STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1b/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of GS-5829 as a Single Agent and In Combination with Enzalutamide in Subjects with Metastatic Castrate-Resistant Prostate Cancer
Name of Test Drug:	GS-5829
Study Number:	GS-US-350-1604
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
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
LTT	lower-level term
LOQ	limit of quantitation
mCRPC	metastatic castrate-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
OS	overall survival
PFS	progression-free survival
PK	pharmacokinetics
PSA	prostate specific antigen
PT	preferred term
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
SOC	system organ class
StD	standard deviation
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings

ULN	upper limit of normal
VR	ventricular rate
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 oral clearance after administration of the drug: 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}
λ_z	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) in the clinical study report (CSR) for Study GS-US-350-1604. This SAP is based on the study protocol amendment 2 dated 30 June 2016 and the electronic case report form (eCRF). The SAP will be finalized before database finalization for the CSR analysis. Any changes made after the finalization of the SAP will be documented in the CSR.

The original study included two phases in the design: phase 1b dose escalation and phase 2 dose expansion. It was decided by the sponsor during the dose escalation phase that this study would be discontinued without moving forward to the 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

This study has two phases: Phase 1b dose escalation and Phase 2 dose expansion. The primary objective of this study is as follows:

Phase 1b Dose Escalation

- To characterize the safety and tolerability of GS-5829 as a single agent and in combination with enzalutamide in subjects with metastatic castrate-resistant prostate cancer (mCRPC)

- To determine the maximum tolerated dose (MTD) of GS-5829 as a single agent and in combination with enzalutamide in subjects with mCRPC

Phase 2 Dose Expansion

- Group 1: To evaluate the efficacy of GS-5829 as a single agent in subjects with mCRPC who have progressed while receiving enzalutamide (**may have** also received abiraterone) as measured by Progression Rate at Week 24 according to Prostate Cancer Working Group 2 (PCWG2) Criteria

- Group 2: To evaluate the efficacy of GS-5829 combined with enzalutamide in subjects with mCRPC who have progressed while receiving treatment with abiraterone (**may not** have previously received enzalutamide) as measured by Progression Rate at Week 24 according to PCWG2 Criteria

- Group 3: To evaluate the efficacy of GS-5829 combined with enzalutamide in subjects with mCRPC who have had Prostate Specific Antigen (PSA) progression, but not radiographic progression, while receiving treatment with enzalutamide (subjects **may** have also previously received abiraterone) as measured by Progression Rate at Week 24 according to PCWG2 Criteria

The secondary objectives of this study are as follows:

Phase 1b Dose Escalation

- To evaluate the pharmacokinetics (PK) of GS-5829 as a single agent and in combination with enzalutamide in subjects with mCRPC

- To evaluate the efficacy of GS-5829 as a single agent and in combination with enzalutamide in subjects with mCRPC as measured by PCWG2 Criteria

Phase 2 Dose Expansion

- To evaluate the safety and tolerability of GS-5829 as a single agent and in combination with enzalutamide in subjects with mCRPC

- Group 1: To evaluate the efficacy of GS-5829 in subjects with mCRPC who have progressed while receiving enzalutamide as measured by PSA at Week 12, progression-free survival (PFS) and overall survival (OS)

- Group 2: To evaluate the efficacy of GS-5829 combined with enzalutamide in subjects with mCRPC who have progressed while receiving abiraterone as measured by PSA at Week 12, PFS and OS

- Group 3: To evaluate the efficacy of GS-5829 combined with enzalutamide in subjects with mCRPC who have had PSA progression, but not radiographic progression, while receiving enzalutamide as measured by PSA at Week 12, PFS and OS

The exploratory objectives of this study are as follows:

- [redacted]

1.2. Study Design

This study has two phases: Phase 1b dose escalation and Phase 2 dose expansion.

Phase 1b: This is an open-label, multicenter, sequential dose-escalation study to evaluate the safety, tolerability, PK, and pharmacodynamics (PD) of GS-5829 as a single agent, and combined with enzalutamide in subjects with metastatic castrate-resistant prostate cancer (mCRPC).

Dose Escalation of GS-5829

Subjects with mCRPC who have progressed on either abiraterone and/or enzalutamide will be sequentially enrolled at progressively higher dose levels to receive oral GS-5829 as a single agent once daily. Dose escalation [3+3] will be performed with cohort sizes of 3 to 6 subjects. Initially 3-4 subjects will be enrolled into each dose level. The study will be initiated at a dose level that has been demonstrated to be safe and tolerable in the ongoing Phase 1 study in patients with solid tumors and lymphomas (Study GS-US-350-1599).

The dose levels for single agent GS-5829 once daily are 2, 3, 4, 6 and 9mg. Dose levels may be modified based on emerging safety, PK, PD, and efficacy results.

Dose Escalation of GS-5829 and enzalutamide

The combination dose escalation using 3+3 design may initiate prior to identification of the MTD of single agent GS-5829 using a starting dose of GS-5829 that has been determined to be safe and tolerable in the single agent dose escalation. The first 3-4 subjects to enroll will receive GS-5829 at a dose less than or equal to the previously determined single agent MTD (or a monotherapy dose that has been determined to be safe) combined with enzalutamide. Enzalutamide is a strong CYP3A4 inducer, which is expected to decrease the exposure of GS-5829 and therefore a higher dose of GS-5829 may be required to achieve target coverage compared to the single agent dose. Subjects will administer enzalutamide 160 mg once daily as a single agent starting on Study Day 1 through Cycle 1, Day 1. On Cycle 1 Day 1 (approximately 14 days after Study Day 1), subjects will administer GS-5829 once daily in combination with enzalutamide 160 mg once daily in order to evaluate the interaction of the 2 agents. Depending on the observed PK interaction, toxicity and tolerability observed in the single agent dose escalation, the dose escalation may continue beyond a dose which has been identified to be safe and tolerable in the single agent arm. Any increase in the dose of GS-5829 will not be by more than 100% in the next cohort.

Phase 2 Dose Expansion:

Group 1: A dose that is less than or equal to the MTD of GS-5829 monotherapy (based on safety, PD and tolerability) will be chosen for an expansion phase. Approximately 20 subjects with mCRPC who have had radiographic disease progression despite adequate testosterone suppression and treatment with enzalutamide will be enrolled. These subjects **may** have

previously received abiraterone. Enrollment into this group may initiate as soon as the MTD of single agent GS-5829 has been identified.

Group 2: A dose that is less than or equal to the MTD of GS-5829 + enzalutamide (based on safety, PD and tolerability) will be chosen for an expansion phase. Approximately 20 subjects with mCRPC who have had radiographic disease progression despite adequate testosterone suppression and treatment with abiraterone will be enrolled. These subjects may **not** have previously received enzalutamide. Enzalutamide will be initiated on Study Day 1 and GS-5829 will initiate on Cycle 1, Day 1 (approximately 15 days later).

Group 3: A dose equivalent to the dose chosen for Group 2 will be chosen for an expansion phase. A maximum of 20 subjects with mCRPC who have had PSA only progression, but not radiographic progression, despite adequate testosterone suppression and treatment with enzalutamide, will be enrolled. These subjects **may** have received prior abiraterone (similar to Group 1). These subjects will continue the enzalutamide therapy they have been receiving (must be receiving continuous enzalutamide for at least 12 weeks prior to Cycle 1, Day 1) and GS-5829 will initiate on Cycle 1, Day 1.

The choice of enrolling a subject into a specific dose escalation cohort or dose expansion group will be based on the treatment slots open at the time of screening, inclusion/exclusion enrollment criteria and the discretion of the investigator.

1.3. Sample Size and Power

Number of subjects planned:

- Phase 1b Dose Escalation: Approximately 72 subjects will be enrolled
- Phase 2 Dose Expansion: Up to 60 subjects will be enrolled

The sample size is not determined by statistical hypothesis testing. The sample size of phase 1b monotherapy phase will be determined based on the number of dose levels evaluated and the emerging GS-5829-related toxicities. The phase 1b study will consist of up to 72 subjects. The phase 2 part will enroll up to 60 subjects to help understand the efficacy effect of GS-5829 as a monotherapy and combination therapy with enzalutamide. The expectation is that at 24 weeks, the non-progression rate will be > 30% with GS-5829 monotherapy in subjects who have progressed on enzalutamide (may have received abiraterone) and/or with GS-5829 combined with enzalutamide in subjects who have progressed on abiraterone only. If the true non-progression rate is above 50%, and we do observe more than 10 non-progression subjects from 20 treated subjects per group, it will guarantee that the lower bound of the 90% confidence interval of the estimated rate will be larger than 30%.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

No formal interim analyses are planned.

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) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

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 treatment group to which subjects were initially assigned 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 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 took at least 1 dose of study drug with treatment group designated according to the planned treatment. This is the primary analysis set for efficacy analyses. Throughout this SAP, study drug is defined as any drug in the therapy (GS-5829 or enzalutamide) unless specified otherwise.

3.1.3. Safety Analysis Set

The Safety Analysis Set includes all subjects who took at least 1 dose of study drug. This is the primary analysis set for safety analyses.

3.1.4. Dose-Limiting Toxicity (DLT) Analysis Set

The DLT Analysis Set includes all subjects in the Safety Analysis Set who complete all or at least 21-day study treatment and have safety assessment through Day 28 of GS-5829, inclusive, or experienced a DLT prior to Day 28, exclusive. During the DLT assessment window, if a subject who fails to receive GS-5829 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 took at least 1 dose of study drug and have at least 1 nonmissing postdose concentration value reported by the PK laboratory. This is the primary analysis set for all PK analyses.

3.2. Subject Grouping

For analyses based on the FAS, subjects will be grouped according to the treatment to which they were assigned. For analyses based on the Safety Analysis Set, subjects will be grouped according to actual treatment received. The actual treatment received will differ from the assigned treatment only when their actual treatment differs from assigned treatment for the entire treatment duration.

For the PK Analysis Set, subjects will be grouped according to the actual treatment they received.

3.3. Strata and Covariates

This study does not use a stratified randomization schedule when enrolling subjects. No 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 AE onset is described 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

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth
- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed

In general, age (in years) collected on the date of the first dose of study drug will be used for analyses and presentation in listings. If age at Day 1 is not available for a subject, then age derived based on date of birth and the Day 1 visit date will be used instead. 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. For screen failures, the date the first informed consent was signed will be used for age derivation. Age required for longitudinal and temporal calculations and analyses (eg, estimates of creatinine clearance, age at date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified.

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, where LOQ is corrected for the dilution factor (ie, reported LOQ/dilution factor) for determination of summary and order statistics.

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 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 dosing 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 analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

If multiple, valid nonmissing 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 nonmissing value on or prior to the first dosing date of study drug (GS-5829 or enzalutamide) will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data, or the measurement with the lowest severity (eg, normal will be selected over abnormal for safety electrocardiogram [ECG] findings) for categorical data.
- For postbaseline visits:

  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 for continuous data and the worse severity will be taken for categorical data, unless otherwise specified.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided by treatment group for each investigator and overall. The summary will present the number and percentage of subjects enrolled. For each column, the denominator for the percentage calculation will be the total number of subjects analyzed for that column.

A summary of subject disposition will be provided by treatment group. This summary will present the number of subjects screened, the number of subjects enrolled, and the number of subjects in each of the categories listed below:

- Full Analysis Set
- Safety Analysis Set
- Discontinued GS-5829 with reasons for discontinuation
- Discontinued Enzalutamide with reasons for discontinuation
- Discontinued the study with reasons for discontinuation of study

For the status of study drug (GS-5829 and Enzalutamide) and study completion and reasons for premature discontinuation, the number and percentage of subjects in each category will be provided. The denominator for the percentage calculation will be the total number of subjects in the Full Analysis Set corresponding to that column.

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

- Reasons for premature study drug or 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 the 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 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 GS-5829 dosing date is missing, the latest date among the 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 day and month are missing but year is available, then the imputed day and month will be the earliest from the following dates: 31 DEC, death date, end of GS-5829 treatment (EOT) date, and (start date of the next dosing period -1); If 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, and (start date of the next dosing period 1).

- For dose start date: If day and month are missing but 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 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 percentage of subjects exposed through the following time periods: 1 day, 4 weeks, 8 weeks, 16 weeks, 24 weeks, 36 weeks, 48 weeks and 60 weeks. Summaries will be provided by treatment group for the Safety Analysis Set.

4.2.2. Adherence to GS-5829

The total amount of doses administered in mg will be summarized using descriptive statistics.

The presumed total amount of doses 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

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

4.2.2.1. On-Treatment Adherence

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

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

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

If there are treatment periods that bottles are not returned, or the return information is missing, these periods will be excluded from the on-treatment adherence calculation for both total amount of study drug administered, and study drug expected to be administered. If subjects never returned any bottle, the adherence will be set as missing.

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

A by-subject listing of study drug administration and drug accountability will be provided separately for GS-5829 by subject ID number (in ascending order) and visit (in chronological order). Separate listing of enzalutamide administration will also be provided.

4.3. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry but 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. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that subjects did not meet and related comments, if collected.

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 treatment group 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 and Baseline Characteristics

Subject demographic variables (ie, age, sex, race, and ethnicity) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2]) will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary of demographic data will be provided for the All Enrolled 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

Not applicable.

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 but will be listed only. A by-subject listing of general medical history will be provided by subject ID number in ascending order.

5.4. Prior Anticancer Therapy

Number of prior regimens, time since the completion of last regimen, and specific prior treatment (enzalutamide, abiraterone, and chemotherapy) will be summarized by treatment group using descriptive statistics based on the Full Analysis Set. A partial completion date will be imputed using the algorithm defined below.

All partial dates of the completion of last regimen will be identified, and the partial dates 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-study anticancer therapies, prior and on-study radiation therapy, and prior and on-study surgery and procedures each by subject ID number in ascending order.

6. EFFICACY ANALYSES

6.1. Primary Efficacy Endpoint

6.1.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint of this study is non-progression rate at Week 24 defined as the proportion of subjects who don't progress by Week 24. The progression is determined by the investigators based on Prostate Cancer Working Group 2 (PCWG2) Criteria for lesion scans, bone scans and PSA assessments together. Subjects will be considered as having definitive disease progression if any of three progression criteria meets. Progression-free survival (PFS), defined as the interval from start of study drug to the earlier of the first documentation of definitive disease progression or death from any cause. Definitive disease progression is determined by investigator based on PCWG2 criteria.

The date of definitive progression will be the time point at which progression is first identified. The death from any cause to be considered as PFS event should occur within the time window of 2 consecutive scheduled tumor assessments after the last tumor assessment. Non-evaluable (NE) and no disease (ND) are considered as not adequate.

Subjects will be censored on the date of Study Day 1 if

- no adequate baseline target lesion assessment nor bone scan is available (note: baseline PSA assessment missing is allowed) and subject didn't die before or on the 2nd scheduled post-baseline tumor assessment without receiving anti-cancer therapy;
- or if no adequate post-baseline tumor assessment is available and subjects didn't die
- or if no adequate post-baseline tumor assessment is available and subjects died after the 2nd scheduled tumor assessment.

Subjects will be censored on the date of last adequate post-baseline tumor assessment, or Day 1 if the last post-baseline adequate tumor assessment doesn't exist, for the following situations:

- 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 post-baseline tumor assessments immediately before documented progression, or
- who have ≥ 2 consecutive missing post-baseline tumor assessments immediately before death without documented progression

Table 6-1 below provides detailed event/censoring scheme for PFS derivation and the derivation diagram provides all decisions on event/censoring indicators and time.

Table 6-1. Event/Censoring Scheme of Analysis for PFS

PFS Derivation Step	Situation	Date of Progression or Censoring	Outcome
1	No adequate baseline tumor assessments and subjects didn't die before or on the 2nd scheduled post-baseline tumor assessment	Study Day 1	Censored
1	No adequate baseline tumor assessments and subjects died before or on the 2nd scheduled post-baseline tumor assessment without receiving anti-cancer therapy	Date of death	Event
1	No adequate baseline tumor assessments, subjects died before or on the 2nd scheduled post-baseline tumor assessment and received anti-cancer therapy	Study Day 1	Censored
2	No adequate post-baseline tumor assessments and subjects did not die	Study Day 1	Censored
2	No adequate post-baseline tumor assessments and subjects died after the 2nd scheduled post-baseline tumor assessment	Study Day 1	Censored
2	No adequate post-baseline tumor assessments and subjects died before or on the 2nd scheduled post-baseline tumor assessment without receiving anti-cancer therapy	Date of death	Event
2	No adequate post-baseline tumor assessments, subjects died before the 2nd scheduled post-baseline tumor assessment and received anti-cancer therapy	Study Day 1	Censored
3	Documented progression and didn't receive anti-cancer therapy or have ≥ 2 consecutive missing post-baseline tumor assessments immediately before documented progression	Date of the first documented progression	Event
3	Death without progression and within the time window of 2 consecutive scheduled post-baseline tumor assessments after the last tumor assessment and didn't receive anti-cancer therapy or have ≥ 2	Date of death	Event

PFS Derivation Step	Situation	Date of Progression or Censoring	Outcome
	consecutive missing post-baseline tumor assessments immediately before death		
3	No documented progression or death and didn't receive anti-cancer therapy or have ≥ 2 consecutive missing post-baseline tumor assessments	Date of the last adequate post-baseline tumor assessment	Censored
4	Start new anticancer therapy without or before documented progression or death or have ≥ 2 consecutive missing post-baseline tumor assessments immediately before documented progression or death	The later one of 1) Date of the last adequate post-baseline tumor assessment on/prior to the new anticancer therapy start date and/or the consecutive missing 2) Study Day 1	Censored

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 first day of the month.
- If 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 adequate disease 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 day is missing but the month and year are available, then the imputed date will be the 1st day of the month or the last known alive date + 1, whichever is later.
- If day and month are missing but year is available, then the imputed date will be 01Jan of that year or the last known alive date + 1, whichever is later.

6.1.2. Analysis of the Primary Efficacy Endpoint

The non-progression rate at Week 24 and 95% confidence interval (CI) will be estimated using Kaplan-Meier method through PFS analysis. The number and percentage of subject who had no progressive disease at Week 24 by counting will also be provided for each treatment group.

The analysis of PFS will be performed using the Kaplan-Meier method for the Full Analysis Set. Medians, Q1, Q3, the proportion of subjects who have no progression or death events at 24 and

48 weeks from the first dosing date will be provided along with corresponding 95% CIs. Kaplan-Meier curves for PFS will be provided by treatment group.

6.2. Secondary Efficacy Endpoints

6.2.1. Definition of Secondary Efficacy Endpoints

PSA response, defined as ≥ 30% decline in PSA from baseline at 12 weeks.

Overall response by lesion scan only: subjects will be categorized based on PCWG2 criteria of lesion scans (same with RECIST v. 1.1 for lesion scans) as complete response (CR), partial response (PR), stable disease (SD), non-complete response or non-progressive disease, progressive disease (PD) or not evaluable (NE) at each visit of assessment.

Overall survival (OS), defined as the interval from start of study drug to death from any cause. Subjects who are lost to follow-up or survived until the end of the study will be censored at the last date that they were known to be alive.

6.2.2. Analysis Methods for Secondary Efficacy Endpoints

Number of subjects with ≥ 30% or ≥ 50% PSA reduction from baseline at 12 weeks and during the whole treatment period will be summarized separately.

The number and percentage of subjects in each overall response category by lesion scans (eg, CR, PR, SD, and PD) will be summarized by treatment group for the FAS.

The analysis of OS will be performed using the Kaplan-Meier method for the FAS Analysis Set. Medians, Q1, Q3, the proportion of subjects who have no events at 24 weeks and 48 weeks from the first dosing date will be provided along with corresponding 95% CIs. Kaplan-Meier curves for OS will be provided by treatment group.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

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 case report form (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 SAE 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 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 based on the Safety Analysis Set.

7.1.6.1. Summaries of AE Incidence by Severity Grades

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, HLT PT, and treatment group. For other AEs described below, summaries will be provided by SOC, PT, and treatment group:

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

- TE SAEs related to GS-5829
- TEAEs leading to premature discontinuation of GS-5829
- TEAEs leading to death
- TEAEs leading to temporary interruption of GS-5829
- TEAEs leading to dose reduction of GS-5829

A brief, high-level summary of AEs described above will be provided by treatment group and by the number and percentage of subjects who experienced the above AEs.

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 HLT within each SOC (if applicable), and then by PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

In addition to the above summary tables, all TEAEs and TE SAEs will be summarized by PT only, in descending order of total frequency. All TEAEs and TEAEs related to GS-5829 will be summarized by SOC, PT and severity.

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

- All AEs, indicating whether the event is treatment emergent
- All AEs with Grade 3 or higher
- All SAEs
- All deaths
- All AEs leading to death
- AEs leading to premature discontinuation of GS-5829
- AEs leading to temporary interruption of GS-5829
- AEs leading to dose reduction of GS-5829

7.1.6.2. Summary of Deaths

A summary (number and percentage of subjects) of deaths will be provided by treatment group. Summary will include the following categories:

- All deaths
- Deaths within 30 days of the last dosing of study drug
- Deaths beyond 30 days of the last dosing of study drug

7.1.7. Additional Analysis of Adverse Events

7.1.7.1. Dose Limiting Toxicity

A 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

The following AEs of interest defined by the medical search term (MST) provided by Gilead Pharmacovigilance and Epidemiology (PVE) Department will be summarized similarly to TEAEs by treatment group.

- Decreased Platelets
- Diarrhoea
- Haemorrhage

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. Hemolized test results will not be included in the analysis, but they will be listed in by-subject laboratory listings.

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology, serum chemistry, coagulation and urinalysis 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 treatment group for each laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each postbaseline visit
- Change and percentage 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 dose of study drug. Change from baseline to a postbaseline visit will be defined as the visit value minus the baseline value. The mean, 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 analysis window, 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

The CTCAE Version 4.03 will be used for assigning 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

Laboratory data that are categorical will be summarized using the number and percentage of subjects in the study with the given response at baseline and each scheduled postbaseline visit.

The following summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided by lab test and treatment group; subjects will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Baseline 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 all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values up to 30 days after the last dosing date.

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 and total bilirubin: (a) > 1.5 x ULN; (b) > 2 x ULN
- AST or ALT > 3 x ULN and 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 of all relevant tests at the same postbaseline visit date. A listing of subjects who met at least 1 of the above criteria will be provided.

7.2.4. Shifts Relative to the Baseline Value

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

7.3. Vital Signs

Descriptive statistics will be provided by 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 dose 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. High or low values for vital signs will be flagged.

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 general 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 for each treatment group. 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

Electrocardiogram (ECG) analysis results are intended to identify meaningful changes in the QT interval. If potential abnormalities of interest are identified, further analyses may be conducted. Summaries of ECG data 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/time point. No formal statistical testing is planned.

A by-subject listing for ECG assessment results will be provided by subject ID number and visit 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:

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

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 time point and change from baseline at each visit and time point will be summarized for the Safety Analysis Set by 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 ventricular rate (VR) 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 treatment group:

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

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

7.6. ECOG Performance Status

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

7.7. Other Safety Measures

No additional safety measures are specified in the protocol.

7.8. Changes from Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC ANALYSES

8.1. PK Sample Collection

PK samples will be collected at the time points listed in Protocol 6.2.11.

8.2. PK Analyses Related to Intensive PK Sampling

Concentrations of GS-5829 and its metabolite in plasma will be determined using validated bioanalytical assays. The first dose and steady-state PK will be determined in subjects in the PK analysis set.

8.2.1. Estimation of Pharmacokinetic Parameters

Pharmacokinetic (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. Pharmacokinetic Parameters

Pharmacokinetic parameters will be generated for all subjects in the PK analysis set for whom PK parameters can be derived. The analytes presented in Table 8-1 will be evaluated if data are available.

Table 8-1. Pharmacokinetic Parameters for Each Analyte

	GS-5829	GS-697412
Cycle 1 Day 1 (enzalutamide combination groups)	C_{max}, T_{max}, $AUC_{0\text{-}24h}$, AUC_{last}, C_{24h}, C_{last}, T_{last}, λz, $T_{1/2}$	C_{max}, T_{max}, $AUC_{0\text{-}24h}$, AUC_{last}, C_{24h}, C_{last}, T_{last}, λz, $T_{1/2}$,
Cycle 1 Day 8 (monotherapy group, fasted) Cycle 2 Day 1 (monotherapy group, fed)	C_{max}, T_{max}, AUC_{tau}, AUC_{last}, C_{tau}, C_{last}, T_{last}, λz, $T_{1/2}$, V_z F, CL_{SS} F	C_{max}, T_{max}, AUC_{tau} AUC_{last}, C_{tau}, C_{last}, T_{last}, λz, $T_{1/2}$,
Cycle 1 Day 15 (enzalutamide combination group)	C_{max}, T_{max}, AUC_{tau}, AUC_{last}, C_{tau}, C_{last}, T_{last}, λz, $T_{1/2}$, V_z F, CL_{SS} F	C_{max}, T_{max}, AUC_{tau} AUC_{last}, C_{tau}, C_{last}, T_{last}, λz, $T_{1/2}$,

Individual subject concentration data and individual subject PK parameters will be listed and summarized using descriptive statistics by treatment. 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 by treatment. 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 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.

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 each analyte by treatment:

- Individual subject concentration data and summary statistics
- Individual subject plasma PK parameters and summary statistics

The following figures may be provided for each analyte by treatment:

- 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.

8.2.3. PK/PD Analyses

Not applicable.

9. REFERENCES

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10. SOFTWARE

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

nQuery Advisor(R) Version 8.3. Statistical Solutions, Cork, Ireland.

11. SAP REVISION

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

12. APPENDICES

Appendix 1. Schedule of Assessments

Study Procedures Table – Phase 1b and 2 Monotherapy

Study Phase	Screening		First 28 Days			Cycle 2 Day 1 and Every 4 weeks	Every 12 weeks	EOT	30-day Safety Follow-up[18]	Survival Follow-Up[20]
Cycle Day	Day -28	Cycle 1 Day 1*	Day 8	Day 15	Day 22					
Window (day)	**-28**		**±1**	**±2**	**±3**	**±7**	**±7**	**±7**	**±7**	
Informed Consent	X									
Medical and Medication History[1]	X									
Physical Examination[2]	X	X	X	X	X	X		X	X	
ECOG Performance Status	X	X	X		X	X		X	X	
Vital Signs[3]	X	X	X	X	X	X		X	X	
Triplicate 12 lead ECG[4]	X	X	X			X		X		
Adverse events/Concomitant medications[7]	X	X	X	X	X	X	X	X	X	
GS 5829 Accountability and/or Dispensing[5]		X				X		X		
Dosing Diary Accountability and/or Dispensing		X				X		X		
Enrollment	X									
CBC with Differential	X[8]	X	X	X	X	X		X	X	

Study Phase	Screening		First 28 Days			Cycle 2 Day 1 and Every 4 weeks	Every 12 weeks	EOT	30-day Safety Follow-up[18]	Survival Follow-Up[20]
Cycle Day	**Day -28**	**Cycle 1 Day 1***	**Day 8**	**Day 15**	**Day 22**					
Window (day)	**-28**		**±1**	**±2**	**±3**	**±7**	**±7**	**±7**	**±7**	
Chemistry	X[8]	X	X	X	X	X		X	X	
Coagulation[9]	X[8]	X	X					X		
Urinalysis	X[8]	X	X			X		X	X	
GS 5829 Intensive PK[10]		X	X			X				
GS 5829 Sparse PK[10]		X		X		X				
GS 5829 pharmacodynamic[11]		X	X	X		X				
CCI										
Tumor Markers PSA[13]		X				X		X		
Archival Tumor Tissue[14]		X								
CCI										
CT/MRI[16]	X						X	X		
Radionuclide Bone Scan[17]	X						X	X		

Study Phase	Screening		First 28 Days			Cycle 2 Day 1 and Every 4 weeks	Every 12 weeks	EOT	30-day Safety Follow-up[18]	Survival Follow-Up[20]
Cycle Day	**Day -28**	**Cycle 1 Day 1***	**Day 8**	**Day 15**	**Day 22**					
Window (day)	**-28**		**±1**	**±2**	**±3**	**±7**	**±7**	**±7**	**±7**	
Treatment Response Assessment[19]							X	X		
Phone call										X

* Day 1 pre GS 5829 lab samples may be drawn up to two days prior to the Day 1 visit.

1 Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti cancer therapies, historical PSA levels and any concurrent medical illnesses.

2 Screening and End of Treatment 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 C1D1 Vital Signs will be taken within 15 min 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. Oxygen saturation will be tested with a pulse oximeter.

4 Triplicate ECG will be collected at any time during Screening window, Day 1 of Cycles 2 6 (at pre dose), and at EOT. In Phase 1b monotherapy, triplicate ECGs will be collected on C1D1 at pre dose and 1 4 hrs post dose and on C1D8 at pre dose, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, and 8 hours post dose (+/ 20 min). In Phase 2 dose expansion, triplicate ECGs will be collected on C1D1 at pre dose and 1 4 hrs post dose and on C1D8 at pre dose, 1 hour, 2 hours, 4 hours, and 6 hours post dose (+/ 20 min). ECGs should always be collected prior to PK (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 (eg, TV, conversation) for 10 minutes prior to ECG collection and ECGs should be collected over a 5 minute window at each time point.

5 Administer GS 5829 in a fed state on C2D1 in selected dose level.

6 Beginning on C1D1, subjects will receive GS 5829 daily.

7 Adverse event 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 IP dose to assess AEs and SAEs. At screening, all medications taken up to 30 days prior to screening will be documented in the eCRF.

8 Screening chemistry, hematology, coagulation, and urinalysis to be collected within 7 days of C1D1 for central lab assessment.

9 Coagulation assessment includes PT/PTT, fibrinogen, Factor VII, fibrinogen degradation products (FDP).

10 In Phase 1b monotherapy: plasma samples for GS 5829 PK will be collected on Day 8 of Cycle 1 at pre dose, 0.5, 1, 2, 3, 4, 6, 8, and 24 hours post dose as well as pre dose and 1 4 hours after GS 5829 administration on Day 1 and Day 15 of Cycle 1 and anytime on Day 1 of Cycles 2 through 6. At one or more dose levels, PK samples will be collected on Day 1 of Cycle 2 at pre dose and 0.5, 1, 2, 3, 4, 6, 8, and 24 hours post dose. (C2D1: If intensive PK is collected for that cohort, then sparse PK does not need to be collected.) In Phase 2 dose expansion Group 1: PK samples will be collected on Day 8 of Cycle 1 at pre dose and 1, 2, 4, and 6 hours post dose. Sparse PK samples will be collected at pre dose and 1 4 hours post dose on Cycle 1 Day 1 and Day 15 and anytime on Day 1 of Cycles 2 through 6.

11 In Phase 1b monotherapy: PD biomarker sampling will be collected at pre dose, 0.5, 1, 2, 3, 4, 6, 8 and 24 hours post dose relative to GS 5829 administration on Cycle 1 Day 8. PD samples will also be collected pre dose and 1 4 hours post dose on Cycle 1 Day 1 and Cycle 1 Day 15. Additional PD samples will be collected at anytime on Day 1 of Cycles 2 through 6.In phase 2 dose expansion Group 1: PD samples will be collected on Day 8 of Cycle 1 at pre dose and 1, 2, 4, and 6 hrs post dose. Sparse PD will be collected at pre dose and 1 4 hours post dose on Cycle 1 Day 1 and Day 15 and anytime on Day 1 of Cycles 2 through 6.

CCI [redacted]

13 Tumor markers PSA will be collected on C1D1 at pre dose and on Day 1 of every subsequent Cycle at pre dose.

14 If available, paraffin embedded archival tumor tissue block for shipment to Gilead or its designee will be requested at C1D1.

CCI [redacted]

16 Tumor evaluation by CT/MRI or applicable scan will be performed during screening (within 8 weeks of Cycle 1 Day 1) and every 12 weeks thereafter. 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.

17 Subjects will also undergo a bone scan. Scan at EOT visit is not necessary if the previous scan is performed within 4 weeks of the EOT.

18 For Phase 1b Dose Escalation subjects, the 30 Day Safety Follow Up will be the final study visit. Phase 2 Dose Expansion subjects will complete the 30 Day Safety Follow Up Visit and proceed to Long Term Survival Follow Up.

19 Tumor burden as assessed by PCWG2 Guidelines.

20 LTFU will begin for subjects participating in phase 2 after the 30 day Safety Follow Up visit for up to 2 years after the last dose of IP.

Study Procedures Table – Phase 1b and 2 Combination Therapy

Study Phase	Screening	Study Day 1	First 28 Days				Cycle 2 Day 1 and Every 4 weeks	Every 12 weeks	EOT	30-day Safety Follow-up[18]	Survival Follow-Up[20]
Cycle Day	Day -28		Cycle 1 Day 1*	Day 8	Day 15	Day 22					
Window (day)	**-28**	3	**±3**	**±1**	**±2**	**±3**	**±7**	**±7**	**±7**	**±7**	
Informed Consent	X										
Medical and Medication History[1]	X										
Physical Examination[2]	X	X	X	X	X	X	X		X	X	
ECOG Performance Status	X	X	X	X		X	X		X	X	
Vital Signs[3]	X	X	X	X	X	X	X		X	X	
Triplicate 12 lead ECG[4]	X		X		X		X		X		
Adverse events/Concomitant medications[7]	X	X	X	X	X	X	X	X	X	X	
GS 5829/enzalutamide Accountability and/or Dispensing[5]			X				X		X		
Enzalutamide Accountability and/or Dispensing[6]		X	X				X		X		
Dosing Diary Accountability and/or Dispensing			X				X		X		

Study Phase	Screening	Study Day 1	First 28 Days			Cycle 2 Day 1 and Every 4 weeks	Every 12 weeks	EOT	30-day Safety Follow-up[18]	Survival Follow-Up[20]
Cycle Day	**Day -28**		**Cycle 1 Day 1***	**Day 8**	**Day 15**	**Day 22**				
Window (day)	**-28**	3	**±3**	**±1**	**±2**	**±3**	**±7**	**±7**	**±7**	**±7**	
Enrollment	X										
CBC with Differential	X[8]	X	X	X	X	X	X		X	X	
Chemistry	X[8]	X	X	X	X	X	X		X	X	
Coagulation[9]	X[8]	X	X	X					X		
Urinalysis	X[8]	X	X	X			X		X	X	
GS 5829 Intensive PK[10]			X		X		X				
GS 5829 Sparse PK[10]			X		X		X				
GS 5829 pharmacodynamic[11]			X	X	X		X				
CCI											
Tumor Markers PSA[13]			X				X		X		
Archival Tumor Tissue[14]			X								
CCI											
CT/MRI[16]	X							X	X		

Study Phase	Screening	Study Day 1	First 28 Days				Cycle 2 Day 1 and Every 4 weeks	Every 12 weeks	EOT	30-day Safety Follow-up[18]	Survival Follow-Up[20]
Cycle Day	**Day -28**		**Cycle 1 Day 1***	**Day 8**	**Day 15**	**Day 22**					
Window (day)	**-28**	3	**±3**	**±1**	**±2**	**±3**	**±7**	**±7**	**±7**	**±7**	
Radionuclide Bone Scan[17]	X							X	X		
Treatment Response Assessment[19]								X	X		
Phone call											X

* Day 1 pre GS 5829 lab samples may be drawn up to two days prior to the Day 1 visit.

1 Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti cancer therapies, historical PSA levels and any concurrent medical illnesses.

2 Screening and End of Treatment 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 Study Day 1 vital signs will be take 15 min pre enzalutamide dose. C1D1 Vital Signs will be taken within 15 min 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. Oxygen saturation will be tested with a pulse oximeter.

4 Triplicate ECG will be collected at any time during Screening window, Day 1 of Cycles 2 6 (at pre dose), and at EOT. In Phase 1b dose escalation with enzalutamide, triplicate ECGs will be collected on Cycle 1, Day 1 and Day 15 at pre dose, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, and 8 hours post dose (+/ 20 min). In Phase 2 dose expansion, triplicate ECGs will be collected on C1D1 and C1D15 at pre dose and 1 4 hrs post dose and on C2D1 at pre dose, 1 hour, 2 hours, 4 hours, and 6 hours post dose (+/ 20 min). ECGs should always be collected prior to PK (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 (eg, TV, conversation) for 10 minutes prior to ECG collection and ECGs should be collected over a 5 minute window at each time point.

5 Administer GS 5829 in a fed state on C2D1 in selected dose level.

6 Subjects in phase 1b dose escalation with enzalutamide and Phase 2 Group 2 receive enzalutamide alone beginning on Study Day 1, then in combination with GS 5829 beginning C1D1.

7 Adverse event 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 IP dose to assess AEs and SAEs. At screening, all medications taken up to 30 days prior to screening will be documented in the eCRF.

8 Screening chemistry, hematology, coagulation, and urinalysis to be collected within 7 days of C1D1 for central lab assessment.

9 Coagulation assessment includes PT/PTT, fibrinogen, Factor VII, fibrinogen degradation products (FDP).

10 In Phase 1b dose escalation with enzalutamide: PK samples 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. In Phase 2 dose expansion Group 2: PK samples will be collected on Cycle 2, Day 1 at pre dose and 1, 2, 4, and 6 hours post dose. Sparse PK will be collected at pre dose and 1 4 hours post dose on Cycle 1 Day 1 and Day 15 and anytime on Day 1 of Cycles 3 through 6.

11 In Phase 1b dose escalation with enzalutamide: PD biomarker samples 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. In Phase 2 dose expansion Group 2: PD samples will be collected on Day 15 of Cycle 1 at pre dose and 1, 2, 4, and 6 hrs post dose. Spare PD will be collected at pre dose and 1 4 hours post dose on Cycle 1 Day 1 and Day 8 and anytime on Day 1 of Cycles 2 through 6.

CCI [redacted]

13 Tumor markers PSA will be collected on C1D1 at pre dose and on Day 1 of every subsequent Cycle at pre dose.

14 If available, paraffin embedded archival tumor tissue block for shipment to Gilead or its designee will be requested at C1D1.

CCI [redacted]

16 Tumor evaluation by CT/MRI or applicable scan will be performed during screening (within 8 weeks of Cycle 1 Day 1) and every 12 weeks thereafter. 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.

17 Subjects will also undergo a bone scan. Scan at EOT visit is not necessary if the previous scan is performed within 4 weeks of the EOT.

18 For Phase 1b Dose Escalation subjects, the 30 Day Safety Follow Up will be the final study visit. Phase 2 Dose Expansion subjects will complete the 30 Day Safety Follow Up Visit and proceed to Long Term Survival Follow Up.

19 Tumor burden as assessed by PCWG2 Guidelines.

20 LTFU will begin for subjects participating in phase 2 after the 30 day Safety Follow Up visit for up to 2 years after the last dose of IP.