STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1b/2 Study of GS-5829 in Combination with Fulvestrant or Exemestane in Subjects with Advanced Estrogen Receptor Positive, HER2 Negative-Breast Cancer
Name of Test Drug:	GS-5829
Study Number:	GS-US-350-1937
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
AEI	adverse event of interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
BOR	best overall response
CBR	clinical benefit rate
CI	confidence interval
CR	complete response
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
ECG	electrocardiogram
ET	early termination
FAS	Full Analysis Set
HLT	high-level term
HR	heart rate
KM	Kaplan-Meier
LTT	lower-level term
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MST	medical search term
MTD	maximum tolerated dose
NE	not evaluable
ORR	overall response rate
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PT	preferred term
PVE	Pharmacovigilance and Epidemiology
Q1, Q3	first quartile, third quartile
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave representing time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula

RR	electrocardiographic interval representing the time measurement between the R wave of one heartbeat and the R wave of the preceding heartbeat
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
StD	standard deviation
SMQs	standardised MedDRA queries
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
$AUC_{x–xx}$	partial area under the plasma/serum concentration versus time curve from time "x" to time "xx"
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum observed concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval
CLss/F	apparent clearance after non-intravenous administration of the drug: after a single dose: CL/F = Dose/AUCinf; at steady state: CLss/F = Dose/AUC_{tau} , where "Dose" is the dose of the drug
Vz/F	apparent volume of distribution during terminal phase after non-intravenous administration of the drug
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
λz	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) of the final analysis for Study GS-US-350-1937. This SAP is based on the study protocol Amendment 2.2 dated 20 November 2017 and the electronic case report form (eCRF). The SAP will be finalized prior to data finalization for the final analysis. Any changes made after the finalization of the SAP will be documented in the clinical study report (CSR).

The study protocol included two phases in the design: phase 1b dose escalation and randomized phase 2 dose espansion. The study was discontinued during the dose escalation phase based on sponsor decision without moving forward to the randomized phase 2 dose expansion. All subjects who were enrolled in phase 1b have discontinued study drug and conducted the safety follow-up visit.

1.1. Study Objectives

The primary objectives are as follows:

Phase 1b Dose Escalation:

- To characterize the safety and tolerability of GS-5829 in combination with fulvestrant and exemestane in subjects with advanced estrogen receptor positive, HER2 negative breast cancer (ER+/HER2- BrCa)

- To determine the Maximum Tolerated Dose (MTD), or the recommended Phase 2 Dose (RP2D) of GS-5829 in combination with fulvestrant in subjects with advanced ER+/HER2- BrCa

Randomized Phase 2 Dose Expansion:

To evaluate the efficacy of GS-5829 in combination with fulvestrant compared to fulvestrant alone in subjects with advanced ER+/HER2- BrCa as measured by progression-free survival (PFS).

The secondary objectives are as follows:

Phase 1b Dose Escalation

- To evaluate the pharmacokinetics of GS-5829 in combination with fulvestrant in subjects with advanced ER+/HER2- BrCa

Randomized Phase 2 Dose Expansion

- To evaluate the efficacy of GS-5829 in combination with fulvestrant compared to fulvestrant alone in subjects with advanced ER+/HER2- BrCa, as measured by overall response rate (ORR) and clinical benefit rate (CBR) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1. ORR is defined as the proportion of subjects with response (complete response [CR], or partial response [PR]). CBR is defined as proportion of subjects with CR, PR, or stable disease (SD) that lasts for ≥ 24 weeks

- To evaluate the safety and tolerability of GS-5829 in combination with fulvestrant compared to fulvestrant alone in subjects with advanced ER+/HER2- BrCa

- To evaluate the overall survival (OS) for subjects with advanced ER+/HER2- BrCa who receive GS-5829 in combination with fulvestrant compared to fulvestrant alone

The exploratory objectives are as follows:

1.2. Study Design

Phase 1b Dose Escalation:

In the study, cohorts of postmenopausal women with advanced ER+/HER2- BrCa, for whom no standard curative therapy exists and who are candidates for exemestane or fulvestrant, will be sequentially enrolled at progressively higher dose levels of oral GS-5829 in combination with standard doses of exemestane or fulvestrant. The starting dose of GS-5829 has been determined to be 4 mg once daily based on safety information, pharmacokinetic and biomarker data from two ongoing GS-5829 studies (GS-US-350-1599, GS-US-350-1604) and the recommendation by the Bayesian Logistic Regression Model (BLRM) of dose-dose limiting toxicity (DLT) relationship.

Eligible subjects will be assigned to either Group A or B based on prior treatment. Group A will initiate with GS-5829 orally once daily on Cycle 1 Day 1 (C1D1) combined with 25 mg of exemestane administered orally once daily (or in accordance with locally approved labeling). The subject may initiate exemestane any time prior to, or on, C1D1. Enrollment in Group A will be stopped after completion of the 4 mg GS-5829 dose level safety assessments. Subjects who were previously enrolled/treated in Group A will continue to be followed and managed.

Group B will initiate GS-5829 orally once daily on C1D1, with fulvestrant administered intramuscularly (in accordance with locally approved labeling) every 28 days (± 3 days). The subject may initiate fulvestrant any time prior to, or on, C1D1. For subjects whom are treatment

naïve (in metastatic setting) and for all subjects for whom C1D1 is the subject's first dose of fulvestrant, a one-time additional dose of 500 mg fulvestrant should be administered on Cycle 1 Day 15 (C1D15).

Subjects may continue receiving GS-5829 once daily until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or death, whichever comes first. Following treatment discontinuation, subjects will be followed for safety for 30 days from the last dose of study drug.

Study procedures at screening, baseline, and during the study treatment and follow-up are outlined in the protocol and presented in Appendix 1: Study Procedures Table of this SAP.

Randomized Phase 2 Dose Expansion:

Approximately 120 female subjects who are post-menopausal with ER+/HER2- BrCa and who have had disease progression following endocrine therapy will be randomized in a 2:1 ratio to receive fulvestrant + GS-5829 or fulvestrant alone. Randomization will be stratified by prior cyclin-dependent kinase 4/6 (CDK4/6) inhibitor plus aromatase inhibitor (AI) status (naïve vs. progressed). The target number of subjects in each of the 2 strata will be approximately 60 (40 for GS-5829 in combination with fulvestrant and 20 for fulvestrant alone). GS-5829 and fulvestrant will be initiated on C1D1. Each cycle consists of 28 days.

Subjects may continue receiving GS-5829 once daily until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or death whichever comes first.

1.3. Sample Size and Power

Up to approximately 40 subjects will be enrolled in the Phase 1b Dose Escalation portion of the study.

Total enrollment will be approximately 120 subjects in Randomized Phase 2 Dose Expansion portion. Approximately 80 subjects will be randomized to receive GS-5829 in combination with fulvestrant and 40 subjects will receive fulvestrant alone in a 2:1 ratio. One hundred twenty subjects will provide 88 events in total and greater than 90% power to detect the difference in PFS between the two treatment arms with 0.1 one-sided significance level, assuming a median PFS of 4 months for subjects who receive fulvestrant alone, a median PFS of 8 months in subjects who receive GS-5829 in combination with fulvestrant, accrual period of 9 months and total study duration of 19 months and a drop-out rate of 10% by 12 months. Within each stratum of naïve or progressed prior CDK4/6 inhibitor subjects, the power will be 80% with target number of 60 subjects (44 events).

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

No formal interim analysis is planned for this study. Safety and tolerability will be monitored regularly for subjects in the study.

2.2. Final Analysis

After all subjects have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the final analysis of the data will be performed.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (StD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

No formal statistical testing will be performed.

By-subject listings will be presented for all subjects in the All Enrolled Analysis Set and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the subject. The assigned treatment group and dose cohort will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of subjects eligible for inclusion will be summarized by dose cohort within each treatment group.

A listing of reasons for exclusion from analysis sets will be provided by subject.

3.1.1. All Enrolled Analysis Set

All Enrolled Analysis Set includes all subjects who received a study subject identification number in the study after screening.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who were enrolled and received at least 1 dose of any study drug (GS-5829, fulvestrant or exemestane). This is the primary analysis set for the analyses of efficacy. Throughout this SAP, study drug is defined as any drug in the combination therapy (GS-5829, fulvestrant or exemestane) unless specified otherwise.

3.1.3. Safety Analysis Set

The Safety Analysis Set includes all subjects who were enrolled and received at least 1 dose of any study drug. This is the primary analysis set for the analyses of safety, study drug administration and study drug compliance.

3.1.4. Dose-Limiting Toxicity (DLT) Analysis Set

The DLT Analysis Set includes all subjects in the Safety Analysis Set who complete all treatment and safety procedures through Day 28, inclusive, or experienced a DLT prior to Day 28, exclusive. During the DLT assessment window, if a subject who fails to receive study drug for at least 21 days for reasons other than DLT, another subject will be enrolled at the same dose level for replacement. For subjects who are replaced but received at least 1 dose of study drug, they will be included in the Safety Analysis Set and not in the DLT Analysis Set.

3.1.5. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all enrolled subjects who received at least 1 dose of study drug and have at least 1 nonmissing postdose concentration value reported by the PK laboratory. Subjects who received concomitant medications prohibited in this study will be excluded from the PK analysis set. This is the primary analysis set for all PK analyses.

3.2. Subject Grouping

Subjects will be categorized by treatment group (A [GS-5829 + exemestane] or B [GS-5829 + fulvestrant]) and dose cohort. Summaries will be presented by dose cohort within each treatment group and overall, unless specified otherwise.

Subjects will be grouped according to the actual treatment they received.

3.3. Strata and Covariates

No stratum and covariates will be included in efficacy and safety analyses.

3.4. Examination of Subject Subgroups

There are no prespecified subject subgroupings for efficacy and safety analyses.

3.5. Multiple Comparisons

Adjustments for multiplicity will not be made, because no formal statistical testing will be performed in this study.

3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

For missing last dosing date of study drug, imputation rules are described in Section 4.2.1. The handling of missing or incomplete dates for the completion of prior anticancer therapy is described in Section 5.4, for death and the initiation of new anticancer therapy in Section 6.1.1, for AE onset in Section 7.1.5.2, and for prior and concomitant medications in Section 7.4.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.7. Data Handling Conventions and Transformations

Age (in years) on the first dosing date of study drug will be used for analyses and presentation in listings. If an enrolled subject was not dosed with any study drug, the enrollment date will be used instead of the first dosing date of study drug. If only the birth year is collected on the CRF, "01 July" will be used for the unknown birth day and month for the purpose of age calculation. If only birth year and month are collected, "01" will be used for the unknown birth day.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

- A value that is 1 unit above the LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). Values with decimal points will follow the same logic as above.

- The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data or nonparametric analysis methods may be used, as appropriate.

Natural logarithm transformation will be used for plasma/blood concentrations and analysis of PK parameters. Plasma concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points, and one-half the value of the LOQ at postbaseline time points.

The following conventions will be used for the presentation of summary and order statistics:

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."

- If more than 25% of the subjects have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."

- If more than 50% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."

- If more than 75% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."

- If all subjects have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ."

PK parameters that are BLQ will be imputed as one-half LOQ before log transformation or statistical model fitting.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day will be calculated from the first dosing date of study drug and derived as follows:

- For postdose study days: Assessment Date – First Dosing Date + 1

- For days prior to the first dose: Assessment Date – First Dosing Date

Therefore, study day 1 is the day of the first dose of study drug administration.

3.8.2. Analysis Visit Windows

The nominal visit as recorded on the CRF will be used when data are summarized by visit. Any data relating to unscheduled visits will not be assigned to a particular visit or time point.

However, the following exceptions will be made:

- An unscheduled visit prior to the first dosing of study drug may be included in the calculation of the baseline value, if applicable.

- Unscheduled visits after the first dose of study drug will be included in determining the maximum postbaseline toxicity grade.

- For subjects who prematurely discontinue from the study, early termination (ET) data will be assigned to what would have been the next scheduled visit where the respective data were scheduled to be collected.

- Data collected on a follow-up visit will be summarized as a separate visit, and labeled "Follow-up Visit."

- Data obtained after the follow-up visit or last dose date plus 30 days (whichever is later) will be excluded from the summaries, but will be included in the listings.

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values may be required for each visit. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per visit.

If multiple valid, nonmissing, continuous measurements exist in an visit, records will be chosen based on the following rules if a single value is needed:

- In general, the baseline value will be the last nonmissing value on or prior to Study Day 1, unless specified differently. If multiple measurements occur on the same day, the last nonmissing value prior to the first dosing date of study drug will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the average of these measurements (for continuous data) will be considered the baseline value.

- For postbaseline values:

  — The record closest to the nominal day for that visit will be selected.

  — If there are 2 records that are equidistant from the nominal day, the later record will be selected.

  — If there is more than 1 record on the selected day, the average will be taken, unless otherwise specified.

For central ECG data, there may be triplicates at the same nominal day/timepoint for each subject. The average of the tripcates should be used as baseline or postbaseline values at each visit and for selecting the maximum postbaseline values.

If multiple valid, nonmissing, categorical measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

— For baseline, the last available record on or prior to the date of the first dose of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected (eg, normal will be selected over abnormal for safety electrocardiogram (ECG) findings).

— For postbaseline visits, if there are multiple records with the same time or no time recorded on the same day, the value with the worst severity within the window will be selected (eg, abnormal will be selected over normal for safety ECG findings).

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

The summary of subject disposition will present the number of subjects screened, subjects enrolled and subjects in the following categories by dose cohort within each treatment group, and overall:

- Safety Analysis Set
- Full Analysis Set
- DLT Analysis Set
- Discontinued study drug with reasons for discontinuation of study drug
- Completed study
- Discontinued the study with reasons for discontinuation of study

For the status of study drug and study completion and reasons for discontinuation, the number and percentage of the subjects in each category will be provided. The denominator for the percentage calculation will be the total number of subjects in the safety analysis set corresponding to that column.

The following by-subject listing will be provided by subject identification (ID) number inascending order to support the above summary tables:

- Reasons for premature study drug and study discontinuation.

4.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to GS-5829 will be examined by assessing the total duration of exposure to GS-5829 and the level of adherence to GS-5829 specified in the protocol.

4.2.1. Duration of Exposure to GS-5829

Total duration of exposure to GS-5829 will be defined as last dosing date of GS-5829 minus first dosing date of GS-5829 plus 1, regardless of any temporary interruptions in GS-5829 administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks).

If the last dosing date of GS-5829 is missing, the latest date among GS-5829 end date, clinical visit date, laboratory sample collection date, and vital signs assessment date that occurred during the on-treatment period will be used.

Partial dose start or stop dates for each dosing period will be imputed using the following algorithm:

- For dose stop date: If the day and month are missing but the year is available, then the imputed day and month will be the earliest from the following dates: 31 DEC, death date, end of treatment (EOT) date, EOS date, and (start date of the next dosing period – 1); If the day is missing but the month and year are available, , then the imputed day will be the earliest from the following dates: last day of the month, death date, EOT date, EOS date, and (start date of the next dosing period – 1).

- For dose start date: If the day and month are missing but the year is available, then the imputed day and month will be the earliest from the following dates: later of (01 JAN, and [stop date of the previous dosing period + 1]), and stop date of the associated dosing period; If the day is missing but the month and year are available, then the imputed day will be the earliest from the following dates: later of (first day of the month, and [stop date of the previous dosing period + 1]), and stop date of the associated dosing period.

The total duration of exposure to GS-5829 will be summarized using descriptive statistics and using number and percentage of subjects exposed through the following time periods: 1 day, 4 weeks, 8 weeks, 16 weeks, 24 weeks, 36 weeks and 48 weeks. Summaries will be provided by dose cohort within each treatment group for the Safety Analysis Set.

4.2.2. Adherence to GS-5829

4.2.2.1. On-Treatment Adherence

The level of on-treatment adherence to GS-5829 will be determined by the total amount of GS-5829 administered relative to the total amount of GS-5829 expected to be administered during a subject's actual on-treatment period. Investigator-prescribed interruption, reductions and escalations as specified in the protocol will be taken into account.

The total amount of GS-5829 in mg administered to a subject will be determined by the data collected on the drug accountability CRF using the following formula:

Total amount of Doses Administered (mg) =

$$(\sum \text{Amount. of Doses Dispensed in mg}) - (\sum \text{Amount. of Doses Returned in mg})$$

The level of on-treatment adherence will be expressed as a percentage using the following formula:

$$\text{On-Treatment Adherence (\%)} = \left(\frac{\text{Total Amount of Study Drug Administered}}{\text{Study Drug Expected to be Administered on Treatment}} \right) \text{x } 100$$

Descriptive statistics for the level of on-treatment adherence with the number and percentage of subjects belonging to adherence categories ($< 75\%$, $\geq 75\%$) will be provided by dose cohort within each treatment group for the Safety Analysis Set.

4.2.2.2. Average Daily Dose

The average daily dose in mg of GS-5829 administered will be summarized using descriptive statistics.

The average daily dose in mg will be calculated using the following formula:

$$\text{Average Daily Dose (mg)} = \frac{\sum(\text{Daily Dose in mg})}{\text{Total Number of Days on Study Drug}},$$

where Total Number of Days on Study Drug = Last Dosing Date – First Dosing Date + 1.

By-subject listings of study drug administration and drug accountability will be provided by subject ID number in ascending order and visit in chronological order as appropriate.

4.3. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry, but were enrolled in the study will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of subjects who did not meet at least 1 eligibility criterion and the number of subjects who did not meet specific criteria by treatment group based on the All Enrolled Analysis Set. A by-subject listing will be provided for those subjects who did not meet at least 1 eligibility (inclusion or exclusion) criterion.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason (eg, nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by dose cohort within each treatment group and total for the All Enrolled Analysis Set. A by-subject listing will be provided for those subjects with any important protocol deviation.

5. BASELINE CHARACTERISTICS

5.1. Demographics

Subject demographic variables (ie, age, sex at birth, race, and ethnicity) will be summarized by dose cohort within each treatment group and overall using descriptive statistics for age, and using number and percentage of subjects for sex, race, and ethnicity. The summary of demographic data will be provided for the Safety Analysis Set.

A by-subject demographic listing, including the informed consent date, will be provided by subject ID number in ascending order.

5.2. Other Baseline Characteristics

Other baseline characteristics include body weight (in kg), height (in cm), body mass index (BMI; in kg/m^2). These baseline characteristics will be summarized by dose cohort within each treatment group and overall using descriptive statistics. The summary of baseline characteristics will be provided for the Safety Analysis Set.

A by-subject listing of these baseline characteristics will be provided by subject ID number in ascending order.

5.3. Medical History

Medical history will be collected at screening for disease-specific and general conditions (ie, conditions not specific to the disease being studied).

General medical history data will not be coded.

A by-subject listing of disease-specific and general medical history will be provided by subject ID number in ascending order.

5.4. Prior Anticancer Therapy

For prior anticancer therapies that a subject received before the start of the study drug, the number of prior regimens and the time since the completion of last regimen (ie, the most recent regimen that a subject received prior to the first dose date of the study drug) will be summarized by dose cohort within each treatment group and overall using descriptive statistics based on the the Safety Analysis Set.

For the completion of last regimen, a partial completion date will be imputed as follows:

- If day and month are missing but year is available, then the imputed day and month will be 01 Jan.

- If day is missing but the month and year are available, then the imputed day will be the first day of the month.

- Partial date will not be imputed if the year is missing.

A by-subject listing will be provided for prior anticancer therapies, on and post study anticancer therapies, prior and on-study radiation therapy, and prior and on-study surgery or procedures each by subject ID number in ascending order.

6. EFFICACY ANALYSES

6.1. Definitions of Efficacy Endpoints

6.1.1. Progression-free survival (PFS)

Progression-free survival (PFS), defined as the interval from first dosing date of study drug to the earlier of the first documentation of definitive disease progression or death from any cause. Definitive disease progression is determined based on RECIST Version 1.1 {Eisenhauer 2009}.

The date of definitive progression will be the time point at which progression is first identified by relevant radiographic, imaging, or clinical data. Data will be censored on the date of last adequate tumor assessment (i.e. not "Not Evaluable" [NE]) for subjects:

- who do not have documented progression or die, or
- who start new anticancer therapy before documented progression, or
- who start new anticancer therapy before death without documented progression, or
- who have ≥ 2 consecutive missing tumor assessments immediate before documented progression, or
- who have ≥ 2 consecutive missing tumor assessments immediate before death without documented progression

Subjects without any post-baseline tumor assessment will be censored at Study Day 1. If a subject does not have a baseline tumor assessment, then PFS will be censored at Study Day 1, regardless of whether or not definitive progression or death has been observed.

When the date of initiation of anticancer therapy other than the study treatment is incomplete or missing, the following algorithm will be followed:

- If the day is missing but the month and year are available, then the imputed day will be the last day of the month.
- If the day and month are missing but year is available, then the imputed day and month will be 01Jan or the last day of the month for the last non-NE tumor assessment if they have the same year, whichever is later.

Every attempt will be made to ensure that complete death dates are recorded. In those rare instances where complete death dates are not recorded, the following algorithm will be used:

- If the day is missing but the month and year are available, then the imputed day will be the midpoint of the month or the last assessment date + 1, whichever is later.

- If the day and month are missing but year is available, then the imputed day and month will be 01Jan or the last day of the latest month that the subject was known to be alive if they have the same year, whichever is later.

6.1.2. Overall Response Rate (ORR)

For each subject, the overall response will be categorized as CR, PR, SD, noncomplete reponse or non progressive disease, progressive disease (PD) or NE at each visit of assessment.

ORR is defined as the proportion of subjects who achieve best overall response (BOR) of CR or PR during the study based on RECIST Version 1.1. Confirmation of CR or PR at the subsequesnt time point is required for best overall response of CR or PR. Subjects, who do not have sufficient baseline or on-study tumor status information to be adequately assessed for response status (ie, those with best overall response of NE) or received anticancer therapy other than the study treatment prior to achieving CR or PR, will be considered as nonresponders. All subjects in the FAS will be included in the denominator in calculation of ORR.

6.1.3. Clinical Benefit Rate (CBR)

CBR is defined as the proportion of subjects who achieve best overall response of CR, PR or SD that lasts for ≥ 24 weeks during the study based on RECIST Version 1.1. Duration of SD is calculated from the first dose date of study drug to the first date of disease progression. All subjects in the FAS will be included in the denominator in the calculation of CBR.

6.2. Analysis of the Efficacy Endpoints

6.2.1. Progression-free Survival

Progression-free survival based on investigators' assessments will be summarized using Kaplan-Meier (KM) methods by dose cohort within treatment group for the FAS. The KM curve for PFS will be provided. All the drived endpoints will be listed.

6.2.2. Overall Response Rate And Clinical Benefit Rate

The number and percentage of subjects in each response category (eg, CR, PR, SD, SD that lasts for ≥ 24 weeks, PD, and NE) will be summarized by dose cohort within treatment group for the FAS. ORR and CBR based on investigators' assessments will be calculated along with their 95% confidence intervals (CIs) based on the Clopper-Pearson method and summarized by dose cohort within treatment group for the FAS.

A by-subject listing of the overall response assessment data will be provided.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

All Adverse Events (AEs) will be listed. The focus of AE summarization will be on treatment-emergent adverse events (TEAEs). AEs that occur before the first dose of study drug or > 30 days after the subject has been discontinued from study drug will be included in data listings.

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to CTCAE Version 4.03. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Pharmacovigilance and Epidemiology (PVE) Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drug.

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The AE onset date is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug.

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

In case when the AE onset date is incomplete and needs to be imputed, the following algorithm will be followed:

- If the day is missing but the month and year are available, then the imputed day will be the first day of the month or the first dosing date if they have the same month and year, whichever is later.
- If the day and month are missing but year is available, then the imputed day and month will be 01Jan or the first dosing date if they have the same year, whichever is later.

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized by dose cohort within each treatment group and overall based on the Safety Analysis Set.

7.1.6.1. Summaries of AE Incidence by Severity

The number and percentage of subjects who experienced at least one TEAE will be provided and summarized by SOC, HLT and PT. For other AEs described below, summaries will be provided by SOC and PT:

- TEAEs
- TEAEs with Grade 3 or higher
- TEAEs related to GS-5829
- Treatment-emergent SAEs

- Treatment-emergent SAEs related to GS-5829
- TEAEs leading to premature discontinuation of GS-5829
- TEAEs leading to dose modification of GS-5829
- TEAEs leading to temporary interruption of GS-5829
- TEAEs leading to death

For TEAEs and TEAEs related to GS-5829, summaries will be provided by SOC, PT and severity.

A brief, high-level summary of AEs described above will be provided to show the number and percentage of subjects who experienced the above AEs as well as the following:

- TEAEs related to exemstane or fulvestrant
- TEAEs related to GS-5829 with Grade 3 or higher
- TEAEs related to exemstane or fulvestrant with Grade 3 or higher
- Treatment-emergent SAEs related to exemstane or fulvestrant

In addition to the above summary tables, TEAEs and treatment emergent SAEs will be summarized by PT only in descending order of total frequency.

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and then by PT in descending order of total frequency within each SOC. For summaries by severity, the most severe severity will be used for those AEs that occurred more than once in a given subject during the study.

In addition, by-subject data listings will be provided for the following:

- All AEs
- All AEs of Grade 3 or higher
- SAEs
- Deaths
- AEs leading to death
- AEs leading to premature discontinuation of GS-5829

- AEs leading to dose reduction of GS-5829
- AE leading to dose interruption of GS-5829.

A flag will be included in the listings to indicate whether the event is treatment emergent.

7.1.6.2. Summary of Deaths

Summary of deaths will not be provided given that there is no occurrence of death reported during this study.

7.1.7. Additional Analysis of Adverse Events

7.1.7.1. Dose Limiting Toxicity

A by-subject listing of the DLT AEs will be provided following the standard AE listing format.

7.1.7.2. Treatment-Emergent Adverse Events (TEAE) of Interest

TEAEs of interest are determined baesd on the customized medical search terms (MSTs) provided by PVE based on the Standardized MedDRA Queries (SMQs). Analyses for TEAEs of interest will be performed for the following:

- Decreased Platelets: (The list of selected PTs is provided in Appendix 3.)
- Haemorrhage: (The list of selected PTs is provided in Appendix 4.)
- Diarrhoea: (The list of selected PTs is provided in Appendix 5.)

The number and percentage of subjects who experienced at least one TEAE of interest will be provided and summarized by adverse event of interest (AEI) category, preferred term and severity in a way similar to the summaries of TEAEs (Section 7.1.6).

A by-subject listing of TEAEs of interest will be provided.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days for subjects who have permanently discontinued study drug. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

A by-subject listing for all lab test results will be provided by subject ID number and time point in chronological order for hematology, serum chemistry and coagulation, separately. Values falling outside of the relevant reference range and/or having a severity Grade of 1 or higher on the CTCAE severity grade will be flagged in the data listings, as appropriate.

7.2.1. Summaries of Numeric Laboratory Results

Descriptive statistics will be provided by dose cohort within each treatment group for each laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dosing date of study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean (StD), median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; StD values will be displayed to the reported number of digits plus 1.

In the case of multiple values in an visit, data will be selected for analysis as described in Section 3.8.3. In the event that both central and local lab results are collected in the clinical database, only central lab results will be included in the summary by visits. All central and local laboratory values will be listed.

7.2.2. Graded Laboratory Values

CTCAE Version 4.03 will be used to assign toxicity Grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

Local labs will be graded based on central lab normal ranges with in-house macro. In the event that both central and local lab results are collected in the clinical database, the worst toxicity grade will be used for the summary of lab toxicities.

All central and local laboratory values will be listed.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days for subjects who permanently discontinued study drug. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.2.2. Summaries of Laboratory Abnormalities

The following summaries (number and percentage of subjects) for laboratory abnormalities will be provided by lab test and dose cohort within each treatment group:

- Basline grade (Grade 0 to 4 separately, Grade 3 or 4, and Grade 1 to 4)
- Worst treatment-emergent laboratory abnormalities postbaseline grade (Grade 1 to 4 separately, Grade 3 or 4, and Grade 1 to 4)

For baseline grade, the denominator for percentage is the number of subjects in the safety analysis set who have nonmissing baseline values; for the worst treatment-emergent laboratory abnormalities postbaseline grade, the denominator for percentage is the number of subjects with nonmissing postbaseline values up to 30 days after last dosing date.

7.2.2.3. Shifts Relative to the Baseline Value

Shift tables for graded lab values will be presented by showing change in severity grade from baseline to the worst postbaseline grade.

7.2.3. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of subjects who were reported to have the following laboratory test values for postbaseline measurements:

- Aspartate aminotransferase (AST): (a) > 3 times of the upper limit of reference range (ULN); (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Alanine aminotransferase (ALT): (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- AST or ALT: (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Total bilirubin: (a) > 1 x ULN; (b) > 2 x ULN
- Alkaline phosphatase (ALP) > 1.5 x ULN
- AST or ALT > 3 x ULN: (a) total bilirubin > 1.5 x ULN; (b) total bilirubin > 2 x ULN; (c) total bilirubin > 2 x ULN and ALP < 2 x ULN

The summary will include data from all postbaseline visits up to 30 days after the last dose of study drug. For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. For both the composite endpoint of AST or ALT and total bilirubin, subjects will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of subjects in the Safety Analysis Set who have nonmissing

postbaseline values. In addition, a listing of subjects who met at least 1 of the above criteria will be provided.

7.3. Vital Signs

Descriptive statistics will be provided by dose cohort within each treatment group for vital signs as follows:

- Baseline value
- Values at each postbaseline visit
- Change from baseline at each postbaseline visit

A baseline value will be defined as the last available value collected on or prior to the date/time of first dosing date of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. vital signs measured at unscheduled visits will be included for the baseline value selection.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. A by-subject listing of vital signs will be provided by subject ID number and visit in chronological order.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

7.4.1. Prior Medications

Prior medications are defined as any medications taken before a subject took the first study drug. A summary of prior medications will not be provided. Prior medications will be included in a listing together with concomitant medications.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant medications will be summarized by preferred name using the number and percentage of subjects by dose level within each treatment group and overall. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered by preferred term in descending overall frequency. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant

medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary, unless otherwise specified. Summaries will be based on the Safety Analysis Set.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

7.5. Electrocardiogram Results

Summaries of ECG readings will be provided for the Safety Analysis Set for each scheduled time point based on central ECG results. The local ECG assessment results will be used in the data summary if only local ECG measurements are available at a visit/timepoint.

A by-subject listing for both central and local ECG assessment results will be provided by subject ID number and visit/time point in chronological order.

7.5.1. Corrected QT Intervals

The QT interval (measured in millisecond [msec]) is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. The QT interval is affected by heart rate, and a number of methods have been proposed to correct QT for heart rate.

Corrected QT (QTc) intervals will be derived using Fridericia's correction (QTcF) as follows:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

where QT is measured in msec; RR = 60/Heart Rate (beats per min [bpm]) and RR is measured in seconds

The maximum postdose QTcF interval values obtained during the study will be summarized within the following categories:

- > 450 msec
- > 480 msec
- > 500 msec

The maximum postdose change in QTcF interval values obtained during the study will also be summarized within the following categories:

- > 30 msec
- > 60 msec

QTcF and uncorrected QT values at each visit and change from baseline at each time point will be summarized for the Safety Analysis Set by dose cohort within each treatment group using descriptive statistics.

7.5.2. PR and QRS Intervals

The PR interval (measured in msec) is a measure of the time between the start of the P wave (the onset of atrial depolarization) and the beginning of the QRS complex (the onset of ventricular depolarization). The QRS interval measures the duration of the QRS complex. The maximum heart rate (HR) and PR and QRS intervals observed during the study will be categorized. The number and percentage of subjects having values in the following ranges will be presented by dose cohort within each treatment group:

- HR > 100 bpm
- PR interval > 200 msec
- QRS interval > 110 msec

In addition, HR, PR, RR, and QRS values at each visit and time point and change from baseline at each visit and time point will be summarized from the Safety Analysis Set for each dose cohort within each treatment group using descriptive statistics.

7.6. Echocardiogram

A by-subject listing will be provided for echocardiogram and multigated acquisition (MUGA) scan results by subject ID number and visit/time point in chronological order.

7.7. ECOG Performance Status

A by-subject listing will be provided for ECOG Performance Status assessments by subject ID number and visit/time point in chronological order.

7.8. Other Safety Measures

No additional safety measures are specified in the protocol.

7.9. Changes From Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.

8. PHARMACOKINETIC (PK) ANALYSES

8.1. PK Sample Collection

PK samples for GS-5829 will be collected on Day 1 and Day 15 of Cycle 1 at pre-dose, and 0.5, 1, 2, 3, 4, 6, 8 and 24 hours at post-dose, and anytime on Day 1 of Cycles 2 through 6. Refer to Appendix 2 of the SAP. All GS-5829 post-dose pharmacokinetic samples have a ± 10 minute window.

8.2. PK Analyses Related to Intensive PK Sampling

8.2.1. Estimation of PK Parameters

PK parameters will be estimated using Phoenix WinNonlin® software using standard noncompartmental methods. The linear/log trapezoidal rule will be used in conjunction with the appropriate noncompartmental model, with input values for dose level, dosing time, plasma concentration, and corresponding real-time values, based on drug dosing times whenever possible.

All predose sample times before time-zero will be converted to 0.

For area under the curve (AUC), samples BLQ of the bioanalytical assays occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of 0 to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data in WinNonlin. The nominal time point for a key event or dosing interval (τ) may be used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach will be assessed by the PK scientist on a profile-by-profile basis.

Pharmacokinetic parameters such as AUC_{tau}, λ_z and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK scientist.

8.2.2. PK Parameters

PK parameters will be generated for all subjects in the PK analysis set. The analytes presented in Table 1 will be evaluated if data are available.

Table 1. PK Parameters for Analytes

	GS-5829	GS-697412	Metabolite/parent ratio
Cycle 1 Day 1	C_{max}, T_{max}, $AUC_{0\text{-}24h}$, AUC_{last}, AUC_{inf}, $\%AUC_{exp}$, C_{24h}, C_{last}, T_{last}, λ_z, $T_{1/2}$, V_z_F, CL_F	C_{max}, T_{max}, $AUC_{0\text{-}24h}$, AUC_{last}, AUC_{inf} , $\%AUC_{exp}$, C_{24h}, C_{last}, T_{last}, λ_z, $T_{1/2}$	C_{max}, $AUC_{0\text{-}24h}$, and C_{24h}
Cycle 1 Day 15	C_{max}, T_{max}, AUC_{tau}, AUC_{last}, C_{tau}, C_{last}, T_{last}, λ_z, $T_{1/2}$, V_z_F, CL_{ss}_F	C_{max}, T_{max}, AUC_{tau}, AUC_{last}, C_{tau}, C_{last}, T_{last}, λ_z, $T_{1/2}$	C_{max} , AUC_{tau}, and C_{tau},

Individual subject concentration data and individual subject PK parameters for GS-5829 and its metabolite GS-697412 will be listed and summarized using descriptive statistics by dose cohort within each treatment group. Summary statistics (n, mean, StD, coefficient of variation [%CV], median, min, max, Q1, and Q3) will be presented for both individual subject concentration data by time point and individual subject PK parameters. Moreover, the geometric mean, 95% CI, and the mean and StD of the natural log-transformed values will be presented for individual subject PK parameter data.

Individual metabolite to parent molar ratios will be calculated for $AUC_{0\text{-}24h}$, C_{max}, and C_{24h} on Cycle 1 Day 1, and for AUC_{tau}, C_{max}, and C_{tau} on Cycle 1 Day 15, when available, and summarized similarly to the PK parameters. Metabolite to parent ratios will be calculated as (PK parameter of metabolite analyte / PK parameter of parent analyte * 0.96), where 0.96 is parent to metabolite molecule weight ratio.

Individual concentration data listings and summaries will include all subjects with concentration data. The sample size for each time point will be based on the number of subjects with nonmissing concentration data at that time point. The number of subjects with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as 0 at predose and one-half of the lower limit of quantitation (LLOQ) for postdose time points.

Individual PK parameter data listings and summaries will include all subjects for whom PK parameter(s) can be derived. The sample size for each PK parameter will be based on the number of subjects with nonmissing data for that PK parameter.

The following tables will be provided for GS-5829 by by dose cohort within each treatment group:

- Individual subject concentration data and summary statistics
- Individual subject plasma PK parameters and summary statistics
- Individual metabolite to parent ratios for $AUC_{0\text{-}24h}$, C_{max}, and C_{24h} on Cycle 1 Day 1, and for AUC_{tau}, C_{max}, and C_{tau}, on Cycle 1 Day 15 and its summary statistics.

The following figures may be provided for GS-5829 by by dose cohort within each treatment group:

- Mean (± StD) concentration data versus time (on linear and semilogarithmic scales)
- Median (Q1, Q3) concentration data versus time (on linear and semilogarithmic scales)

Individual, mean, and median postdose concentration values that are ⩽ LLOQ will not be displayed in the figures and remaining points connected.

PK sampling details by subject, including procedures, differences in scheduled and actual draw times, and sample age will be provided in listings.

9. REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1). Eur J Cancer 2009;45 (2):228-47.

10. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

11. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

12. APPENDICES

Appendix 1. Study Procedures Table

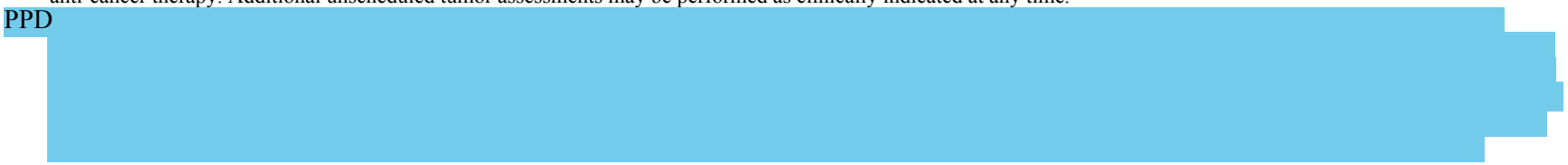
	Screening	***Treatment Period***					**End of Treatment**	**30 Day Safety Follow Up[8]**
Study Phase Cycle Day	**Day -28**	***Cycle 1***		***Cycle 2***		***Cycle 3 and every 4 weeks***		
		Day 1 [7]	***Day 15***	***Day 1***	***Day 15***	***Day 1***		
Window (days)	-28	*+3*	*±2*	*+3*	*±2*	*+3*	±7	±5
Informed Consent	X							
Medical and Medication History [1]	X							
Physical Examination [2]	X	*X*		*X*		*X*	X	X
ECOG Performance Status [3]	X	*X*		*X*			X	X
Vital Signs [4]	X	*X*	*X*	*X*	*X*	*X*	X	X
Triplicate 12-lead ECG [5]	X	*X*	*X*	*X*		*X*	X	
Echocardiogram [6]	X			*X*			X	
Adverse Events/Concomitant Medication [9]	X	*X*	*X*	*X*	*X*	*X*	X	X
GS-5829 and Exemestane (Group A Phase 1b) Accountability and Dispensing [10]		*X*		*X*		*X*	X	
Exemestane (Group A Phase 1b) or Fulvestrant Administration [11]		*Subjects will self-administer exemestane (Group A Phase 1b) orally once daily starting on or before C1D1.* *Subjects will receive fulvestrant during visits on C1D1 and then every 28 days (±3 days). For subjects initiating fulvestrant on this study, a single dose of fulvestrant should be administered on C1D15 (± 3 days).*						

Study Phase Cycle Day	Screening	Treatment Period					End of Treatment	30 Day Safety Follow Up[8]
	Day -28	Cycle 1		Cycle 2		Cycle 3 and every 4 weeks		
		Day 1 [7]	Day 15	Day 1	Day 15	Day 1		
CBC with Differential [12]	X	X	X	X		X	X	X
Chemistry [12]	X	X	X	X	X	X	X	X
Coagulation [13]	X	X	X	X			X	
25-hydroxy vitamin D	X							
Serum Pregnancy Test, Serum Estradiol and FSH (if applicable), Urine Pregnancy Test (if applicable) [14]	X	X[14]		X[14]		X[14]	X	
HBV, HCV, HIV Virology [15]	X							
Archival Tumor Tissue [16]		X						
PPD								
Treatment Response Assessment [17]	X	CT/MRI Performed every 8 weeks (±7 days) for the first year and then every 12 weeks (±7 days) from the date of C1D1.					X	
CT/MRI [18]	X						X	
Radionuclide Bone Scan [19]	X						X	
Phone Call								
PPD								

1 Medical history includes significant past medical events (e.g., prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies and any concurrent medical illnesses. At screening, all medications taken up to 30 days prior to screening will be documented in the eCRF.
2 Screening and EOT Physical Examinations (PE) will be a complete PE. Beginning at C1D1, a modified physical examination will be performed. Weight (without shoes) should be measured at each PE. Height (without shoes) is measured at Screening only.
3 ECOG will be scored using the scale index in study protocol Appendix 6.
4 C1D1 Vital Signs will be taken within 15 minutes pre-GS-5829 dose and 2 and 4 hours post dose (+/- 15 min); vital signs will be taken pre-dose only at all subsequent visits.

5 Triplicate ECGs will be collected at any time during Screening window, C1D1, Day 1 of Cycles 2-6 (at pre-dose), and at EOT. In the Phase 1b Dose Escalation phase of the study, triplicate ECGs will be collected on C1D1 at pre-dose and 1-4 hrs post-dose and on C1D15 at pre-dose, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, and 8 hours post dose (± 20 minutes). In the Randomized Phase 2 Dose Expansion phase of the study, triplicate ECGs will be collected on C1D1 at pre-dose and 1-4 hrs post-dose and on C1D15 at pre-dose, 1 hour, 2 hours, 4 hours, and 6 hours post dose (±20 minutes). ECGs should always be collected prior to pharmacokinetics (or any other blood draw) if they are to be collected at the same nominal time point. Subjects should be resting quietly and free of distraction (e.g., TV, conversation) for 10 minutes prior to ECG collection and ECGs should be collected over a 5 minute window at each time point.
6 Multigated acquisition scan (MUGA) is acceptable. The same modality must be used throughout study participation.
7 Day 1 pre-GS-5829 lab samples may be drawn up to two days prior to the Day 1 visit.
8 For Phase 1b Dose Escalation subjects, the 30-Day Safety Follow-Up Visit (±5 days) will be the final study visit. Randomized Phase 2 Dose Expansion subjects will complete the 30-Day Safety Follow-Up Visit (±5 days) and proceed to Long Term Survival Follow-Up.
9 LTFU will begin for subjects participating in the Randomized Phase 2 Dose Expansion phase of the study after the 30 day Safety Follow-Up visit for up to 2 years after the last dose of study drug. A phone call will be made every 3 months (± 7 days) to confirm whether subject has had disease progression.
10 AE reporting period begins once the Informed Consent Form has been signed. AEs will be assessed using NCI CTCAE (v 4.03) criteria at pre- and post-GS-5829 dosing during applicable clinic visits. Subjects will also return to clinic at 30-day post last study drug dose to assess AEs and SAEs.
11 Beginning on C1D1, subjects will receive GS-5829 daily.
12 Subjects assigned to receive exemestane in combination with GS-5829 in the study will self-administer exemestane orally once daily starting on or before on C1D1 and thereafter at approximately the same time each day until the end of treatment. Subjects assigned to receive fulvestrant in combination with GS-5829 in this study will receive fulvestrant 500 mg IM on C1D1 and every 28 days (± 3 days) until the end of treatment. For subjects initiating fulvestrant on this study a single dose of fulvestrant 500 mg should be administered on Cycle 1 Day 15 (± 3 days).
13 C1D1 pre-dose samples may be drawn up to 2 days prior to the visit.
14 Coagulation assessment includes PT/INR, aPTT to be done at Screening and predose of: C1D1, C1D15 and C2D1.
15 Subjects who are on goserelin will have serum pregnancy, serum estradiol, and FSH checked first day of Cycle 1 to Cycle 3, and a urine pregnancy test will be performed monthly thereafter starting cycle 4.
16 HCV RNA Reflex is required.
17 If available, paraffin embedded archival tumor tissue block or freshly sectioned unstained slides will be requested to be shipped to Gilead or designee. These samples will be requested on or after C1D1.
18 Tumor burden as assessed by RECIST v. 1.1 Guidelines (refer to Appendix 7).
19 The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject. CT/MRI to be done at EOT visit if not done within the previous 4 weeks. Subjects who discontinue study treatment for reasons other than disease progression will continue to have tumor assessments performed during the follow up visits every 8 weeks for the first year and then every 12 weeks until disease progression, initiation of new anti-cancer therapy, or discontinuation from the overall study participation (death, subject's request, lost to follow-up) whichever happens first. Every effort should be made to perform a last tumor assessment before starting a new anti-cancer therapy. Additional unscheduled tumor assessments may be performed as clinically indicated at any time.

PPD



21 Subjects who discontinue study treatment for reasons other than disease progression will continue to have tumor assessments performed during the follow up visits every 8 weeks for the first year and then every 12 weeks until disease progression, initiation of new anti-cancer therapy, or discontinuation from the overall study participation (death, subject's request, lost to follow-up) whichever happens first. Every effort should be made to perform a last tumor assessment before starting a new anticancer therapy. Additional unscheduled tumor assessments may be performed as clinically indicated at any time.

22 Pre-treatment (anytime during the screening window and prior to the first dose) and on-treatment biopsies (obtained between 4 and 8 weeks post C1D1) will be obtained from subjects who provide their specific consent to the collection of these samples. Core biopsies or excisional biopsies are requested and fine needle aspirates will not be accepted. Please refer to the laboratory manual for tissue requirements.

Appendix 2. Pharmacokinetics, Pharmacodynamic Time Point Collection Tables

Phase 1b Dose Escalation[1]

Time point in hours from GS-5829 dose	Screening	C1D1	C1D15	C2D1	C3D1 and every 4 weeks [2]	EOT
Pre-dose		X	X			
0.5 Post-dose (± 10 minutes)		X	X			
1 Post-dose (± 10 minutes)		X	X			
2 Post-dose (± 10 minutes)		X	X			
3 Post-dose (±10 minutes)		X	X	X	X	
4 Post-dose (± 10 minutes)		X	X			
6 Post-dose (±10 minutes)		X	X			
8 Post-dose (±10 minutes)		X	X			
24 Post-dose (± 10 minutes)		X	X			

1 Pharmacokinetic and pharmacodynamic samples for GS-5829 will be collected on Day 1 and Day 15 of Cycle 1 at pre-dose 0.5, 1, 2, 3, 4, 6, 8 and 24 hours post-dose and anytime on Day 1 of Cycles 2 through 6.
2 The last pharmacokinetics/pharmacodynamics collection will be at C6D1.

Appendix 3. List of Medical Search Terms for Decreased Platelets

MedDRA Preferred Terms	MedDRA Code
Acquired amegakaryocytic thrombocytopenia	10076747
Amegakaryocytic thrombocytopenia	10076744
Cutaneovisceral angiomatosis with thrombocytopenia	10069098
HELLP syndrome	10049058
Immune thrombocytopenic purpura	10074667
Megakaryocytes abnormal	10027118
Megakaryocytes decreased	10027119
Platelet count abnormal	10035526
Platelet count decreased	10035528
Platelet disorder	10035532
Platelet maturation arrest	10035537
Platelet production decreased	10035540
Platelet toxicity	10059440
Plateletcrit abnormal	10064785
Plateletcrit decreased	10064784
Severe fever with thrombocytopenia syndrome	10078387
Thrombocytopenia	10043554
Thrombocytopenia neonatal	10043557
Thrombocytopenic purpura	10043561
Thrombotic thrombocytopenic purpura	10043648

Note: Selected preferred terms were based on MedDRA Version 21.0.

Appendix 4. List of Medical Search Terms for Haemorrhage

MedDRA Preferred Terms	MedDRA Code
Haemorrhagic adrenal infarction	10079902
Eye haematoma	10079891
Spontaneous hyphaema	10080110
Anal fissure haemorrhage	10079765
Paranasal sinus haemorrhage	10080108
Peripheral artery aneurysm rupture	10079908
Aortic annulus rupture	10079586
Abdominal wall haematoma	10067383
Abdominal wall haemorrhage	10067788
Abnormal clotting factor	10049862
Abnormal withdrawal bleeding	10069195
Acquired dysfibrinogenaemia	10051122
Acquired haemophilia	10053745
Acquired haemophilia with anti FVIII, XI, or XIII	10056496
Acquired protein S deficiency	10068370
Acquired Von Willebrand's disease	10069495
Activated partial thromboplastin time abnormal	10000631
Activated partial thromboplastin time prolonged	10000636
Activated partial thromboplastin time ratio abnormal	10075284
Activated partial thromboplastin time ratio fluctuation	10075286
Activated partial thromboplastin time ratio increased	10075287
Acute haemorrhagic leukoencephalitis	10058994
Acute haemorrhagic ulcerative colitis	10075634
Administration site bruise	10075094
Administration site haematoma	10075100
Administration site haemorrhage	10075101
Adrenal haematoma	10059194
Adrenal haemorrhage	10001361
Anal haemorrhage	10049555
Anal ulcer haemorrhage	10063896

MedDRA Preferred Terms	MedDRA Code
Anastomotic haemorrhage	10056346
Anastomotic ulcer haemorrhage	10002244
Aneurysm ruptured	10048380
Angina bullosa haemorrhagica	10064223
Anorectal varices haemorrhage	10068925
Anti factor IX antibody positive	10058748
Anti factor V antibody positive	10058745
Anti factor VII antibody positive	10058746
Anti factor VIII antibody positive	10049013
Anti factor X activity abnormal	10077670
Anti factor X activity increased	10077671
Anti factor X antibody positive	10058747
Anti factor XI antibody positive	10058749
Anti factor XII antibody positive	10058750
Antithrombin III increased	10051115
Aortic aneurysm rupture	10002886
Aortic dissection rupture	10068119
Aortic intramural haematoma	10067975
Aortic perforation	10075729
Aortic rupture	10060874
Aponeurosis contusion	10075330
Application site bruise	10050114
Application site haematoma	10068317
Application site haemorrhage	10072694
Application site purpura	10050182
Arterial haemorrhage	10060964
Arterial intramural haematoma	10074971
Arterial ligation	10003165
Arterial perforation	10075732
Arterial rupture	10003173
Arteriovenous fistula site haematoma	10055150

MedDRA Preferred Terms	MedDRA Code
Arteriovenous fistula site haemorrhage	10055123
Arteriovenous graft site haematoma	10055152
Arteriovenous graft site haemorrhage	10055126
Atrial rupture	10048761
Auricular haematoma	10003797
Basal ganglia haematoma	10077031
Basal ganglia haemorrhage	10067057
Basilar artery perforation	10075736
Benign familial haematuria	10060876
Bladder tamponade	10062656
Bleeding time abnormal	10049227
Bleeding time prolonged	10005140
Bleeding varicose vein	10005144
Blood blister	10005372
Blood fibrinogen abnormal	10005518
Blood fibrinogen decreased	10005520
Blood thrombin abnormal	10005818
Blood thrombin decreased	10005820
Blood thromboplastin abnormal	10005824
Blood thromboplastin decreased	10005826
Blood urine	10005863
Blood urine present	10018870
Bloody discharge	10057687
Bloody peritoneal effluent	10067442
Bone contusion	10066251
Bone marrow haemorrhage	10073581
Brain contusion	10052346
Brain stem haematoma	10073230
Brain stem haemorrhage	10006145
Brain stem microhaemorrhage	10071205
Breast haematoma	10064753

MedDRA Preferred Terms	MedDRA Code
Breast haemorrhage	10006254
Broad ligament haematoma	10006375
Bronchial haemorrhage	10065739
Bronchial varices haemorrhage	10079163
Bursal haematoma	10077818
Capillary fragility abnormal	10007192
Capillary fragility increased	10007194
Capillary permeability increased	10007200
Cardiac contusion	10073356
Carotid aneurysm rupture	10051328
Carotid artery perforation	10075728
Catheter site bruise	10063587
Catheter site haematoma	10055662
Catheter site haemorrhage	10051099
Central nervous system haemorrhage	10072043
Cephalhaematoma	10008014
Cerebellar haematoma	10061038
Cerebellar haemorrhage	10008030
Cerebellar microhaemorrhage	10071206
Cerebral aneurysm perforation	10075394
Cerebral aneurysm ruptured syphilitic	10008076
Cerebral arteriovenous malformation haemorrhagic	10008086
Cerebral artery perforation	10075734
Cerebral haematoma	10053942
Cerebral haemorrhage	10008111
Cerebral haemorrhage foetal	10050157
Cerebral haemorrhage neonatal	10008112
Cerebral microhaemorrhage	10067277
Cervix haematoma uterine	10050020
Cervix haemorrhage uterine	10050022
Chest wall haematoma	10076597

MedDRA Preferred Terms	MedDRA Code
Choroidal haematoma	10068642
Choroidal haemorrhage	10008786
Chronic gastrointestinal bleeding	10050399
Chronic pigmented purpura	10072726
Ciliary body haemorrhage	10057417
Circulating anticoagulant	10053627
Clot retraction abnormal	10009669
Clot retraction time prolonged	10009675
Coagulation disorder neonatal	10009732
Coagulation factor decreased	10009736
Coagulation factor deficiency	10067787
Coagulation factor IX level abnormal	10061770
Coagulation factor IX level decreased	10009746
Coagulation factor mutation	10065442
Coagulation factor V level abnormal	10061771
Coagulation factor V level decreased	10009754
Coagulation factor VII level abnormal	10061772
Coagulation factor VII level decreased	10009761
Coagulation factor VIII level abnormal	10061773
Coagulation factor VIII level decreased	10009768
Coagulation factor X level abnormal	10061774
Coagulation factor X level decreased	10009775
Coagulation factor XI level abnormal	10061775
Coagulation factor XI level decreased	10009779
Coagulation factor XII level abnormal	10061776
Coagulation factor XII level decreased	10009783
Coagulation factor XIII level abnormal	10061777
Coagulation factor XIII level decreased	10009787
Coagulation time abnormal	10009791
Coagulation time prolonged	10009799
Coagulopathy	10009802

MedDRA Preferred Terms	MedDRA Code
Coital bleeding	10065019
Colonic haematoma	10009996
Congenital coagulopathy	10063563
Congenital dysfibrinogenaemia	10051123
Conjunctival haemorrhage	10010719
Contusion	10050584
Corneal bleeding	10051558
Cullen's sign	10059029
Cystitis haemorrhagic	10011793
Deep dissecting haematoma	10074718
Diarrhoea haemorrhagic	10012741
Dilutional coagulopathy	10060906
Disseminated intravascular coagulation	10013442
Diverticulitis intestinal haemorrhagic	10013541
Diverticulum intestinal haemorrhagic	10013560
Duodenal ulcer haemorrhage	10013839
Duodenitis haemorrhagic	10013865
Dysfunctional uterine bleeding	10013908
Ear haemorrhage	10014009
Ecchymosis	10014080
Encephalitis haemorrhagic	10014589
Endometriosis	10014778
Enterocolitis haemorrhagic	10014896
Epidural haemorrhage	10073681
Epistaxis	10015090
Ethanol gelation test positive	10062650
Exsanguination	10015719
Extra-axial haemorrhage	10078254
Extradural haematoma	10015769
Extravasation blood	10015867
Eye contusion	10073354

MedDRA Preferred Terms	MedDRA Code
Eye haemorrhage	10015926
Eyelid bleeding	10053196
Eyelid contusion	10075018
Eyelid haematoma	10064976
Factor I deficiency	10016075
Factor II deficiency	10016076
Factor III deficiency	10052473
Factor IX deficiency	10016077
Factor V deficiency	10048930
Factor VII deficiency	10016079
Factor VIII deficiency	10016080
Factor X deficiency	10052474
Factor Xa activity abnormal	10078667
Factor Xa activity decreased	10078676
Factor XI deficiency	10016082
Factor XII deficiency	10051806
Factor XIII deficiency	10016083
Femoral artery perforation	10075739
Femoral vein perforation	10075745
Fibrin abnormal	10016575
Fibrin D dimer decreased	10016579
Fibrin D dimer increased	10016581
Fibrin decreased	10016584
Fibrin degradation products	10016585
Fibrin degradation products increased	10016588
Fibrinolysis abnormal	10016604
Fibrinolysis increased	10016607
Foetal-maternal haemorrhage	10016871
Gardner-Diamond syndrome	10078888
Gastric haemorrhage	10017788
Gastric occult blood positive	10067855

MedDRA Preferred Terms	MedDRA Code
Gastric ulcer haemorrhage	10017826
Gastric ulcer haemorrhage, obstructive	10017829
Gastric varices haemorrhage	10057572
Gastritis alcoholic haemorrhagic	10017857
Gastritis haemorrhagic	10017866
Gastroduodenal haemorrhage	10053768
Gastroduodenitis haemorrhagic	10048712
Gastrointestinal angiectasia	10078142
Gastrointestinal haemorrhage	10017955
Gastrointestinal organ contusion	10078655
Gastrointestinal polyp haemorrhage	10074437
Gastrointestinal ulcer haemorrhage	10056743
Genital contusion	10073355
Genital haemorrhage	10061178
Gingival bleeding	10018276
Graft haemorrhage	10063577
Grey Turner's sign	10075426
Haemarthrosis	10018829
Haematemesis	10018830
Haematochezia	10018836
Haematocoele	10018833
Haematoma	10018852
Haematoma evacuation	10060733
Haematoma infection	10051564
Haematosalpinx	10050468
Haematospermia	10018866
Haematotympanum	10063013
Haematuria	10018867
Haematuria traumatic	10018871
Haemobilia	10058947
Haemophilia	10061992

MedDRA Preferred Terms	MedDRA Code
Haemophilia A with anti factor VIII	10056492
Haemophilia A without inhibitors	10056493
Haemophilia B with anti factor IX	10056494
Haemophilia B without inhibitors	10056495
Haemophilic arthropathy	10065057
Haemophilic pseudotumour	10073770
Haemoptysis	10018964
Haemorrhage	10055798
Haemorrhage coronary artery	10055803
Haemorrhage foetal	10061191
Haemorrhage in pregnancy	10018981
Haemorrhage intracranial	10018985
Haemorrhage neonatal	10061993
Haemorrhage subcutaneous	10018999
Haemorrhage subepidermal	10019001
Haemorrhage urinary tract	10055847
Haemorrhagic anaemia	10052293
Haemorrhagic arteriovenous malformation	10064595
Haemorrhagic ascites	10059766
Haemorrhagic breast cyst	10077443
Haemorrhagic cerebral infarction	10019005
Haemorrhagic cyst	10059189
Haemorrhagic diathesis	10062713
Haemorrhagic disease of newborn	10019008
Haemorrhagic disorder	10019009
Haemorrhagic erosive gastritis	10067786
Haemorrhagic hepatic cyst	10067796
Haemorrhagic infarction	10019013
Haemorrhagic necrotic pancreatitis	10076058
Haemorrhagic ovarian cyst	10060781
Haemorrhagic pneumonia	10077933

MedDRA Preferred Terms	MedDRA Code
Haemorrhagic stroke	10019016
Haemorrhagic thyroid cyst	10072256
Haemorrhagic transformation stroke	10055677
Haemorrhagic tumour necrosis	10054096
Haemorrhagic urticaria	10059499
Haemorrhagic varicella syndrome	10078873
Haemorrhagic vasculitis	10071252
Haemorrhoidal haemorrhage	10054787
Haemostasis	10067439
Haemothorax	10019027
Henoch-Schonlein purpura	10019617
Hepatic haemangioma rupture	10054885
Hepatic haematoma	10019676
Hepatic haemorrhage	10019677
Hereditary haemorrhagic telangiectasia	10019883
Hermansky-Pudlak syndrome	10071775
Hyperfibrinolysis	10074737
Hyphaema	10020923
Hypocoagulable state	10020973
Hypofibrinogenaemia	10051125
Hypoprothrombinaemia	10021085
Hypothrombinaemia	10058517
Hypothromboplastinaemia	10058518
Iliac artery perforation	10075731
Iliac artery rupture	10072789
Iliac vein perforation	10075744
Immune thrombocytopenic purpura	10074667
Implant site bruising	10063850
Implant site haematoma	10063780
Implant site haemorrhage	10053995
Incision site haematoma	10059241

MedDRA Preferred Terms	MedDRA Code
Incision site haemorrhage	10051100
Increased tendency to bruise	10021688
Induced abortion haemorrhage	10052844
Inferior vena cava perforation	10075742
Infusion site bruising	10059203
Infusion site haematoma	10065463
Infusion site haemorrhage	10065464
Injection site bruising	10022052
Injection site haematoma	10022066
Injection site haemorrhage	10022067
Instillation site bruise	10073630
Instillation site haematoma	10073609
Instillation site haemorrhage	10073610
Internal haemorrhage	10075192
International normalised ratio abnormal	10022592
International normalised ratio increased	10022595
Intestinal haematoma	10069829
Intestinal haemorrhage	10059175
Intestinal varices haemorrhage	10078058
Intra-abdominal haematoma	10056457
Intra-abdominal haemorrhage	10061249
Intracerebral haematoma evacuation	10062025
Intracranial haematoma	10059491
Intracranial tumour haemorrhage	10022775
Intraocular haematoma	10071934
Intrapartum haemorrhage	10067703
Intraventricular haemorrhage	10022840
Intraventricular haemorrhage neonatal	10022841
Iris haemorrhage	10057418
Joint microhaemorrhage	10077666
Kidney contusion	10023413

MedDRA Preferred Terms	MedDRA Code
Lacrimal haemorrhage	10069930
Large intestinal haemorrhage	10052534
Large intestinal ulcer haemorrhage	10061262
Laryngeal haematoma	10070885
Laryngeal haemorrhage	10065740
Lip haematoma	10066304
Lip haemorrhage	10049297
Liver contusion	10067266
Lower gastrointestinal haemorrhage	10050953
Lower limb artery perforation	10075730
Lymph node haemorrhage	10074270
Mallory-Weiss syndrome	10026712
Mediastinal haematoma	10049941
Mediastinal haemorrhage	10056343
Medical device site bruise	10075570
Medical device site haematoma	10075577
Medical device site haemorrhage	10075578
Melaena	10027141
Melaena neonatal	10049777
Meningorrhagia	10052593
Menometrorrhagia	10027295
Menorrhagia	10027313
Mesenteric haematoma	10071557
Mesenteric haemorrhage	10060717
Metrorrhagia	10027514
Mouth haemorrhage	10028024
Mucocutaneous haemorrhage	10076048
Mucosal haemorrhage	10061298
Muscle contusion	10070757
Muscle haemorrhage	10028309
Myocardial haemorrhage	10048849

MedDRA Preferred Terms	MedDRA Code
Myocardial rupture	10028604
Naevus haemorrhage	10062955
Nail bed bleeding	10048891
Nasal septum haematoma	10075027
Neonatal gastrointestinal haemorrhage	10074159
Nephritis haemorrhagic	10029132
Nipple exudate bloody	10029418
Occult blood positive	10061880
Ocular retrobulbar haemorrhage	10057571
Oesophageal haemorrhage	10030172
Oesophageal intramural haematoma	10077486
Oesophageal ulcer haemorrhage	10030202
Oesophageal varices haemorrhage	10030210
Oesophagitis haemorrhagic	10030219
Optic disc haemorrhage	10030919
Optic nerve sheath haemorrhage	10030941
Oral contusion	10078170
Oral mucosa haematoma	10074779
Osteorrhagia	10051937
Ovarian haematoma	10033263
Ovarian haemorrhage	10065741
Palpable purpura	10056872
Pancreatic contusion	10078654
Pancreatic haemorrhage	10033625
Pancreatitis haemorrhagic	10033650
Papillary muscle haemorrhage	10059164
Paranasal sinus haematoma	10069702
Parathyroid haemorrhage	10059051
Parotid gland haemorrhage	10051166
Pelvic haematoma	10054974
Pelvic haematoma obstetric	10034248

MedDRA Preferred Terms	MedDRA Code
Pelvic haemorrhage	10063678
Penile contusion	10073352
Penile haematoma	10070656
Penile haemorrhage	10034305
Peptic ulcer haemorrhage	10034344
Pericardial haemorrhage	10034476
Perineal haematoma	10034520
Periorbital haematoma	10034544
Periorbital haemorrhage	10071697
Periosteal haematoma	10077341
Peripartum haemorrhage	10072693
Perirenal haematoma	10049450
Peritoneal haematoma	10058095
Peritoneal haemorrhage	10034666
Periventricular haemorrhage neonatal	10076706
Petechiae	10034754
Pharyngeal haematoma	10068121
Pharyngeal haemorrhage	10034827
Pituitary haemorrhage	10049760
Placenta praevia haemorrhage	10035121
Plasminogen activator inhibitor	10059620
Plasminogen activator inhibitor decreased	10059619
Plasminogen decreased	10035493
Plasminogen increased	10035495
Platelet factor 4 decreased	10060220
Polymenorrhagia	10064050
Post abortion haemorrhage	10036246
Post procedural contusion	10073353
Post procedural haematoma	10063188
Post procedural haematuria	10066225
Post procedural haemorrhage	10051077

MedDRA Preferred Terms	MedDRA Code
Post transfusion purpura	10072265
Postmenopausal haemorrhage	10055870
Postpartum haemorrhage	10036417
Post-traumatic punctate intraepidermal haemorrhage	10071639
Procedural haemorrhage	10071229
Proctitis haemorrhagic	10036778
Prostatic haemorrhage	10036960
Protein C increased	10060230
Protein S abnormal	10051736
Protein S increased	10051735
Prothrombin level abnormal	10037048
Prothrombin level decreased	10037050
Prothrombin time abnormal	10037057
Prothrombin time prolonged	10037063
Prothrombin time ratio abnormal	10061918
Prothrombin time ratio increased	10037068
Pulmonary alveolar haemorrhage	10037313
Pulmonary contusion	10037370
Pulmonary haematoma	10054991
Pulmonary haemorrhage	10037394
Puncture site haemorrhage	10051101
Purpura	10037549
Purpura fulminans	10037556
Purpura neonatal	10037557
Purpura non-thrombocytopenic	10057739
Purpura senile	10037560
Putamen haemorrhage	10058940
Radiation associated haemorrhage	10072281
Rectal haemorrhage	10038063
Rectal ulcer haemorrhage	10038081
Renal artery perforation	10075737

MedDRA Preferred Terms	MedDRA Code
Renal cyst haemorrhage	10059846
Renal haematoma	10038459
Renal haemorrhage	10038460
Respiratory tract haemorrhage	10038727
Respiratory tract haemorrhage neonatal	10038728
Retinal aneurysm rupture	10079121
Retinal haemorrhage	10038867
Retinopathy haemorrhagic	10051447
Retroperitoneal haematoma	10058360
Retroperitoneal haemorrhage	10038980
Retroplacental haematoma	10054798
Ruptured cerebral aneurysm	10039330
Russell's viper venom time abnormal	10059759
Scleral haemorrhage	10050508
Scrotal haematocoele	10061517
Scrotal haematoma	10039749
Shock haemorrhagic	10049771
Skin haemorrhage	10064265
Skin neoplasm bleeding	10060712
Skin ulcer haemorrhage	10050377
Small intestinal haemorrhage	10052535
Small intestinal ulcer haemorrhage	10061550
Soft tissue haemorrhage	10051297
Spermatic cord haemorrhage	10065742
Spinal cord haematoma	10076051
Spinal cord haemorrhage	10048992
Spinal epidural haematoma	10050162
Spinal epidural haemorrhage	10049236
Spinal subarachnoid haemorrhage	10073564
Spinal subdural haematoma	10050164
Spinal subdural haemorrhage	10073563

MedDRA Preferred Terms	MedDRA Code
Spleen contusion	10073533
Splenic artery perforation	10075738
Splenic haematoma	10041646
Splenic haemorrhage	10041647
Splenic varices haemorrhage	10068662
Splinter haemorrhages	10041663
Spontaneous haematoma	10065304
Spontaneous haemorrhage	10074557
Stoma site haemorrhage	10074508
Stomatitis haemorrhagic	10042132
Subarachnoid haematoma	10076701
Subarachnoid haemorrhage	10042316
Subarachnoid haemorrhage neonatal	10042317
Subchorionic haematoma	10072596
Subchorionic haemorrhage	10071010
Subclavian artery perforation	10075740
Subclavian vein perforation	10075743
Subcutaneous haematoma	10042345
Subdural haematoma	10042361
Subdural haematoma evacuation	10042363
Subdural haemorrhage	10042364
Subdural haemorrhage neonatal	10042365
Subgaleal haematoma	10069510
Subretinal haematoma	10071935
Superior vena cava perforation	10075741
Testicular haemorrhage	10051877
Thalamus haemorrhage	10058939
Third stage postpartum haemorrhage	10043449
Thoracic haemorrhage	10062744
Thrombin time abnormal	10051319
Thrombin time prolonged	10051390

MedDRA Preferred Terms	MedDRA Code
Thrombin-antithrombin III complex abnormal	10053972
Thrombin-antithrombin III complex increased	10053968
Thrombocytopenic purpura	10043561
Thrombotic thrombocytopenic purpura	10043648
Thyroid haemorrhage	10064224
Tongue haematoma	10043959
Tongue haemorrhage	10049870
Tonsillar haemorrhage	10057450
Tooth pulp haemorrhage	10072228
Tooth socket haemorrhage	10064946
Tracheal haemorrhage	10062543
Traumatic haematoma	10044522
Traumatic haemorrhage	10053476
Traumatic haemothorax	10074487
Traumatic intracranial haematoma	10079013
Traumatic intracranial haemorrhage	10061387
Tumour haemorrhage	10049750
Ulcer haemorrhage	10061577
Umbilical cord haemorrhage	10064534
Umbilical haematoma	10068712
Umbilical haemorrhage	10045455
Upper gastrointestinal haemorrhage	10046274
Ureteric haemorrhage	10065743
Urethral haemorrhage	10049710
Urinary bladder haemorrhage	10046528
Urogenital haemorrhage	10050058
Uterine haematoma	10063875
Uterine haemorrhage	10046788
Vaccination site bruising	10069484
Peripheral artery haematoma	10081077
Subgaleal haemorrhage	10080900

MedDRA Preferred Terms	MedDRA Code
Von Willebrand's factor antibody	10080829
Nephritis haemorrhagic	10029132
Renal cyst haemorrhage	10059846
Renal haematoma	10038459
Renal haemorrhage	10038460
Ureteric haemorrhage	10065743
Extraischaemic cerebral haematoma	10080347
Gastrointestinal vascular malformation haemorrhagic	10080561
Vaccination site haematoma	10069472
Vaccination site haemorrhage	10069475
Vaginal haematoma	10046909
Vaginal haemorrhage	10046910
Varicose vein ruptured	10046999
Vascular access site bruising	10077767
Vascular access site haematoma	10077647
Vascular access site haemorrhage	10077643
Vascular access site rupture	10077652
Vascular graft haemorrhage	10077721
Vascular pseudoaneurysm ruptured	10053949
Vascular purpura	10047097
Vascular rupture	10053649
Vein rupture	10077110
Venous haemorrhage	10065441
Venous perforation	10075733
Ventricle rupture	10047279
Vertebral artery perforation	10075735
Vessel puncture site bruise	10063881
Vessel puncture site haematoma	10065902
Vessel puncture site haemorrhage	10054092
Vitreous haematoma	10071936
Vitreous haemorrhage	10047655

MedDRA Preferred Terms	MedDRA Code
Von Willebrand's disease	10047715
Von Willebrand's factor antibody positive	10066358
Von Willebrand's factor multimers abnormal	10055165
Vulval haematoma	10047756
Vulval haematoma evacuation	10047757
Vulval haemorrhage	10063816
White nipple sign	10078438
Withdrawal bleed	10047998
Wound haematoma	10071504
Wound haemorrhage	10051373

Note: Selected preferred terms were based on MedDRA Version 21.0.

Appendix 5. List of Medical Search Terms for Diarrhoea

MedDRA Preferred Terms	MedDRA Code
Defaecation urgency	10012110
Diarrhoea	10012735
Diarrhoea haemorrhagic	10012741
Diarrhoea neonatal	10012743
Frequent bowel movements	10017367
Gastrointestinal hypermotility	10052402
Post procedural diarrhoea	10057585
Abnormal faeces	10000133
Allergic gastroenteritis	10075308
Anal incontinence	10077605
Antidiarrhoeal supportive care	10055660
Bowel movement irregularity	10063541
Change of bowel habit	10008399
Colitis	10009887
Colitis erosive	10058358
Colitis ischaemic	10009895
Colitis microscopic	10056979
Colitis psychogenic	10053397
Culture stool negative	10011630
Encopresis	10014643
Enteritis	10014866
Enteritis leukopenic	10014877
Enterocolitis	10014893
Enterocolitis haemorrhagic	10014896
Eosinophilic colitis	10057271
Faecal containment device insertion	10073732
Faecal volume increased	10049939
Faeces discoloured	10016100
Gastroenteritis	10017888
Gastroenteritis eosinophilic	10017902
Gastroenteritis radiation	10017912
Gastrointestinal inflammation	10064147

MedDRA Preferred Terms	MedDRA Code
Gastrointestinal motility disorder	10061173
Gastrointestinal toxicity	10059024
Gastrointestinal tract irritation	10070840
Intestinal angioedema	10076229
Intestinal transit time abnormal	10074724
Intestinal transit time decreased	10074598
Irritable bowel syndrome	10023003
Low anterior resection syndrome	10080023
Neutropenic colitis	10062959
Radiation proctitis	10037766

Note: Selected preferred terms were based on MedDRA Version 21.0.

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