Official Title: A Phase 1, Open-Label, Single-Dose, Randomized, Three-Period Crossover Study to Evaluate the Relative Bioavailability and Food Effect of GDC-9545 in Healthy Female Subjects of Non-Childbearing Potential

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A PHASE 1, OPEN-LABEL, SINGLE-DOSE, RANDOMIZED, THREE-PERIOD CROSSOVER STUDY TO EVALUATE THE RELATIVE BIOAVAILABILITY AND FOOD EFFECT OF GDC-9545 IN HEALTHY FEMALE SUBJECTS OF NON-CHILDBEARING POTENTIAL

Protocol GP42006

Covance Study 8418446

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ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the concentration-time curve from Hour 0 extrapolated to infinity
AUC_{0-24}	area under the concentration-time curve from Hour 0 to 24 hours postdose
AUC_{0-t}	area under the concentration-time curve from Hour 0 to the last measurable concentration
BMI	body mass index
CBC	complete blood count
CCOD	clinical cut-off date
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	apparent total clearance
C_{max}	maximum observed concentration
CPET	Clinical Pharmacology Protocol Execution Team
CSR	Clinical Study Report
C_t	last measurable concentration
CV%	coefficient of variation
CYP	cytochrome P450
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
eMC	Electronic Medicines Compendium
ER	estrogen receptor
ET	Early Termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HDYF?	How do you feel?
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form

ICH	International Conference on Harmonisation/International Council for Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
λz	apparent terminal elimination rate constant
LHRH	luteinizing hormone-releasing hormone
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PLD	phospholipidosis
PPD	purified protein derivative
PK	pharmacokinetic(s)
PSS	Patient Safety Solutions
RBC	red blood cell
RBR	Research Biosample Repository
SAE	serious adverse event
SAP	Statistical Analysis Plan
SERD	selective estrogen receptor degrader
SERM	selective estrogen receptor modulator
SOC	System Organ Class
SOP	standard operating procedure
$t_{1/2}$	apparent terminal elimination half-life
TB	tuberculosis
t_{max}	time to maximum observed concentration
UA	urinalysis
ULN	upper limit of normal
US	United States
V_Z/F	apparent volume of distribution during the terminal elimination phase
WBC	white blood cell

1 SYNOPSIS

Title of Study:	A Phase 1, Open-Label, Single-Dose, Randomized, Three-Period Crossover Study to Evaluate the Relative Bioavailability and Food Effect of GDC-9545 in Healthy Female Subjects of Non-Childbearing Potential
Objectives:	The primary objectives of this study are: • To evaluate the relative bioavailability of GDC-9545 Phase 3 capsule as compared to the Phase 1 tablet in the fasted state in healthy adult female subjects of non-childbearing potential • To assess the impact of food on GDC-9545 PK for the Phase 3 capsule in healthy adult female subjects of non-childbearing potential. The secondary objective of this study is: • To explore the safety and tolerability of single oral doses of 30 mg GDC-9545 as a Phase 3 capsule in the fasted and fed states in healthy adult female subjects of non-childbearing potential.
Methodology/Study Design:	This study will be an open-label, randomized, three-period, six-sequence crossover study of GDC-9545 administered to healthy females of non-childbearing potential to determine the relative bioavailability of the Phase 3 capsule formulation to the Phase 1 tablet formulation in the fasted state and the effect of food on the Phase 3 capsule formulation. Potential subjects will be screened to assess their eligibility to enter the study within 34 days (Days -35 to -2) prior to dosing on Period 1 Day 1. Dosing will be on Day 1 of each period.
Number and General Description of Subjects:	Eighteen subjects will be enrolled in the study to complete a minimum of 12 subjects.
Diagnosis and Main Criteria for Inclusion:	Healthy females of non-childbearing potential, between 18 and 65 years of age, inclusive, within body mass index range of 8.0 to 30.0 kg/m^2, inclusive, who are in good health, as determined by no clinically significant findings from medical history, 12-lead electrocardiogram (ECG), vital signs, and clinical laboratory evaluations.
Test Product(s), Dose, and Mode of Administration:	Subjects will receive the following treatments, according to a randomization schedule generated by a Covance Biostatistician: **Treatment A:** 30-mg dose of GDC-9545 (three 10-mg tablets) administered orally with approximately 240 mL room temperature water after at least an 8-hour fast. **Treatment B:** 30-mg dose of GDC-9545 (one 30-mg capsule) administered orally with approximately 240 mL room temperature water after at least an 8-hour fast. **Treatment C:** 30-mg dose of GDC-9545 (one 30-mg capsule) administered orally with approximately 240 mL room temperature water within 30 minutes of eating a high-fat meal.
Duration of Treatment:	Planned Enrollment/Screening Duration: approximately 5 weeks. Length of Each Confinement: subjects will be confined at the study site from the time of Check-in (Day -1) until Clinic Discharge on Day 8 of each period. The washout period between doses will be a minimum of 10 days. All subjects will receive 3 doses of GDC-9545. A Follow-up visit will occur 12 to 14 days after the last dose of GDC-9545. Planned Study Conduct Duration: approximately 10 weeks.
Criteria for Evaluation: Safety	Safety and tolerability assessments will include recording of adverse events, clinical laboratory evaluations, 12-lead ECGs, vital sign measurements, and physical examinations.
Criteria for Evaluation: Pharmacokinetics	The following pharmacokinetic (PK) parameters will be derived from the plasma concentrations of GDC-9545 using the model independent approach: maximum observed concentration (C_{max}), time to C_{max} (t_{max}), area under the concentration-time curve from Hour 0 to the last measurable concentration (AUC_{0-t}), area under the concentration-time curve from Hour 0 extrapolated to infinity ($AUC_{0-\infty}$), apparent

	terminal elimination rate constant (λ_z), apparent terminal elimination half-life ($t_{1/2}$), apparent total clearance (CL/F), and apparent volume of distribution during the terminal elimination phase (V_z/F).
Statistical Methods:	Descriptive statistics (mean, median, minimum, maximum, standard deviation, coefficient of variation [CV%], geometric mean, and geometric CV%) will be calculated for all PK parameters for GDC-9545. The PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for GDC-9545 will be analyzed to evaluate the relative bioavailability of GDC-9545 as a Phase 3 capsule formulation compared to a Phase 1 tablet formulation under fasted conditions and to assess the food effect on GDC-9545 PK for a Phase 3 capsule formulation. The mixed-effect analysis of variance model for three-period crossover design will be used for formulation comparison and fasted state and fed state comparison of capsule. The model will include sequence, formulation, and period as fixed effects and a random effect for subject within sequence. Appropriate covariance structure will be used. Log transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ values will be evaluated to estimate ratios of geometric mean values and the corresponding 90% confidence intervals (CIs). (Relative bioavailability-Test: capsule, Reference: tablet; food effect-Test: fed, Reference: fasted.) The parameter t_{max} will be analyzed nonparametrically using the Wilcoxon signed-rank test. The median difference between the test and reference investigational products and the corresponding 90% CI will be calculated. All safety data will be listed and summarized using standard descriptive statistics for the Safety Population. No formal statistical analyses are planned.

2 INTRODUCTION

2.1 BACKGROUND

Breast cancer is the most frequent cancer diagnosed in women, and accounts for approximately 15% (approximately 522,000 cases) of all cancer deaths (Ferlay et al. 2013). Approximately 80% of all breast cancers express estrogen receptor (ER), and the vast majority of these cancers are dependent on ER for tumor growth and progression. Modulation of estrogen activity and/or synthesis is the mainstay of therapeutic approaches in women with ER+ breast cancer. However, despite the effectiveness of available endocrine therapies, many patients ultimately relapse or develop resistance. The growth and survival of the majority of tumors are thought to remain dependent on ER signaling. Consequently, patients with ER+ breast cancer can still respond to second/third line endocrine treatment after progression on prior therapy (Di Leo et al. 2010; Baselga et al. 2012). GDC-9545 is a small-molecule therapeutic agent that is being developed for the treatment of patients with ER+ breast cancer. GDC-9545 antagonizes the effects of estrogens via competitive binding to the ligand-binding domain of both wild-type and mutant ER. In addition to its direct antagonist properties, GDC-9545 reduces levels of ERα protein through proteasome-mediated degradation. Degradation of ER is hypothesized to enable full suppression of ER signaling, which is not achieved by first generation ER therapeutics.

2.2 PHARMACOLOGY

GDC-9545 has demonstrated growth inhibition in vitro as a single agent in human breast cancer cell lines expressing wild-type or mutant forms of ERα and in vivo in breast cancer xenograft models that harbor ERα mutations. In addition, GDC-9545 enhances the in vivo efficacy of the CDK4/6 inhibitor palbociclib, a standard-of-care drug for treatment of patients with hormone receptor+/HER2- metastatic breast cancer, in the ER+ MCF7 xenograft model. GDC-9545, unlike 17α-ethinylestradiol and tamoxifen, did not induce ER agonism when assessed in immature rat uteri. Moreover, GDC-9545 is anticipated to have a low risk of adverse cardiovascular, neurologic, and respiratory effects at pharmacologically active doses and at doses used in the first-in-human Phase 1 clinical trial.

2.3 PHARMACOKINETICS

No human-specific metabolites were detected in studies in human, mouse, rat, rabbit, dog, or monkey hepatocytes. In vitro data showed that plasma protein binding of GDC-9545 was high across all species, ranging from 98% to 99% bound.
Uridine 5'-diphospho-glucuronosyltransferase 1A4 glucuronidation was the major in vitro metabolic pathway of GDC-9545. The contribution from cytochrome P450 (CYP) isoforms was

minor and included CYP3A4 and CYP2C9. In vitro studies suggest a low-to-moderate potential for drug-drug interaction.

2.4 TOXICOLOGY AND SAFETY PHARMACOLOGY

Adverse organ effects identified in pivotal toxicity studies in rat and monkey were dose-dependent, largely confined to the kidney and liver, and readily monitorable in the clinic using standard laboratory assessments. The findings in reproductive organs in both species are consistent with the anti-estrogenic mode of action of GDC-9545 and were partially reversible in monkeys but not rats, likely due to the maintenance of pharmacologically active exposures of GDC-9545 at the end of the recovery period. In both rats and monkeys, there was dose-dependent phospholipidosis (PLD) in numerous organs, including liver and kidney. In rats, PLD was not noted at 10 mg/kg, but increased in incidence and severity from 30 to 100 mg/kg. In monkeys, PLD was present at all doses, but was limited to minimal changes in the lung at 20 mg/kg. In general, PLD is of greatest concern when accumulations occur in critical cell types such as cardiomyocytes, neurons, and retinal epithelium (Chatman et al. 2009), but PLD was not seen in any of these cell types.

No significant inhibition was observed on cloned human sodium or calcium channels in vitro. GDC-9545 inhibited human ether à go go related gene potassium current with a 50% inhibitory concentration 339-fold higher than the unbound maximum observed concentration of the 100-mg dose in humans from the Phase 1 first-in-human trial. There were no GDC-9545-related changes in cardiovascular parameters in cynomolgus monkey after single doses up to the maximum dose tested. In a four-week study in monkeys, there was a dose-dependent decrease in heart rate that was not considered to be toxicologically relevant. GDC-9545 was not mutagenic in the bacterial mutagenesis assay, did not induce micronucleus formation in human lymphocytes, and was not phototoxic in mammalian cells.

2.5 CLINICAL RESULTS

GDC-9545 is currently being evaluated in a Phase 1 study in patients. As of the clinical cut-off date (CCOD) of 4 September 2019, safety data is available on 120 patients with ER+/HER2-, locally recurrent or metastatic breast cancer that have been treated with GDC-9545 at 10- to 250-mg doses given once daily, including 74 patients in single-agent dose-escalation or expansion cohorts ± luteinizing hormone-releasing hormone (LHRH) agonist and 46 patients in palbociclib combination dose-escalation cohorts. Single-dose pharmacokinetic (PK) parameters for GDC-9545 as a single agent are shown in Table 2-1.

Table 2-1 GDC-9545 Single-Dose Pharmacokinetic Parameters

Dose	t_{max} (hr)	C_{max} (ng/mL)	AUC_{0-24} (hr•ng/mL)	$AUC_{0-\infty}$ (hr•ng/mL)	$t_{1/2}$ (hr)
10 mg (n = 6)	2.50 (1.00-4.00)	53.7 (55.3)	782 (50.5)	1910 (66.6)	38.9 (32.2)
30 mg (n = 6)	1.75 (1.00-3.00)	177 (23.5)	2110 (25.6)	5070 (28.3)	41.4 (8.7)
90 mg (n = 6)	3.0 (1.50-4.00)	382 (31.8)	5570 (31.8)	12200 (31.3)	36.9 (20.9)
250 mg (n = 3)	3.0 (3.0-3.0)	1190 (7.46)	16600 (6.95)	32300 (11.8)	26.2 (17.7)

$AUC_{0-\infty}$ = area under the concentration-time curve from Hour 0 extrapolated to infinity; AUC_{0-24} = area under the concentration-time curve from Hour 0 to 24 hours postdose; C_{max} = maximum observed concentration; $t_{1/2}$ = apparent terminal elimination half-life; t_{max} = time to maximum observed concentration.

Geometric mean (geometric coefficient of variation) is presented for all parameters except t_{max}, for which median (range) is reported.

Robust ER target engagement across all doses as evidenced by [^{18}F]-fluoroestradiol-positron emission tomography data was demonstrated. Of the 39 patients with post-baseline tumor assessments, 2 patients had confirmed partial responses and 28 patients had stable disease or non-complete response/non-progressive disease.

There were no withdrawals due to adverse events (AEs), and no dose-limiting toxicities were reported. GDC-9545 was well tolerated at all dose levels. As of the CCOD of 4 September 2019, 74 patients treated with single-agent GDC-9545 (including arms co-administered with LHRH agonist) at doses ranging from 10 to 250 mg including 10 patients treated at 30 mg GDC-9545 (which is the selected dose for this study).

Of the 74 patients treated with single-agent GDC-9545, AEs attributed to GDC-9545 occurring in 5% or more of patients included: fatigue (14 patients [19%]), arthralgia (9 patients [12%]), nausea (8 patients [11%]); diarrhea (7 patients [10%]); bradycardia (6 patients [8%]); hot flush, alanine aminotransferase (ALT) increased, and aspartate aminotransferase (AST) increased (5 patients each [7%]); and constipation and dyspepsia (4 patients each [5%]). Related events have been Grade 1 or 2 in severity with the exception of three Grade 3 events of fatigue, transaminase increased, and diarrhea (all were in patients treated with 100 mg GDC-9545 and confounded by metastatic sites and disease progression).

In the single-agent GDC-9545 30-mg cohort, the AEs attributed to GDC-9545 occurring in 3 or more patients with Grade 1 or 2 severity included: fatigue, nausea, diarrhea, and dyspepsia (3 patients each [30%]).

Of the 74 patients treated with single-agent GDC-9545, five serious AEs (SAEs) occurred in 4 patients (5%) including: appendiceal abscess, small intestinal obstruction, fatigue, migraine, and paraesthesia. All SAEs except fatigue were considered unrelated to GDC-9545 by the Investigators. In the 30-mg single-agent cohort, only a single patient experienced SAEs of migraine and paraesthesia; both of which were considered unrelated to GDC-9545.

GDC-9545 treatment resulted in a dose-dependent decrease in heart rate. Of the 74 patients treated with single-agent GDC-9545, 7 patients (9.5%) experienced AEs that are mapped into the cardiac disorder System Organ Class (SOC). This includes AEs of bradycardia in 7 patients (9.5%; 6 patients at 90/100-mg and 1 patient at 250-mg cohorts) and palpitation in 2 patients (3%; 1 patient at 90-mg and 1 patient at 250-mg cohorts). All AEs were Grade 1 and asymptomatic. No cardiac-related events have been reported at 30 mg.

Refer to the GDC-9545 Investigator's Brochure (IB) for details on nonclinical and clinical studies.

2.6 STUDY RATIONALE

The purpose of this study is to evaluate the bioavailability of the GDC-9545 Phase 3 capsule relative to the Phase 1 tablet and to assess the effect of food on the GDC-9545 PK of the Phase 3 capsule. These evaluations will support the use of the Phase 3 capsule in future clinical studies.

2.7 DOSE RATIONALE

GDC-9545 is a potent, orally bioavailable, small-molecule therapeutic agent that is being developed for the treatment of patients with ER+ breast cancer. GDC-9545 antagonizes the effects of estrogens via competitive binding to the ligand-binding domain of both wild-type and mutant ER with nanomolar potency.

Based on interim data from safety, PK, and early signs of target modulation/activity in the first-in-human study of GDC-9545 in patients, 30 mg was selected as the optimal dose for future clinical development.

As of the CCOD, a total of 120 postmenopausal women with locally advanced or metastatic ER+/HER2− breast cancer received at least one dose of GDC-9545 in the ongoing Phase Ia/Ib Study GO39932. This includes 74 patients who have been treated with single-agent GDC-9545 (± LHRH agonist) at doses ranging from 10 to 250 mg. The single-agent dose escalation was completed in October 2018 after enrolling 29 patients. At the end of the dose-escalation stage, no

patients had experienced dose-limiting toxicities, SAEs, or protocol-defined AEs of special interest (AESIs) during dose escalation. The maximum tolerated dose was not reached.

As of the CCOD, the most frequent AEs related to GDC-9545 in ≥5% (n=74) patients treated with single-agent GDC-9545 (± LHRH agonist) were: fatigue (14 patients [19%]); arthralgia (9 patients [12%]); nausea (8 patients [11%]); diarrhea (7 patients [9.5%]); bradycardia (6 patients [8%]); hot flush, ALT increased, and AST increased (5 patients each [7%]); constipation and dyspepsia (4 patients each [5%]). All treatment-related events have been Grade 1 or 2 severity with the exception of three Grade 3 events of fatigue, transaminase increased, and diarrhea (all were in patients treated with 100 mg GDC-9545 and confounded by metastatic sites and disease progression). One patient has experienced a treatment-related SAE (Grade 3 fatigue) considered related to both GDC-9545 and disease progression. The dose of GDC-9545 was reduced in 2 patients (both receiving 100 mg); no patients were withdrawn from treatment due to AEs.

Of the 74 patients treated with single-agent GDC-9545, 7 patients (9.5%) experienced AEs that are mapped into the cardiac disorder SOC. No cardiac-related events have been reported at 30 mg. GDC-9545 was well tolerated at all dose levels with no trend for an increase in frequency or severity of AEs.

All observations of AEs described above are at higher dose levels with continuous daily dosing. Consequently, the single dose of 30 mg represents an acceptable dosage for this study.

3 STUDY OBJECTIVES AND CORRESPONDING ENDPOINTS

3.1 PRIMARY OBJECTIVES

The primary objectives of this study are:

- To evaluate the relative bioavailability of GDC-9545 Phase 3 capsule as compared to the Phase 1 tablet in the fasted state in healthy adult female subjects of non-childbearing potential
- To assess the impact of food on GDC-9545 PK for the Phase 3 capsule in healthy adult female subjects of non-childbearing potential.

3.2 SECONDARY OBJECTIVES

The secondary objective of this study is:

- To explore the safety and tolerability of single oral doses of 30 mg GDC-9545 as a Phase 3 capsule in the fasted and fed states in healthy adult female subjects of non-childbearing potential.

3.3 ENDPOINTS

The primary endpoints are the PK parameters outlined in Section 9.2. The secondary endpoints are the incidence and severity of AEs and incidence of abnormalities in laboratory safety assessments, 12-lead electrocardiograms (ECGs), vital signs measurements, and physical examinations.

4 STUDY DESIGN

4.1 DESCRIPTION OF THE STUDY

This study will be an open-label, randomized, three-period, six-sequence crossover study of GDC-9545 administered at 30 mg in healthy females of non-childbearing potential to determine the relative bioavailability of the Phase 3 capsule formulation to the Phase 1 tablet formulation in the fasted state and the effect of food on the Phase 3 capsule formulation. Eighteen subjects will be enrolled in the study at a single study site to complete a minimum of 12 subjects. Study treatments are as follows:

Treatment A: 30-mg dose of GDC-9545 (three 10-mg tablets) administered orally with approximately 240 mL room temperature water after at least an 8-hour fast.

Treatment B: 30-mg dose of GDC-9545 (one 30-mg capsule) administered orally with approximately 240 mL room temperature water after at least an 8-hour fast.

Treatment C: 30-mg dose of GDC-9545 (one 30-mg capsule) administered orally with approximately 240 mL room temperature water within 30 minutes of eating a high-fat meal.

A summary of the sequences is presented in Table 4-1.

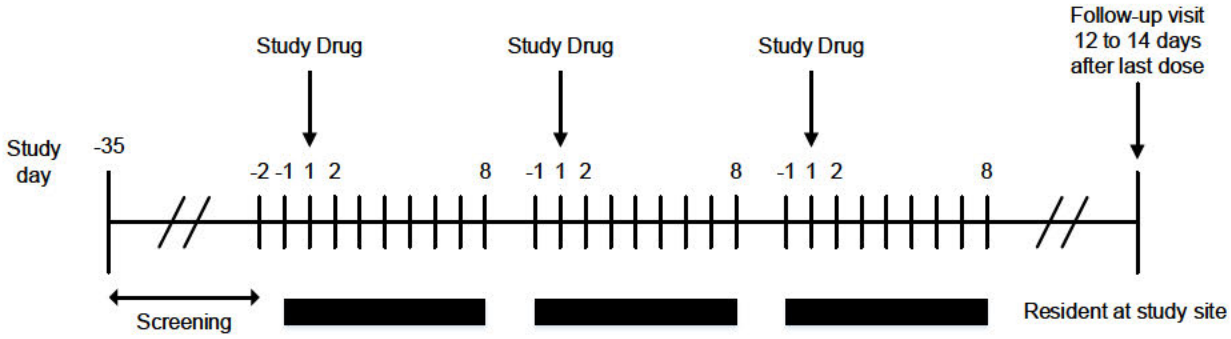
Table 4-1 Three-Period, Six-Sequence Crossover Study Design

Sequence	Number of Subjects	Period 1[a]	Period 2[a]	Period 3[a]
I	3	Treatment A	Treatment B	Treatment C
II	3	Treatment B	Treatment C	Treatment A
III	3	Treatment C	Treatment A	Treatment B
IV	3	Treatment A	Treatment C	Treatment B
V	3	Treatment B	Treatment A	Treatment C
VI	3	Treatment C	Treatment B	Treatment A

[a] A minimum of 10 days between doses, with 7-day pharmacokinetic collection postdose and washout.
Treatment A: 30-mg dose of GDC-9545 (three 10-mg tablets) administered orally with approximately 240 mL room temperature water after at least an 8-hour fast.
Treatment B: 30-mg dose of GDC-9545 (one 30-mg capsule) administered orally with approximately 240 mL room temperature water after at least an 8-hour fast.
Treatment C: 30-mg dose of GDC-9545 (one 30-mg capsule) administered orally with approximately 240 mL room temperature water within 30 minutes of eating a high-fat meal.

The study schematic is displayed in Figure 4-1.

Figure 4-1 Study Schematic



There will be a minimum 10-day washout between doses.

Potential subjects will be screened to assess their eligibility to enter the study within 34 days (Days -35 to -2) prior to dosing on Period 1 Day 1. Replacement subjects will not be enrolled. For all subjects, routine Screening procedures, as outlined in Section 5.1, will be performed.

Eligible subjects will be admitted to the study site on the day prior to GDC-9545 dosing (Check-in [Day -1]) of Period 1 to collect baseline data and familiarize the subjects with study procedures that will be used during the rest of the study. On Period 1 Day 1, subjects will be randomly assigned to one of six possible treatment sequences and the first dose of GDC-9545 in the assigned sequence will be administered in the morning. The washout period between doses will be a minimum of 10 days based on the GDC-9545 geometric mean apparent terminal elimination half-life ($t_{1/2}$) of approximately 40 hours.

Subjects will be confined at the study site from the time of Check-in (Day -1) until Clinic Discharge on Day 8 of each period. Subjects will return to the study site for a Follow-up visit 12 to 14 days after the last dose of GDC-9545. A detailed list of assessments during confinement is included in Table 7-1.

In this study design, physical examinations, 12-lead ECGs, vital signs, How do you feel? (HDYF?) inquiries, clinical laboratory evaluations (Appendix A), and PK sampling will be performed at Screening, at specified times during the study, and/or at Follow-up/Early Termination (ET; 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 (Period 1 Day 1), only SAEs caused by protocol-mandated interventions will be reported. After initiation of study drug administration on Period 1 Day 1, all AEs, whether volunteered, elicited, or noted upon physical examination, will be recorded throughout the study (i.e., from Period 1 Day 1 until Follow-up/ET). The Sponsor should be notified if the Investigator becomes aware of any SAE that occurs after the follow-up period (defined as 12 to 14 days after the last dose of GDC-9545) if the event is believed to be related to prior study drug treatment.

A schedule of activities is presented in Table 7-1.

4.2 RATIONALE FOR STUDY DESIGN

A crossover design will be used to reduce the residual variability as every subject acts as their own control. A single-dose, crossover design is the standard design to compare PK. Subjects will be randomized to one of six treatment sequences to minimize assignment bias.

This study is an open-label investigation because the PK parameters are believed not to be subject to bias. The crossover design further minimizes the effect of inter-subject variability. Blood sampling up to 168 hours postdose will allow the PK parameters of GDC-9545 to be adequately characterized based on prior data. The 10-day washout between GDC-9545 doses is considered sufficient to prevent carryover effects of the treatments based on the GDC-9545 geometric mean $t_{1/2}$ of 26.2 to 41.4 hours.

4.3 RATIONALE FOR SUBJECT POPULATION

This study will enroll only female subjects since there is no information on safety in males. Healthy adult female subjects were chosen for inclusion in this study because they are free of health problems that could otherwise make them more susceptible to drug toxicity or confound the interpretation of the study results, are not routinely using concomitant medications that could

interact with the study drug, and can provide a standard basis for comparison (i.e., control) with less variability.

Female subjects will be of non-childbearing potential as no studies assessing the reproductive and developmental toxicity of GDC-9545 have been conducted to date. It is not known whether GDC-9545 can cross the placenta or cause harm to the fetus when administered to pregnant women or whether it affects reproductive capacity. Microscopic evidence of disruption of the estrus cycle was present in both rats and cynomolgus monkeys administered GDC-9545 and did not reverse during a 4-week recovery period. Additional studies with longer recovery periods are required to adequately assess the reversibility of these findings.

4.4 RATIONALE FOR EXPLORATORY ASSESSMENTS

Not applicable.

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 C_{max} (t_{max}), and $t_{1/2}$.

5 SUBJECT SELECTION

Eighteen healthy female volunteer subjects who meet all the protocol inclusion criteria and none of the exclusion criteria will be enrolled into the study.

5.1 SCREENING PROCEDURES

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

5.2 CHECK-IN PROCEDURES

Refer to Table 7-1 for procedures performed at Check-in (Day -1) for each period, when subjects will report to the study site.

For subjects to continue their participation in the study, the drug screen and the pregnancy test must be negative and the clinical laboratory evaluations must be within the normal laboratory range (unless deemed not clinically significant by the Investigator). 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 of non-childbearing potential including non-pregnant, non-lactating, and either postmenopausal defined as:
   - Age >60 years;
   - Age ≤60 years and amenorrhea ≥12 months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and estradiol levels and follicle-stimulating hormone (FSH) levels in the postmenopausal range;

   or surgically sterile for at least 90 days prior to Screening defined as:
   - Bilateral tubal ligation;
   - Bilateral salpingectomy;
   - Hysterectomy;
   - Bilateral oophorectomy;

   The pregnancy test result must be negative at Screening and Check-in (Day -1) of Period 1;
2. Females between 18 and 65 years of age, inclusive;
3. Females with body mass index (BMI) range 18.5 to 30.0 kg/m^2, inclusive at Screening;
4. Females in good health, determined by no clinically significant findings from medical history, 12-lead ECG, or vital signs;
5. Clinical laboratory evaluations (including chemistry panel [fasted at least 8 hours], complete blood count [CBC], and urinalysis [UA] with complete microscopic analysis at Screening) within the reference range for the test laboratory, unless deemed not clinically significant by the Investigator. Congenital nonhemolytic hyperbilirubinemia (e.g., suspicion of Gilbert's syndrome based on total and direct bilirubin) is acceptable. In case of borderline or questionable results, tests may be repeated to confirm eligibility;
6. Negative test for selected drugs of abuse at Screening (does not include alcohol) and at Check-in (Day -1) for Period 1 (does include alcohol; Appendix A);
7. Negative hepatitis panel (hepatitis B surface antigen and hepatitis C virus antibody) and negative human immunodeficiency virus (HIV) antibody screens (Appendix A);
8. Subject must receive an explanation of the mandatory Research Biosample Repository (RBR) component of the study and be 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. Female subject having a significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal (GI), neurological, or psychiatric disorder (as determined by the Investigator);
2. Female subject having a history of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator;
3. History of allergy to GDC-9545 or any of its excipients;
4. Female subject having a history of stomach or intestinal surgery (including cholecystectomy) or resection that would potentially alter absorption and/or excretion of orally administered drugs except that appendectomy and hernia repair will be allowed;
5. Female subject having a history or presence of an abnormal ECG that, in the Investigator's opinion, is clinically significant including complete left bundle branch block; right bundle branch block; first-, second-, or third-degree heart block; sick sinus syndrome; or evidence of prior myocardial infarction;
6. Having a QTc interval >470 msec, PR interval >210 msec, or QRS complex >120 msec. If the ECG parameters are out-of-range, the ECG will be repeated 2 additional times and a triplicate average will be used to determine eligibility;
7. Confirmed (e.g., 2 consecutive measurements) baseline heart rate ≤50 bpm prior to enrollment;
8. Female subject having a history of alcoholism or drug addiction within 1 year prior to Check-in (Day -1) of Period 1;
9. The 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) of Period 1;
10. History of active or latent tuberculosis (TB), regardless of treatment history;
11. History of previous use of tamoxifen, aromatase inhibitors, or any other endocrine agent for the treatment of breast cancer;
12. The use of hormone replacement therapy or selective ER modulators (SERMs; e.g., raloxifene) within 1 year prior to Check-in (Day -1) of Period 1;
13. The use of oral antibiotics within 4 weeks or intravenous antibiotics within 8 weeks prior to Check-in (Day -1) of Period 1;
14. The use or intent to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to Check-in (Day -1) of Period 1;

15. The participation in any other investigational study drug trial in which receipt of an investigational study drug occurred within 5 half-lives or 30 days, whichever is longer, prior to Check-in (Day -1) of Period 1;
16. The use of drugs of abuse (including opioids) within 4 weeks of Screening;
17. The use of any prescription medications/products within 14 days prior to Check-in (Day -1) of Period 1, unless deemed acceptable by the Investigator;
18. The use of any over-the-counter, non-prescription preparations (including vitamins; minerals; and phytotherapeutic-, herbal-, and plant-derived preparations) within 7 days prior to Check-in (Day -1) of Period 1, unless deemed acceptable by the Investigator;
19. The use of poppy seed-containing foods or beverages within 7 days prior to Check-in (Day -1) of Period 1, unless deemed acceptable by the Investigator;
20. The use of alcohol- or caffeine-containing foods or beverages within 72 hours prior to Check-in (Day -1) of Period 1, unless deemed acceptable by the Investigator;
21. Female subjects will refrain from strenuous exercise from 7 days prior to Check-in (Day -1) of Period 1;
22. The need to follow a special diet and unable to consume the high-fat meal;
23. Poor peripheral venous access;
24. Female subject having a history of malignancy, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer (must be cancer-free for at least 5 years);
25. The donation of blood from 90 days prior to Screening through Follow-up, inclusive, or of plasma from 2 weeks prior to Screening;
26. Receipt of blood products within 2 months prior to Check-in (Day -1) of Period 1;
27. Any acute or chronic condition that, in the opinion of the Investigator, would limit the subject's ability to complete and/or participate in this clinical study;
28. In the opinion of the Investigator or Sponsor, are unsuitable for inclusion 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 Investigator may remove a subject from the study if, in the Investigator's 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 that jeopardize the subject's safety if she continues in the study, 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 7.15). 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 Investigator to have stabilized or returned to baseline.

Replacement subjects will not be enrolled in this study. 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.

The entire study may be discontinued at the discretion of the Investigator, Sponsor, or Sponsor's Medical Monitor based on the occurrence of 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.

6 ASSESSMENT OF SAFETY

6.1 SAFETY PLAN

GDC-9545 is not approved, and clinical development is ongoing. The safety plan for subjects in this study is based on clinical experience with GDC-9545 in ongoing studies. The anticipated important safety risks for GDC-9545 are outlined below. Please refer to the IB for a complete summary of safety information.

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. In addition, guidelines for managing AEs are provided below.

6.1.1 RISKS ASSOCIATED WITH GDC-9545

6.1.1.1 IDENTIFIED RISKS AND ADVERSE DRUG REACTIONS

At this time no risks or adverse drug reactions have been identified for GDC-9545.

6.1.1.2 POTENTIAL RISKS

On the basis of the established class effects of estrogen antagonists in patients with breast cancer, knowledge of similar molecules, as well as the nonclinical data and clinical experience from Phase Ia/Ib Study GO39932, gastrointestinal toxicities (including: nausea, vomiting, and diarrhea), venous thromboembolic events, bradycardia, hepatotoxicity, renal dysfunction, and female infertility are the specific safety concerns for GDC-9545.

Table 6-1 summarizes the key clinical safety data for each of the safety concerns based on the cumulative review of clinical data as of CCOD (04 September 2019). Patients received daily doses of GDC-9545.

Table 6-1 Potential Risks for GDC-9545

Potential Risks	Assessment of Risks	Clinical Data
Gastrointestinal toxicities (nausea, vomiting, and diarrhea)	Gastrointestinal toxicities (e.g., nausea, vomiting, and diarrhea) have been reported in association with some oral SERD molecules currently in early development.	The following treatment-related GI toxicities were reported in patients who received doses of 10-250 mg of GDC-9545 as a single-agent (n=74): nausea (11%), diarrhea (9.5%), constipation (5%), and vomiting (4%). All AEs were Grade 1 or 2, except Grade 3 diarrhea in 1 patient at 100 mg. The following treatment-related GI toxicities were reported in patients who received 30 mg single-agent GDC-9545 (n=10): nausea and, diarrhea (3 patients each [30%]), vomiting (2 patients [20%]), and constipation (1 patient [10%]); all events were Grade 1 or 2..
Venous thromboembolic events	Thromboembolic events occur in patients with malignancies. Against this background of malignancy, they are reported to occur commonly in patients receiving fulvestrant (≥1/100 to <1/10; Falsodex eMC 2016a). The SERM tamoxifen is reported to carry a 2- to 3-fold increased risk of thromboembolic events in the adjuvant setting (Tamoxifen eMC 2016b).	No patients treated with GDC-9545 have experienced thromboembolic events as defined by MedDRA SMQ narrow of "Embolic and thrombotic events, venous."
Bradycardia	During the nonclinical 4-week toxicity study in cynomolgus monkeys, GDC-9545 related reductions in heart rate (surface and telemetry leads) were observed on	Seven (9.5%) patients who received single-agent GDC-9545 (all treated at 90 mg or higher dose level), had reported Grade 1 asymptomatic bradycardia/sinus bradycardia. No

Potential Risks	Assessment of Risks	Clinical Data
	Day 13 at 20, 60, and 200 mg/kg and on Day 23 at 60 mg/kg. These changes were considered related to GDC-9545 but were within the normal range for the cynomolgus monkey and not considered adverse. At completion of the dose-escalation portion of Study GO39932, 3 patients (10%) in the 90-mg cohort had reported Grade 1 asymptomatic bradycardia. Upon further review of clinical safety data (e.g., vital signs/ECGs) at least 1 patient at all dose levels was noted to have asymptomatic bradycardia and/or asymptomatic heart rate decrease. In those patients with a decreased heart rate, there were no clinically significant ECG changes or evidence of exercise intolerance. Until there is a clear understanding of the clinical profile of decreased heart rate with GDC-9545, ECGs will continue to be collected. Caution should be taken with the co-administration of drugs known to cause decreases in heart rate.	clinically significant ECG changes (e.g., conduction abnormality), exercise intolerance, or changes in systolic or diastolic blood pressure have been reported as a result of bradycardia. No cardiac-related events have been reported at 30 mg.
Hepatotoxicity	Liver enzyme elevation has been reported in association with some oral SERD molecules currently in early development. Changes in liver enzymes have been reported with the oral SERM tamoxifen (common, ≥1% to <10%) and the injectable SERD fulvestrant (very common, ≥10%; Falsodex eMC 2016a; Tamoxifen eMC 2016b). Hepatitis, hepatic failure, and hepatic necrosis are reported as rare (≥0.01% and <0.1%) in patients receiving tamoxifen. Hepatic failure and hepatitis are reported as uncommon (≥1/1,000 to <1/100) in patients receiving fulvestrant.	Events of ALT or AST increased (all Grade 1) were reported in 8% and 7%, respectively, of patients who received doses of 10-250 mg of GDC-9545 as a single-agent. In addition, 1 patient in Cohort A4 (GDC-9545 100 mg + LHRH agonist) had experienced Grade 3 transaminase increased that was considered related to GDC-9545 by the Investigator. The event resolved and the patient was able to continue GDC-9545 treatment at a reduced dose of 60 mg/day with no recurrences. In the 30 mg single-agent GDC-9545 cohort, only 1 patient has experienced Grade 1 ALT increased.
Renal dysfunction	Renal failure or acute kidney injury are not listed as unwanted effects of fulvestrant (Falsodex eMC 2016a).	No cases of acute kidney injury as defined by MedDRA High Level Group Terms of "Renal disorders (excluding nephropathies)" or AEs of creatinine increase have been reported.

Potential Risks	Assessment of Risks	Clinical Data
Changes in female reproductive organs and menopausal symptoms	Based on the anti-estrogenic pharmacological activity of GDC-9545, its effects are anticipated to be similar to but potentially more severe than those of normal menopause, such as loss of muscle and bone, hot flashes, vaginal dryness or discharge, irritation, mood swings, and decreased libido. Hot flushes and vaginal discharge have been reported in association with oral SERD molecules currently in early development. Unlike GDC-9545, the SERM tamoxifen promotes the growth of endometrial tissue in vitro, acting as an agonist of ER in that tissue (Tamoxifen eMC 2016b). Endometrial changes including polyps (≥1% and <10%) and endometrial cancer (uncommon, ≥0.1% and <1%) are listed as undesirable effects of tamoxifen. GDC-9545 and fulvestrant (both SERDs) are not agonistic in endometrial cells. The effects of GDC-9545 in human endometrial tissue are unknown, but endometrial agonism is not anticipated.	The following AEs have been reported in the SOC of reproductive system and breast disorders in patients who received single-agent GDC-9545 (n=74): vulvovaginal dryness, vaginal discharge, and vulvovaginal pruritus (1 patient each [1.4%]). All events were Grade 1. In the 30 mg single-agent GDC-9545 cohort, 2 patients have experienced an event mapped to the reproductive disorder SOC including Grade 1 vulvovaginal dryness and Grade 1 vaginal discharge (1 patient each [10%]).

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECG = electrocardiogram; eMC = Electronic Medicines Compendium; ER = estrogen receptor; GI = gastrointestinal; LHRH = luteinizing hormone-releasing hormone; MedDRA = Medical Dictionary for Regulatory Activities; SERD = selective estrogen receptor degrader; SERM = selective estrogen receptor modulator; SMQ = Standardised MedDRA Query; SOC = System Organ Class.

Source: RO7197597 (GDC-9545). Investigator's Brochure. Genentech, Inc. Version 3. June 2019.

6.1.2 MANAGEMENT OF SUBJECTS WHO EXPERIENCE SPECIFIC ADVERSE EVENTS

The majority of risks identified for GDC-9545 are following continuous daily dosing over an extended period and not likely to occur with single dose administration. Guidelines for management of specific AEs are outlined in Table 6-2.

Table 6-2 Guidelines for Management of Subjects Who Experience Specific Adverse Events

Event	Action to be Taken
Gastrointestinal toxicities (nausea, vomiting, diarrhea)	• Infectious or alternate etiology should be excluded. • Treat and manage per standard-of-care, including use of antidiarrheals (e.g., lomotil) and appropriate supportive care including hydration if clinically indicated. • Do not administer antidiarrheals until at least 4 hours postdose. • Hold GDC-9545 until resolution to Grade ≤1.
Elevation of hepatic transaminases	• Rule out alternative etiologies (e.g., concomitant medications or biliary obstruction). • Treat and manage per local standard-of-care. • For Grade ≥3 transaminase increased, withdraw the subject from the study.
Bradycardia	• Monitor patients closely for symptomatic bradycardia. • For Grade ≥2, withdraw the subject from the study.
Venous thromboembolic event	Any grades: • Subjects should be advised to seek immediate medical attention if they become aware of any symptoms of pulmonary embolism or deep vein thrombosis, such as acute onset of chest pain, shortness of breath, or swelling in extremities. • Manage and treat subjects according to institutional guidelines and local standards of care. • Withdraw the subject from the study.
Abnormal vaginal bleeding or uterine hemorrhage	Any grades: • Evaluate with a complete gynecological workup including consultation with a specialist. • Consider transvaginal ultrasound. • Withdraw the subject from the study.
Creatinine increase	• For Grade ≥2, withdraw the subject from the study.

In the unlikely event that any other toxicity is suspected, please contact the Medical Monitor. All AEs must be reported according to the procedures documented in Section 8.

7 STUDY PROCEDURES

7.1 SCHEDULE OF STUDY ACTIVITIES

The schedule of activities is presented in Table 7-1. The PK sampling scheme is presented in Table 7-2. The clinical laboratory and safety assessment windows are presented in Table 7-3.

Table 7-1 Schedule of Activities

	Screening	Periods 1, 2, and 3[a]								Follow-up
		Day								
Study Procedures	Days -35 to -2	Check-in -1	1	2	3	4	5	6	7 Discharge/ET 8	12 to 14 days after last dose
Confined to the Study Site		X	X	X	X	X	X	X	X	X	
Ambulatory (outpatient) Study Site Visit	X										X
Informed Consent	X										
Demographics	X										
Previous Medication and Compliance with Inclusion/Exclusion Criteria	X	X									
Medical History	X	X[b]									
Height, Weight, and BMI[c]	X	X									X
Physical Examination[d]		X									X
Single 12-Lead ECG	X	X	X[e]	X						X	X
Vital Signs[f]	X	X	X[e]	X	X	X	X	X	X	X	X
Chemistry Panel, CBC, and UA[g]	X	X		X						X	X
Drug and Alcohol Screen[h]	X	X									
Hepatitis B, C, and HIV Screen[g]	X										
Tuberculosis testing[i]	X										
Serum Pregnancy Test[j]	X	X									X
FSH[j]	X										
Concomitant Medication			X	X	X	X	X	X	X	X	X
AE Evaluations (HDYF? Inquiry)			X	X	X	X	X	X	X	X	X
Randomization			X[k]								
GDC-9545 Dose			X								
PK Blood Samples[l]			X	X	X	X	X	X	X	X	
Blood Sample for RBR[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; RBR = Research Biosample Repository; TB = tuberculosis; UA = urinalysis.

[a] There will be a minimum 10-day washout between doses.

[b] Interim medical history only. Includes any medical history that occurred between the end of the Screening visit and the Period 1 Check-in.

[c] Body weight recorded at Screening, Check-in (Day -1), and Follow-up, and height and BMI recorded at Screening only.

[d] Routine physical examination at Check-in (Day -1) of Period 1, and abbreviated physical examination at Check-in (Day -1) of Periods 2 and 3 and Follow-up. (Section 7.13).

[e] Predose and 4 hours postdose.

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

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

[h] Includes alcohol testing at Check-in (Day -1) only.

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

[j] Qualitative serum pregnancy test at Screening and urine pregnancy test at all other times. A positive urine pregnancy test will be confirmed with a serum pregnancy test. Follicle-stimulating hormone testing performed on postmenopausal females.

[k] Prior to Period 1 dose.

[l] For PK blood samples collected during the study, refer to Table 7-2.

[m] Sample collected prior to the GDC-9545 dose in Period 1.

Table 7-2 Pharmacokinetic Sampling Scheme

Study Day	PK Sampling Timepoints	Window (±)	Analyte (Matrix)
Day 1	Predose (0 Hour) any time prior to study drug administration	NA	GDC-9545 (Plasma)
	30 minutes	5 minutes	GDC-9545 (Plasma)
	1 hour	10 minutes	GDC-9545 (Plasma)
	1.5 hours	10 minutes	GDC-9545 (Plasma)
	2 hours	10 minutes	GDC-9545 (Plasma)
	2.5 hours	10 minutes	GDC-9545 (Plasma)
	3 hours	10 minutes	GDC-9545 (Plasma)
	4 hours	10 minutes	GDC-9545 (Plasma)
	5 hours	10 minutes	GDC-9545 (Plasma)
	6 hours	10 minutes	GDC-9545 (Plasma)
	8 hours	10 minutes	GDC-9545 (Plasma)
	12 hours	20 minutes	GDC-9545 (Plasma)
Day 2	24 hours	20 minutes	GDC-9545 (Plasma)
Day 3	48 hours	20 minutes	GDC-9545 (Plasma)
Day 4	72 hours	20 minutes	GDC-9545 (Plasma)
Day 5	96 hours	20 minutes	GDC-9545 (Plasma)
Day 6	120 hours	20 minutes	GDC-9545 (Plasma)
Day 7	144 hours	20 minutes	GDC-9545 (Plasma)
Day 8	168 hours	20 minutes	GDC-9545 (Plasma)

NA = not applicable; PK = pharmacokinetic.

Table 7-3 Clinical Laboratory and Safety Assessment Windows

Safety Assessment Timepoints[a]	Window (±)
Predose	45 minutes
0 to 24 hours postdose	15 minutes
Days 2 to 7	6 hours
Days 8 to 29	6 hours

[a] Safety assessments may include vital signs, electrocardiograms, physical examinations, and clinical laboratory assessments. Not all safety assessments will be performed at each timepoint specified.

7.2 STUDY TREATMENT

The Investigational Medicinal Product for this study is GDC-9545.

7.2.1 DRUG SUPPLIES AND ACCOUNTABILITY

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

Table 7-4 Study Drugs

Study Drug	GDC-9545	GDC-9545
Formulation[a]	Tablet (Phase 1 Reference Product)	Capsule (Phase 3 Test Product)
Strength	10 mg	30 mg
Supplier	Genentech	Roche
Manufacturer	Patheon	Roche

[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(s) will be provided to the study site by the supplier/manufacturer as soon as available.

GDC-9545 tablet will be stored between 2°C and 8°C and GDC-9545 capsule will be stored at the recommended condition of "do not store above 25°C" under secure conditions. The study drugs 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 Investigator 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 United States (US) Title 21 Code of Federal Regulations (CFR) 320.38 and 320.63.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

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 consecutively numbered subjects. 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. The approximate amount of the high-fat meal consumed by the subject will also be recorded.

Each dose will be administered orally with approximately 240 mL of room temperature water. A hand and mouth check will be performed to verify that the dose administered was swallowed. Fasted 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. For fed dosing, subjects will be required to fast for at least 8 hours until 30 minutes prior to their scheduled GDC-9545 dose on Day 1, when they will be given a high-fat meal that must be entirely consumed within 30 minutes. Details regarding the high-fat meal are as follows:

Standardized High-Fat Breakfast
2 eggs fried in butter
2 strips of bacon
2 slices of toast with butter
4 oz of hash brown potatoes (fried with butter)
8 oz (240 mL) of whole milk

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.

7.3 REMOVAL OF STUDY BLIND

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

7.4 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) of Period 1 and during the entire study.

Subjects will refrain from strenuous exercise from 7 days prior to Check-in (Day -1) of Period 1 and during the entire study and will otherwise maintain their normal level of physical activity (i.e., will not begin a new exercise program or participate in any unusually strenuous physical exertion).

Subjects will remain seated upright and/or ambulatory 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 preparations, 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 the first dose in Period 1 through Follow-up.

7.5.1 PERMITTED MEDICATIONS

Acetaminophen (paracetamol) may be administered as needed up to 1 g every 4 to 6 hours (maximum 3 g/day). Prune juice may be given for constipation.

The administration of any other concomitant medications during the study is prohibited without prior approval of the Investigator, 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.

7.5.2 PROHIBITED MEDICATIONS

Subjects will refrain from use of hormone replacement therapy and SERMs (e.g., raloxifene) from 1 year prior to Check-in (Day -1) of Period 1 until Follow-up. Subjects must not have any history of previous use of tamoxifen, aromatase inhibitors, or any other endocrine agent for the treatment of breast cancer.

Subjects may not take oral antibiotics within 4 weeks or intravenous antibiotics within 8 weeks prior to Check-in (Day -1) of Period 1 until Follow-up.

Subjects will not have received any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to Check-in (Day -1) of Period 1 until Follow-up. Subjects will not have received any investigational study drug within 5 half-lives or 30 days, whichever is longer, prior to Check-in (Day -1) of Period 1 until Follow-up.

Subjects will refrain from the use of any other prescription medications during the interval from 14 days prior to Check-in (Day -1) of Period 1 until Follow-up, unless deemed acceptable by the Investigator. In addition, subjects will refrain from the use of any over-the-counter non-prescription preparations (including vitamins; minerals; and phytotherapeutic-, herbal-, and plant-derived preparations) from 7 days prior to Check-in (Day -1) of Period 1 until Follow-up, unless deemed acceptable by the Investigator.

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.

7.5.3 PROHIBITED FOOD

Subjects will abstain from consuming poppy seed-containing foods and beverages for 7 days prior to Check-in (Day -1) of Period 1 and during the entire study, unless deemed acceptable by the Investigator. Subjects will abstain from consuming alcohol- or caffeine-containing foods and beverages for 72 hours prior to Check-in (Day -1) of Period 1 and during the entire study, unless deemed acceptable by the Investigator.

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.

See Section 7.2.2 for diet and fluid restrictions in regards to dose administration.

7.6 PHARMACOKINETIC BLOOD SAMPLE COLLECTION AND PROCESSING

Blood samples for PK analysis of GDC-9545 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 7-2.

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

After the plasma samples collected in the study are analyzed for GDC-9545 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 pharmacodynamic assays. Residual 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. Sample retention may be detailed in the laboratory manual.

7.7 ANALYTICAL METHODOLOGY

Plasma concentrations of GDC-9545 will be determined by Covance Laboratories Inc. using a validated/qualified analytical procedure.

7.8 CLINICAL LABORATORY EVALUATIONS

Clinical laboratory evaluations (including chemistry panel [fasted at least 8 hours], CBC, and UA) will be collected at the timepoints listed in Table 7-1. Clinical laboratory evaluations are listed in Appendix A.

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 test) at Check-in (Day -1) of each period. A qualitative serum pregnancy test will be performed at Screening, and a urine pregnancy test will be performed at Check-in (Day -1) of each period and Follow-up. A positive urine pregnancy test will be confirmed with a serum pregnancy test. If a qualitative serum pregnancy test is positive, then a quantitative serum pregnancy test may be performed for confirmation. An FSH test (postmenopausal females) will be performed at Screening.

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 purified protein derivative (PPD) skin test
    - A positive purified 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 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 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 analyzed to achieve one or more of 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 OR ETHICS COMMITTEE

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)/Ethics Committee (EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, Section 7.9 through Section 7.9.7 of this protocol will not be applicable at that site.

7.9.3 MANDATORY SAMPLES FOR COLLECTION

A mandatory whole blood sample will be collected for DNA extraction for RBR and may be sent to one or more laboratories for analysis.

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 Investigators 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 Investigator 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; Section 7.9.6). A separate, specific signature will be required to document a subject's agreement to provide an RBR specimen.

The Investigator (or authorized 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. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the subject. If a subject wishes to withdraw consent to the testing of their specimens, the Investigator must inform the Medical Monitor in writing of the subject's wishes and the Investigator (or authorized designee) must complete the 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/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

7.10 12-LEAD ELECTROCARDIOGRAMS

A single 12-lead ECG will be obtained at the timepoints specified in Table 7-1.

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, the blood draws will be obtained at the scheduled timepoint, and the 12-lead ECGs will be obtained as close to the scheduled blood draw as possible, but prior to the blood draw.

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.

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 vital signs 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?” at the timepoints specified in

Table 7-1. 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 or abbreviated physical examination will be performed at the timepoints specified in Table 7-1.

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. An abbreviated physical examination will consist of an assessment of general appearance, skin, thorax/lungs, cardiovascular system, and abdomen.

7.14 CLINIC DISCHARGE PROCEDURES

Refer to Table 7-1 for procedures performed on the day of discharge.

7.15 FOLLOW-UP/EARLY TERMINATION PROCEDURES

Refer to Table 7-1 for procedures performed at Follow-up or 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 Investigators, 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
- Adverse events 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 Investigator, 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 Investigator's 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 [NCI CTCAE]); 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 AE recorded on the eCRF.

Serious AEs are required to be reported by the Investigator to the Sponsor via Covance Patient Safety Solutions (PSS) 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 Investigator to the Sponsor via Covance PSS immediately (i.e., no more than 24 hours after learning of the event; see Section 8.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (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
- Grade ≥3 nausea/vomiting/diarrhea
- Grade ≥2 thromboembolic events (pulmonary embolism, deep vein thrombosis, and embolism)
- Grade ≥3 renal failure (including acute kidney injury or other similar medical concepts)
- Grade ≥3 hepatitis or elevation in ALT or AST
- Grade ≥2 vaginal or uterine hemorrhage

- Grade ≥2 bradycardia
- Any grade of endometrial cancer.

8.2 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The Investigator is responsible for ensuring that all AEs (as defined in Section 8.1) are recorded on the AE eCRF in accordance with protocol instructions (see Section 8.4.2).

For each AE recorded on the AE eCRF, the Investigator will make an assessment of seriousness (see Section 8.1.2 for seriousness criteria), severity (see Section 8.2.3), and causality (see Section 8.2.4).

8.2.1 ADVERSE EVENT REPORTING PERIOD

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 administration, 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 recorded throughout the study until Follow-up (defined as 12 to 14 days after the last dose of GDC-9545). The Sponsor should be notified if the Investigator becomes aware of any SAE that occurs after the follow-up period (defined as 12 to 14 days after the last dose of GDC-9545) if the event is believed to be related to prior study drug treatment.

Instructions for reporting AEs that occur after the AE reporting period are provided in Section 8.6.

The Investigator 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 until Follow-up, 12 to 14 days after the final dose of study drug). However, the Sponsor should be notified if the Investigator 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 Investigator 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 AE severity grading scale for the NCI CTCAE (version 5.0) will be used for assessing AE severity. Table 8-1 will be used for assessing AE severity for AEs that are not specifically listed in the NCI CTCAE.

Table 8-1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living[a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living[b,c]
4	Life-threatening consequences or urgent intervention indicated[d]
5	Death related to adverse event[d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by subjects who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as an SAE (see Section 8.4.2 for reporting instructions), per the definition of SAE in Section 8.1.2.

[d] Grade 4 and 5 events must be reported as SAEs (see Section 8.4.2 for reporting instructions), per the definition of SAE in Section 8.1.2.

8.2.4 ASSESSMENT OF CAUSALITY OF ADVERSE EVENTS

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. **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	**Adverse events 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 Investigator's 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 serious adverse events against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators and applicable regulatory authorities. **Attribution of serious adverse events 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 adverse events in other subjects)**.

8.3 PROCEDURES FOR RECORDING ADVERSE EVENTS

8.3.1 RECORDING ADVERSE EVENTS ON THE CASE REPORT FORM

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 Investigator 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 to Covance PSS 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 Covance PSS 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 Investigator's judgment.

It is the Investigator's responsibility 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 5 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 Investigator's judgment.

It is the Investigator's responsibility 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, Investigators must report the occurrence of either of the following as an AE:

- 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 Covance PSS 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 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 Covance PSS immediately (i.e., no more than 24 hours after learning of the event; see Section 8.4.2). For GDC-9545, 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-9545, 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.

8.3.1.8 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 Covance PSS (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 8.6.

8.3.1.9 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").

8.3.1.10 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 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 Investigator must report such events to the Sponsor immediately via Covance PSS; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event. The following is a list of events that the Investigator 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).

For SAEs and AESIs, the Investigator must report new significant follow-up information for these events to the Sponsor immediately via Covance PSS (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.

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 Investigator 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: [redacted], M.D., Ph.D.
Genentech, Inc.
[redacted] (Office Telephone No.)
[redacted] (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 Investigator should be completed and submitted to the Sponsor via Covance PSS 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.

Covance PSS to receive the Investigator-generated SAE reports:
Email: saeintake@covance.com
Fax: 1-888-887-8097

8.4.2.2 EVENTS THAT OCCUR AFTER STUDY DRUG INITIATION

After initiation of study drug, SAEs and AESIs will be reported after Follow-up (12 to 14 days after the final dose of study drug). 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 Covance PSS) 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 Covance PSS 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.

8.4.2.3 REPORTING REQUIREMENTS FOR PREGNANCIES

8.4.2.3.1 PREGNANCIES IN FEMALE SUBJECTS

Female subjects will be instructed to immediately inform the Investigator if they become pregnant during the study or within 90 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed by the Investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and emailed to Covance PSS (see Section 8.4.2 for reporting instructions). Pregnancy should not be recorded on the AE eCRF. The Investigator 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 Investigator 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 Covance PSS (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). All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

8.5 FOLLOW-UP OF SUBJECTS AFTER ADVERSE EVENTS

8.5.1 INVESTIGATOR FOLLOW-UP

The Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, 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.

8.5.2 SPONSOR FOLLOW-UP

For SAEs, AESIs, 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.

8.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

At the Follow-up/ET visit, the Investigator should instruct each subject to report to the Investigator 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 Investigator becomes aware of any SAE that occurs after the end of the AE reporting period (defined as until Follow-up, 12 to 14 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 Investigator 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 Investigators.

Genentech United Kingdom Drug Safety
Email Address: welwyn.uk_dsc@roche.com
Fax No.: 44 1707 367 582

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

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

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

- GDC-9545 IB

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

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

The IRB will be notified by the investigative site in writing (e.g., email) within the timeframe required per local IRB regulations 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 at least one dose of study drug.

The PK Population will consist of all subjects who received at least one dose of study drug and have at least one evaluable postdose PK sample.

Baseline is defined as the last result prior to the first dose of study drug on Period 1 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, clinical laboratory assessments, vital signs, and ECGs. Clinical laboratory assessments, vital signs (including oral temperature, respiratory rate, and supine blood pressure and pulse), and ECGs will be listed by subject number and scheduled time, and changes from baseline will be summarized.

Verbatim descriptions of AEs will be coded according to current Medical Dictionary for Regulatory Activities version 22.0 (or higher) guidelines. Adverse events will be summarized. 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-9545 using the model independent approach (Gibaldi and Perrier 1982):

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 from Hour 0 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 $t_{1/2} = (\ln 2)/\lambda_z$
CL/F	apparent total clearance
V_Z/F	apparent volume of distribution during the terminal elimination phase

Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as Phoenix WinNonlin (Certara Inc., version 8.1 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 INTERIM ANALYSIS

No interim analyses are planned

9.4 STATISTICAL ANALYSIS OF PHARMACOKINETIC DATA

Descriptive statistics (mean, median, minimum, maximum, standard deviation, coefficient of variation [CV%], geometric mean, and geometric CV%) will be calculated for all PK parameters for GDC-9545.

The PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for GDC-9545 will be analyzed to evaluate the relative bioavailability of GDC-9545 as a Phase 3 capsule formulation compared to a Phase 1 tablet formulation under fasted conditions and to assess the food effect on GDC-9545 PK for a Phase 3 capsule formulation. The mixed-effect analysis of variance model for three-period crossover design will be used for formulation comparison and fasted state and fed state comparison of capsule. The model will include sequence, formulation, and period as fixed effects and a random effect for subject within sequence. Appropriate covariance structure will be used.

Log transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ values will be evaluated to estimate ratios of geometric mean values and the corresponding 90% confidence intervals (CIs). (Relative bioavailability-Test: capsule, Reference: tablet; food effect-Test: fed, Reference: fasted.)

The parameter t_{max} will be analyzed nonparametrically using the Wilcoxon signed-rank test. The median difference between the test and reference investigational products and the corresponding 90% CI will be calculated.

Caution should be used when interpreting results since this study was not based on power calculations.

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 (CSR) and/or SAP as appropriate.

9.5 STATISTICAL ANALYSES OF SAFETY DATA

All safety data will be listed and summarized using standard descriptive statistics for the Safety Population. No formal statistical analyses are planned.

9.6 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. Eighteen subjects will be enrolled so that a minimum of 12 subjects will complete the study without the need for replacement subjects.

9.7 QUALITY CONTROL AND QUALITY ASSURANCE

Quality control and quality assurance will be performed in Data Management according to Covance standard operating procedures (SOPs) or per client request and as applicable according to the contract between Covance and the Sponsor, including but not limited to Covance's validated EDC system, specifications, and quality checks.

10 ADMINISTRATIVE ASPECTS

10.1 CHANGE IN PROTOCOL

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

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

10.2 INVESTIGATOR MEETING; SITE INITIATION

Prior to the start of the clinical study, the representative(s) of the Sponsor will meet with the Investigator(s) and appropriate clinical staff to familiarize the Investigator 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 Investigator 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 Investigator(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 Investigator and Investigator's 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 21 CFR 56, the protocol, advertisement, and ICF will be reviewed and approved by the IRB. The Sponsor will supply relevant material for the Investigator 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 Investigator.

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

The Investigator 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 Investigator's 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 Investigator 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 Investigator. 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, 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.

10.7.1 ELECTRONIC CASE REPORT FORMS

Electronic Case Report Forms 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 Case Report Forms 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 Investigator 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 Investigator 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 Investigator and institution(s) must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC 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 SOP 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 SOP 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 Investigators 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 US FDA and other regulatory agencies, national and local health authorities, Genentech monitors/representatives and collaborators, and the IRB/EC 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 CSRs and other summary reports will be provided upon request.

10.7.6 RETENTION OF RECORDS

United States 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 Investigator 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 US under a US Investigational New Drug (IND), the Investigator must comply with the record retention requirements set forth in the US 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 US CFR governing Protection of Human Subjects (21 CFR 50), Financial Disclosure by Clinical Investigators (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 US 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.

[redacted]

03 Dec 2019

[redacted], D.O.

Date

Principal Investigator
Covance Clinical Research Unit

SPONSOR AGREEMENT

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

[redacted] 27 Nov. 2019

[redacted], B.S. [redacted] Date

[redacted]

Genentech, Inc.

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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/creatine phosphokinase
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)
Cotinine[b]
Methadone
Opiates
Phencyclidine

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[d]
Follicle-stimulating hormone (postmenopausal females)[b]
QuantiFERON® TB Gold tuberculosis test[b]

[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 testing will be performed at Check-in (Day -1) of each period.

[d] Serum qualitative pregnancy test at Screening and urine pregnancy test at all other times. A positive urine pregnancy test will be confirmed with a serum pregnancy test. If a qualitative serum pregnancy test is positive, then a quantitative serum pregnancy test may be performed for confirmation.

APPENDIX B – APPROXIMATE MAXIMUM BLOOD VOLUME COLLECTED

Note: Additional samples may be drawn for safety purposes.

	Sample Volume (mL)	Number of Samples	Total Volume (mL)
Serology	7.0	1	7.0
Tuberculosis (Quantiferon® TB Gold)	3.0	1	3.0
Chemistry panel (includes serum pregnancy, estradiol, and follicle-stimulating hormone)	8.5	11	93.5
Complete blood count	4.0	11	44.0
PK samples	4.0	57	228.0
RBR sample	6.0	1	6.0
		Total	**381.5**

PK = pharmacokinetic; TB = tuberculosis; RBR = Research Biosample Repository.