transmitted to the PI.

The IRB will be informed by the PI of subsequent protocol amendments and of serious and unexpected AEs. Approval for protocol amendments will be transmitted in writing to the PI. If requested, the PI will permit audits by the IRB and regulatory inspections by providing direct access to source data and documents.

The PI will provide the IRB with progress reports at appropriate intervals (not to exceed 1 year) and a Study Progress Report following the completion, termination, or discontinuation of the PIs participation in the study.

10.6 INFORMED CONSENT

Written informed consent for the study will be obtained from all subjects before protocol-specific procedures are carried out. The ICF will be approved (along with the protocol) by the IRB and will be acceptable to the Sponsor.

The PI or designee will explain the nature of the study and the action of the test product. The subjects will be informed that participation is voluntary and that they can withdraw from the study at any time. In accordance with 21 CFR 50, the informed consent process shall be

documented by the use of a written ICF approved by the IRB and signed by the subject prior to protocol-specific procedures being performed.

The subject will sign two copies of the ICF. One copy will be given to the subject, and the other will be maintained with the subject's records.

10.7 RECORDS

The results from Screening and data collected during the study will be recorded in the subject's eCRF. To maintain confidentiality, the subjects will be identified only by numbers.

The completed eCRFs will be transferred to the Sponsor or designee. Copies of each eCRF will be retained by the PI. All source documents, records, and reports will be retained by the study site in accordance with 21 CFR 312.62(c).

All primary data, or copies thereof (e.g., laboratory records, case report forms [CRFs], data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report, will be retained in the study site archives.

10.7.1 ELECTRONIC CASE REPORT FORMS

Electronic CRFs are to be completed using the Medidata RAVE EDC system. The site will receive training and have access to a manual for appropriate eCRF completion. Electronic CRFs will be submitted electronically to Covance and should be handled in accordance with instructions from Genentech/Covance. All eCRFs should be completed by designated, trained examining personnel as appropriate.

The results from Screening and data collected during the study will be recorded in the subject's eCRF. To maintain confidentiality, the subjects will be identified only by numbers. The PI will ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRF by providing an electronic signature. The completed eCRFs will be transferred to the Sponsor or designee.

In addition, at the end of the study, the PI will receive subject data for the site in a readable format (e.g., a compact disc) that must be kept with the study records.

10.7.2 SOURCE DATA DOCUMENTATION

Study Monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which subject data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, subject files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in a clinical trial. Source documents that are required to verify the validity and completeness of data entered into the eCRFs must never be obliterated or destroyed. To facilitate source data verification and review, the PI and institution(s) must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB review. The study site must also allow inspection by applicable health authorities.

10.7.3 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with FDA requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system (for clinical research purposes) would be one that (1) allows data entry only by authorized individuals; (2) prevents the deletion or alteration of previously entered data and provides an audit trail for such data changes (e.g., modification of file); (3) protects the database from tampering; and (4) ensures data preservation.

In collaboration with the Study Monitor, Genentech's or Covance's Quality Assurance group may assist in assessing whether electronic records generated from computerized medical record systems used at study sites can serve as source documents for the purposes of this protocol. If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents must be maintained to ensure that critical protocol data entered into the eCRFs can be verified.

10.7.4 STUDY MEDICATION ACCOUNTABILITY

The recipient of study medication will acknowledge receipt by returning the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced. Accurate records of all study drug received at, dispensed from, returned to, and disposed of by the study site should be recorded by using the Drug Inventory Log.

Study drug will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to Genentech with the appropriate documentation, as determined by the Sponsor. If the study site is able to destroy study drug, the method of destruction must be documented. Genentech must evaluate and approve the study site's drug destruction standard operating procedure prior to the initiation of drug destruction by the study site.

10.7.5 DISCLOSURE OF DATA

Subject medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization to use and disclose personal health information) signed by the subject or unless permitted or required by law. Medical information may be given to a subject's personal physician or other appropriate medical personnel responsible for the subject's welfare for treatment purposes.

Given the complexity and exploratory nature of the analyses, data derived from exploratory biomarker specimens will generally not be provided to study PIs or subjects unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other regulatory agencies, national and local health authorities, Genentech monitors/representatives and collaborators, and the IRB for the study site, if appropriate.

Study data, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

10.7.6 RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, ICFs, laboratory test results, and medication inventory records, must be retained by the PI for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the study drug. All state and local laws for retention of records also apply. No records should be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location. For studies conducted outside the United States under a U.S. IND, the PI must comply with the record retention requirements set forth in the U.S. FDA IND regulations and the relevant national and local health authorities, whichever is longer.

All primary data, or copies thereof (e.g., laboratory records, eCRFs, data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report will be retained in the study site archives.

10.8 REFERENCE TO DECLARATION OF HELSINKI/BASIC PRINCIPLES

The study procedures outlined in this protocol will be conducted in accordance with the U.S. CFR governing Protection of Human Subjects (21 CFR 50), Financial Disclosure by Clinical PIs (21 CFR 54), IRBs (21 CFR 56), IND Application (21 CFR 312), and Applications for FDA Approval to Market a New Drug (21 CFR 314), as appropriate. As such, these sections of U.S. Title 21 CFR, along with the applicable ICH Guidelines, are commonly known as GCP, which are consistent with the Declaration of Helsinki.

PRINCIPAL INVESTIGATOR AGREEMENT

I have read the foregoing protocol and agree to conduct the study as described herein.

20DEC2018

~~Hugh Coleman, D.O.~~ Date

SUB- Principal Investigator
Covance Clinical Research Unit
Daytona Beach, FL
LAWRENCE GALITZ MD
Signing for Dr. Coleman

PRINCIPAL INVESTIGATOR AGREEMENT

I have read the foregoing protocol and agree to conduct the study as described herein.

T. Alex King, M.D.
Principal Investigator
Covance Clinical Research Unit
Dallas, TX.

Date

SPONSOR AGREEMENT

I have read the foregoing protocol and agree to the conduct of the study as described herein.

Sravanthi Cheeti, B.Pharm., M.S.
Clinical Pharmacologist
Genentech, Inc.

12/19/2018
Date

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APPENDIX A – CLINICAL LABORATORY EVALUATIONS

Clinical Chemistry Panel (Fasted at least 8 hours):
Alanine aminotransferase
Albumin
Alkaline phosphatase
Aspartate aminotransferase
Blood urea nitrogen
Calcium
Chloride
Cholesterol
Creatinine
Creatine kinase (CK)/Creatine phosphokinase (CPK)
Direct bilirubin
Glucose
Potassium
Sodium
Total bilirubin
Total protein
Triglycerides
Uric acid

Complete Blood Count:
Hematocrit
Hemoglobin
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Mean corpuscular volume
Platelet count
Red blood cell (RBC) count
RBC distribution width
White blood cell (WBC) count
WBC differential (absolute):
Basophils
Eosinophils
Lymphocytes
Monocytes
Neutrophils

Urinalysis:
Bilirubin
Color and appearance
Glucose
Ketones
Leukocyte esterase
Nitrite
Occult blood
pH and specific gravity
Protein
Urobilinogen
Microscopic exam including bacteria, casts, crystals, epithelial cells, RBCs, and WBCs (if protein, leukocyte esterase, nitrite, or blood is positive) [a]

Drug Screen:
Including but not limited to the following:
Alcohol (ethanol) [c]
Amphetamines
Barbiturates
Benzodiazepines
Cannabinoids (THC)
Cocaine (metabolite)
Methadone
Opiates
Phencyclidine
Cotinine

Other Tests:
Hepatitis B virus core antibody [b]
Hepatitis B surface antigen [b]
Hepatitis C virus antibody [b]
Human Immunodeficiency Virus antibody [b]
Pregnancy test (serum qualitative)
Follicle-stimulating hormone (FSH) [b]
QuantiFERON® TB Gold
Tuberculosis test [b]

Coagulation Profile
Prothrombin time (PT)
Activated partial thromboplastin time (aPTT)/Partial thromboplastin time (PTT)
International normalized ratio (INR)
Fibrinogen

[a] A microscopic examination will be performed at Screening. During other scheduled urinalysis assessments, a microscopic examination will only be performed if protein, leukocyte esterase, nitrite, or blood is positive.

[b] Measured at the Screening visit only.

[c] Alcohol breath or urine testing will be performed at Check-in (Day -1) for both periods only.

APPENDIX B – APPROXIMATE MAXIMUM BLOOD VOLUME COLLECTED

Number of samples collected in each part of the study

	Sample Volume (mL)	Number of Samples	Total Volume (mL)
Serology	7	1	7
Clinical Laboratory Evaluations (including serum pregnancy and serum FSH)	12.5	5	62.5
Coagulation	3	3	9
Tuberculosis (Quantiferon® TB Gold)	4	1	4
PK Samples	4	31	124
WGS Sample	6	1	6
		Total per part	**212.5**

FSH = follicle-stimulating hormone; PK = pharmacokinetic; TB = tuberculosis; WGS = whole genome sequencing.

Note: Additional samples may be drawn for safety purposes.

If subjects participate in both parts of the study, the total blood volume will be approximately double that indicated in the table (~425 mL).