# PROTOCOL

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| **TITLE:** | **A PHASE I, SINGLE CENTER, OPEN-LABEL, PARTIALLY RANDOMIZED, TWO PART STUDY TO INVESTIGATE THE ABSORPTION, METABOLISM, AND EXCRETION OF [$^{14}$C]-GDC-9545 FOLLOWING A SINGLE ORAL DOSE (PART 1) AND TO EVALUATE THE ABSOLUTE BIOAVAILABILITY OF ORAL CAPSULE FORMULATIONS OF GDC-9545 F12 AND F18 AND THE RELATIVE BIOAVAILABILITY OF F18 COMPARED TO F12 (PART 2) IN HEALTHY FEMALE SUBJECTS OF NON-CHILDBEARING POTENTIAL** |
| **PROTOCOL NUMBER:** | GP42662 (QSC204283) |
| **VERSION NUMBER:** | 4 |
| **EUDRACT NUMBER:** | 2020-004650-29 |
| **IND NUMBER:** | Not applicable |
| **NCT NUMBER:** | NCT04680273 |
| **TEST PRODUCT:** | GDC-9545 (RO7197597) |
| **CLINICAL PHARMACOLOGY:** | [redacted] MS, PharmD |
| **SPONSOR:** | Genentech, Inc. |
| **DATE FINAL:** | 18 Feb 2021 |

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| **SPONSOR:** | Genentech, Inc. |

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

Nand Singh BSc, MD, DPM, MFPM

Principal Investigator's Name

[redacted]

Principal Investigator's [redacted]nature

[redacted]

Date

Please retain the signed original of this form for your study files.

## PROTOCOL ACCEPTANCE FORM

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

[redacted] MS, Pharm D, [redacted]

[redacted]

2/19/2021

Sponsor Representative's Signature | Date

Please retain the signed original of this form for your study files.

## PROTOCOL SYNOPSIS

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|---|---|
| **TITLE:** | **A Phase I, Single Center, Open-Label, Partially Randomized, Two Part Study to Investigate the Absorption, Metabolism, and Excretion of [$^{14}$C]-GDC-9545 following a Single Oral Dose (Part 1) and to Evaluate the Absolute Bioavailability of Oral Capsule Formulations of GDC-9545 F12 and F18 and the Relative Bioavailability of F18 Compared to F12 (Part 2) in Healthy Female Subjects of Non-childbearing Potential** |
| **PROTOCOL NUMBER:** | GP42662 (QSC204283) |
| **VERSION NUMBER:** | 4 |
| **EUDRACT NUMBER:** | 2020-004650-29 |
| **IND NUMBER:** | Not applicable |
| **NCT NUMBER:** | NCT04680273 |
| **TEST PRODUCT:** | GDC-9545 (RO7197597) |
| **PHASE:** | I |
| **INDICATION:** | Not applicable |
| **SPONSOR:** | Genentech, Inc. |

**Objectives and Endpoints**

Part 1 of this study will evaluate the absorption, metabolism, excretion, pharmacokinetics and safety of GDC-9545 in healthy volunteers. Part 2 of this study will evaluate the absolute and relative bioavailability, and safety of GDC-9545 in healthy volunteers. Specific objectives and corresponding endpoints for the study are outlined below.

| | Objectives | Endpoints |
|---|---|---|
| Primary | Part 1: To determine the mass balance and routes of elimination of [$^{14}$C]-GDC-9545 following a single oral dose of [$^{14}$C]-GDC-9545 capsule, 30 mg containing not more than (NMT) 4.6 megabecquerel (MBq; 124 microcurie [µCi]) | Mass balance recovery of total radioactivity (TR) in all excreta (urine and feces): $CumA_e$ and $CumF_e$<br>Determination of routes and rates of elimination of [$^{14}$C]-GDC-9545 by $A_e$, $CumA_e$, $F_e$ and $CumF_e$ by interval for all excreta (urine and feces) |
| | Part 1: To assess the pharmacokinetics (PK) of GDC-9545 and total drug-derived material in plasma following a single oral dose of [$^{14}$C]-GDC-9545 capsule, 30 mg (NMT 4.6 MBq [124 µCi]) | Calculation of PK parameters as appropriate for GDC-9545 (plasma only) and TR (plasma and whole blood)<br>Assessment of the concentrations of TR in whole blood and plasma<br>Evaluation of whole blood:plasma concentration ratios for TR |

| | | |
|---|---|---|
| | Part 2: To determine the absolute bioavailability of an oral GDC-9545/F12 capsule, 30 mg and an oral GDC-9545/F18 capsule, 30 mg | Absolute bioavailability assessment based on the PK parameter $AUC_{0\text{-}inf}$ for GDC-9545 |
| | Part 2: To determine the relative bioavailability of GDC-9545/F18 capsule, 30 mg compared to the GDC-9545/F12 capsule, 30 mg | Relative bioavailability assessment based on the PK parameters $C_{max}$ and $AUC_{0\text{-}inf}$ for GDC-9545 |
| Secondary | Part 1: To characterize and identify metabolites of [$^{14}$C]-GDC-9545 in plasma, urine, and feces | Characterization of abundant metabolites by liquid chromatography-high resolution mass spectrometry |
| | Part 2: To characterize the PK of GDC-9545 following oral and intravenous (IV) administration | Calculation of PK parameters as appropriate for GDC-9545 in plasma only |
| | Part 1 and Part 2: To evaluate the safety and tolerability of single doses of GDC-9545 | Incidence and severity of adverse events<br>Incidence of abnormalities in laboratory safety tests, 12-lead ECGs and vital sign measurements |

Metabolite profiling and identification will be reported separately from the Clinical Study Report as a standalone document.

## Study Design

### Description of Study

This is an open-label, single-center, two part study in heathy female subjects of non-childbearing potential to investigate the absorption, metabolism, and excretion of [$^{14}$C]-GDC-9545 (Part 1), the absolute bioavailability of formulations Roformis Number RO7197597/F12-01 (F12) and Roformis Number RO7197597/F18-01 (F18) (i.e., GDC-9545/F12 capsule, 30 mg and GDC-9545/F18 capsule, 30 mg), and relative bioavailability of GDC-9545 oral capsule F18 to the F12 formulation (Part 2).

***Part 1***

Part 1 is an open-label, single-treatment design. It is planned to enroll 6 subjects to ensure data in a minimum of 4 evaluable subjects. An evaluable subject for Part 1 of the study is defined as a subject who has provided mass balance and PK samples for up to 480 hours (up to Day 21) or until they have met the mass balance discharge criteria (i.e., cumulative recovery of radioactivity exceeds 90% of the administered dose; OR radioactivity in urine and feces is less than 1% of the administered dose over a 24 hour period on 2 consecutive PK sample collection days, as determined by quick counts).

Each subject will receive a single oral dose of [$^{14}$C]-GDC-9545 capsule, 30 mg (NMT 4.6 MBq [124 µCi]) with approximately 240 mL water in the fasted state (Treatment A).

Subjects will undergo preliminary screening procedures for the study up to 28 days (Day -28 to Day -2) before [$^{14}$C]-GDC-9545 administration on Day 1. Subjects will be admitted in the morning on the day prior to [$^{14}$C]-GDC-9545 administration (Day -1) and will be dosed in the morning of Day 1 following an overnight fast of a minimum of 10 hours.

Urine and feces samples for measurement of TR will be collected pre-dose and at intervals until study completion including after discharge, if needed.

Blood samples for measurement of plasma GDC-9545 and TR in plasma and whole blood will be collected pre-dose and at intervals until study completion including after discharge, if needed.

Safety and tolerability will be monitored by clinical and laboratory assessments at intervals throughout the study.

It is planned that subjects will remain resident in the clinical unit until 480 hours post-dose (Day 21) when they will be discharged from the clinical unit.

***Part 2***

Part 2 is a randomized, open-label, three-treatment, two-sequence crossover design conducted over three periods. It is planned to enroll 10 subjects to ensure data in a minimum of 8 evaluable subjects. An evaluable subject for Part 2 of the study is defined as a subject who has received an investigational medicinal product (IMP) and has sufficient drug concentration measurements up to 168 hours after dosing for evaluation of defined PK parameters for each treatment, and have completed all planned safety assessments up to 168 hours after dosing for each treatment.

Subjects will be randomly allocated to one of two treatment sequences (BCD and BDC). In each treatment period, subjects will receive a single 30 mg dose of GDC-9545 in the fasted state. GDC-9545 will be administered as one of three possible formulations according to the randomization schedule:

- Treatment B: 30 mg GDC-9545 as a Solution for Infusion, 3 mg/mL administered intravenously in 10 mL as an infusion over 30 minutes
- Treatment C: GDC-9545/F12 capsule, 30 mg, administered with approximately 240 mL water
- Treatment D: GDC-9545/F18 capsule, 30 mg, administered with approximately 240 mL water

Subjects will undergo preliminary screening procedures for the study up to 28 days (Day -28 to Day -2) before GDC-9545 administration on Day 1 of Period 1. Subjects will be admitted in the morning on the day prior to the first GDC-9545 administration (Day -1 of Period 1). Subjects will be resident in the clinical unit from the morning of Day -1 in Period 1 until Day 8 in Period 3 (i.e., for 28 to 29 consecutive nights that will cover all 3 treatment periods).

For each treatment period, subjects will be dosed in the morning of Day 1 following an overnight fast of a minimum of 10 hours.

For Treatment B, to assess tolerability of the IV administration, the first subject will be dosed as a sentinel; then, at least 4 hours later, the second subject will be dosed only if there are no acute safety findings for the first subject. If the first two subjects tolerated the IV dose, in the opinion of the Principal Investigator and Medical Monitor, the remaining subjects will be dosed. The third subject will be dosed at least 20 hours after the second subject (i.e., at least 24 hours after the first subject). All subsequent dosing of the IV formulation will be staggered by at least 15 minutes.

Blood samples for measurement of plasma GDC-9545 will be collected pre-dose and at intervals until Day 8 of each period.

Safety and tolerability will be monitored by clinical and laboratory assessments at intervals throughout the study.

There will be a minimum washout of 10 days between each IMP administration and a follow-up call will take place 13 to 15 days post-final dose.

**Number of Subjects**

For Part 1, it is planned to enroll 6 subjects to ensure data in a minimum of 4 evaluable subjects. For Part 2, it is planned to enroll 10 subjects to ensure data in a minimum of 8 evaluable subjects. No replacement subjects are to be used in Part 1 of this study. Up to 4 replacement subjects are permitted in Part 2 of this study to ensure there are 8 evaluable subjects.

**Target Population**

Inclusion Criteria

Subjects must meet the following criteria for study entry:

- Able and willing to comply with the study restrictions and to give written informed consent before any study procedure.

- Healthy female subjects of non-childbearing potential that are non-pregnant, non-lactating females, who are either postmenopausal or surgically sterile, aged 30 to 65 years, inclusive, at time of signing Informed Consent Form (ICF)
    - Postmenopausal females are defined as:
        - Age >60 years;
        - Age ≤60 years and amenorrhea ≥12 months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression. Estradiol levels and/or follicle-stimulating hormone (FSH) levels in the postmenopausal range;
    - Surgically sterile females for at least 90 days prior to screening are defined as:
        - Bilateral salpingectomy;
        - Hysterectomy;
        - Bilateral oophorectomy;
    - For all subjects, the pregnancy test result must be negative at screening and admission (Day -1 for Part 1 and Day -1 of Period 1 for Part 2)
- A body mass index (BMI) between 18.5 and 32.0 kg/$m^2$, inclusive, at screening
- Ability to comply with the study protocol
- Must have regular bowel movements (i.e., average stool production of ≥1 and ≤3 stools per day) (Part 1 only)
    - Female subjects of non-childbearing potential do not need to use any methods of contraception.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from study entry:

- Women of childbearing potential, women who are pregnant or breastfeeding.
    - All women must have a negative highly sensitive serum pregnancy test result at screening and a negative highly sensitive urine pregnancy test at admission.
- Subjects who have received any IMP in a clinical research study within the 90 days prior to Day 1 (Part 1) or Day 1 of Period 1 (Part 2)
- History of serious adverse reaction or serious hypersensitivity to any drug or allergy to the study drug formulation excipients
- Subjects who are, or are immediate family members of, a study site or Sponsor employee
- Subjects who have previously been administered IMP in this study. Subjects who have taken part in Part 1 are not permitted to take part in Part 2.
- Evidence of current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; i.e., the virus that causes Coronavirus Disease 2019 [COVID-19]) infection
- Positive for hepatitis C virus (HCV) antibody, hepatitis B surface antigen (HBsAg), or human immunodeficiency virus (HIV) antibody at screening
- History of any drug or alcohol abuse in the past 2 years
- Regular alcohol consumption >14 units per week (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 Units = 125 mL glass of wine, depending on type)
- A confirmed positive alcohol breath test at screening or admission
- Current smokers and those who have smoked within the last 12 months. A confirmed breath carbon monoxide reading of greater than 10 ppm at screening or admission.
- Current users of e-cigarettes and nicotine replacement products and those who have used these products within the last 12 months
- Confirmed positive drugs of abuse test result at screening or admission
- Radiation exposure, including that from the present study, excluding background radiation but including diagnostic x-rays and other medical exposures, exceeding 5 mSv in the last 12 months or 10 mSv in the last 5 years. No occupationally exposed worker, as defined in the Ionising Radiation Regulations 2017, shall participate in the study (Part 1 only)

- Subjects who do not have suitable veins for multiple venipunctures/cannulation as assessed by the Investigator or delegate at screening
- Clinically significant abnormal clinical chemistry, hematology, coagulation or urinalysis as judged by the Investigator. Subjects with Gilbert's Syndrome are allowed
- Evidence of renal impairment at screening, as indicated by an estimated creatinine clearance (CLcr) of <70 mL/min using the Cockcroft-Gault equation
- History of clinically significant cardiovascular, renal, hepatic, dermatological, chronic respiratory or gastrointestinal (GI) disease (especially peptic ulceration, GI bleeding, ulcerative colitis, Crohn's Disease or Irritable Bowel Syndrome), neurological or psychiatric disorder, as judged by the Investigator
- Presence or history of clinically significant allergy requiring treatment, as judged by the Investigator. Hay fever is allowed unless it is active
- Donation of blood or plasma within the previous 3 months or loss of greater than 400 mL of blood
- Subjects who are taking, or have taken, any medication (e.g., prescription drugs, over-the-counter drugs, hormone replacement therapy [HRT], vaccines, topical medications, herbal or homeopathic remedies, nutritional supplements), other than up to 4 g of paracetamol per day, in the 14 days before IMP administration. Exceptions may apply on a case by case basis, if considered not to interfere with the objectives of the study, as determined by the Investigator.
- Subjects who are taking, or have taken, oral antibiotics within 4 weeks or IV antibiotics within 8 weeks prior to admission.
- Subjects who are taking, or have taken, any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to admission.
- History of GI surgery (with the exception of appendectomy unless it was performed within the previous 12 months) (Part 1 only)
- Acute diarrhea or constipation in the 7 days before the predicted Day 1. If screening occurs >7 days before the Day 1, this criterion will be determined on Day 1. Diarrhea will be defined as the passage of liquid feces and/or a stool frequency of greater than 3 times per day. Constipation will be defined as a failure to open the bowels for 3 days (Part 1 only)
- Malabsorption syndrome or other condition that would interfere with enteral absorption
- History or presence of an abnormal ECG that is clinically significant in the Investigator's opinion, including complete left bundle branch block, second- or third-degree atrioventricular heart block, or evidence of prior myocardial infarction
- QT interval corrected through use of Fridericia's formula (QTcF) $>$ 440 msec demonstrated by at least two ECGs $>$ 30 minutes apart
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (e.g., severe left ventricular systolic dysfunction, left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome
- Confirmed (e.g., 2 consecutive measurements) baseline heart rate ≤50 bpm prior to enrollment
- Current treatment with medications that are well known to prolong the QT interval
- Absolute neutrophil count $<1.3 \times 10^9$/L (1300/$\mu$L)
- Failure to satisfy the Investigator of fitness to participate for any other reason

**End of Study**

The end of this study is defined as the date when the last subject, last visit (LSLV), occurs or the date at which the last data point required for statistical analysis (i.e., mass balance, PK and/or metabolite profiling and identification data for Part 1 and PK data for Part 2) or safety follow-up is received from the last subject, whichever occurs later. The end of the study is expected to occur approximately 9 weeks after the last subject is enrolled in Part 2.

**Length of Study**

The total length of Part 1 of the study, from screening of the first subject to the end of the study, is expected to be approximately 10 weeks. The total length of Part 2 of the study, from screening of the first subject to the end of the study, is expected to be approximately 9 weeks.

**Investigational Medicinal Products**

**Test Product (Investigational Drug)**

***Part 1***

A single oral dose of [$^{14}$C]-RO7197597 Capsule, 30 mg (NMT 4.6 MBq [124 µCi]), which is referred to as [$^{14}$C]-GDC-9545 capsule in this protocol (Treatment A)

***Part 2***

A single dose of 30 mg GDC-9545 in each of three treatment periods; the following formulations will be administered:

- Treatment B: RO7197597 Solution for Infusion, 3 mg/mL, (referred to as GDC-9545 Solution for Infusion in this protocol) administered in a 10 mL volume intravenously over 30 minutes (as an infusion)
- Treatment C: Hard Capsules GDC-9545, 30 mg (referred to as GDC-9545/F12 capsule in this protocol), administered orally
- Treatment D: Hard Capsules GDC-9545, 30 mg F18 (referred to as GDC-9545/F18 capsule in this protocol), administered orally

**Statistical Methods**

**Primary Analysis**

***Mass balance Analyses (Part 1 only)***

The following mass balance parameters will be calculated from urine and feces separately and total (urine and feces combined):

- $A_{eu}$: amount of TR excreted in urine
- $CumA_{eu}$: cumulative amount of TR excreted in urine
- $F_{eu}$: amount of TR excreted in urine expressed as a percentage of the radioactive dose administered
- $CumF_{eu}$: cumulative amount of TR excreted in urine expressed as a percentage of the radioactive dose administered
- $A_{ef}$: amount of TR eliminated in feces
- $CumA_{ef}$: cumulative amount of TR eliminated in feces
- $F_{ef}$: amount of TR eliminated in feces expressed as a percentage of the radioactive dose administered
- $CumF_{ef}$: cumulative amount of TR eliminated in feces expressed as a percentage of the radioactive dose administered
- $A_{etotal}$: amount of TR excreted in urine and feces combined
- $CumA_{etotal}$: cumulative amount of TR excreted in urine and feces combined
- $F_{etotal}$: amount of TR excreted in urine and feces combined expressed as a percentage of the radioactive dose administered
- $CumF_{etotal}$: cumulative amount of TR excreted in urine and feces combined expressed as a percentage of the radioactive dose administered

***Pharmacokinetic Analyses***

The PK of GDC-9545 in plasma and TR in whole blood and plasma will be summarized by estimating the following parameters (as appropriate for data collected):

- $C_{max}$: maximum observed concentration
- $t_{max}$: time of maximum observed concentration
- $AUC_{0\text{-}t}$: area under the curve from time 0 to the time of last measurable concentration
- $AUC_{0\text{-}inf}$: area under the curve from time 0 extrapolated to infinity
- $\lambda_Z$: first order rate constant associated with the terminal (log-linear) portion of the curve
- $t_{1/2}$: terminal elimination half-life
- CL: total body clearance calculated after a single IV administration (for GDC-9545 only; Part 2 IV dose only)
- CL/F: total body clearance calculated after a single extravascular administration where F (fraction of dose bioavailable) is unknown (for GDC-9545 only; oral doses only)
- $V_z$: volume of distribution based on the terminal phase calculated using $AUC_{0\text{-}inf}$ after a single IV administration (for GDC-9545 only; Part 2 IV dose only)
- $V_z$/F: apparent volume of distribution (for GDC-9545 only; oral doses only)
- Ratio between whole blood and plasma concentrations for TR (Part 1 only)
- Ratio between whole blood and plasma $AUC_{0\text{-}inf}$ values for TR (Part 1 only)
- F: Absolute bioavailability calculated using $AUC_{0\text{-}inf}$ (for GDC-9545 only; oral doses in Part 2 only)
- Frel $C_{max}$: Relative bioavailability based on $C_{max}$ (for GDC-9545 only; GDC-9545/F18 capsule, 30 mg in Part 2 only)
- Frel $AUC_{0\text{-}t}$: Relative bioavailability based on $AUC_{0\text{-}t}$ (for GDC-9545 only; GDC-9545/F18 capsule, 30 mg in Part 2 only)
- Frel $AUC_{0\text{-}inf}$: Relative bioavailability based on $AUC_{0\text{-}inf}$ (for GDC-9545 only; GDC-9545/F18 capsule, 30 mg in Part 2 only)

The absolute bioavailability of GDC-9545/F12 capsule and GDC-9545/F18 capsule will be calculated using the $AUC_{0\text{-}inf}$ values obtained after oral and IV administration of GDC-9545. The mixed-effect analysis of variance model will be used for absolute bioavailability determination. The model will include formulation and period as fixed effects and a random subject effect.

To evaluate the relative bioavailability of GDC-9545 as GDC-9545/F18 capsule compared to GDC-9545/F12 capsule, the PK parameters $C_{max}$ and $AUC_{0\text{-}inf}$ for GDC-9545 will be analyzed. The mixed-effect analysis of variance model for the two-period crossover design will be used for formulation comparison. The model will include formulation and period as fixed effects and random subject effect (i.e., assuming a compound symmetry covariance structure).

Log-transformed $C_{max}$, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ values will be evaluated to estimate ratios of geometric mean values and the corresponding 90% confidence intervals (CIs) (test: GDC-9545/F18 capsule, reference: GDC-9545/F12 capsule; or test: GDC-9545/F12 capsule, reference: GDC-9545 Solution for Infusion; or test: GDC-9545/F18 capsule, reference: GDC-9545 Solution for Infusion).

**Determination of Sample Size**

For Part 1, it is planned to enroll 6 subjects to ensure data in a minimum of 4 evaluable subjects. For Part 2, it is planned to enroll 10 subjects to ensure data in a minimum of 8 evaluable subjects. No replacement subjects are to be used in Part 1 of this study. Up to 4 replacement subjects are permitted in Part 2 of this study to ensure there are 8 evaluable subjects.

The study is exploratory, and no formal sample size calculation has been made. Based on experience from previous studies of a similar design, a sample size of 6 subjects for Part 1 and 10 subjects for Part 2 is considered appropriate to meet the objectives of the study.

**Interim Analyses**

No interim analyses are planned for Part 1.

The following in-study decision will be made during Part 2 of this study:

- Progression from sentinel group to main group where sentinel dosing is used for Treatment B

For Treatment B, to assess tolerability of the IV administration, the first subject will be dosed as a sentinel; then, at least 4 hours later, the second subject will be dosed only if there are no acute safety findings for the first subject. If the first two subjects tolerated the IV dose, in the opinion of the Principal Investigator and Medical Monitor, the remaining subjects will be dosed. The third subject will be dosed at least 20 hours after the second subject (i.e., at least 24 hours after the first subject). All subsequent dosing of the IV formulation will be staggered by at least 15 minutes.

The decision to proceed with the main group will be made by the Investigator, based on safety data until up to 24 hours post-dose for the two sentinel subjects. The Investigator will inform the sponsor of any safety concerns.

The decision to proceed to the next dose level will be based on safety and tolerability data. The following data are required:

- Adverse events
- ECGs
- Vital signs

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| $^{14}C$ | carbon-14 |
| ALT | alanine aminotransferase |
| APTT | activated partial thromboplastin time |
| ARSAC | Administration of Radioactive Substances Advisory Committee |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| BMI | body mass index |
| CI | confidence interval |
| CLcr | creatinine clearance |
| COVID-19 | Coronavirus Disease 2019 |
| CRO | contract research organization |
| CV% | coefficient of variation |
| EC | Ethics Committee |
| ECG | electrocardiogram |
| eCRF | electronic Case Report Form |
| EDC | electronic data capture |
| EMA | European Medicines Agency |
| ER | estrogen receptor |
| ESR1 | estrogen receptor 1 |
| FDA | Food and Drug Administration |
| F12 | Roformis Number RO7197597/F12-01 |
| F18 | Roformis Number RO7197597/F18-01 |
| FSH | follicle stimulating hormone |
| GCP | Good Clinical Practice |
| GGT | gamma glutamyl transferase |
| GI | gastrointestinal |
| HBsAg | hepatitis B surface antigen |
| HCV | hepatitis C virus |
| HER2 | human epidermal growth factor receptor 2 |
| HIV | human immunodeficiency virus |
| HRT | hormone replacement therapy |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| IMP | investigational medicinal product |

| Abbreviation | Definition |
|---|---|
| IND | Investigational New Drug (Application) |
| INR | international normalized ratio |
| ISF | Investigator Site File |
| IV | intravenous |
| LBD | ligand-binding domain |
| LHRH | luteinizing hormone-releasing hormone |
| LSLV | last subject, last visit |
| MBq | megabecquerel |
| µCi | microcurie |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NMT | not more than |
| PCR | polymerase chain reaction |
| PK | pharmacokinetic(s) |
| PLD | phospholipidosis |
| PT | prothrombin time |
| QTcF | QT interval corrected through use of Fridericia's formula |
| RBC | red blood cell |
| SAP | Statistical Analysis Plan |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SUSAR | suspected unexpected serious adverse reaction |
| TR | total radioactivity |
| ULN | upper limit of normal |
| WBC | white blood cell |

# 1. BACKGROUND

## 1.1 BACKGROUND ON BREAST CANCER

Breast cancer is the most commonly diagnosed cancer in women, with an estimated global incidence of 2,088,849 new cases and 626,679 deaths reported in 2018 (Bray et al. 2018). Approximately 80% of all breast cancers express estrogen receptor (ER) and the vast majority of these cancers are dependent on the 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 such as ER antagonists (e.g., tamoxifen), aromatase inhibitors (e.g., anastrozole, letrozole, and exemestane), and full ER antagonists/degraders (e.g., fulvestrant), many patients ultimately relapse or develop resistance to these agents and therefore require further treatment for optimal disease control.

## 1.2 BACKGROUND ON GDC-9545

GDC-9545 (RO7197597) 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 (LBD) of both wild-type and mutant ER with nanomolar potency. Upon binding, GDC-9545 induces an inactive conformation to the ER LBD, as measured by displacement of co-activator peptides. In addition to its direct antagonist properties, the mechanism of action of GDC-9545 includes reducing 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 such as tamoxifen, which display partial agonism. GDC-9545 potently inhibits the proliferation of multiple ER+ breast cancer cell lines in vitro, including cells engineered to express clinically relevant mutations in ER.

GDC-9545 exhibited dose-dependent anti-tumor activity in xenograft models of ER+ breast cancer, including in a patient-derived xenograft model that harbors an estrogen receptor 1 (ESR1) mutation (ER.Y537S). The efficacious dose range was 0.1 to 10 mg/kg/day, and all doses were well tolerated. Fulvestrant, when dosed according to a clinically relevant dosing scheme, was less efficacious than GDC-9545 in the assessed xenograft models. Thus, GDC-9545 demonstrated robust nonclinical activity in ER+ breast cancer models of ESR1-wildtype- and ESR1-mutation-bearing disease.

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

### 1.2.1 Toxicology and Safety Pharmacology

Doses used in the pivotal 4- and 26-week toxicity studies were appropriate based on evidence of dose-limiting (monkeys) or potentially dose-limiting (rats) toxicities, and achievement of systemic exposures that are similar to or in excess of anticipated

therapeutic exposures. Adverse organ effects identified in both pivotal toxicity studies were dose-responsive, largely confined to the kidney and liver, and monitorable in the clinic using standard laboratory assessments. Liver findings were partially to completely reversible, while nephropathy observed at 30 mg/kg in rats after 26 weeks of dosing did not reverse. 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 both species.

In both rats and monkeys, there was a dose-dependent phospholipidosis (PLD) observed in numerous organs, including in the retinal pigmented epithelium of the eye and choroid plexus epithelium at 30 mg/kg in rats. In rats, PLD was not noted at 3 mg/kg, but increased in incidence and severity with increasing dose. In monkeys, dose-dependent PLD was present at all doses but was limited to minimal changes in the liver and lymph nodes at 7 mg/kg, the lowest dose tested. In the 26-week chronic toxicity studies, the severity and incidence of PLD observed via light microscopy were reduced in some organs for both rats and monkeys suggesting partial reversibility in some organs after a 16-week recovery period.

For the 26-week toxicity study in rats, dose levels of 3, 10, and 30 mg/kg/day resulted in area under the concentration-time curve (AUC)-based exposure factor that were 1x, 4x, and 13x relative to the 30 mg clinical dose with 30 mg/kg/day being considered the severely toxic dose for 10% of animals. For the 26-week toxicity study in monkeys, dose levels of 7, 20, and 60 mg/kg/day resulted in AUC-based exposure factors that were 0.4x, 0.9x, and 2.5x relative to the 30 mg clinical dose with 20 mg/kg/day being considered the highest non-severely toxic dose.

GDC-9545 was not mutagenic in the bacterial mutagenesis assay, did not induce an increase in micronucleus formation in human lymphocytes in in vitro studies and was not phototoxic in an in vitro mammalian cell-based assay.

Results from the nonclinical toxicity and safety pharmacology studies completed to date provide a robust characterization of the toxicity profile of GDC-9545 to support administration to patients with ER+ breast cancer in ongoing clinical trials.

### 1.2.2 Clinical Summary

As of the data cutoff of 31 Jan 2020, GDC-9545 has been administered in two Phase I clinical studies, GO39932 and GO40987, and one clinical pharmacology trial, a relative bioavailability study, GP42006, is ongoing to evaluate the tablet and capsule formulations.

Study GO39932 is a first-in-human Phase Ia/Ib, multicenter, open-label study evaluating the safety, pharmacokinetics (PK), and activity of GDC-9545 alone (at doses of 10 to 250 mg) or in combination (doses of 100 mg GDC-9545) with palbociclib and/or

luteinizing hormone-releasing hormone (LHRH) agonist in patients with ER+ (human epidermal growth factor receptor 2 [HER2]-) breast cancer.

Study GO40987 is a Phase I, open-label, multicenter, preoperative study to assess changes in Ki67 levels and to evaluate the pharmacodynamics, PK, safety, and biologic activity of GDC-9545 in patients with Stage I to III operable ER+ (HER2-) untreated breast cancer.

GDC-9545 administered at 30 mg once daily is also being evaluated in a Phase III trial in metastatic breast cancer in combination with palbociclib (BO41843; NCT04546009), in a Phase II trial in untreated ER+ HER2- early breast cancer, in combination with palbociclib (WO42133; NCT04436744) and in a Phase II trial in previously treated ER+ HER2- metastatic breast cancer (WO42312; NCT04576455).

#### 1.2.2.1 Safety

The single agent dose escalation portion of Study GO39932 enrolled 29 patients (dose levels of 10, 30, 90 and 250 mg). No dose-limiting toxicities, serious adverse events, or adverse events of special interest were reported and a maximum tolerated dose was not determined. Initially 100 mg and 250 mg (±LHRH agonist) GDC-9545 doses were chosen for single-agent dose expansion, and an escalation cohort combined 100 mg GDC-9545 with 125 mg palbociclib. [redacted]. Enrollment was completed for the 100 mg single agent expansion and 100 mg in combination with palbociclib expansion; at the time of the data cutoff (31 Jan 2020), enrollment was ongoing in the 30 mg GDC-9545 expansion cohort.

As of the data cutoff of 31 Jan 2020, within the dose escalation and dose expansion stages combined, a total of 87 patients have been treated with single-agent GDC-9545 (±LHRH agonist) including 22 patients within the GDC-9545 30 mg cohort. Forty-eight patients have been treated with 100 mg GDC-9545 in combination with 125 mg palbociclib (±LHRH agonist), and one patient participated in cardiac Cohort C1 (100 mg GDC-9545 in combination with 125 mg palbociclib).

GDC-9545 is tolerated well as single−agent at all dose levels (10 mg to 250 mg) and in combination at 100 mg with palbociclib.

Of the 87 patients treated with single-agent GDC-9545 at doses ranging from 10 to 250 mg, regardless of attribution to study drug, adverse events occurring in 10% or more patients were: fatigue, back pain, nausea, arthralgia, cough, diarrhea, constipation, and pain in extremity. Grade ≥3 adverse events irrespective of causality occurring in 2 or more patients were: diarrhea, decreased appetite, and fatigue.

In the single agent cohorts, 7 patients (8%) experienced 8 serious events including: pleural effusion, pulmonary embolism, duodenal ulcer perforation, appendiceal abscess, small intestinal obstruction, fatigue, migraine, and paresthesia. All serious adverse events were considered unrelated to GDC-9545 by the Investigators, except fatigue, which was also considered related to progressive disease. One patient died due to a serious adverse event of duodenal ulcer perforation that was considered unrelated to GDC-9545 by the Investigator.

Of the 48 patients treated with 100 mg GDC-9545 in combination with palbociclib, 8 patients (17%) experienced 9 serious adverse events including: dyspnea, urinary tract infection, electrocardiogram QT prolonged, deep vein thrombosis, thrombocytopenia and fatal breast cancer progression (in one patient each), and neutropenia (3 patients); only Grade 3 QT prolonged was considered related to GDC-9545 by the Investigator.

In Study GO40987, patients received GDC-9545 daily for approximately 14 days at one of three treatment cohorts (10, 30, and 100 mg).

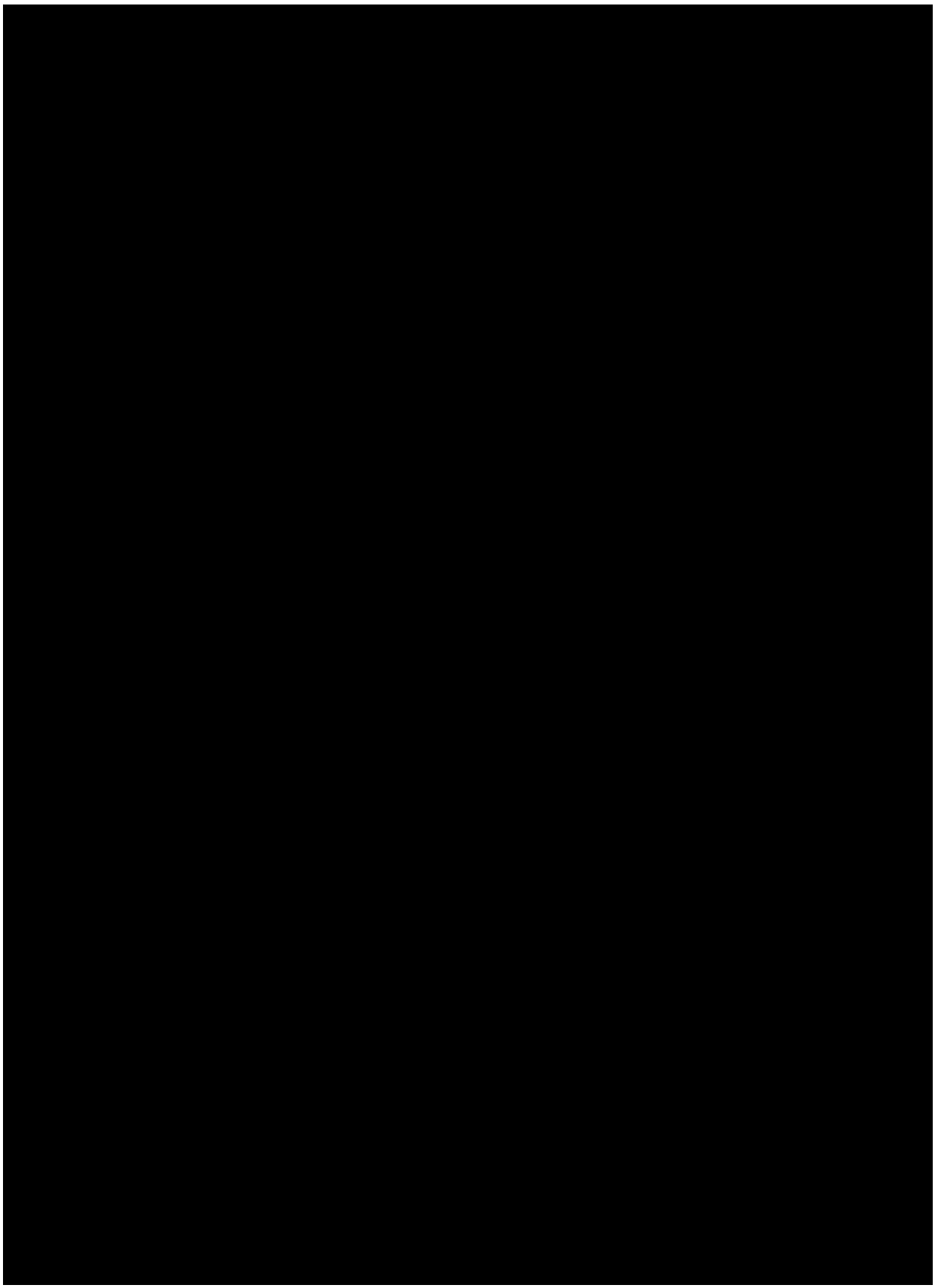
As of the data cutoff date of 31 Jan 2020, a total of 30 postmenopausal women with Stage I to III operable ER+ (HER2-) untreated breast cancer were treated with single-agent GDC-9545 at doses ranging from 10 to 100 mg in Study GO40987. Adverse events reported in ≥10% of patients irrespective of attribution to study drug were: nausea, procedural pain and hot flush, asthenia and arthralgia. In this study, one patient experienced serious adverse event of breast abscess (Grade 3), following surgery, in the GDC-9545 10 mg dose group. However, it was not related to study treatment. No other Grade ≥3 adverse events or serious adverse events irrespective of causality, thromboembolic events, or issues with wound healing have been reported.

Therefore, overall GDC-9545 was well tolerated at all dose levels in patients with early breast cancer.

[redacted]

[redacted]

[redacted]



[redacted]

## 1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The study population rationale and the dose rationale for the study drugs are discussed in Sections 3.3.1 and 3.3.2, respectively.

### 1.3.1 Study Rationale

GDC-9545 is being investigated for the treatment of ER+ breast cancer, using a capsule formulation. The efficacy of GDC-9545 is currently being assessed in breast cancer patients and as of the data cutoff of 31 Jan 2020, clinical benefit rate was reported in 71 (60%) of 119 patients overall (in Study GO39932). Additionally, GDC-9545 is being progressed into Phase III studies in metastatic breast cancer patients.

To support the regulatory clinical pharmacology package for GDC-9545, a radiolabeled human mass-balance study (absorption, distribution, metabolism and elimination) is required to characterize the overall disposition and biotransformation of GDC-9545. Part 1 of this study is being conducted to investigate the mass balance recovery and metabolic profiling and identification for orally administered carbon-14 ([$^{14}$C])-GDC-9545. The study will use oral administration to determine the metabolite profile of GDC-9545, as this is the intended therapeutic route.

Part 2 of this study is being conducted to investigate the absolute and relative bioavailability of two GDC-9545 oral capsules, in order to aid formulation optimization for the development of a capsule formulation that will be successfully administered to patients. Formulation Roformis Number RO7197597/F12-01 (F12) is a 30 mg [redacted] capsule formulation manufactured using standard excipients and a [redacted]. For Formulation Roformis Number RO7197597/F18-01 (F18), the encapsulation process of Formulation F12 was further improved and a [redacted] was selected as the manufacturing technology. [redacted]

### 1.3.2 Risk-Benefit Assessment

There will be no therapeutic benefit for the volunteers participating in the study. The development of a product to improve the treatment of ER+ breast cancer will be of benefit to the wider community/patients with such symptoms.

The risks of participation are primarily those associated with adverse reactions to the study drug, although there may also be some discomfort from collection of blood samples and other study procedures. The tolerability profile of GDC-9545 from administration of single agent daily doses up to 250 mg to ER+ breast cancer patients has been characterized from previous clinical studies. There have been few adverse drug reactions following GDC-9545 dosing in previous clinical studies in patients. With the exception of one event of fatigue (which was also considered related to progressive disease), no serious adverse drug reactions have been reported in the single agent studies. No specific safety concerns have been identified about the use of 30 mg GDC-9545 in healthy volunteers in this study.

Because an intravenous (IV) dose of GDC-9545 has not been previously administered in a clinical study, a sentinel dosing design will be used for Treatment B in Part 2, i.e., the

second subject administered Treatment B will be dosed at least 4 hours after the first subject, and the third subject will be dosed at least 20 hours after the second subject (i.e., at least 24 hours after the first subject). This will allow assessment of the tolerability of the IV administration in the first two subjects prior to dosing the remaining subjects.

Potential risks identified in the IB include hepatotoxicity, venous thromboembolic events, renal dysfunction, bradycardia and QT prolongation, which will be monitored by safety laboratory and electrocardiogram (ECG) assessments as applicable. Potential gastrointestinal (GI) toxicities will be monitored through adverse event monitoring. Potential drug-drug interactions with other medications are addressed by restrictions on concomitant medication use. Potential risks to a developing fetus from GDC-9545 exposure in utero, changes in female reproductive organs and menopausal symptoms and male/female infertility are addressed by exclusion of males and females of childbearing potential from this study. Risks associated with GDC-9545 are further discussed in Section 5.1.1.

Risks associated with radiation and Coronavirus Disease 2019 (COVID-19) associated risks are discussed in Sections 5.1.2 and 5.1.3, respectively, and general risks associated with the conduct of the study are discussed in Section 5.1.4. However, these risks are considered to be small and therefore acceptable.

Overall, no significant safety concerns have been identified about the use of 30 mg GDC-9545 or [$^{14}$C]-GDC-9545 in healthy volunteers. All volunteers will be resident in the clinic and remain under medical supervision following study drug administration and will undergo a standard battery of safety assessments. Hence, the risks to participants in this study are considered acceptable.

# 2. OBJECTIVES AND ENDPOINTS

Part 1 of this study will evaluate the absorption, metabolism, excretion, PK and safety of GDC-9545 in healthy volunteers. Part 2 of this study will evaluate the absolute and relative bioavailability, and safety of GDC-9545 in healthy volunteers. Specific objectives and corresponding endpoints for both parts of the study are outlined below.

## 2.1 MASS BALANCE, PHARMACOKINETIC AND METABOLITE PROFILING AND IDENTIFICATION OBJECTIVES (PRIMARY AND SECONDARY STUDY OBJECTIVES)

### 2.1.1 Part 1

The primary mass balance and PK objectives for Part 1 of this study are as follows:

- To determine the mass balance and routes of elimination of [$^{14}$C]-GDC-9545 following a single oral dose of [$^{14}$C]-GDC-9545 capsule, 30 mg containing not more than (NMT) 4.6 megabecquerel (MBq; 124 microcurie [µCi]) on the basis of the following endpoints:

  - Mass balance recovery of total radioactivity (TR) in all excreta (urine and feces): $CumA_e$ and $CumF_e$
  - Determination of routes and rates of elimination of [$^{14}$C]-GDC-9545 by $A_e$, $CumA_e$, $F_e$ and $CumF_e$ by interval for all excreta (urine and feces)

- To assess the PK of GDC-9545 and total drug-derived material in plasma following a single oral dose of [$^{14}$C]-GDC-9545 capsule, 30 mg (NMT 4.6 MBq [124 µCi]) on the basis of the following endpoints:
  - Calculation of PK parameters as appropriate for GDC-9545 (plasma only) and TR (plasma and whole blood)
  - Assessment of the concentrations of TR in whole blood and plasma
  - Evaluation of whole blood:plasma concentration ratios for TR

The secondary metabolite profiling and identification objective for Part 1 of this study is as follows:

- To characterize and identify metabolites of [$^{14}$C]-GDC-9545 in plasma, urine, and feces on the basis of the following endpoint:
  - Characterization of abundant metabolites by liquid chromatography-high resolution mass spectrometry

Metabolite profiling and identification will be reported separately from the Clinical Study Report as a standalone document.

### 2.1.2 Part 2

The primary PK objectives for Part 2 of this study are as follows:

- To determine the absolute bioavailability of an oral GDC-9545/F12 capsule, 30 mg and an oral GDC-9545/F18 capsule, 30 mg on the basis of the following endpoints:
  - Absolute bioavailability assessment based on the PK parameter $AUC_{0\text{-}inf}$ for GDC-9545
- To determine the relative bioavailability of GDC-9545/F18 capsule, 30 mg compared to the GDC-9545/F12 capsule, 30 mg on the basis of the following endpoint:
  - Relative bioavailability assessment based on the PK parameters $C_{max}$ and $AUC_{0\text{-}inf}$ for GDC-9545

The secondary PK objectives for Part 2 of this study are as follows:

- To characterize the PK of GDC-9545 following oral and IV administration on the basis of the following endpoint:
  - Calculation of PK parameters as appropriate for GDC-9545 in plasma only

## 2.2 SAFETY OBJECTIVE (SECONDARY STUDY OBJECTIVE)

The safety (secondary) objective for both Parts 1 and 2 of this study is to evaluate the safety and tolerability of single doses of GDC-9545 on the basis of the following endpoints:

- Incidence and severity of adverse events
- Incidence of abnormalities in laboratory safety tests, 12-lead ECGs and vital sign measurements

# 3. STUDY DESIGN

## 3.1 DESCRIPTION OF THE STUDY

This is an open-label, single-center, two part study in heathy female subjects of non-childbearing potential to investigate the absorption, metabolism, and excretion of [$^{14}$C]-GDC-9545 (Part 1), the absolute bioavailability of formulations F12 and F18 (i.e., GDC-9545/F12 capsule, 30 mg and GDC-9545/F18 capsule, 30 mg) and relative bioavailability of GDC-9545 oral capsule F18 to the F12 formulation (Part 2).

Subjects who do not meet the criteria for participation in this study (screen failure) may qualify for 1 re-screening opportunity (for a total of 2 screenings per participant) at the Investigator's discretion. Subjects must re-sign the consent form prior to re-screening. The Investigator will record reasons for screen failure in the screening log (see Section 4.5.1).

It is planned that Part 1 will begin prior to Part 2 of the study, and that the two parts of the study will partially overlap.

### 3.1.1 Part 1

Part 1 is an open-label, single-treatment design. It is planned to enroll 6 subjects to ensure data in a minimum of 4 evaluable subjects. An evaluable subject for Part 1 of the study is defined as a subject who has provided mass balance and PK samples for up to 480 hours (up to Day 21) or until they have met the mass balance discharge criteria (i.e., cumulative recovery of radioactivity exceeds 90% of the administered dose; OR radioactivity in urine and feces is less than 1% of the administered dose over a 24 hour period on 2 consecutive PK sample collection days, as determined by quick counts).

Each subject will receive a single oral dose of [$^{14}$C]-GDC-9545 capsule, 30 mg (NMT 4.6 MBq [124 µCi]) with approximately 240 mL water in the fasted state (Treatment A).

Subjects will undergo preliminary screening procedures for the study up to 28 days (Day -28 to Day -2) before [$^{14}$C]-GDC-9545 administration on Day 1. Subjects will be admitted in the morning on the day prior to [$^{14}$C]-GDC-9545 administration (Day -1) and will be dosed in the morning of Day 1 following an overnight fast of a minimum of 10 hours.

Urine and feces samples for measurement of TR will be collected pre-dose and at intervals until study completion including after discharge, if needed.

Blood samples for measurement of plasma GDC-9545 and TR in plasma and whole blood will be collected pre-dose and at intervals until study completion including after discharge, if needed.

Safety and tolerability will be monitored by clinical and laboratory assessments at intervals throughout the study.

It is planned that subjects will remain resident in the clinical unit until 480 hours post-dose (Day 21) when they will be discharged from the clinical unit.

It is planned that subjects will be released as a group when all subjects have achieved the following mass balance discharge criteria:

- Cumulative recovery of radioactivity exceeds 90% of the administered dose; OR
- Radioactivity in urine and feces is less than 1% of the administered dose over a 24 hour period on 2 consecutive PK sample collection days, as determined by quick counts

This may result in the subjects being discharged as a group prior to completion of the planned residency period. Once the mass balance discharge criteria have been achieved, collection of all samples (blood, urine, and feces) may be stopped and the subjects will undergo discharge assessments. If the mass balance discharge criteria have not been met by all subjects by Day 21, subjects will be discharged from the clinical unit and those who have not met the discharge criteria will return for outpatient visits every 7 days for a 24-hour sample collection interval (i.e., subjects will be resident in the clinical unit for 24 hours during each return visit) until the mass balance discharge criteria are met (the maximum number of 24-hour return visits will not exceed 3). Discharged subjects may be asked to return for these visits if samples are needed post-discharge, prior to study completion. During the period of weekly collection, mass balance cumulative recovery will be estimated by means of interpolation.

If additional residency is not considered appropriate or necessary, then home collections of urine and/or feces may be requested at the discretion of the Investigator for individual subjects.

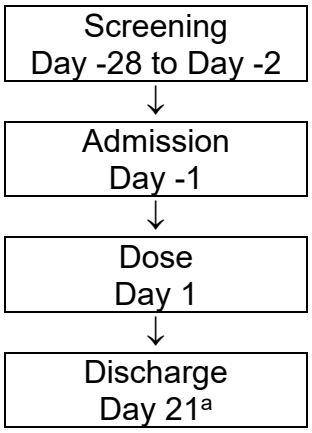
The total duration of Part 1 of the study for each enrolled subject (screening through to end of study) will be approximately 10 weeks, divided as follows:

- Screening: up to 28 days before the first dose of study drug.
- A single treatment period, with admission on Day -1 and discharge from the clinical unit on or before Day 21

- If mass balance discharge criteria have not been met by Day 21: return visits every 7 days for a 24-hour sample collection interval until the radioactivity recovery criteria are met (maximum number of 24-hour outpatient visits will not exceed 3). Discharged subjects may be asked to return for these visits if samples are needed post-discharge, prior to study completion.

Figure 3 presents an overview of the study design for Part 1. A schedule of activities is provided in Appendix 1.

**Figure 3 Overview of Part 1 Design**




[a] Subjects may be discharged as a group earlier if the mass balance discharge criteria have been achieved. If the criteria have not been met by Day 21, subjects will be discharged from the clinical unit and those who have not met the discharge criteria will return for outpatient visits every 7 days for a 24-hour sample collection interval until the mass balance discharge criteria are met (the maximum number of 24-hour return visits will not exceed 3). Discharged subjects may be asked to return for these visits if samples are needed post-discharge, prior to study completion. If additional residency is not considered appropriate or necessary, then home collections of urine and/or feces may be requested at the discretion of the Investigator for individual subjects.

### 3.1.2 Part 2

Part 2 is a randomized, open-label, three-treatment, two-sequence crossover design conducted over three periods. It is planned to enroll 10 subjects to ensure data in a minimum of 8 evaluable subjects. An evaluable subject for Part 2 of the study is defined as a subject who has received an investigational medicinal product (IMP) and has sufficient drug concentration measurements up to 168 hours after dosing for evaluation of defined PK parameters for each treatment, and have completed all planned safety assessments up to 168 hours after dosing for each treatment.

Subjects will be randomly allocated to one of two treatment sequences (BCD and BDC; see Section 4.2.2). In each treatment period, subjects will receive a single 30 mg dose of GDC-9545 in the fasted state. GDC-9545 will be administered as one of three possible formulations according to the randomization schedule:

- Treatment B: 30 mg GDC-9545 as a Solution for Infusion, 3 mg/mL administered intravenously in 10 mL as an infusion over 30 minutes

- Treatment C: GDC-9545/F12 capsule, 30 mg, administered with approximately 240 mL water
- Treatment D: GDC-9545/F18 capsule, 30 mg, administered with approximately 240 mL water

Subjects will undergo preliminary screening procedures for the study up to 28 days (Day -28 to Day -2) before GDC-9545 administration on Day 1 of Period 1. Subjects will be admitted in the morning on the day prior to the first GDC-9545 administration (Day -1 of Period 1). Subjects will be resident in the clinical unit from the morning of Day -1 in Period 1 until Day 8 in Period 3 (i.e., for 28 to 29 consecutive nights that will cover all 3 treatment periods).

For each treatment period, subjects will be dosed in the morning of Day 1 following an overnight fast of a minimum of 10 hours.

For Treatment B, to assess tolerability of the IV administration, the first subject will be dosed as a sentinel; then, at least 4 hours later, the second subject will be dosed only if there are no acute safety findings for the first subject. If the first two subjects tolerated the IV dose, in the opinion of the Principal Investigator and Medical Monitor per the criteria in Section 6.8.1, the remaining subjects will be dosed. The third subject will be dosed at least 20 hours after the second subject (i.e., at least 24 hours after the first subject). All subsequent dosing of the IV formulation will be staggered by at least 15 minutes.

Blood samples for measurement of plasma GDC-9545 will be collected pre-dose and at intervals until Day 8 of each period.

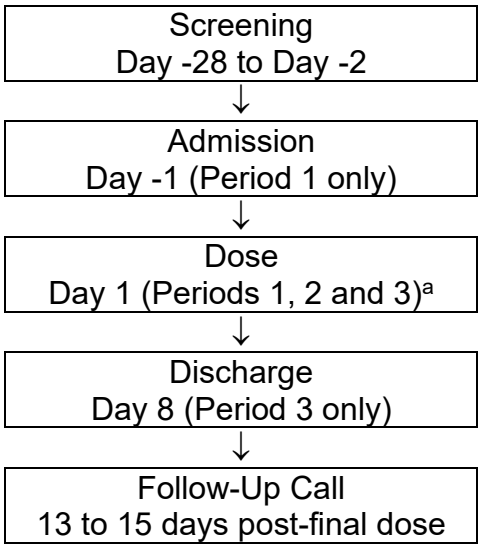
Safety and tolerability will be monitored by clinical and laboratory assessments at intervals throughout the study.

The total duration of Part 2 of the study for each enrolled subject (screening through to end of study) will be approximately 9 weeks, divided as follows:

- Screening: up to 28 days before the first dose of study drug.
- Three treatment periods, separated by a treatment-free washout so there are at least 10 days between each of the three study drug administrations.
- Safety follow-up call: 13 to 15 days after the last dose of study drug.

Figure 4 presents an overview of the study design for Part 2. A schedule of activities is provided in Appendix 2.

**Figure 4 Overview of Part 2 Design**




[a] Subjects will receive Treatments B, C and D in Periods 1, 2 and 3 in a randomized manner. There will be a minimum washout of 10 days between each IMP administration.

## 3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last subject, last visit (LSLV), occurs or the date at which the last data point required for statistical analysis (i.e., mass balance, PK and/or metabolite profiling and identification data for Part 1 and PK data for Part 2) or safety follow-up is received from the last subject, whichever occurs later. The end of the study is expected to occur approximately 9 weeks after the last subject is enrolled in Part 2.

In addition, the Sponsor may decide to terminate the study at any time.

The total length of Part 1 of the study, from screening of the first subject to the end of the study, is expected to be approximately 10 weeks. The total length of Part 2 of the study, from screening of the first subject to the end of the study, is expected to be approximately 9 weeks.

## 3.3 RATIONALE FOR STUDY DESIGN

### 3.3.1 Rationale for Subject Population

Healthy volunteers, instead of a patient population, have been chosen for this study in order to safely assess the absorption, metabolism, excretion, PK and safety properties of GDC-9545.

As this is a Phase I study assessing the absorption, metabolism, excretion, PK, relative bioavailability and safety of GDC-9545, the most relevant population is healthy volunteers, as recommended by the U.S. Food and Drug Administration (FDA, (2002) and the European Medicines Agency (EMA, 2010). Subjects who are non-smokers

without a history of alcohol or drug abuse or regular co-medication are proposed to avoid interaction on drug metabolism and to avoid non-compliance.

The target patient population for GDC-9545 is female ER+ breast cancer patients; therefore, it is necessary to assess the absorption, metabolism, excretion, PK and safety properties of GDC-9545 in female subjects. Based on the anti-estrogenic pharmacological activity of GDC-9545, administration during pregnancy is expected to have an adverse effect and poses a risk to the human fetus, including birth defects and miscarriage. Additionally, only female subjects are to be enrolled owing to there being no previous clinical information on safety in males. Therefore, only female subjects of non-childbearing potential will be allowed to participate in the study.

We acknowledge the Administration of Radioactive Substances Advisory Committee (ARSAC) Notes for Guidance recommend that wherever possible, healthy subjects selected for research projects should be aged over 50 years (2020). However, the current study is designed to generate data for supporting the investigation of the human absorption, metabolism and excretion of a drug, as well as generating samples for metabolite profiling and structural identification.

There are two main reasons for generating these data within a clinical development program. The first is to provide human metabolite data that can be used to interpret the metabolism profiles seen in the preclinical species employed in the longer term toxicity studies, to ensure that there is adequate toxicology coverage for the safe development of the drug in patients. The second is to provide data to understand how the drug is processed in physiologically normal subjects, because understanding the routes of metabolism and elimination in a healthy population generates the appropriate data to guide the clinical pharmacology package required to fulfil the regulatory requirements of a New Drug Application.

In order to address these two main aims of an absorption, metabolism and excretion study, investigation of the drug under development is required in a population with normal physiological function, as it is recognized that certain physiological processes e.g., renal function, deteriorate with age and therefore it is preferable to use as healthy population as possible, to mitigate against factors which may make interpretation of the data difficult. Also, healthy subjects as a trial population are ideal since they have a relatively stable physiological, biochemical and hormonal status, which removes any disease-related variations and variations due to concomitant medications.

Additionally, healthy volunteers are considered more suitable for this study than for the following reasons:

- Patients would not be expected to derive clinically meaningful benefit from GDC-9545 in this study because of the short duration of treatment

- Patients participating in this study would need to discontinue standard-of-care therapy so that the study could achieve its objective of assessing the absorption, metabolism, excretion, PK profile safety and tolerability of GDC-9545
- Healthy volunteers are expected to have the best systemic reserve to respond to any unexpected reactions to GDC-9545, such as hypersensitivity reactions

Based on the above considerations and target population, healthy female subjects of non-childbearing potential (i.e., surgically sterilized or post-menopausal), aged ≥30 and ≤65 years are considered suitable for this study.

### 3.3.2 Rationale for [$^{14}$C]-GDC-9545 and GDC-9545 Doses and Schedule

The planned therapeutic dose for GDC-9545 (which is currently being evaluated in a Phase III trial in metastatic breast cancer patients) is 30 mg once daily; therefore, 30 mg is the chosen dose for both Parts 1 and 2 of this study. Single doses of GDC-9545 up to 250 mg have been administered in previous Phase I clinical studies (in ER+ breast cancer patients), and have been found to be well tolerated.

GDC-9545 will be given in the fasted state in order to avoid the potential for a food effect.

This is an open-label study, because the parameters (i.e., mass balance recovery of TR in urine and feces, TR concentrations in plasma and whole blood, and GDC-9545 concentrations in plasma) on which the primary endpoints are based are considered to be objective measures.

#### 3.3.2.1 Part 1

In order to assess the absorption, metabolism and excretion of GDC-9545, a single oral dose of [$^{14}$C]-GDC-9545 capsule, 30 mg [NMT 4.6 MBq [124 µCi]) in Part 1.

The dose of radioactivity has been determined following review of nonclinical quantitative whole body autoradiography data and the consequential human dosimetry prediction. The effective dose will be 0.7 millisievert (mSv) and will fall within International Commission on Radiological Protection (1992) Guidelines for Category IIa studies (0.1 to 1 mSv). The dose of radioactivity will be no more than 4.6 MBq (124 µCi).

To ensure that the [$^{14}$C] drug product(s) does not exceed the limit for radioactive dose approved by ARSAC, the target specific activity of the drug substance will be set at 90% of 90% of the threshold radioactive dosing limit. This will allow for tolerances in the manufacturing processes for both drug substance and drug product thereby providing continued assurance for compliance with the ARSAC approved limit for drug product radioactivity dose.

#### 3.3.2.2 Part 2

In order to assess the relative and absolute bioavailability of different oral formulations of GDC-9545, a single IV administration of 30 mg GDC-9545 as a Solution for Infusion, 3 mg/mL will be administered (as an infusion) for Treatment B and single oral doses of capsule formulations F12 and F18 (i.e., GDC-9545/F12 capsule, 30 mg and GDC-9545/F18 capsule, 30 mg) will be administered for Treatments C and D, respectively.

An IV dose of 30 mg was selected to be equal to the oral dose in order to prevent any difficulties in comparison of the IV and oral dose that may arise if there is non-linearity in the PK. Simulations for the IV dose of 30 mg in 10 mL infused over 30 minutes using the population PK model and the physiologically based PK model for GDC-9545 predicted peak concentrations that were within the range of concentrations observed previously in clinic (the highest $C_{max}$ observed previously being 1650 ng/mL at steady-state following administration of 250 mg GDC-9545 once daily).

For Treatment B, to assess tolerability of the IV administration, the first subject will be dosed as a sentinel; then, at least 4 hours later, the second subject will be dosed only if there are no acute safety findings for the first subject. If the first two subjects tolerated the IV dose, in the opinion of the Principal Investigator and Medical Monitor per the criteria in Section 6.8.1, the remaining subjects will be dosed. The third subject will be dosed at least 20 hours after the second subject (i.e., at least 24 hours after the first subject). All subsequent dosing of the IV formulation will be staggered by at least 15 minutes.

A crossover design was chosen for Part 2 for Treatments C and D because it utilizes within-subject, as well as between-subject, comparisons and is consequently more efficient than a standard parallel group design. As each subject acts as their own control, the impact of confounding factors is also minimized. Subjects were randomized between treatment sequences BCD and BDC to minimize allocation and selection bias.

### 3.3.3 Rationale for PK Sampling Schedule

The PK sampling schedule has been selected on the basis of data from previous studies in which single doses of GDC-9545 have been administered to patients. The frequent sampling schedule that follows the single doses of GDC-9545 is designed to capture data at a sufficient number of time points to provide a detailed profile of the absorption, distribution, and elimination of this drug, including time to maximum observed concentration ($t_{max}$) and terminal half-life ($t_{1/2}$).

## 4. MATERIALS AND METHODS

### 4.1 SUBJECTS

Approximately 16 (6 in Part 1 and 10 in Part 2) healthy female volunteers of non-childbearing potential will be enrolled at one investigative site located in the UK.

No replacement subjects are to be used in Part 1 of this study. Up to 4 replacement subjects are permitted in Part 2 of this study to ensure there are 8 evaluable subjects; a maximum of 6 subjects in Part 1 and 14 subjects in Part 2 may be dosed.

Subjects will be recruited from the Quotient Sciences panel or by direct advertising to the public. Quotient Sciences (the Clinical Research Unit) must have a full medical history from each subject's General Practitioner as follows:

- Within the last 24 months prior to enrollment in the study for all volunteers who have previously participated in a clinical research study at Quotient Sciences.
- Within the last 12 months prior to enrollment in the study for all new volunteers.

Before subjects are admitted to the clinic, The Over Volunteering Prevention System will be checked to ensure that each subject has not been dosed in a study within 90 days of the planned Day 1 (Part 1) or Day 1 of Period 1 (Part 2) of this study.

### 4.1.1 Inclusion Criteria

Subjects must meet the following criteria for study entry:

1. Able and willing to comply with the study restrictions and to give written informed consent before any study procedure.
2. Healthy female subjects of non-childbearing potential that are non-pregnant, non-lactating females, who are either postmenopausal or surgically sterile, aged 30 to 65 years, inclusive, at time of signing the Informed Consent Form (ICF)
    - Postmenopausal females are defined as:
        - Age >60 years;
        - Age ≤60 years and amenorrhea ≥12 months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression. Estradiol levels and/or follicle-stimulating hormone (FSH) levels in the postmenopausal range;
    - Surgically sterile females for at least 90 days prior to screening are defined as:
        - Bilateral salpingectomy;
        - Hysterectomy;
        - Bilateral oophorectomy;
    - For all subjects, the pregnancy test result must be negative at screening and admission (Day -1 for Part 1 and Day -1 of Period 1 for Part 2)
3. A body mass index (BMI) between 18.5 and 32.0 kg/$m^2$, inclusive, at screening
4. Ability to comply with the study protocol
5. Must have regular bowel movements (i.e., average stool production of ≥1 and ≤3 stools per day) (Part 1 only)

- Female subjects of non-childbearing potential do not need to use any methods of contraception.

For both study parts, inclusion criterion 2 from the list above will be re-assessed at admission/pre-dose of Part 1 and admission/pre-dose of Part 2 Period 1.

### 4.1.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from study entry:

1. Women of childbearing potential, women who are pregnant or breastfeeding.
   - All women must have a negative highly sensitive serum pregnancy test result at screening and a negative highly sensitive urine pregnancy test at admission.
2. Subjects who have received any IMP in a clinical research study within the 90 days prior to Day 1 (Part 1) or Day 1 of Period 1 (Part 2)
3. History of serious adverse reaction or serious hypersensitivity to any drug or allergy to the study drug formulation excipients
4. Subjects who are, or are immediate family members of, a study site or Sponsor employee
5. Subjects who have previously been administered IMP in this study. Subjects who have taken part in Part 1 are not permitted to take part in Part 2.
6. Evidence of current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; i.e., the virus that causes COVID-19) infection
7. Positive for hepatitis C virus (HCV) antibody, hepatitis B surface antigen (HBsAg), or human immunodeficiency virus (HIV) antibody at screening
8. History of any drug or alcohol abuse in the past 2 years
9. Regular alcohol consumption >14 units per week (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 Units = 125 mL glass of wine, depending on type)
10. A confirmed positive alcohol breath test at screening or admission
11. Current smokers and those who have smoked within the last 12 months. A confirmed breath carbon monoxide reading of greater than 10 ppm at screening or admission.
12. Current users of e-cigarettes and nicotine replacement products and those who have used these products within the last 12 months
13. Confirmed positive drugs of abuse test result at screening or admission
14. Radiation exposure, including that from the present study, excluding background radiation but including diagnostic x-rays and other medical exposures, exceeding 5 mSv in the last 12 months or 10 mSv in the last 5 years. No occupationally exposed worker, as defined in the Ionising Radiation Regulations 2017, shall participate in the study (Part 1 only)
15. Subjects who do not have suitable veins for multiple venipunctures/cannulation as assessed by the Investigator or delegate at screening

16. Clinically significant abnormal clinical chemistry, hematology, coagulation or urinalysis as judged by the Investigator (laboratory parameters are listed in Appendices 1 and 2). Subjects with Gilbert's Syndrome are allowed
17. Evidence of renal impairment at screening, as indicated by an estimated creatinine clearance (CLcr) of <70 mL/min using the Cockcroft-Gault equation
18. History of clinically significant cardiovascular, renal, hepatic, dermatological, chronic respiratory or GI disease (especially peptic ulceration, GI bleeding, ulcerative colitis, Crohn's Disease or Irritable Bowel Syndrome), neurological or psychiatric disorder, as judged by the Investigator
19. Presence or history of clinically significant allergy requiring treatment, as judged by the Investigator. Hay fever is allowed unless it is active
20. Donation of blood or plasma within the previous 3 months or loss of greater than 400 mL of blood
21. Subjects who are taking, or have taken, any medication (e.g., prescription drugs, over-the-counter drugs, hormone replacement therapy [HRT], vaccines, topical medications, herbal or homeopathic remedies, nutritional supplements), other than up to 4 g of paracetamol per day, in the 14 days before IMP administration. Exceptions may apply on a case by case basis, if considered not to interfere with the objectives of the study, as determined by the Investigator.
22. Subjects who are taking, or have taken, oral antibiotics within 4 weeks or IV antibiotics within 8 weeks prior to admission.
23. Subjects who are taking, or have taken, any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to admission.
24. History of GI surgery (with the exception of appendectomy unless it was performed within the previous 12 months) (Part 1 only)
25. Acute diarrhea or constipation in the 7 days before the predicted Day 1. If screening occurs >7 days before the Day 1, this criterion will be determined on Day 1. Diarrhea will be defined as the passage of liquid feces and/or a stool frequency of greater than 3 times per day. Constipation will be defined as a failure to open the bowels for 3 days (Part 1 only)
26. Malabsorption syndrome or other condition that would interfere with enteral absorption
27. History or presence of an abnormal ECG that is clinically significant in the Investigator's opinion, including complete left bundle branch block, second- or third-degree atrioventricular heart block, or evidence of prior myocardial infarction
28. QT interval corrected through use of Fridericia's formula (QTcF) $>$440 msec demonstrated by at least two ECGs $>$30 minutes apart
29. History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias such as structural heart disease (e.g., severe left ventricular systolic dysfunction, left ventricular hypertrophy), coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), clinically significant electrolyte abnormalities

(e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome

30. Confirmed (e.g., 2 consecutive measurements) baseline heart rate ≤50 bpm prior to enrollment
31. Current treatment with medications that are well known to prolong the QT interval
32. Absolute neutrophil count $<1.3 \times 10^9$/L (1300/μL)
33. Failure to satisfy the Investigator of fitness to participate for any other reason

For Part 1, exclusion criteria 1, 6, 10, 11, 13, 16, 20, 21, 25, 27, 28, 29, 30, 31, 32 and 33 from the list above will be re-assessed at admission/pre-dose.

For Part 2, exclusion criteria 1, 6, 10, 11, 13, 16, 20, 21, 27, 28, 29, 30, 31, 32 and 33 from the list above will be re-assessed at admission/pre-dose in Period 1.

## 4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This study is open-label; no blinding is required.

### 4.2.1 Part 1

Part 1 is non-randomized; therefore, a randomization schedule will not be produced. A treatment allocation will be produced prior to dosing with IMP, which will dictate the order in which each subject is administered the treatment. The treatment allocation will be retained in the Investigator Site File (ISF).

Eligible subjects will be assigned a unique identification number on the morning of dosing (Day 1) according to the code [redacted] to [redacted] for Part 1, using the lowest number available.

### 4.2.2 Part 2

Using a computer-generated randomization schedule, subject numbers will be allocated to one of two treatment sequences (Table 4) in Part 2. The allocation will be balanced with 5 subjects assigned to each of the treatment sequences.

**Table 4 Part 2 Treatment Sequences**

| Treatment Sequence | Period 1 | Period 2 | Period 3 |
|---|---|---|---|
| BCD | Treatment B | Treatment C | Treatment D |
| BDC | Treatment B | Treatment D | Treatment C |

B; Treatment B = 30 mg GDC-9545 as a Solution for Infusion, 3 mg/mL administered intravenously in 10 mL as an infusion over 30 minutes
C; Treatment C = GDC-9545/F12 capsule, 30 mg, administered with approximately 240 mL water
D; Treatment D = GDC-9545/F18 capsule, 30 mg, administered with approximately 240 mL water

Eligible subjects will be assigned a unique identification number on the morning of dosing in Period 1 according to the code [redacted] to [redacted] for Part 2, using the lowest number

available. Replacement subjects will be allocated subject numbers [redacted] to [redacted], where the last 2 digits are the same as those of the original subject (e.g., if Subject [redacted] withdraws the replacement will have Subject Number [redacted]). Replacement subjects will be assigned to the same treatment sequence as the subject they replaced and will receive any treatments that the replaced subject did not receive in addition to any treatments that are required to make the required comparison of interest.

A treatment allocation list will be produced prior to dosing using the randomization schedule and will be retained in the ISF.

The original randomization schedule and proof of quality control procedures will be held by the Data Sciences department at Quotient Sciences until the study is archived, at which time the randomization materials will be retained in the ISF.

## 4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The IMP for Part 1 of this study is:

- For Treatment A: [$^{14}$C]-RO7197597 Capsule, 30 mg (NMT 4.6 MBq [124 µCi]), which is referred to as [$^{14}$C]-GDC-9545 capsule in this protocol

The IMPs for Part 2 of this study are:

- For Treatment B: RO7197597 Solution for Infusion, 3 mg/mL, (referred to as GDC-9545 Solution for Infusion in this protocol)
- For Treatment C: Hard Capsules GDC-9545, 30 mg (referred to as GDC-9545/F12 capsule in this protocol)
- For Treatment D: Hard Capsules GDC-9545, 30 mg F18 (referred to as GDC-9545/F18 capsule in this protocol)

### 4.3.1 Study Treatment Formulations and Packaging

For Part 1, the [$^{14}$C]-GDC-9545 will be supplied by Pharmaron UK Ltd, Rushden, Northamptonshire, UK (Pharmaron) as a powder.

For Part 2, the GDC-9545 active pharmaceutical ingredient will be supplied by the Sponsor.

In Part 1, the radiolabeled Treatment A, [$^{14}$C]-GDC-9545 capsule, 30 mg (NMT 4.6 MBq [124 µCi]), will be manufactured by Quotient Sciences as capsules for oral administration.

In Part 2, two oral capsule formulations will be investigated (GDC-9545/F12 capsule, 30 mg and GDC-9545/F18 capsule, 30 mg); both formulations will be manufactured by the Sponsor and will be supplied as 30 mg capsules.

In Part 2, for the purposes of assessment of the absolute bioavailability of the oral formulations, an IV formulation (GDC-9545 as a Solution for Infusion, 3 mg/mL) will also be administered; this will be manufactured by Quotient Sciences.

For information on the formulation and handling of [$^{14}$C]-GDC-9545 and GDC-9545, see the Investigational Medicinal Product Dossier.

### 4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Sections 3.1.1 and 3.1.2 for Parts 1 and 2 of the study, respectively.

Refer to the dosing instructions for detailed instructions on drug preparation, storage, and administration.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.11.

Guidelines for treatment interruption or discontinuation for subjects who experience adverse events are provided in Section 4.6.

#### 4.3.2.1 [$^{14}$C]-GDC-9545 and GDC-9545

In Part 1, each subject will receive a single oral dose of [$^{14}$C]-GDC-9545 capsule, 30 mg (NMT 4.6 MBq [124 µCi]) (Treatment A). The test formulation will be swallowed whole with approximately 240 mL water following an overnight fast of a minimum of 10 hours.

In Part 2, each subject will be randomized to receive a single dose of 30 mg GDC-9545 in each of three treatment periods; the following formulations will be administered:

- Treatment B: GDC-9545 Solution for Infusion, 3 mg/mL
- Treatment C: GDC-9545/F12 capsule, 30 mg
- Treatment D: GDC-9545/F18 capsule, 30 mg

Treatment B will be administered in a 10 mL volume intravenously over 30 minutes (as an infusion) following an overnight fast of a minimum of 10 hours.

To assess tolerability of the IV administration, the first subject will be dosed as a sentinel; then, at least 4 hours later, the second subject will be dosed only if there are no acute safety findings for the first subject. If the first two subjects tolerated the IV dose, in the opinion of the Principal Investigator and Medical Monitor per the criteria in Section 6.8.1, the remaining subjects will be dosed. The third subject will be dosed at least 20 hours after the second subject (i.e., at least 24 hours after the first subject). All subsequent dosing of the IV formulation will be staggered by at least 15 minutes. To allow for potential interruptions and pump variations, up to a 10% difference in duration

of the IV administration will not be considered as a protocol deviation provided that the full planned dose is administered as these minor discrepancies should not have a significant impact on the overall study objectives.

The planned administration time will be 30 minutes; the actual IV administration start and stop time will be recorded in the source.

- The IV administration will finish within ± 3 minutes of the nominal time point

Treatments C and D will be swallowed whole with approximately 240 mL water following an overnight fast of a minimum of 10 hours.

There will be a minimum washout of 10 days between each IMP administration.

[$^{14}$C]-GDC-9545 and GDC-9545 doses are expressed as the free base equivalent.

### 4.3.3 Investigational Medicinal Product Handling and Accountability

Quotient Sciences will manufacture the [$^{14}$C]-GDC-9545 capsules and the GDC-9545 Solution for Infusion. The Sponsor will manufacture the GDC-9545/F12 and GDC-9545/F18 capsules. The study site (i.e., Investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each subject, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that subjects are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of GDC-9545 capsules. The study site will acknowledge receipt of GDC-9545 capsules supplied by the Sponsor to confirm the shipment condition and content. Any damaged shipments will be replaced. The Investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized staff.

Only subjects enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the Pharmaceutical Development and Control Strategy Report, dosing instructions and/or the GDC-9545 IB for information on IMP handling, including preparation and storage, and accountability.

#### 4.3.3.1 Retention of Study Drug Samples

According to Title 21, Part 320 of the U.S. Code of Federal Regulations, reserve samples of the clinical supplies used in a bioavailability or bioequivalence study must be retained by the organization that conducted the study and stored under conditions that will maintain the integrity, identity, strength, quality and purity of the samples. The samples for retention will be randomly selected by the Investigator or by a representative of the Investigator. All samples must be retained at the study site for a period of at least 5 years following the date on which the application or supplemental application is approved by the U.S. FDA. If such application is not approved, all samples must be retained for at least 5 years following the date of completion of any bioavailability or bioequivalence study from which the reserve samples were obtained.

### 4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, HRT, vaccines, topical medications, herbal or homeopathic remedies, nutritional supplements) used by a subject in addition to protocol-mandated treatment from 14 days before IMP administration until discharge from the study.

All such medications should be reported to the Investigator and recorded on the Concomitant Medications eCRF.

#### 4.4.1 Permitted Therapy

Subjects are permitted to use the following therapies during the study:

- Up to 4 g of paracetamol per day
- Medications to treat adverse events

If any medication is required, the name, strength, frequency of dosing and reason for its use will be documented in the subject's source data.

#### 4.4.2 Prohibited Therapy

Subjects should not take any medication (e.g., prescription drugs, over the counter drugs, HRT, vaccines, topical medications, herbal or homeopathic remedies, nutritional supplements), with the exception of up to 4 grams of paracetamol per day, from 14 days before IMP administration until discharge from the study unless the Investigator has given prior consent. The following categories of medication are specifically prohibited:

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 90 days prior to initiation of study treatment and during study treatment.
- Subjects may not take oral antibiotics within 4 weeks or IV antibiotics within 8 weeks prior to admission until discharge from the study, with the exception of any medications that are required to treat adverse events.
- 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 admission until discharge from the study.

### 4.4.3 Prohibited Food and Drink

Use of the following foods and drinks is prohibited as described below:

- Consumption of liquids or foods containing grapefruit, cranberry, caffeine or other xanthines from 24 hours prior to admission until discharge from the clinical unit.
- Consumption of food containing poppy seeds for 48 hours prior to screening and for 48 hours prior to admission until discharge from the clinical unit.

### 4.4.4 Additional Restrictions

For Part 1, subjects must not consume anything likely to disturb GI transit (e.g., spicy or high-fat meals such as curry or fish and chips or foods of a high-fiber content such as All-Bran) for 24 hours prior to admission until discharge from the study.

For both study parts, subjects must not consume alcohol during the 24 hours prior to screening and the 24 hours prior to admission until discharge from the clinical unit.

Subjects must not take part in any unaccustomed strenuous exercise from the 72 hours before the screening visit and then from 72 hours prior to admission until discharge from the clinical unit.

Subjects must not donate blood or plasma (outside of this study), from clinical unit admission, throughout the study duration, and for at least 90 days following last dose of study medication.

No food or fluids other than water will be allowed from 8 hours prior to each study visit until after study laboratory samples are obtained.

In each study period, subjects will be provided with a light snack on the evening of Day -1 and no food will be allowed until 4 hours after dosing.

Lunch will be provided at approximately 4 hours post-dose, an evening meal at approximately 10 hours post-dose and an evening snack at approximately 14 hours post-dose.

On subsequent days, meals will be provided at appropriate times. Meals will be similar among cohorts.

Subjects will be allowed water up to 1 hour before the scheduled dosing time and will be provided with 240 mL of water at 1 hour post-dose. Water will be allowed ad libitum after 1 hour post-dose. Decaffeinated fluids will be allowed ad libitum from lunch time on the day of dosing.

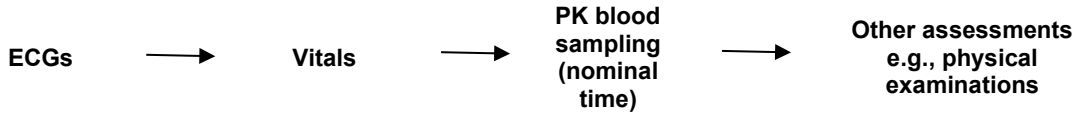
## 4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1 for Part 1 and in Appendix 2 for Part 2. All activities should be performed and documented for each subject.

There are times where the protocol requires more than one procedure to be completed at the same time point. In these instances, the following will apply to post-dose time points:

- PK samples should take priority over other procedures scheduled at the same time point
- ECGs should be taken prior to vital signs when both measurements are scheduled at the same time point
- Other assessments, e.g., physical examinations etc., will be performed within the required time windows

As guidance, the preferred order of assessments is:




All assessments will be timed and performed relative to the start of dosing.

### 4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled subjects and for subjects who are not subsequently enrolled will be maintained at the study site.

Subjects will be provided with a written explanation of the study at least the day before the screening visit. A physician or nurse will explain to each subject the nature of the study, its purpose, expected duration and the benefits and risks involved in study participation. Subjects will be informed that, for safety reasons, brief details of their involvement in the study may be revealed to other units and companies that carry out clinical studies in the local area. Subjects will then be given the opportunity to ask questions and will be informed of their right to withdraw from the study without prejudice. After this explanation and before entering the study, the subject will voluntarily sign an ICF. Until written consent has been obtained from the subject, no study specific procedure or investigation will be performed. If an amendment is made to the participant

information sheet, participants will be re consented to the most current version of the ICF(s) where appropriate.

All screening evaluations must be completed and reviewed to confirm that subjects meet all eligibility criteria before enrollment. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Although only women of non-childbearing potential will be enrolled, and so the risk of pregnancy is very low, the risk associated with exposure to ionizing radiation to women who may be pregnant, will be discussed with female subjects. They will be tested using a highly sensitive pregnancy screening kit prior to each study period. Any subject found to be pregnant, or in whom pregnancy cannot reasonably be excluded, will be withdrawn from the study.

If the start of the study is delayed for any reason so that the interval between screening and first dose exceeds 28 days, all or part of the screening procedures may be repeated at the discretion of the Investigator.

This study permits the re-screening of a subject who has discontinued the study as a pre-treatment failure (i.e., subject has not been randomized/has not been treated); the reason for failure must be temporary and expected to resolve. If re-screened, the subject must be re-consented.

### 4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, HRT, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the subject within 14 days prior to initiation of study treatment will be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity. Height and weight will be recorded at screening.

### 4.5.3 Physical Examinations

A complete physical examination, performed at screening, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, GI, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the Medical History.

Limited, symptom-directed physical examinations should be performed at specified timepoints and as clinically indicated. Changes from baseline abnormalities should be

recorded in subject notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

### 4.5.4 Vital Signs

Vital signs will include measurements of pulse rate, and systolic and diastolic blood pressure while the subject is in a supine position for 5 minutes, and oral temperature.

The acceptable deviations from the nominal vital signs measurements time points are:

- The pre-dose vital signs measurements will be taken ≤2 hours before dosing.
- Post-dose vital signs measurements will be taken ± 15 minutes from the nominal post-dose time points.
- Discharge vital signs measurements will be taken ± 1 hour from the nominal time point.

Record abnormalities observed at baseline on the Medical History. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

### 4.5.5 Laboratory and Other Biological

When a subject withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the subject specifically requests 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.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.5.

For sampling procedures, storage conditions, and shipment instructions, see the Clinical Sample Processing Manual.

#### 4.5.5.1 Safety Laboratory Assessments

Samples for the following laboratory tests will be sent to The Doctors Laboratory for analysis:

- Hematology: white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin, hematocrit (packed cell volume), mean cell hemoglobin, mean cell hemoglobin concentration, mean cell volume, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes)
- Chemistry panel (serum):magnesium, sodium, potassium, chloride, glucose, fasting glucose, urea, creatinine, creatine kinase, total protein, albumin, phosphate (inorganic), calcium, total bilirubin, direct bilirubin (only if total is elevated), alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), and bicarbonate

- Coagulation: international normalized ratio (INR), activated partial thromboplastin time (APTT), thrombin time and prothrombin time (PT)
- Virology: HBsAg, HCV Antibody, HIV Antibody at screening
- Estradiol and FSH (post-menopausal female subjects only)
- Pregnancy test
  - All women will have a highly sensitive serum pregnancy test at screening and a highly sensitive urine pregnancy test at admission.
- Urinalysis (pH, specific gravity, glucose, protein, ketones, blood, bilirubin, leukocytes, nitrites, urobilinogen) and urine drug screen samples will be analyzed by dipstick at the clinic. Microbiology and/or microscopic urinalysis examination, at the discretion of the Investigator based on urinalysis results (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)
- The urine drug screen will test for the following: amphetamines, barbiturates, benzodiazepines, cocaine, marijuana/cannabis, methadone, methamphetamine/ecstasy, morphine/opiates, phencyclidine, and tricyclic anti-depressants.

Scheduled blood samples for safety laboratory tests will be taken following an 8-hour fast. The acceptable deviation from the nominal time points are as follows:

- The pre-dose samples will be taken ≤2 hours before dosing
- Post-dose samples will be taken ± 1 hour from the nominal sampling time

CLcr will be calculated at screening by The Doctors Laboratory using the Cockcroft-Gault equation and body weight for eligibility purposes:

$$\text{CLcr (mL/min)} = \frac{\text{(140-age [years]) x (body weight [kg]) (× 1.04)}}{\text{serum creatinine (µmol/L)}}$$

Alcohol breath tests and carbon monoxide breath tests will be performed at the clinic. A positive alcohol breath test will exclude that subject from dosing during that admission. A carbon monoxide result of greater than 10 ppm will exclude the subject from the study.

#### 4.5.5.2 Mass Balance, Pharmacokinetic and Metabolite Profiling and Identification Assessments

Samples for the following laboratory tests will be sent to Covance for analysis:

- Plasma samples for PK analysis of GDC-9545

Samples for the following laboratory tests will be sent to Pharmaron for analysis:

- Plasma, whole blood, urine and feces samples for analysis of TR (Part 1 only)
- Other accidental sources of elimination for analysis of TR (Part 1 only)

Samples for the following laboratory tests will be sent to the Sponsor for analysis:

- Plasma, urine and feces samples for metabolite profiling and identification (Part 1 only)

Consent will be collected from the subjects for use of these samples for the purposes of the proposed study.

In Part 1, a single urine sample will be taken at pre-dose (or the first void of the day) for the mass balance analysis. Where a sample is not provided, this will not be considered a deviation. All individual urine voids will be collected and shipped to Pharmaron for TR analysis, according to Quotient Sciences' standard operating procedures, unless indicated otherwise by the Sponsor.

In Part 1, the pre-dose fecal sample will be taken in the 24 hours period before dosing (between admission and pre-dose). If a pre-dose fecal sample cannot be obtained, the subject will still be dosed. Where a sample is not provided, this will not be considered a deviation. Samples will be shipped to Pharmaron for the analysis of TR.

During Part 1 of the study, other accidental sources of elimination will be collected as voided (e.g., emesis). Samples will be shipped to Pharmaron for the analysis of TR.

Venous blood samples will be withdrawn via an indwelling cannula or by venipuncture (see Appendices 3 and 4 for detailed schedules for Parts 1 and 2, respectively). The acceptable deviations from the nominal PK and metabolite profiling and identification blood sampling times are as follows:

- The pre-dose samples will be taken ≤1 hour before dosing
- 0.25 to 0.5 hours post-dose samples will be taken within ± 2 minutes of the nominal post-dose sampling time
- 0.58 to 1 hour post-dose samples will be taken within ± 5 minutes of the nominal post-dose sampling time
- 1.5 to 8 hours post-dose samples will be taken within ± 15 minutes of the nominal post-dose sampling time
- 12 to 24 hours post-dose samples will be taken within ± 30 minutes of the nominal post-dose sampling time
- 48 to 480 hours post-dose samples will be taken within ± 4 hours of the nominal post-dose sampling time
- 648 to 984 hours post-dose samples will be taken within ± 1 day of the nominal post-dose sampling time

For Treatment B, PK samples will be timed and performed relative to the start of the IV administration.

The total blood volume for each subject will not exceed 550 mL in a 4-week period. The first 0.5 mL of blood withdrawn via cannula will be discarded.

Residual PK samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

### 4.5.6 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1 for Part 1 and Appendix 2 for Part 2). The acceptable deviations from the nominal ECG measurement time points are:

- The pre-dose ECG measurements will be taken ≤2 hours before dosing
- Post-dose ECG measurements will be taken ± 15 minutes from the nominal post-dose time point.
- Discharge ECG measurements will be taken ± 1 hour from the nominal time point.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the subject has been resting in a supine position for at least 5 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal, whenever feasible. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the Investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the subject's permanent study file at the site. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular post-dose timepoint the mean QTcF is $>$ 500 msec and/or 60 msec longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs taken 30 minutes apart. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the Investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 4.6.1. The Investigator should also evaluate the subject for potential concurrent

risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

## 4.6 TREATMENT, SUBJECT, STUDY, AND SITE DISCONTINUATION

### 4.6.1 Stopping Criteria

The study will be halted, and the risk to other subjects evaluated if any of the following criteria are met:

- A serious adverse reaction (i.e., a serious adverse event considered at least possibly related to the IMP administration) in one subject.
- Severe non-serious adverse reactions (i.e., severe non-serious adverse event considered as, at least possibly related to the IMP administration) in two subjects in the same cohort, independent of within or not within the same system organ class.

Relatedness will be determined by the Investigator.

If the study is halted, a temporary halt will be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and ethics committee (EC) in the form of a substantial amendment. The study may be resumed or terminated; however, it will not be resumed until a further substantial amendment to resume the study is submitted and approved by MHRA and EC.

The ARSAC Practitioner will also be informed of the temporary halt.

In addition, subjects must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the Investigator or Sponsor determines may jeopardize the subject's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the subject
- Pregnancy
- Concurrent illness that would adversely affect subject safety or data integrity or requirement for prohibited medication
- Experiencing a serious or severe adverse event including but not limited to:
  - corrected QT interval by Fridericia's formula (QTcF) of >500 msec or increase in QTcF interval of >60 msec from baseline (confirmed following a repeat ECG)
  - ALT concentration >3 × the upper limit of the reference range (confirmed following a repeat ALT blood test)
- Evidence of current SARS-CoV-2 infection

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

For a subject who withdraws because of an IMP-related adverse event, every effort will be made to ensure the subject completes follow-up procedures. Any subject withdrawn or discontinuing the study prematurely because of an IMP-related adverse event or termination of the study will be considered to have completed the study, and will not be replaced.

Subjects who withdraw from Part 1 of the study will not be replaced.

For Part 2 only, subjects who discontinue study treatment may be replaced at the discretion of the Sponsor and the Investigator to ensure a minimum of 8 evaluable subjects. An evaluable subject for Part 2 of the study is defined as a subject who has received an IMP and has sufficient drug concentration measurements up to 168 hours after dosing for evaluation of defined PK parameters for each treatment, and have completed all planned safety assessments up to 168 hours after dosing for each treatment.

### 4.6.2 Subject Discontinuation from the Study

Subjects have the right to voluntarily withdraw from the study at any time for any reason. In addition, the Investigator has the right to withdraw a subject from the study at any time.

Reasons for subject discontinuation from the study may include, but are not limited to, the following:

- Subject withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Subject non-compliance, defined as failure to comply with protocol requirements as determined by the Investigator or Sponsor

Every effort should be made to obtain a reason for subject discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a subject requests to be withdrawn from the study, this request must be documented in the source documents and signed by the Investigator.

For a subject who withdraws because of an IMP-related adverse event, every effort will be made to ensure the subject completes follow-up procedures. Any subject withdrawn or discontinuing the study prematurely because of an IMP-related adverse event or termination of the study will be considered to have completed the study, and will not be replaced.

Subjects who withdraw from Part 1 of the study will not be replaced.

For Part 2 only, subjects who discontinue study treatment may be replaced at the discretion of the Sponsor and the Investigator to ensure a minimum of 8 evaluable subjects. An evaluable subject for Part 2 of the study is defined as a subject who has received an IMP and has sufficient drug concentration measurements up to 168 hours after dosing for evaluation of defined PK parameters for each treatment, and have completed all planned safety assessments up to 168 hours after dosing for each treatment.

### 4.6.3 Study Discontinuation

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

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

The Sponsor will notify the Investigator if the Sponsor decides to discontinue the study.

After the start of protocol activities but prior to the commencement of dosing, the study may be terminated by the Sponsor and Investigator without consultation with the MHRA, EC, ARSAC Practitioner or ARSAC. The ARSAC Practitioner and ARSAC (if ARSAC research application has been submitted or approved) must be notified promptly, in writing, that the study will no longer be taking place. Notification of early termination should also be provided to the EC and MHRA within 15 days, clearly explaining the reasons for the termination.

If the study is abandoned prior to commencement of any protocol activities, the Investigator or Sponsor must notify the EC, MHRA, ARSAC Practitioner and ARSAC (if ARSAC research application has been submitted or approved) in writing outlining the reasons for abandonment of the trial.

New information regarding the safety of the IMP that indicates a change in the risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study may also mean termination of the study prior to dosing.

Once exposure to dosing has begun, the study will be completed as planned unless the following criteria are satisfied that require a temporary halt or early termination of the study.

- The occurrence of serious or severe adverse event(s), if considered to be related to the IMP, on the dosing day.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

If any of the above occurs, the study will be terminated if careful review of the overall risk/benefit analysis demonstrates that the assumptions have changed and that the overall balance is no longer acceptable. In these circumstances, termination can only take place with the agreement of the Investigator and Sponsor. The MHRA, EC, ARSAC Practitioner and ARSAC will be informed of study termination.

If it becomes necessary to consider termination of the study on the dosing day, dosing may be suspended pending discussion between the Investigator, Sponsor and ARSAC Practitioner). Dosing will be stopped immediately on safety grounds.

The study may be terminated or suspended at the request of the MHRA or EC.

### 4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for GCP
- No study activity (i.e., all subjects have completed the study and all obligations have been fulfilled)

## 5. ASSESSMENT OF SAFETY

### 5.1 SAFETY PLAN

GDC-9545 is not approved, and clinical development is ongoing. The safety plan for volunteers in this study is based on clinical experience with GDC-9545 in completed and ongoing studies. The anticipated important safety risks for this study are outlined below. Please refer to the GDC-9545 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 adverse events.

### 5.1.1 Risks Associated with GDC-9545

As of the data cutoff of 31 Jan 2020, the safety of GDC-9545 has previously been evaluated in a comprehensive pre-clinical safety program and in clinical studies in more than 160 ER+ breast cancer patients. Preclinical and clinical findings for GDC-9545 are summarized in Section 1.2.

Overall, GDC-9545 was well tolerated at all dose levels in patients with early breast cancer; all reported adverse events have been Grade 1 or 2 severity, except a Grade 3 serious adverse event of breast abscess in one patient at 10 mg dose level, which was considered unrelated to GDC-9545 by the Investigator. With the exception of one event of fatigue (which was also considered related to progressive disease), no serious adverse drug reactions have been reported in the single agent studies; additionally, no identified risks have been confirmed for GDC-9545.

On the basis of nonclinical toxicology findings for GDC-9545 and known toxicities associated with other drugs in the ER antagonist class, the potential risks of GDC-9545 are hepatotoxicity, GI toxicities, venous thromboembolic events, bradycardia, renal dysfunction, changes in female reproductive organs and menopausal symptoms, male/female infertility, QT prolongation and embryofetal toxicity. These potential risks will be managed as outlined in Section 1.3.2.

GDC-9545 has been assessed to have a low potential for clinically relevant Cytochrome P450 mediated drug-drug interactions. Nonetheless, potential drug-drug interactions with other medications will be avoided by restrictions on concomitant medication use.

In pre-clinical toxicity studies, GDC-9545 was found to be not mutagenic in the bacterial mutagenesis assay, did not induce an increase in micronucleus formation in human lymphocytes in in vitro studies and was not phototoxic in an in vitro mammalian cell-based assay.

Overall, no significant safety concerns have been identified about the use of 30 mg GDC-9545 in healthy volunteers.

### 5.1.2 Risks Associated with Radiation

Subjects will be exposed to ionizing radiation of NMT 4.6 MBq (124 µCi) [$^{14}$C]. The effective dose that each subject will receive from one administration of 4.6 MBq (124 µCi) [$^{14}$C] will not exceed 0.7 mSv. This is approximately 3.1 months of the average radiation exposure received in the UK each year (2.7 mSv; data obtained from Public Health England Ionising Radiation Exposure of the UK Population: 2010 Review) and is equivalent to slightly less than the radiation dose that would result from 2 x-rays of the abdomen. An increase in the amount of radiation that is received above natural radiation carries a risk of later developing serious and possibly fatal conditions. However, the risk associated with the maximum possible dose of radiation in this study is very small indeed and is considered to be acceptable.

### 5.1.3 COVID-19 Related Risks and Risk Mitigation Measures

The following risks and risk mitigating measures apply to the time in which the study is conducted during the COVID-19 pandemic.

#### 5.1.3.1 IMP-Related Risk

Against the background of the COVID-19 pandemic, the potential risk of a subject developing COVID-19 has been considered in terms of the risk-benefit evaluation. The mode of action of the IMP – as ER antagonist – has been considered alongside available pre-clinical and clinical data (including class effects) and it is considered that a subject would not be at increased risk of either becoming infected with SARS-CoV-2 (the virus that causes COVID-19) or experiencing a more severe illness. That is, the IMP has no known immunomodulatory effect that would confer an increased risk to healthy subjects enrolled in the study.

#### 5.1.3.2 General COVID-19-Related Risk Mitigation Measures

General risk mitigation against COVID-19 will be implemented in accordance with Quotient Sciences' monitoring and prevention control measures.

The risk mitigation measures, where applicable, will be amended based on emerging government guidance.

### 5.1.4 General Risks

Collecting a blood sample from a vein may cause pain, swelling, bruising, light headedness, fainting, and very rarely, clot formation, nerve damage and/or infection at the site of the needle stick.

During cannulation, more than one attempt may be needed to insert the cannula in a vein of a subject and it is possible that bruising and/or inflammation may be experienced at the site of cannulation.

Electrocardiogram (ECG) stickers on the subjects' chests and limbs may cause some local irritation and may be uncomfortable to remove but subjects will be closely monitored to ensure any local irritation does not persist.

## 5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, 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.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

### 5.2.1 Adverse Events

According to the ICH guideline for GCP, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event 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) (see Section 5.3.5.9 for more information)
- 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)

### 5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the Investigator, places the subject at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs subject hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event 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)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see

Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

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

Serious adverse events are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

### 5.2.3 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 immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 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 5.3.5.7)
- Cases of potential drug-induced kidney injury
- 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.
- 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. This term applies only when a contamination of the study drug is suspected.

## 5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The Investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the Investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

### 5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

### 5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event 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?"

### 5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

**Table 5 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 a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

### 5.3.4 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 adverse event 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 6:

- 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 6 Causal Attribution Guidance**

| Is the adverse event suspected to be caused by the study drug on the basis of 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. |
| NO | An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting 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). |

For subjects receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

### 5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

#### 5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction" or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a subject experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

#### 5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event 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 Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event

report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

#### 5.3.5.3 Adverse Events That Are Secondary to Other Events

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

#### 5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between subject evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event 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 serious adverse events.

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

#### 5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event 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 adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event 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 adverse event. 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 Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

#### 5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event 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 adverse event.

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 Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

### 5.3.5.7 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

### 5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

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 Adverse Event 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 Adverse Event 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 adverse event reporting period should be reported as described in Section 5.6.

### 5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the Medical History.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept

that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

#### 5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for a preexisting 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 adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of subject requirement for outpatient care outside of normal outpatient clinic operating hours

#### 5.3.5.11 Cases of Accidental Overdose or Medication Error

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

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For GDC-9545 and [$^{14}$C]-GDC-9545, adverse events associated with special situations should be recorded as described below for each situation:

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

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

In addition, all special situations associated with GDC-9545 or [$^{14}$C]-GDC-9545, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (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 two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

## 5.4 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; 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 after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the Investigator must report new significant follow-up information to the Sponsor immediately (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 serious adverse events to the local health authority and EC.

### 5.4.1 Emergency Medical Contacts

**Medical Monitor Contact Information**

Genentech Medical Monitor contact information:

Medical Monitors: [redacted] MD, MPH (Primary)

Telephone Nos.: [redacted] (Mobile – USA)

[redacted] (Office – USA)

**ARSAC Practitioner Contact Information**

CRO ARSAC Practitioner contact information:

ARSAC Practitioner: [redacted] MB BChir, MRCGP, MFPM

Telephone No.: [redacted] (Mobile – UK)

Email: [redacted]

### 5.4.2 Reporting Requirements for Serious Adverse Events, Adverse Events of Special Interest

#### 5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Sponsor or its designee 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 to Investigators:

– Fax: [redacted] or [redacted] or [redacted] or [redacted]

– Email: welwyn.pds-pc@roche.com

#### 5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 28 days after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Sponsor or its designee 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 to Investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur $>$28 days after the final dose of study treatment are provided in Section 5.6.

### 5.4.3 Reporting Requirements for Pregnancies

#### 5.4.3.1 Pregnancies in Female Subjects

Subjects will be instructed to immediately inform the Investigator if they become pregnant during the study or within 30 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to Investigators. Pregnancy should not be recorded on the Adverse Event 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 serious adverse events 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 Adverse Event eCRF. In addition, the Investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

#### 5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event,

recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

#### 5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female subject exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

## 5.5 FOLLOW-UP OF SUBJECTS AFTER ADVERSE EVENTS

### 5.5.1 Investigator Follow-Up

The Investigator should follow each adverse event 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 serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event 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.

### 5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, 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.

## 5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the Investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 28 days after the final dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the Investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special

Interest Reporting Form using the fax number or email address provided to Investigators.

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

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

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the following reference document:

- 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.

It is the responsibility of the Sponsor to determine whether an event requires expedited reporting and to notify the Investigator of their decision as soon as possible.

Where expedited reporting is required, the following procedures should be followed.

Fatal or life-threatening SUSARs

Suspected unexpected serious adverse reactions (SUSARs) are adverse events that are believed to be related to an IMP and are both unexpected (i.e., the nature or severity is not expected from the information provided in the IB) and serious. SUSARs are subject to expedited reporting to the MHRA, EMA, and EC.

It is the responsibility of the Sponsor to report fatal or life-threatening SUSARs to the MHRA as soon as possible, but no later than 7 calendar days after they first became aware of the reaction. Any additional relevant information should be sent within 8 days of the report.

The Sponsor is required to notify the EC of any SUSAR as soon as possible, but no later than 7 calendar days after they first became aware of the reaction. Any additional relevant information should be sent within 8 days of the report. The task of reporting fatal or life-threatening SUSARs may be delegated to the Investigator.

The ARSAC Practitioner will be notified of any fatal or life-threatening SUSAR that is considered related to the exposure to radioactivity.

Other SUSARs

It is the responsibility of the Sponsor to report other SUSARs to the MHRA as soon as possible, but no later than 15 calendar days after they first became aware of the reaction.

The Sponsor is required to notify the EC of other SUSARs as soon as possible, but no later than 15 calendar days after they first became aware of the reaction. The task of reporting other SUSARs may be delegated to the Investigator.

The ARSAC Practitioner will be notified of any SUSAR that is considered related to the exposure to radioactivity.

# 6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary objectives of Part 1 of this study is to characterize the absorption, metabolism, excretion, PK of GDC-9545. No formal statistical analysis will be performed for Part 1 of this study.

The primary objectives of Part 2 of this study are to evaluate the absolute and relative bioavailability of GDC-9545. A mixed-effect analysis of variance model for the two-period crossover design will be used for formulation comparison. A separate mixed-effect analysis of variance model will be used for the absolute bioavailability comparison.

Descriptive statistics (e.g., mean, median, standard deviation, minimum, maximum and number of subjects with an observation [n]) will be calculated for PK, mass balance and safety data in both Parts 1 and 2 of the study. Additional statistics will be provided for PK-related data, including coefficient of variation (CV%), geometric mean and geometric CV%.

All safety, mass balance recovery, and PK data will be listed.

A study specific Statistical Analysis Plan (SAP) will be produced which will detail the statistical and reporting requirement for the study in more detail. The SAP will be finalized prior to database lock.

## 6.1 DETERMINATION OF SAMPLE SIZE

For Part 1, it is planned to enroll 6 subjects to ensure data in a minimum of 4 evaluable subjects. For Part 2, it is planned to enroll 10 subjects to ensure data in a minimum of 8 evaluable subjects. No replacement subjects are to be used in Part 1 of this study. Up to 4 replacement subjects are permitted in Part 2 of this study to ensure there are 8 evaluable subjects.

The study is exploratory and no formal sample size calculation has been made. Based on experience from previous studies of a similar design, a sample size of 6 subjects for Part 1 and 10 subjects for Part 2 is considered appropriate to meet the objectives of the study.

## 6.2 SUMMARIES OF CONDUCT OF STUDY

The number of subjects who enroll, are randomized (Part 2 only), are dosed, discontinue, or complete the study will be summarized. Reasons for premature study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

## 6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race/ethnicity, height, weight, and BMI) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. For Part 1, summaries will be presented overall. For Part 2, summaries will be presented by treatment sequence; if all subjects receive all treatments, summaries will be presented overall only, unless a sequence effect is observed in the formal statistical analyses described below. Additionally, all data will be listed.

Demographic and baseline characteristics will be recorded at screening.

## 6.4 MASS BALANCE ANALYSES (PART 1 ONLY)

Urine and fecal samples will be collected for the analysis of TR in Part 1. The following mass balance parameters will be calculated by Quotient Sciences from urine and feces separately and total (urine and feces combined):

- $A_{eu}$: amount of TR excreted in urine
- $CumA_{eu}$: cumulative amount of TR excreted in urine
- $F_{eu}$: amount of TR excreted in urine expressed as a percentage of the radioactive dose administered
- $CumF_{eu}$: cumulative amount of TR excreted in urine expressed as a percentage of the radioactive dose administered
- $A_{ef}$: amount of TR eliminated in feces
- $CumA_{ef}$: cumulative amount of TR eliminated in feces
- $F_{ef}$: amount of TR eliminated in feces expressed as a percentage of the radioactive dose administered
- $CumF_{ef}$: cumulative amount of TR eliminated in feces expressed as a percentage of the radioactive dose administered
- $A_{etotal}$: amount of TR excreted in urine and feces combined

- $CumA_{etotal}$: cumulative amount of TR excreted in urine and feces combined
- $F_{etotal}$: amount of TR excreted in urine and feces combined expressed as a percentage of the radioactive dose administered
- $CumF_{etotal}$: cumulative amount of TR excreted in urine and feces combined expressed as a percentage of the radioactive dose administered

## 6.5 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of subjects with sufficient data to enable estimation of key parameters (e.g., AUC, time to maximum concentration [$t_{max}$], maximum concentration [$C_{max}$], half-life [$t_{1/2}$) with subjects grouped according to treatment received.

Plasma GDC-9545, plasma TR and whole blood TR concentration data will be listed and summarized by treatment using descriptive statistics. Individual and mean concentration versus time profiles will be plotted.

The PK of GDC-9545 in plasma and TR in whole blood and plasma will be summarized by estimating the following parameters (as appropriate for data collected):

- $C_{max}$: maximum observed concentration
- $t_{max}$: time of maximum observed concentration
- $AUC_{0-t}$: area under the curve from time 0 to the time of last measurable concentration
- $AUC_{0-inf}$: area under the curve from time 0 extrapolated to infinity
- $\lambda_z$: first order rate constant associated with the terminal (log-linear) portion of the curve
- $t_{1/2}$: terminal elimination half-life
- CL: total body clearance calculated after a single IV administration (for GDC-9545 only; Part 2 IV dose only)
- CL/F: total body clearance calculated after a single extravascular administration where F (fraction of dose bioavailable) is unknown (for GDC-9545 only; oral doses only)
- $V_z$: volume of distribution based on the terminal phase calculated using $AUC_{0-inf}$ after a single IV administration (for GDC-9545 only; Part 2 IV dose only)
- $V_z$/F: apparent volume of distribution (for GDC-9545 only; oral doses only)
- Ratio between whole blood and plasma concentrations for TR (Part 1 only)
- Ratio between whole blood and plasma $AUC_{0-inf}$ values for TR (Part 1 only)
- F: Absolute bioavailability calculated using $AUC_{0-inf}$ (for GDC-9545 only; oral doses in Part 2 only)

- Frel $C_{max}$: Relative bioavailability based on $C_{max}$ (for GDC-9545 only; GDC-9545/F18 capsule, 30 mg in Part 2 only)
- Frel $AUC_{0-t}$: Relative bioavailability based on $AUC_{0-t}$ (for GDC-9545 only; GDC-9545/F18 capsule, 30 mg in Part 2 only)
- Frel $AUC_{0-inf}$: Relative bioavailability based on $AUC_{0-inf}$ (for GDC-9545 only; GDC-9545/F18 capsule, 30 mg in Part 2 only)

The absolute bioavailability of GDC-9545/F12 capsule and GDC-9545/F18 capsule will be calculated using the $AUC_{0-inf}$ values obtained after oral and IV administration of GDC-9545. The mixed-effect analysis of variance model will be used for absolute bioavailability determination. The model will include formulation and period as fixed effects and a random subject effect.

To evaluate the relative bioavailability of GDC-9545 as GDC-9545/F18 capsule compared to GDC-9545/F12 capsule, the PK parameters $C_{max}$ and $AUC_{0-inf}$ for GDC-9545 will be analyzed. The mixed-effect analysis of variance model for the two-period crossover design will be used for formulation comparison. The model will include formulation and period as fixed effects and random subject effect (i.e., assuming a compound symmetry covariance structure).

Log-transformed $C_{max}$, $AUC_{0-t}$, and $AUC_{0-inf}$ values will be evaluated to estimate ratios of geometric mean values and the corresponding 90% confidence intervals (CIs) (test: GDC-9545/F18 capsule, reference: GDC-9545/F12 capsule; or test: GDC-9545/F12 capsule, reference: GDC-9545 Solution for Infusion; or test: GDC-9545/F18 capsule, reference: GDC-9545 Solution for Infusion).

## 6.6 METABOLITE PROFILING AND IDENTIFICATION ANALYSES

Metabolite profiling of plasma, urine and feces will be performed using liquid chromatography-high resolution mass spectrometry where appropriate.

These aspects will be reported separately from the Clinical Study Report as a standalone document.

## 6.7 SAFETY ANALYSES

The safety analysis population will consist of all subjects who received at least one dose of study drug, with subjects grouped according to treatment received.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded from 1 to 5 based on the adverse event severity grading scale for the NCI CTCAE (see Section 5.3.3). Adverse events of special interest will also be collected and reported (see Section 5.4.2).

Summary tables will be presented by treatment. If a subject has more than one episode of a particular event, only one episode (the most severe or the strongest causal relationship to study drug) will be counted. A subject with more than one different adverse event within a particular body system will only be counted once in the total number of subjects experiencing adverse events for the body system. Similarly, a subject who experiences an adverse event in more than one body system will only be counted once in the total number of subjects experiencing adverse events in all body systems.

Selected laboratory and vital sign anomalies will be presented by shift tables and will be listed.

## 6.8 INTERIM ANALYSES

### 6.8.1 Planned Interim Analysis

Part 1 and Part 2 will be analyzed separately.

No interim analyses are planned for Part 1.

The following in-study decision will be made during Part 2 of this study:

- Progression from sentinel group to main group where sentinel dosing is used for Treatment B

For Treatment B, to assess tolerability of the IV administration, the first subject will be dosed as a sentinel; then, at least 4 hours later, the second subject will be dosed only if there are no acute safety findings for the first subject. If the first two subjects tolerated the IV dose, in the opinion of the Principal Investigator and Medical Monitor, the remaining subjects will be dosed. The third subject will be dosed at least 20 hours after the second subject (i.e., at least 24 hours after the first subject). All subsequent dosing of the IV formulation will be staggered by at least 15 minutes.

The decision to proceed with the main group will be made by the Investigator, based on safety data until up to 24 hours post-dose for the two sentinel subjects. The Investigator will inform the sponsor of any safety concerns.

The decision to proceed to the next dose level will be based on safety and tolerability data. The following data are required:

- Adverse events
- ECGs
- Vital signs

# 7. DATA COLLECTION AND MANAGEMENT

## 7.1 DATA QUALITY ASSURANCE

A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. The CRO will supply eCRF specifications for this study. Data entered manually will be collected via EDC through use of eCRFs. The site will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO's Data Management department will request data clarification from the site, which Data Management will resolve electronically in the EDC system.

The CRO will produce a Data Management Plan that describes the quality checking to be performed on the data. Laboratory data will be sent directly to the CRO, using the CRO's standard procedures to handle and process the electronic transfer of these data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's Data Management Plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

AEs, medical histories and medications will be coded as detailed in the Data Management Plan. An independent coding review will also be performed within the Data Sciences department.

## 7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. The site will receive training for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the Investigator or a designee.

At the end of the study, the Investigator will receive subject data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

## 7.3 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, 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 pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the Investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and EC review. The study site must also allow inspection by applicable health authorities.

## 7.4 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 health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

## 7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, , Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by

relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may 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.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

# 8. ETHICAL CONSIDERATIONS

## 8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

## 8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before EC submission. The final EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

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

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

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

If the Consent Forms are revised (through an amendment or an addendum) while a subject is participating in the study, the subject or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and EC policy. For any updated or revised Consent Forms, the case history or clinical records for each subject shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

## 8.3 ETHICS COMMITTEE

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

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

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

## 8.4 ADMINISTRATION OF RADIATION

Dr [redacted] will be the ARSAC Practitioner for this study, which includes the administration of radiation at Quotient Sciences. Administration will be conducted in accordance with Dr [redacted]'s current ARSAC Practitioner license and Quotient Sciences' current ARSAC Employer license. Additionally, a research application will be submitted to ARSAC to obtain approval for the conduct of the study before dosing.

The protocol will be reviewed and the final version will be approved by the ARSAC Practitioner, Dr [redacted].

## 8.5 CONFIDENTIALITY

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

Subject medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the subject, 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 exploratory biomarker analyses, data derived from these analyses 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 (see Section 9.5).

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

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

## 8.6 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate

financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

# 9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

## 9.1 STUDY DOCUMENTATION

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

## 9.2 PROTOCOL DEVIATIONS

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

## 9.3 SITE INSPECTIONS

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

## 9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by Genentech, Inc.

The study will be conducted at a single-center: Quotient Sciences, Mere Way, Ruddington Fields, Ruddington, Nottingham, NG11 6JS, UK.

Central facilities will be used for certain study assessments throughout the study (e.g., clinical laboratory tests, PK analyses and metabolite profiling and identification) as specified in Section 4.5.

Monitoring will be performed by [redacted] Wirral Clinical Consultancy Ltd, 76 Pipers Lane, Lower Heswall Wirral, Cheshire, CH60 9HN, UK.

The ARSAC Practitioner will be [redacted] MB BChir, MRCGP, MFPM, Tel: [redacted] email: [redacted]

## 9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.5 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

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

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

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

## 9.6 PROTOCOL AMENDMENTS

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

Approval must be obtained from the EC and regulatory authorities (as locally required) before implementation of any substantial changes, except for changes necessary to eliminate an immediate hazard to subjects or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

Any amendments relating to the administration of radioactive substances will be reviewed by the ARSAC Practitioner prior to submission to ARSAC as required by the current ARSAC Notes for Guidance. The ARSAC Practitioner will also be notified of any substantial amendments to the PIS and ICF and/or protocol.

## 10. REFERENCES


Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394–424.

FDA Guidance: Food effect bioavailability and fed bioequivalence studies. 2002.

EMA – Guidance on the investigation of bioequivalence. 20 Jan 2010.

Health and Safety. Ionising Radiation (Medical Exposure) Regulations 2017. Statutory Instrument 2017 No. 1322.

Ionising Radiation Exposure of the UK population: 2010 Review. Public Health England. Apr 2016. https://www.gov.uk/government/publications/ionising-radiation-exposure-of-the-uk-population-2010-review

Notes for guidance on the clinical administration of radiopharmaceuticals and use of sealed radioactive sources. Administration of Radioactive Substances Advisory Committee. Sep 2020.

RO7197597 (GDC-9545) Investigator's Brochure. F. Hoffmann-La Roche Ltd. Version 4, May 2020.

# Appendix 1
# Part 1 Schedule of Activities

| Study Procedures | Screening | Residency in Clinical Unit | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Days | –28 to –2 | –1[a] | 1 | | | | | | | | | | | | 2 | 3 | 4 | 5 | 6 |
| Time after study drug dosing (hours) [b] | | | Pre-dose | 0 | 1 | 1.5 | 2 | 2.5 | 3 | 4 | 5 | 6 | 8 | 12 | 24 | 48 | 72 | 96 | 120 |
| Informed consent | X[c] | | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | X | X | | | | | | | | | | | | | | | | |
| Medical history | X | X[d] | | | | | | | | | | | | | | | | | |
| Complete physical examination [e] | X | | | | | | | | | | | | | | | | | | |
| Limited physical examination [f] | | X | | | | | | | | | | | | | | | | | |
| Height, weight and BMI | X | | | | | | | | | | | | | | | | | | |
| Vein assessment | X | | | | | | | | | | | | | | | | | | |
| 12-lead safety ECG | X | | X | | X | | | | | X | | | | | X | | | | |
| Vital signs [g] | X | | X | | X | | | | | X | | | | | X | | | | |
| Laboratory safety tests [h] | X | X | | | | | | | | | | | | | | | | | |
| Urinalysis [i] | X | X | | | | | | | | | | | | | | | | | |
| Urine drug screen [j] | X | X | | | | | | | | | | | | | | | | | |
| Alcohol breath test | X | X | | | | | | | | | | | | | | | | | |
| Carbon monoxide breath test | X | X | | | | | | | | | | | | | | | | | |
| Virology screen [k] | X | | | | | | | | | | | | | | | | | | |
| Estradiol and FSH [l] | X | | | | | | | | | | | | | | | | | | |
| Pregnancy test [m] | X | X | | | | | | | | | | | | | | | | | |

**Appendix 1: Part 1 Schedule of Activities**

| Study Procedures | Screening | Residency in Clinical Unit | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Days | –28 to –2 | –1[a] | 1 | | | | | | | | | | | 2 | 3 | 4 | 5 | 6 | |
| Time after study drug dosing (hours) [b] | | | Pre-dose | 0 | 1 | 1.5 | 2 | 2.5 | 3 | 4 | 5 | 6 | 8 | 12 | 24 | 48 | 72 | 96 | 120 |
| Adverse event monitoring [n] | ◄ | ► | | | | | | | | | | | | | | | | | |
| Prior and concomitant medications [o] | ◄ | ► | | | | | | | | | | | | | | | | | |
| Study drug administration | | | | X | | | | | | | | | | | | | | | |
| Plasma samples for GDC-9545 and total radioactivity PK [p] | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Whole blood samples for total radioactivity PK [p] | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Plasma samples for metabolite profiling and ID [p] | | | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Urine samples for total radioactivity and metabolite profiling and identification [q] | | | ◄ | ► | | | | | | | | | | | | | | | |
| Feces samples for total radioactivity and metabolite profiling and identification [r] | | ◄ | ► | | | | | | | | | | | | | | | | |
| Confinement in the clinic | | ◄ | ► | | | | | | | | | | | | | | | | |

**Appendix 1: Part 1 Schedule of Activities**

| Study Procedures | Residency in Clinical Unit | | | | | | | | | | | | | | | Return Visits | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Days | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21[s] | 28[s] | 35[s] | 42[s] |
| Time after study drug dosing (hours) [b] | 144 | 168 | 192 | 216 | 240 | 264 | 288 | 312 | 336 | 360 | 384 | 408 | 432 | 456 | 480 | 648 | 816 | 984 |
| Limited physical examination [f] | | | | | | | | | | | | | | | X | | | |
| 12-lead safety ECG | | | | | | | | | | | | | | | X | | | |
| Vital signs [g] | | | | | | | | | | | | | | | X | | | |
| Laboratory safety tests [h] | | | | | | | | | | | | | | | X | | | |
| Urinalysis [i] | | | | | | | | | | | | | | | X | | | |
| Adverse event monitoring [n] | ← | | | | | | | | | | | | | | → | | | |
| Prior and concomitant medications [o] | ← | | | | | | | | | | | | | | → | | | |
| Plasma samples for GDC-9545 and total radioactivity PK [p] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Whole blood samples for total radioactivity PK [p] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Plasma samples for metabolite profiling and ID [p] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Urine samples for total radioactivity and metabolite profiling and identification [q] | ← | | | | | | | | | | | | | | → | X | X | X |
| Feces samples for total radioactivity and metabolite profiling and identification [r] | ← | | | | | | | | | | | | | | → | X | X | X |
| Confinement in the clinic | ← | | | | | | | | | | | | | | → | X | X | X |

**Appendix 1: Part 1 Schedule of Activities**

| Study Procedures | Residency in Clinical Unit | | | | | | | | | | | | | | | Return Visit | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Days | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21[s] | 28[s] | 35[s] | 42[s] |
| Time after study drug dosing (hours) [b] | 144 | 168 | 192 | 216 | 240 | 264 | 288 | 312 | 336 | 360 | 384 | 408 | 432 | 456 | 480 | 648 | 816 | 984 |
| Return visits | | | | | | | | | | | | | | | | X | X | X |

[a] Admission to the clinical unit. Eligibility will be reassessed at admission/pre-dose.

[b] All assessments will be timed and performed relative to the start of dosing

[c] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

[d] Update only

[e] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, GI, genitourinary, and neurologic systems.

[f] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated.

[g] Includes pulse rate, and systolic and diastolic blood pressure while the subject is in a supine position, and oral temperature at all time points.

[h] Hematology includes white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin, hematocrit (packed cell volume), mean cell hemoglobin, mean cell hemoglobin concentration, mean cell volume, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes). Chemistry panel (serum) includes magnesium, sodium, potassium, chloride, glucose, fasting glucose, urea, creatinine, creatine kinase, total protein, albumin, phosphate (inorganic), calcium, total bilirubin, direct bilirubin (only if total is elevated), alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), and bicarbonate. Creatinine clearance will be estimated at screening from serum creatinine using the Cockcroft-Gault equation for eligibility purposes. Coagulation panel includes international normalized ratio (INR), activated partial thromboplastin time (APTT), thrombin time and prothrombin time (PT).

[i] Includes pH, specific gravity, glucose, protein, ketones, blood, bilirubin, leukocytes, nitrites, urobilinogen. Microbiology and/or microscopic urinalysis examination, at the discretion of the Investigator based on urinalysis results (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

[j] Amphetamines, barbiturates, benzodiazepines, cocaine, marijuana/cannabis, methadone, methamphetamine/ecstasy, morphine/opiates, phencyclidine, and tricyclic anti-depressants.

[k] HBsAg, HCV Antibody, HIV Antibody for all subjects.

[l] Estradiol and FSH for post-menopausal female subjects only.

[m] All subjects must have a negative highly sensitive serum pregnancy test result at screening and a negative highly sensitive urine pregnancy test at admission.

[n] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug. All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6. In addition, the Sponsor should be notified if the Investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[o] Medication (e.g., prescription drugs, over-the-counter drugs, HRT, vaccines, topical medications, herbal or homeopathic remedies, nutritional supplements) used by a subject in addition to protocol-mandated treatment from 14 days prior to initiation of study drug until discharge from the study.

[p] See Appendix 3 for detailed schedule. Blood sample collection will be at pre-dose, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24 hours post-dose, and at 24-hour intervals thereafter until study completion (including after discharge, if needed)/early termination. Permissible time windows for PK sampling are: pre-dose, ≤1 hour before dosing; 1 hour post-dose, ±5 minutes; 1.5 to 8 hours, ±15 minutes; 12 to 24 hours, ±30 minutes; 48 to 480 hours, ±4 hours; 648 to 984 hours, ±1 day

[q] A single urine sample will be collected at pre-dose (the first void of the day) and then at the following collection periods: 0 to 12 hours, 12 to 24 hours, and then daily (24 hour intervals) until the mass balance discharge criteria have been met or until Day 21, and then on a weekly basis starting on Day 28 (until criteria met or Day 42 reached).

[r] The pre-dose feces sample will be taken in the 24 hours period before dosing (between admission and pre-dose). Post-dose feces will be collected at 24 hour intervals until the mass balance discharge criteria have been met or until Day 21, and then on a weekly basis starting on Day 28 (until criteria met or Day 42 reached).

[s] It is planned that subjects will remain resident in the clinical unit until 480 hours post-dose (Day 21) when they will be discharged from the clinical unit. The same procedures are to be performed at early termination/withdrawal as at discharge. Subjects may be discharged as a group earlier if the mass balance discharge criteria have been achieved. If the criteria have not been met by Day 21, subjects will be discharged from the clinical unit and those who have not met the discharge criteria will return for outpatient visits every 7 days for a 24-hour sample collection interval until the mass balance discharge criteria are met (the maximum number of 24-hour return visits will not exceed 3). Discharged subjects may be asked to return for these visits if samples are needed post-discharge, prior to study completion. If additional residency is not considered appropriate or necessary, then home collections of urine and/or feces may be requested at the discretion of the Investigator for individual subjects. Safety discharge assessments will be performed at the time of actual discharge or early termination/withdrawal from the clinical unit. PK, TR and metabolite profiling and identification blood samples to be collected at 480 hours post-dose or at time of actual discharge/early termination if earlier. Any subject who discontinues or is withdrawn from the study after being discharged from the clinical unit will be asked to return to the clinical unit to undergo early termination/withdrawal procedures.

# Appendix 2
# Part 2 Schedule of Activities

| Study Procedures | Screening | Study days in each period | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | –28 to –2 | -1[a] | 1 | | | | | | | | | | | | | | | | 2 |
| Time after study drug dosing (hours) – (relative to start of IV infusion for Treatment B) [b] | | | Pre-dose | 0 | 0.25 | 0.5 | 0.58 | 0.67 | 1 | 1.5 | 2 | 2.5 | 3 | 4 | 5 | 6 | 8 | 12 | 24 |
| Informed consent | X[c] | | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | X | X[d] | X | | | | | | | | | | | | | | | | |
| Medical history | X | X[e] | | | | | | | | | | | | | | | | | |
| Complete physical examination [f] | X | | | | | | | | | | | | | | | | | | |
| Limited physical examination [g] | | X[h] | | | | | | | | | | | | | | | | | |
| Height, weight and BMI | X | | | | | | | | | | | | | | | | | | |
| Vein assessment | X | | | | | | | | | | | | | | | | | | |
| 12-lead safety ECG | X | | X | | | X | | | X | | | | | X | | | | | X |
| Vital signs [i] | X | | X | | | X | | | X | | | | | X | | | | | X |
| Laboratory safety tests [j] | X | X[h] | | | | | | | | | | | | | | | | | |
| Urinalysis [k] | X | X[h] | | | | | | | | | | | | | | | | | |
| Urine drug screen [l] | X | X[d] | | | | | | | | | | | | | | | | | |
| Alcohol breath test | X | X[d] | | | | | | | | | | | | | | | | | |
| Carbon monoxide breath test | X | X[d] | | | | | | | | | | | | | | | | | |
| Randomization | | | X[d] | | | | | | | | | | | | | | | | |
| Virology screen [m] | X | | | | | | | | | | | | | | | | | | |
| Estradiol and FSH [n] | X | | | | | | | | | | | | | | | | | | |
| Pregnancy test [o] | X | X[d] | | | | | | | | | | | | | | | | | |

**Appendix 2: Part 2 Schedule of Activities**

| Study Procedures | Screening | Study days in each period | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | –28 to –2 | -1[a] | 1 | | | | | | | | | | | | | | | | 2 |
| Time after study drug dosing (hours) – (relative to start of IV infusion for Treatment B) [b] | | | Pre-dose | 0 | 0.25 | 0.5 | 0.58 | 0.67 | 1 | 1.5 | 2 | 2.5 | 3 | 4 | 5 | 6 | 8 | 12 | 24 |
| Adverse event monitoring [p] | ◄ | ► | | | | | | | | | | | | | | | | | |
| Prior and concomitant medications [q] | ◄ | ► | | | | | | | | | | | | | | | | | |
| Study drug administration [r] | | | | X | | | | | | | | | | | | | | | |
| Plasma samples for GDC-9545 PK [s] | | | X | | X[t] | X[t] | X[t] | X[t] | X | X | X | X[u] | X | X | X[u] | X | X | X | X |
| Confinement in the clinic | | ◄ | ► | | | | | | | | | | | | | | | | |

**Appendix 2: Part 2 Schedule of Activities**

| Study Procedures | Study days in each period | | | | | | Follow-Up Phone Call |
|---|---|---|---|---|---|---|---|
| | 3 | 4 | 5 | 6 | 7 | 8[v] | 14 to 16[w] |
| Time after study drug dosing (hours) – (relative to start of IV infusion for Treatment B) [b] | 48 | 72 | 96 | 120 | 144 | 168 | |
| Limited physical examination [g] | | | | | | X[x] | |
| 12-lead safety ECG | | | | | | X[x] | |
| Vital signs [i] | | | | | | X[x] | |
| Laboratory safety tests [j] | | | | | | X[x] | |
| Urinalysis [k] | | | | | | X[x] | |
| Adverse event monitoring [p] | ← | — | — | — | — | → | |
| Prior and concomitant medications [q] | ← | — | — | — | — | → | |
| Plasma samples for GDC-9545 PK [s] | X | X | X | X | X | X[y] | |
| Confinement in the clinic | ← | — | — | — | — | → | |

0.25 hours = 15 minutes, 0.5 hours = 30 minutes, 0.58 hours = 35 minutes; 0.67 hours = 40 minutes

[a] Admission to the clinical unit (Period 1 only). Subjects will be resident in the clinical unit for 28 to 29 consecutive nights that will cover all 3 treatment periods. Eligibility will be reassessed at admission/pre-dose.

[b] All assessments will be timed and performed relative to the start of dosing

[c] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

[d] Period 1 only

[e] Update only (Period 1 only).

[f] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, GI, genitourinary, and neurologic systems.

[g] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated.

[h] Periods 1, 2 and 3

[i] Includes pulse rate, and systolic and diastolic blood pressure while the subject is in a supine position, and oral temperature at all time points.

[j] Hematology includes white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin, hematocrit (packed cell volume), mean cell hemoglobin, mean cell hemoglobin concentration, mean cell volume, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes). Chemistry panel (serum) includes magnesium, sodium, potassium, chloride, glucose, fasting glucose, urea, creatinine, creatine kinase, total protein, albumin, phosphate (inorganic), calcium, total bilirubin, direct bilirubin (only if total is elevated), alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), and bicarbonate. Creatinine clearance will be estimated at screening from serum creatinine using the Cockcroft-Gault equation for eligibility purposes. Coagulation panel includes international normalized ratio (INR), activated partial thromboplastin time (APTT), thrombin time and prothrombin time (PT).

[k] Includes pH, specific gravity, glucose, protein, ketones, blood, bilirubin, leukocytes, nitrites, urobilinogen. Microbiology and/or microscopic urinalysis examination, at the discretion of the Investigator based on urinalysis results (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

[l] Amphetamines, barbiturates, benzodiazepines, cocaine, marijuana/cannabis, methadone, methamphetamine/ecstasy, morphine/opiates, phencyclidine, and tricyclic anti-depressants.

[m] HBsAg, HCV Antibody, HIV Antibody for all subjects.

[n] Estradiol and FSH for post-menopausal female subjects only.

[o] All subjects must have a negative highly sensitive serum pregnancy test result at screening and a negative highly sensitive urine pregnancy test at admission.

[p] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug. All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6. In addition, the Sponsor should be notified if the Investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[q] Medication (e.g., prescription drugs, over-the-counter drugs, HRT, vaccines, topical medications, herbal or homeopathic remedies, nutritional supplements) used by a subject in addition to protocol-mandated treatment from 14 days prior to initiation of study drug until discharge from the study.

[r] Treatment B will be administered intravenously over 30 minutes (as an infusion). For Treatment B only, to assess tolerability of the IV administration, the first subject will be dosed as a sentinel; then, at least 4 hours later, the second subject will be dosed only if there are no acute safety findings for the first subject. If the first two subjects tolerated the IV dose, in the opinion of the Principal Investigator and Medical Monitor, the remaining subjects will be dosed. The third subject will be dosed at least 20 hours after the second subject (i.e., at least 24 hours after the first subject). All subsequent dosing of the IV formulation will be staggered by at least 15 minutes. For Treatments C and D, all subjects will be dosed as a single cohort.

[s] See Appendix 4 for detailed schedule. Permissible time windows for PK sampling and other assessments are: pre-dose, ≤1 hour before dosing; 0.25 to 0.5 hours post-dose, ±2 minutes; 0.58 to 1 hour, ±5 minutes; 1.5 to 8 hours, ±15 minutes; 12 to 24 hours, ±30 minutes; 48 to 168 hours, ±4 hours.

[t] Treatment B (IV dose only). 0.5 hours sample to be taken immediately after IV administration (i.e., 30 minutes after the start of the IV administration)

[u] Treatments C and D (oral doses) only.

[v] Discharge from clinical unit in Period 3 only. The same procedures are to be performed at early termination/withdrawal as at discharge.

[w] Follow-up telephone call at 13 to 15 days post-final dose.

[x] Period 3 only; safety discharge assessments will be performed at the time of actual discharge/early termination from the clinical unit

[y] Periods 1, 2 and 3. In Period 3, PK blood samples to be collected at 168 hours post-dose or at time of actual discharge/early termination if earlier.

# Appendix 3
# Part 1 Schedule of Pharmacokinetic Samples

| Visit [a] | Time point [a] | Sample Type |
|---|---|---|
| Day 1 | Pre-dose | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | | Feces (total radioactivity and metabolite profiling and identification)[c] |
| | 0 to 12.0 hours post-dose | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | 0 to 24.0 hours | Feces (total radioactivity and metabolite profiling and identification)[c] |
| | 1.0 hour | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 1.5 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 2.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 2.5 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 3.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 4.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 5.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 6.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 8.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |

Appendix 3
Part 1 Schedule of Pharmacokinetic Assessments

| Visit [a] | Time point [a] | Sample Type |
|---|---|---|
| Day 1 | 12.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 12.0 to 24.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |
| Day 2 | 24.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 24.0 to 48.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | | Feces (total radioactivity and metabolite profiling and identification)[c] |
| Day 3 | 48.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 48.0 to 72.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | | Feces (total radioactivity and metabolite profiling and identification)[c] |
| Day 4 | 72.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 72.0 to 96.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | | Feces (total radioactivity and metabolite profiling and identification)[c] |
| Day 5 | 96.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 96.0 to 120.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | | Feces (total radioactivity and metabolite profiling and identification)[c] |
| Day 6 | 120.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 120.0 to 144.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | | Feces (total radioactivity and metabolite profiling and identification)[c] |

Appendix 3
Part 1 Schedule of Pharmacokinetic Assessments

| Visit [a] | Time point [a] | Sample Type |
|---|---|---|
| Day 7 | 144.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 144.0 to 168.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | | Feces (total radioactivity and metabolite profiling and identification)[c] |
| Day 8 | 168.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 168.0 to 192.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | | Feces (total radioactivity and metabolite profiling and identification)[c] |
| Day 9 | 192.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 192.0 to 216.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | | Feces (total radioactivity and metabolite profiling and identification)[c] |
| Day 10 | 216.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 261.0 to 240.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | | Feces (total radioactivity and metabolite profiling and identification)[c] |
| Day 11 | 240.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 240.0 to 264.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | | Feces (total radioactivity and metabolite profiling and identification)[c] |
| Day 12 | 264.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 264.0 to 288.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |

Appendix 3
Part 1 Schedule of Pharmacokinetic Assessments

| Visit [a] | Time point [a] | Sample Type |
|---|---|---|
| Day 12 | 264.0 to 288.0 hours | Feces (total radioactivity and metabolite profiling and identification)[c] |
| Day 13 | 288.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 288.0 to 312.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | | Feces (total radioactivity and metabolite profiling and identification)[c] |
| Day 14 | 312.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 312.0 to 336.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | | Feces (total radioactivity and metabolite profiling and identification)[c] |
| Day 15 | 336.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 336.0 to 360.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | | Feces (total radioactivity and metabolite profiling and identification)[c] |
| Day 16 | 360.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 360.0 to 384.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | | Feces (total radioactivity and metabolite profiling and identification)[c] |
| Day 17 | 384.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 384.0 to 408.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | | Feces (total radioactivity and metabolite profiling and identification)[c] |
| Day 18 | 408.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |

Appendix 3
Part 1 Schedule of Pharmacokinetic Assessments

| Visit [a] | Time point [a] | Sample Type |
|---|---|---|
| Day 18 | 408.0 to 432.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | | Feces (total radioactivity and metabolite profiling and identification)[c] |
| Day 19 | 432.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 432.0 to 456.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | | Feces (total radioactivity and metabolite profiling and identification)[c] |
| Day 20 | 456.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 456.0 to 480.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | | Feces (total radioactivity and metabolite profiling and identification)[c] |
| Day 21 | 480.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| Day 28 | 648.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 648.0 to 672.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | | Feces (total radioactivity and metabolite profiling and identification)[c] |
| Day 35 | 816.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 816.0 to 840.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |
| | | Feces (total radioactivity and metabolite profiling and identification)[c] |
| Day 42 | 984.0 hours | GDC-9545 and TR PK, and metabolite profiling and identification (plasma) |
| | | TR PK (whole blood) |
| | 984.0 to 1008.0 hours | Urine (total radioactivity and metabolite profiling and identification)[b] |

Appendix 3
Part 1 Schedule of Pharmacokinetic Assessments

| Visit [a] | Time point [a] | Sample Type |
|---|---|---|
| Day 42 | 984.0 to 1008.0 hours | Feces (total radioactivity and metabolite profiling and identification)[c] |

PK = pharmacokinetic, TR = total radioactivity.

[a] It is planned that subjects will be released as a group when all subjects have achieved the mass balance discharge criteria. This may result in the subjects being discharged as a group prior to completion of the planned residency period. Once the mass balance discharge criteria have been achieved, collection of all samples (blood, urine, and feces) may be stopped and the subjects will undergo discharge assessments. Discharged subjects may be asked to return for these visits if samples are needed post-discharge, prior to study completion, if needed.

Blood sample collection will be at pre-dose, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24 hours post-dose, and at 24-hour intervals thereafter until study completion (including after discharge, if needed)/early termination

Permissible time windows for PK sampling are: pre-dose, ≤1 hour before dosing; 1 hour post-dose, ±5 minutes; 1.5 to 8 hours, ±15 minutes; 12 to 24 hours, ±30 minutes; 48 to 480 hours, ±4 hours; 648 to 984 hours, ±1 day

[b] A single urine sample will be collected at pre-dose (the first void of the day) and then at the following collection periods: 0 to 12 hours, 12 to 24 hours, and then daily (24 hour intervals) until the mass balance discharge criteria have been met or until Day 21, and then on a weekly basis starting on Day 28 (until criteria met or Day 42 reached).

[c] The pre-dose feces sample will be taken in the 24 hours period before dosing (between admission and pre-dose). Post-dose feces will be collected at 24 hour intervals until the mass balance discharge criteria have been met or until Day 21, and then on a weekly basis starting on Day 28 (until criteria met or Day 42 reached).

# Appendix 4
# Part 2 Schedule of Pharmacokinetic Samples

| Visit [a] | Time point [a] | Sample Type |
|---|---|---|
| Day 1 | Pre-dose | GDC-9545 PK (plasma) |
| | 0.25 hours post-dose [b] | GDC-9545 PK (plasma) |
| | 0.5 hours [c] | GDC-9545 PK (plasma) |
| | 0.58 hours [d] | GDC-9545 PK (plasma) |
| | 0.67 hours [e] | GDC-9545 PK (plasma) |
| | 1.0 hours | GDC-9545 PK (plasma) |
| | 1.5 hours | GDC-9545 PK (plasma) |
| | 2.0 hours | GDC-9545 PK (plasma) |
| | 2.5 hours [f] | GDC-9545 PK (plasma) |
| | 3.0 hours | GDC-9545 PK (plasma) |
| | 4.0 hours | GDC-9545 PK (plasma) |
| | 5.0 hours [f] | GDC-9545 PK (plasma) |
| | 6.0 hours | GDC-9545 PK (plasma) |
| | 8.0 hours | GDC-9545 PK (plasma) |
| | 12.0 hours | GDC-9545 PK (plasma) |
| Day 2 | 24.0 hours | GDC-9545 PK (plasma) |
| Day 3 | 48.0 hours | GDC-9545 PK (plasma) |
| Day 4 | 72.0 hours | GDC-9545 PK (plasma) |
| Day 5 | 96.0 hours | GDC-9545 PK (plasma) |
| Day 6 | 120.0 hours | GDC-9545 PK (plasma) |
| Day 7 | 144.0 hours | GDC-9545 PK (plasma) |
| Day 8 | 168.0 hours | GDC-9545 PK (plasma) |

PK = pharmacokinetic.

[a] Visit and time points are applicable to all periods in Part 2, except where indicated. For Treatment B (IV dose), time points are relative to the start of the IV administration.

[b] Treatment B (IV dose) only

[c] Treatment B (IV dose only); sample to be taken immediately after IV administration (i.e., 30 minutes after the start of the IV administration)

[d] Treatment B (IV dose only); sample to be taken 5 minutes after the end of IV administration (i.e., 35 minutes after the start of the IV administration)

[e] Treatment B (IV dose only); sample to be taken 10 minutes after the end of IV administration (i.e., 40 minutes after the start of the IV administration)

[f] Treatments C and D (oral doses) only

Permissible time windows for PK sampling and other assessments are: pre-dose, ≤1 hour before dosing; 0.25 to 0.5 hours post-dose, ±2 minutes; 0.58 to 1 hour, ±5 minutes; 1.5 to 8 hours, ±15 minutes; 12 to 24 hours, ±30 minutes; 48 to 168 hours, ±4 hours