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

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Statistical Analysis Plan

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

SAP Status: Sponsor Final
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Investigational Product: GDC-9545

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Covance Study: 8418446

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LIST OF ABBREVIATIONS

Abbreviations pertain to the statistical analysis plan (SAP) only (not the tables, figures, and listings [TFLs]).

ADaM	Analysis Data Model
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-t}	area under the concentration-time curve calculated from Hour 0 to the last measurable concentration
$AUC_{0-\infty}$	area under the concentration-time curve from Hour 0 extrapolated to infinity
$\%AUC_{extrap}$	percentage of area under the concentration-time curve that is due to extrapolation from the last measurable concentration to infinity
BLQ	below the limit of quantification
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CL/F	apparent total clearance
C_{max}	maximum observed concentration
CSR	clinical study report
CV	coefficient of variation
ECG	electrocardiogram
ICH	International Council for/Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
λ_z	apparent terminal elimination rate constant
NC	not calculated
NR	no result
PK	pharmacokinetic(s)
R^2 adjusted	adjusted coefficient for determination of exponential fit
SAP	statistical analysis plan
SD	standard deviation
TEAE	treatment-emergent adverse event
TFL	table, figure, and listing
t_{last}	time of last quantifiable concentration
t_{lag}	time to first quantifiable concentration
t_{max}	time to maximum observed concentration
$t_{1/2}$	apparent terminal elimination half-life
V_Z/F	apparent volume of distribution during the terminal elimination phase

1. INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 1 dated 26 November 2019) and electronic case report form.

This SAP describes the planned analysis of the pharmacokinetic (PK) and safety and tolerability data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shells document.

In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Genentech, Inc. A limited amount of information about this study (eg, objectives, study design) is given to help the reader's interpretation. This SAP must be finalized prior to the lock of the clinical database for this study. When the SAP and TFL shells are approved, they will serve as the template for this study's CSR.

This SAP supersedes any statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified accordingly in the CSR. Any substantial deviations from this SAP will be agreed with Genentech, Inc. and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline *Statistical Principles for Clinical Trials* and ICH E3 guideline *Structure and Content of Clinical Study Reports*.[1,2]

The document history is presented in Appendix 1.

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objectives of this study are:

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

2.2. Secondary Objective

The secondary objective of this study is:

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

3. STUDY ENDPOINTS

3.1. Primary Endpoints

The following PK parameters will be derived from the plasma concentrations of GDC-9545:

- maximum observed concentration (C_{max})
- time to C_{max} (t_{max})
- area under the concentration-time curve (AUC) calculated from Hour 0 to the last measurable concentration (AUC_{0-t})
- area under the concentration-time curve from Hour 0 extrapolated to infinity ($AUC_{0-\infty}$)
- apparent terminal elimination rate constant (λ_z)
- apparent terminal elimination half-life ($t_{1/2}$)
- apparent total clearance (CL/F)
- apparent volume of distribution during the terminal elimination phase (V_Z/F).

3.2. Secondary Endpoints

The secondary endpoints are:

- Incidence and severity of adverse events (AEs) and incidence of abnormalities in laboratory safety assessments, 12-lead electrocardiograms (ECGs), vital signs measurements, and physical examinations.

4. STUDY DESIGN

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

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

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

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

A summary of the sequences is presented in Table 1.

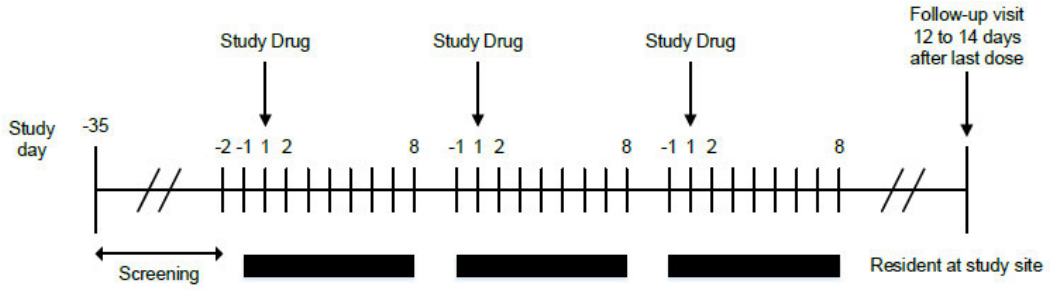
Table 1: Three-Period, Six-Sequence Crossover Study Design

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

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

A schematic of the study design is presented in Figure 1.

Figure 1: Study Design



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

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

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

5. SAMPLE SIZE JUSTIFICATION

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

that a minimum of 12 subjects will complete the study without the need for replacement subjects.

6. STUDY TREATMENTS

The study treatment names, abbreviations, and ordering to be used in the TFLs are presented in Table 2.

Table 2: Presentation of Study Treatments in TFLs

Study Treatment	Abbreviation	Order in TFLs
30-mg dose of GDC-9545 (three 10-mg tablets) fasted	A	1
30-mg dose of GDC-9545 (one 30-mg capsule) fasted	B	2
30-mg dose of GDC-9545 (one 30-mg capsule) fed	C	3

All treatments described above are the planned treatments. The TFLs will reflect the actual treatments received, and dose levels will be displayed in increasing order.

The study treatment sequence names, abbreviations, and ordering to be used in the TFLs are presented in Table 3.

Table 3: Presentation of Study Treatment Sequences in TFLs

Study Treatment Sequence	Abbreviation	Order in TFLs
30-mg dose of GDC-9545 (three 10-mg tablets) fasted/ 30-mg dose of GDC-9545 (one 30-mg capsule) fasted/ 30-mg dose of GDC-9545 (one 30-mg capsule) fed	A/B/C	1
30-mg dose of GDC-9545 (one 30-mg capsule) fasted/ 30-mg dose of GDC-9545 (one 30-mg capsule) fed/ 30-mg dose of GDC-9545 (three 10-mg tablets) fasted	B/C/A	2
30-mg dose of GDC-9545 (one 30-mg capsule) fed/ 30-mg dose of GDC-9545 (three 10-mg tablets) fasted/ 30-mg dose of GDC-9545 (one 30-mg capsule) fasted	C/A/B	3
30-mg dose of GDC-9545 (three 10-mg tablets) fasted/ 30-mg dose of GDC-9545 (one 30-mg capsule) fed/ 30-mg dose of GDC-9545 (one 30-mg capsule) fasted	A/C/B	4
30-mg dose of GDC-9545 (one 30-mg capsule) fasted/ 30-mg dose of GDC-9545 (three 10-mg tablets) fasted/ 30-mg dose of GDC-9545 (one 30-mg capsule) fed	B/A/C	5
30-mg dose of GDC-9545 (one 30-mg capsule) fed/ 30-mg dose of GDC-9545 (one 30-mg capsule) fasted/ 30-mg dose of GDC-9545 (three 10-mg tablets) fasted	C/B/A	6

7. DEFINITIONS OF POPULATIONS

Any protocol deviations will be considered prior to database lock for their importance and taken into consideration when assigning subjects to populations.

7.1. All Subjects Population

The all subjects population will include all subjects who signed the informed consent form and had any study assessment recorded in the database per the protocol.

7.2. Safety Population

The safety population will consist of all subjects who received at least 1 dose of study drug.

7.3. Pharmacokinetic Population

The PK population will consist of all subjects who received at least 1 dose of study drug and have at least 1 evaluable postdose PK sample. A subject may be excluded from the PK summary statistics and statistical analysis if the subject has an AE of vomiting that occurs within 2 times median t_{max}.

8. STATISTICAL METHODOLOGY

8.1. General

Listings will be provided for all data captured in the database. Listings will include all subjects assigned to the all subjects population and include data up to the point of study completion or discontinuation. Subjects are generally considered to have completed the study if they completed all protocol-specified procedures and assessments for the Follow-up visit. Any subject who discontinued the study will be identified accordingly in the listings. Summaries and statistical analyses will include the subjects assigned to the relevant population based on data type.

Data analysis will be performed using the SAS® statistical software package Version 9.4 (or higher if upversioned during the study).

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1 (or higher if upversioned during the study) and CDISC ADaM Implementation Guide Version 1.2 (or higher if upversioned during the study). Pinnacle 21 Community Validator Version 2.2.0 (or higher if upversioned during the study) will be utilized to ensure compliance with CDISC standards.

Caution should be used when interpreting results from the statistical analyses conducted in this study because the sample size is not based on power calculations.

Where reference is made to ‘all calculations’, this includes, but is not limited to, summary statistics, statistical analyses, baseline derivations, changes from baseline, and any parameter derivations.

8.1.1. Calculation of the Summary Statistics

For continuous data the following rules will be applied:

- Missing values will not be imputed, unless specifically stated otherwise.
- Unrounded data will be used in the calculation of summary statistics.
- If the number of subjects with valid observations (n) <3, summary statistics will not be calculated, with the exception of n, minimum, and maximum.
- As Early Termination data is not associated with any scheduled timepoint, it will be excluded from all calculations of summary statistics.

For categorical data the following rules will be applied:

- If the categories of a parameter are ordered (eg, AE severity), all categories between the possible minimum and maximum categories will be included, even if n = 0 for a given category. If the categories are not ordered (eg, race), only those categories for which there is at least 1 subject represented will be included.
- Missing values will not be imputed, with the exception of AEs where the 'worst-case' approach will be taken (see Section 8.6.1), or unless specifically stated otherwise. A 'missing' category will be included for any parameter for which information is missing. This will ensure that the population size totals are consistent across different parameters.

8.1.2. Triplicate Readings

For ECG data only, where triplicate readings are taken, the mean of triplicate readings will replace the original readings in all calculations.

In case of incomplete triplicate readings (eg, only 2 out of 3 readings were recorded), the mean and/or medians will be calculated based on the number of readings available.

8.1.3. Repeat and Unscheduled Readings

For vital signs and ECG data only, any predose value recorded in addition to the original value or a postdose value recorded within 15 minutes of the original value will be defined as a repeat value; any postdose value recorded more than 15 minutes after the original value will be defined as an unscheduled value. For all other data types (eg, laboratory parameters), any value recorded in addition to the original value will be defined as an unscheduled value.

The original value will be replaced by the last associated repeat value in all calculations.

As unscheduled values are not associated with any scheduled timepoint, they will be excluded from all calculations, with the exception of baseline derivations (see Section 8.1.4).

8.1.4. Definitions of Baseline and Change from Baseline

The period specific baseline will be defined as the last value recorded prior to the first dose of study drug in each period. If the date/time of the value is incomplete or missing, it will be excluded from the baseline calculation, unless the incomplete date/time indicates the value was recorded prior to the first dose.

Individual changes from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The mean change from period specific baseline will be defined as the mean of the individual changes from period specific baseline for all subjects.

See Section 8.1.3 for more detail on handling repeat and unscheduled readings in the calculations. See Section 8.1.2 for more detail on handling of triplicate readings in the calculations.

8.2. Subject Disposition and Population Assignment

Subject disposition and population assignment will be listed.

A summary table by treatment sequence will be provided, based on the all subjects population.

8.3. Screening Demographics

The screening demographics including age, sex, race, ethnicity, height, body weight, and body mass index will be listed.

A summary table by treatment sequence will be provided, based on the safety population.

8.4. Prior and Concomitant Medication

Prior medication will be defined as medication that ends prior to the first dose. Concomitant medication will be defined as medication that starts during or after the first dose or starts but does not end prior to the first dose.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary Global, Format B3, Version September 2019 (or later if upversioned during the study). Prior and concomitant medications will be listed.

8.5. Pharmacokinetic Assessments

8.5.1. Pharmacokinetic Analysis

The following PK parameters will be determined where possible from the plasma concentrations of GDC-9545 using non-compartmental methods performed using Phoenix WinNonlin (Certara USA, Inc., Version 8.1 or higher):

Parameter	Definition
C_{max}	maximum observed concentration
t_{max}	time to maximum observed concentration
t_{last}	time of last quantifiable concentration
t_{lag}	time to first quantifiable concentration
AUC_{0-t}	area under the concentration-time curve calculated from Hour 0 to the last measurable concentration, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations
$AUC_{0-\infty}$	area under the concentration-time curve from Hour 0 extrapolated to infinity, calculated using the formula: $AUC_{0-\infty} = AUC_{0-t} + (C_t/\lambda_z)$ where C_t is the last measurable concentration and λ_z is the apparent terminal elimination rate constant
$\%AUC_{extrap}$	percentage of area under the concentration-time curve that is due to extrapolation from the last measurable concentration to infinity
λ_z	apparent terminal elimination rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase
$t_{1/2}$	apparent terminal elimination half-life (wherever possible), where $t_{1/2}$ = natural log(ln)2/λ_z
CL/F	apparent total clearance, calculated as dose/$AUC_{0-\infty}$
V_Z/F	apparent volume of distribution during the terminal elimination phase, calculated as CL/F/λ_z

Additional PK parameters may be determined where appropriate.

The PK analysis will, where possible, be carried out using actual postdose times recorded in the raw data. If actual times are missing, nominal times may be used with sponsor approval.

Concentrations will be used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

The dose level of GDC-9545 will be converted to its free base equivalent for PK analysis if the analytical laboratory reports the free base concentration.

The C_{max} and t_{max} will be obtained directly from the plasma concentration-time profiles.

For multiple peaks, the highest postdose concentration will be reported as C_{max}. In the case that multiple peaks are of equal magnitude, the earliest t_{max} will be reported.

8.5.1.1. Criteria for Handling Concentrations Below the Limit of Quantification in Pharmacokinetic Analysis

Concentration values that are below the limit of quantification (BLQ) will be set to zero, with defined exceptions as follows;

- Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.
- If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.
- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.
- If a predose concentration is missing, these values may be set to zero.

8.5.1.2. Criteria for the Calculation of an Apparent Terminal Elimination Half-life

8.5.1.2.1. Number of Data Points

At least 3 data points will be included in the regression analysis which preferably should not include C_{max}.

8.5.1.2.2. Goodness of Fit

When assessing terminal elimination phases, the adjusted coefficient for determination of exponential fit (R^2 adjusted) will be used as a measure of the goodness of fit of the data points to the determined line.

Regression-based parameters (ie, λ_z, $t_{1/2}$, $AUC_{0-\infty}$, CL/F, V_Z/F) will only be calculated if the R^2 adjusted value of the regression line is ≥0.7.

8.5.1.2.3. Period of Estimation

The time period used for the estimation of $t_{1/2}$ will be over at least 2 half-lives, where possible.

Where elimination half-life is estimated over a time period of less than 2 half-lives, it will be flagged in the data listings at the discretion of the Pharmacokineticist, and the robustness of the value should be discussed in the CSR.

8.5.1.3. Calculation of Area Under the Concentration-time Curve

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the lower limit of quantification, with at least one of these concentrations following C_{max}.

For any partial AUC determination (where applicable), nominal time will generally be used for the end of the interval. Actual times for partial AUC intervals may be used at the discretion of the Pharmacokineticist.

The $AUC_{0-\infty}$ values (and related parameters [CL/F and Vz/F]) where the percentage extrapolation is <30% will be reported. Any $AUC_{0-\infty}$ values (and related parameters) where the percentage extrapolation is ≥30% will be reported and flagged but excluded from statistics.

8.5.1.4. Anomalous Values

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in the raw data and CSR.

Embedded BLQ values may be considered anomalous depending on the route of administration and the characteristics of the drug.

Positive predose values >5% of C_{max} may be excluded from the summary statistics and statistical analysis at the discretion of the Pharmacokineticist.

8.5.2. Presentation of Pharmacokinetic Data

8.5.2.1. Presentation of Pharmacokinetic Concentration Data

The following rules will be applied if there are values that are BLQ or if there are missing values (eg, no result [NR]) in a plasma concentration data series to be summarized.

- For the calculation of summary statistics, BLQ values will be set to zero.
- If an embedded BLQ value is considered anomalous within the concentration-time profile, this value will be excluded from the summary statistics.
- Where there is NR, these will be set to missing.
- If there are fewer than 3 values in the data series, only the minimum, maximum, and n will be presented. The other summary statistics will be denoted as not calculated (NC). A BLQ is considered a value.
- If all the values are BLQ, then the arithmetic mean, arithmetic standard deviation (SD), median, minimum, and maximum will be presented as zero, and the geometric mean and geometric coefficient of variation (CV) will be denoted as NC.
- If the value of the arithmetic mean or median is BLQ, it will be presented as zero and the geometric mean and geometric CV will be denoted as NC.

8.5.2.2. Presentation of Pharmacokinetic Parameters

For the calculation of summary statistics of PK parameters, all NR and NC values in a data series will be set to missing.

The AUC values will be set to NC if they have been calculated using fewer than 3 concentrations, and/or 3 concentrations if the last is C_{max}.

8.5.3. Pharmacokinetic Statistical Methodology

All PK concentrations and parameters will be listed.

Descriptive statistics (mean, median, minimum, maximum, SD, geometric mean, and geometric CV) will be calculated for all PK parameters for GDC-9545.

Summary tables, mean (+ SD) figures, overlaying individual figures, and individual figures by treatment and time postdose will be provided for plasma PK concentrations. All figures will be produced on both linear and semi-logarithmic scales. The +SD bars will only be displayed on the linear scale.

Summary tables by treatment will be provided for all PK parameters, with the exception of regression diagnostic PK parameters.

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

Log transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ values will be evaluated to estimate ratios of geometric mean values and the corresponding 90% confidence intervals (CIs).

The comparisons of interest are:

Relative bioavailability: Treatment B, capsule (Test) vs Treatment A, tablet (Reference)

Food effect on capsule: Treatment C, fed (Test) vs Treatment B, fasted (Reference)

An example of the SAS code that will be used (assuming formulation coding is 1 = Treatment A, 2 = Treatment B and 3 = Treatment C) is as follows:

```
proc mixed data=pk;
   by parcat1n parcat1 pkday paramn param;
   class trtan aperiod trtseqp usubjid;
    model log_pk = trtan aperiod trtseqp / residual ddfm=kr;
   random intercept / subject=usubjid(trtseqp) type=un;
```

```
   estimate 'Capsule - tablet' trtan -1 1 0/ cl alpha=0.1;
   estimate 'fed - fasted' trtan 0 -1 1/ cl alpha=0.1;
run;
```

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

8.6. Safety and Tolerability Assessments

8.6.1. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities Version 22.1 (or higher if upversioned during the study). All AEs will be assigned severity grade using Nationcal Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (or higher if upversioned during the study).

A treatment-emergent AE (TEAE) will be defined as an AE that starts during or after the first dose, or starts prior to the first dose and increases in severity after the first dose.

A treatment-related TEAE will be defined as a TEAE with a relationship of related to the study treatment, as determined by the investigator.

The AEs of special interest for this study are defined as follows:

- Cases of potential drug-induced liver injury that include an elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law
- Suspected transmission of an infectious agent by the study drug as defined below:
    - o Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a subject exposed to a medicinal product. The term applies only when a contamination of the study drug is suspected
- Grade ≥3 nausea/vomiting/diarrhea
- Grade ≥2 thromboembolic events (pulmonary embolism, deep vein thrombosis, and embolism)
- Grade ≥3 renal failure (including acute kidney injury or other similar medical concepts)
- Grade ≥3 hepatitis or elevation in ALT or AST
- Grade ≥2 vaginal or uterine hemorrhage
- Grade ≥2 bradycardia

- Any grade of endometrial cancer.

All AEs, serious AEs and AEs of special interest will be listed. In addition to the data recorded in the database, the listings will include derived onset time and duration. Onset time will be calculated from the time of the last dose for TEAEs only.

The frequency of subjects with TEAEs and the number of TEAEs will be summarized for the following categories:

- TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment
- TEAEs by severity and treatment
- Treatment-related TEAEs (overall, serious, leading to discontinuation, and leading to death) by treatment
- Treatment-related TEAEs by severity and treatment

The frequency of subjects will be summarized separately for TEAEs and treatment-related TEAEs by the following:

- System organ class, preferred term, and treatment
- Preferred term and treatment

The frequency of subjects will be summarized separately for clustered TEAEs, presenting the TEAEs by the combined preferred term and treatment by the following:

- (1) combining the preferred terms “sinus bradycardia” and “bradycardia”
- (2) combining the preferred terms “neutropenia” and “neutrophil count decreased”
- (3) combining the preferred terms “thrombocytopenia” and “platelet count decreased”
- (4) combining the preferred terms “thrombocytosis” and “platelet count increased”
- (5) combining the preferred terms “leukopenia” and “leukocyte count decreased”
- (6) combining the preferred terms “leukocytosis” and “leukocyte count increased”

For the AE data the following rules will apply:

- For the derivation of TEAE status: If the start date/time of an AE is incomplete or missing, an AE will be assumed to be a TEAE, unless the incomplete start date/time or the end date/time indicates an AE started prior to the first dose.
- For the derivation of treatment-related TEAE status: If the study treatment relationship for a TEAE is missing, a TEAE will be assumed to be a treatment-related TEAE.

- For the derivation of onset time: If the start date/time of an AE is missing, onset time will not be calculated. If the start date/time of an AE is incomplete, where possible, the minimum possible onset time will be calculated and presented in '≥DD:HH:MM' format (eg, if the date/time of the last dose is 01MAY2019/08:00 and recorded start date/time of an AE is 03MAY2019, then the minimum possible onset time will be calculated by assuming the AE started at the first hour and minute of 03MAY2019 [03MAY2019/00:00], thus will be presented as onset time ≥01:16:00 in the listing).

- For the derivation of duration: If the end date/time of an AE is missing, duration will not be calculated. If the start or end date/time of an AE is incomplete, where possible, the maximum possible duration will be calculated and presented in '≤DD:HH:MM' format (eg, if the start of an AE date/time is 01MAY2019/08:00 and its recorded end date/time is 03MAY2019, then the maximum possible duration will be calculated by assuming the AE ended at the last hour and minute of 03MAY2019 [03MAY2019/23:59], thus will be presented as duration ≤02:15:59 in the listing).

- For the calculation of summary statistics: If the severity of a TEAE is missing, a TEAE will be counted under the maximum severity possible.

- For the calculation of summary statistics: If a subject experienced multiple TEAEs with the same preferred term for the same treatment, this will be counted as 1 TEAE for that treatment under the maximum severity recorded.

8.6.2. Clinical Laboratory Parameters

All clinical laboratory parameters, with changes from period specific baseline, will be listed; any value outside the clinical reference range will be flagged. Separate listings will be provided for any parameter for which there is any individual subject value outside the respective clinical reference range.

Summary tables and boxplots by treatment and timepoint will be provided for clinical chemistry and complete blood count parameters, with changes from period specific baseline.

Values recorded as <x, ≤x, >x, or ≥x will be displayed in the listings as recorded. For the derivation of listing flags, calculation of summary statistics, and presentation in the figures, <x and ≤x values will be set to half of x, whereas >x and ≥x values will be set to x.

8.6.3. Vital Signs Parameters

All vital signs parameters, with changes from period specific baseline, will be listed; any value outside the clinical reference range will be flagged.

Summary tables and boxplots by treatment and timepoint will be provided for all vital signs parameters, with changes from period specific baseline.

8.6.4. 12-lead Electrocardiogram Parameters

All 12-lead ECG parameters, with changes from period specific baseline, will be listed; any value outside the clinical reference range will be flagged.

Summary tables and boxplots by treatment and timepoint will be provided for all 12-lead ECG parameters, with changes from period specific baseline.

8.6.5. Other Assessments

Medical history and surgical and procedure history will be listed.

All other safety and tolerability assessments not detailed in the above sections will be listed only.

8.6.6. Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

9. INTERIM ANALYSES

No interim analyses are planned.

10. SIGNIFICANT CHANGES FROM THE PROTOCOL-SPECIFIED ANALYSES

There were no significant changes from the protocol-specified analyses.

11. REFERENCES

1. ICH. ICH Harmonised Tripartite Guideline: Statistical principles for clinical trials (E9). 5 February 1998.

2. ICH. ICH Harmonised Tripartite Guideline: Structure and content of clinical study reports (E3). 30 November 1995.

12. APPENDICES

Appendix 1: Document History

Version, Status	Date of Change	Summary/Reason for Changes
Version 1, Final	NA	NA; the first version

NA = not applicable

Statistical Analysis Plan Approval Form

Sponsor Name:	Genentech, Inc
Sponsor Protocol ID:	GP42006
Covance Study ID:	8418446
SAP Text Filename:	GP42006_SAP_Sponsor_Final_V1.pdf
TFL Shells Filename:	GP42006_TFL_Shells_Sponsor_Final_V1.pdf
Version:	1
Date:	03 February 2020

Covance Approval:

[redacted] 04 Feb 2020
Signature Date

[redacted]
Printed Name/Title - Statistician, Qualifications

Sponsor Approval(s):

By signing below when the statistical analysis plan (SAP) is considered final, the signatories agree to the analyses to be performed for this study; and to the format of the associated tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based on this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a work-scope change.

[redacted] 03 FEB 2020
Signature Date

[redacted] / STATISTICIAN
Printed Name/Title

N/A N/A
Signature Date

N/A
Printed Name/Title

Please scan/email completed form(s) to the [redacted] listed below:

Printed Name/Title:	[redacted]
Email:	[redacted]