CLINICAL STUDY PROTOCOL

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
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	124032
EudraCT Number:	2015-003741-26
Clinical Trials.gov Identifier:	NCT02607228
Indication:	Metastatic Castrate-Resistant Prostate Cancer
Protocol ID:	GS-US-350-1604
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PROTOCOL SYNOPSIS

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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
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	124032 2015-003741-26 NCT02607228
Study Centers Planned:	Phase 1b: Approximately 4 centers in the United States Phase 2: Approximately 11 centers in the United States and 4 in the European Union
Objectives:	The primary objectives of this study are 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]

Study Design:

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).

Subjects will return to the clinic for frequent evaluation and monitoring as per Appendix 2 and Appendix 3.The doses for each monotherapy dose level are shown in the table below.

Dose Level	Single agent GS -5829 (once daily)
1*	1.4 mg
2	2 mg
3	3 mg
4	4 mg
5	6 mg
6	9 mg

* The initial dose level may be higher than dose level 1, depending on results in Study GS-US-350-1599

Dose levels may be modified based on emerging safety, PK, PD, and efficacy results.

If a dose limiting toxicity (DLT) occurs within 28 days at the first dose level, this level will be expanded to enroll 2-3 additional subjects (6 subjects total). If ≥ 2 DLTs occur in the first dose level tested, then one dose level lower will be opened to enroll 3-4 additional subjects. If no DLT occurs in 3-4 subjects or < 2 DLTs occur in up to 6 subjects at the lower dose level, then this dose level will be the MTD of single agent GS-5829.

The safety and tolerability of each dose level will be assessed by a Safety Review Team (SRT) after all subjects in the cohort have been followed for at least 28 days after the first dose of monotherapy GS-5829. If no DLTs occur in 3-4 subjects or < 2 DLTs occur in up to 6 subjects on the first dose level after 28 days on treatment, the second dose level will open. Each subsequent dose level will open if the dose level preceding has no DLTs in 3-4 subjects or < 2 DLTs in up to 6 subjects.

If a subject is enrolled in a dose level but does not complete the pharmacokinetic (PK) or pharmacodynamics (PD) analysis in the first 28 days of dosing, they may continue on study but an additional subject may be enrolled at that dose level.

The MTD of monotherapy is the highest dose level with a subject incidence of 0 DLTs in 3-4 subjects or < 2 DLTs in 6 subjects during the first 28 days of study drug dosing. A minimum of 3 subjects need to be treated in a cohort before this dose level is deemed as the MTD.

If the lowest dose evaluated is deemed the MTD, then the lower dose cohort may be enrolled to explore the relationship between exposure and efficacy and safety.

The combination dose escalation 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.

Dose Escalation of GS-5829 and enzalutamide

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.

Similar to the single agent dose escalation, the available safety, tolerability and pharmacokinetics data for each combination therapy dose level will be assessed by a Safety Review Team (SRT) after all subjects in the cohort have been followed for at least 28 days after their first dose of GS-5829. If no DLTs occur in 3-4 subjects or < 2 DLTs occur in up to 6 subjects on the first combination dose level after 28 days on treatment (C1D28), the second dose level will open. Each subsequent dose level will open if the dose level preceding has no DLTs in 3-4 subjects or < 2 DLTs in up to 6 subjects. The dose escalation intended is similar to that for single agent GS-5829 (see the previous table). Depending on the exposure observed, the data (including PK, tolerability, safety and PSA response) will be evaluated to determine the appropriate GS-5829 dose in combination with enzalutamide. The dose of GS-5829 for the next combination therapy dose level will be communicated to the sites by administrative letter.

If a subject is enrolled in a dose level but does not complete the PK or PD analysis in the first 28 days of GS-5829 dosing, they may continue on study but an additional subject may be enrolled at that dose level.

The MTD of the combination therapy is the highest dose level with a subject incidence of 0 DLTs in 3-4 subjects or < 2 DLTs in 6 subjects during the first 28 days of study drug dosing. A minimum of 3 subjects need to be treated at a dose level before this dose level can be deemed as the MTD. Based on tolerability, PK, PD, efficacy and emerging data from other studies using GS-5829, dose escalation may be discontinued prior to reaching the MTD.

Dose Limiting Toxicity Definition

A DLT is a toxicity defined below and considered possibly related to GS-5829 occurring during the DLT assessment window (Day 1 through Day 28) in each monotherapy or combination therapy cohort:

- Grade ≥ 4 neutropenia (absolute neutrophil count [ANC] < 500/mm^3
- Grade ≥ 3 neutropenia (ANC < 1000/mm^3) with fever (a single temperature of > 38.3°C or a sustained temperature of ≥ 38°C for more than one hour)
- Grade ≥ 3 thrombocytopenia
- Grade ≥ 2 bleeding (e.g. gastrointestinal, respiratory, epistaxis, purpura)

- Grade ≥ 3 or higher non-hematologic toxicity, except:
  - Grade 3 nausea or emesis with maximum duration of 48 hours on adequate medical therapy
  - Grade 3 diarrhea which persists for < 72 hours in the absence of maximal medical therapy.
- Grade ≥ 2 non-hematologic treatment-emergent adverse event (TEAE) that in the opinion of the investigator is of potential clinical significance such that further dose escalation would expose subjects to unacceptable risk
- Treatment interruption of ≥ 7 days due to unresolved toxicity

For certain toxicities, such as laboratory assessments without a clear clinical correlate, a discussion between the Investigator and Medical Monitor may take place to determine if this adverse event (AE) should be assessed as a DLT. However, any Grade 3 or Grade 4 elevation in aspartate transaminase (AST) or alanine transaminase (ALT) associated with a Grade 2 elevation in bilirubin that is at least possibly related to study drug will be considered a DLT.

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 on 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.
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
Target Population:	Adult subjects with histologically or cytologically confirmed mCRPC who are chemo-naïve, and have documented disease progression while receiving enzalutamide and/or abiraterone therapy.
Duration of Treatment:	Treatment will continue in the absence of disease progression, unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 3.4.
Diagnosis and Main Eligibility Criteria:	Inclusion Criteria: Subjects must meet all of the following inclusion criteria to be eligible for participation in this study: 1) Male ≥18 years of age 2) Histologically or cytologically confirmed prostate cancer (subjects with primary neuroendocrine carcinoma of prostate are excluded) • Phase 1b Monotherapy Dose Escalation: Subject must have documented progressive disease by meeting at least one of the PCWG2 criteria (Appendix 4) despite treatment with abiraterone and/or enzalutamide • Phase 1b Combination Therapy Escalation **and** Phase 2 Combination Dose Expansion (Group 2): Subjects must have documented progressive disease by meeting at least one of the PCWG2 criteria, despite treatment with abiraterone. They may **not** have received prior enzalutamide or chemotherapy for mCRPC

- Phase 1b Combination Therapy Escalation **and** Phase 2 Combination Dose Expansion (Group 2): Subjects must have documented progressive disease by meeting at least one of the PCWG2 criteria, despite treatment with abiraterone. They may **not** have received prior enzalutamide or chemotherapy for mCRPC
- Phase 2 Monotherapy Dose Expansion (Group 1): Subjects must have documented progressive disease by meeting at least one of the PCWG2 criteria, despite treatment with enzalutamide. They may have received prior abiraterone, but not prior chemotherapy, for mCRPC
- Phase 2 Combination Therapy Dose Expansion (Group 3): Subjects must have documented progressive disease by meeting the PCWG2 criteria for PSA progression, but not radiographic progression, despite treatment with enzalutamide. They may have received prior abiraterone, but not prior chemotherapy, for mCRPC (similar to Group 1); however, they must also have been on continuous enzalutamide therapy for at least 12 weeks prior to Cycle 1, Day 1.

3) Castration-resistant disease defined as ongoing androgen deprivation therapy with GnRH analogue or bilateral orchiectomy and serum testosterone level ≤ 1.73 nmol/L (50 ng/dL) at the screening visit. Subjects who have not had a bilateral orchiectomy must have a plan to maintain effective GnRH-analogue therapy for the duration of the trial
4) Metastatic disease documented by bone lesions on bone scan or by measurable soft tissue disease by CT/MRI. Subjects whose disease spread is limited to regional pelvic lymph nodes are not eligible.
5) All acute toxic effects of any prior antitumor therapy resolved to Grade ≤ 1 before the start of study drug dosing (with the exception of alopecia [Grade 1 or 2 permitted] and neurotoxicity [Grade 1 or 2 permitted])
6) Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1
7) Life expectancy of ≥ 3 months, in the opinion of the Investigator

8) Adequate organ function defined as follows:
   a) Hematologic: Platelets ≥ 100 x 10^9/L; Hemoglobin ≥ 9.0 g/dL; ANC ≥ 1.5 x 10^9/L (without platelet transfusion or any granulocytic growth factors within previous 7 days of the hematologic laboratory values obtained at screening visit)
   b) Hepatic: AST / ALT ≤ 2.5 x upper limit of normal (ULN) (if liver metastases are present, ≤ 5 x ULN); total or conjugated bilirubin ≤ 1.5 x ULN
   c) Renal: Serum Creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 60 mL/min as calculated by the Cockroft-Gault method
9) Coagulation: International Normalized Ratio (INR) ≤ 1.2
10) Male subjects of reproductive potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 7 and refrain from sperm donation for at least 90 days
11) Able and willing to provide written informed consent to participate in the study

Exclusion Criteria:

Subjects who meet any of the following exclusion criteria are not to be enrolled in this study:

1) History or evidence of clinically significant disorder, condition, or disease that, in the opinion of the Investigator or Medical Monitor would pose a risk to subject safety or interfere with the study evaluations, procedures, or completion
2) Known brain metastasis or leptomeningeal disease
3) Uncontrolled intercurrent illness including, but not limited to, active uncontrolled infection, active or chronic bleeding event within 28 days prior to first dose of study drug, uncontrolled cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements as judged by treating physician
4) A history of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the past 12 months, cerebral vascular accident and brain arteriovenous malformation are excluded from combination therapy with enzalutamide.

5) Myocardial infarction, symptomatic congestive heart failure (New York Heart Association Classification > Class II), unstable angina, or serious uncontrolled cardiac arrhythmia within the last 6 months of Cycle 1 Day 1
6) Major surgery, defined as any surgical procedure that involves general anesthesia and a significant incision (ie, larger than what is required for placement of central venous access, percutaneous feeding tube, or biopsy) within 28 days of the first dose of study drug
7) Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of GS-5829, including any unresolved nausea, vomiting, or diarrhea that is Common Terminology Criteria for Adverse Events (CTCAE) Grade > 1
8) Minor surgical procedure(s) within 7 days of enrollment or randomization, or not yet recovered from prior surgery (placement of central venous access device, fine needle aspiration, or endoscopic biliary stent ≥ 1 day before enrollment or randomization is acceptable)
9) Anti-tumor therapy (chemotherapy, antibody therapy, molecular targeted therapy) within 21 days or 5 half-lives, whichever is longer, of study drug dosing (6 weeks for nitrosoureas, mitomycin C, or molecular agents with $t_{1/2}$ > 10 days); concurrent use of an LHRH agonist is permitted for all subjects and ongoing enzalutamide is required in Group 3.
10) History of a concurrent or second malignancy, except for: adequately treated local basal cell or squamous cell carcinoma of the skin; cervical carcinoma in situ; superficial bladder cancer; breast carcinoma in situ; adequately treated Stage 1 or 2 cancer currently in complete remission; any other cancer that has been in complete remission for ≥ 5 years
11) History of long QT syndrome or whose corrected QT interval (QTc) measured (Fridericia method) at screening is prolonged (> 450 ms). Subjects who screen fail due to this criterion are not eligible to be re-screened
12) Prior exposure to bromodomain (BET) inhibitors
13) Clinically significant bleeding within 28 days of Cycle 1 Day 1
14) Known human immunodeficiency virus (HIV) infection
15) HBsAg positive
16) HCV antibody positive

17) Use of moderate/strong cytochrome P450 (CYP)3A4 inhibitors or moderate/strong CYP3A4 inducers within 2 weeks prior to the first dose of study drug (with the exception of enzalutamide in the combination arms)

18) Evidence of bleeding diathesis

19) History of hemoptysis of ≥ 2.5 mL/1 teaspoon within 6 months of Cycle 1 Day 1

20) History of high grade esophageal or gastric varices

21) Anticoagulation therapy within 7 days of Cycle 1 Day 1, including acetylsalicylic acid, low molecular weight heparin, or warfarin.

Study Procedures/ Frequency:

Screening:

Screening will commence with obtaining the subject's signed informed consent and will occur up to 28 days prior to the first dosing of study drug on Study Day 1/Cycle 1 Day 1. Screening procedures will include the following: medical history review, physical exam, vital signs, 12-lead electrocardiogram (ECG), ECOG Performance Status, prior/concomitant medication review, chemistry, hematology and coagulation, PSA, adverse event (AE) assessment, and computed tomography (CT) or magnetic resonance imaging (MRI) (scans that meet protocol requirements that are obtained as part of standard medical practice up to 28 days prior to Study Day 1/Cycle 1 Day 1 are acceptable) and bone scan. Baseline tumor lesions will be measured and characterized prior to Study Day 1/Cycle 1 Day 1 to assess the subject disease status prior to beginning treatment.

Treatment:

Subjects who meet eligibility criteria will receive GS-5829 as a single agent and combined with enzalutamide orally once daily. Each cycle will consist of 28 days. Safety and efficacy assessments will occur on an outpatient basis including an assessment of tumor response, physical exam, vitals, ECG, collection of blood samples (for routine safety labs, GS-5829 PK, PD markers, and biomarkers at applicable visits), and assessment of AEs. In addition, subjects will undergo a bone scan and CT (or MRI) scan every 12 weeks. A subject who does not show evidence of disease progression may continue receiving GS-5829 or GS-5829 plus enzalutamide once daily until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 3.4. Subjects who have progressive disease by PSA measurements alone may continue study drug.

	After discontinuation of study treatment, subjects will be followed for safety for 30 days. **Phase 1b Monotherapy Dose Escalation** PK and PD samples for GS-5829 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. GS-5829 dose will be administered in fed state on Day 1 of Cycle 2. **Phase 1b Dose Escalation with enzalutamide** PK and PD 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. **Phase 2 Dose Expansion (Group 1)** PK and PD samples will be collected on Day 8 of Cycle 1 at pre-dose and 1, 2, 4, and 6 hours post-dose. Sparse PK and PD 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. **Phase 2 Dose Expansion (Group 2)** PK and PD samples will be collected on Cycle 2, Day 1 at pre-dose and 1, 2, 4, and 6 hours post-dose. Sparse PK and PD 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 3 through 6. **Phase 2 Dose Expansion (Group 3)** PK and PD samples will be collected on Cycle 2, Day 1 at pre-dose and 1, 2, 4, and 6 hours post-dose. Sparse PK and PD 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 3 through 6.
Test Product, Dose, and Mode of Administration:	GS-5829 tablets will be self-administered orally once daily, beginning on Cycle 1 Day 1 of the study and thereafter at approximately the same time each day until end of treatment. GS-5829 is supplied as 0.2 mg, 1 mg, 5 mg, and 10 mg tablets. Enzalutamide capsules will be self-administered orally once daily beginning on Study Day 1 of the Dose Escalation portion and Dose Expansion portion (Group 2). Enzalutamide will be supplied as 40 mg capsules; subjects will self-administer 160 mg (4 × 40 mg capsules) once daily.

Reference Therapy, Dose, and Mode of Administration:	Not Applicable
Criteria for Evaluation:	**Phase 1b and Phase 2**
Safety:	Safety will be evaluated by assessment of clinical laboratory tests, physical examination, 12-lead ECG, vital signs measurements, and the documentation of AEs
Efficacy	Disease progression will be assessed according to PCWG2 criteria. Progression/Non-progression rate at Week 12, Progression free survival defined by the time from Study Day 1 to the date of death from any cause or the date of progressive disease which one is earlier, and overall survival will be measured.
Pharmacokinetics:	The following PK parameters for GS-5829 will be calculated as applicable: C_{max}, $AUC_{last,}$ AUC_{tau}, C_{tau}, and T_{max}
Statistical Methods:	**Analysis Methods** The Full Analysis Set (FAS) will be used in the analyses of subject characteristics and efficacy endpoints. The FAS consists of all subjects who receive ≥ 1 dose of study drug. A Safety Analysis Set for this study will be the same as FAS since this study is a non-randomized study. Other analysis sets (DLT evaluable and PK/PD analysis sets) will be used for additional analyses as well. Subject characteristics and study results will be described and summarized by dose level and assessment for the relevant analysis sets. Descriptive summaries will be prepared to show sample size, mean, standard deviation (StD), 90% confidence intervals (CIs) on the mean, median, minimum and maximum for continuous variables, and counts, percentages and 90% CIs on the percentage for categorical variables. Efficacy endpoints: Estimates of progression/non-progression rate at Week 12 will be present with 90% exact CIs: PFS and OS will be visualized using Kaplan-Meier plot, and median survival time estimate will be listed. Based on the Safety Analysis Set, information regarding study drug administration, study drug compliance and safety variables will be described and summarized.

Using data from the PK and PD Analysis Sets, GS-5829 plasma concentrations and PK parameters and whole blood PD markers will also be described and summarized. Plasma concentrations of GS-5829 metabolite(s) may also be determined and PK explored.

Sample Size

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%.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP), including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
AR	androgen receptor
AR-V7	AR splice variant 7
AST	aspartate transaminase
AUC_{last}	area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
AUC_{tau}	area under the plasma concentration-time curve
BCRP	breast cancer resistance protein
BET	bromodomain and extra-terminal
BRD	bromodomain
C_{max}	maximum concentration observed
C_{tau}	concentration at the end of the dosing interval
CFR	Code of Federal Regulations
CI	confidence interval
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CRPC	castrate-resistant prostate cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DSPH	Drug Safety and Public Health
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ER	estrogen receptor
eSAE	electronic serious adverse events
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HBsAg	Hepatitis B surface Antigen

HIV	Human Immunodeficiency Virus
HNSTD	highest non-severely toxic dose
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IP	investigational product
IRB	Institutional Review Board
IxRS	Interactive voice/web Response System
LHRH	luteinizing hormone releasing hormone
mCRPC	metastatic castrate-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	overall response rate
OS	overall survival
PCWG	Prostate Cancer Working Group
PD	pharmacodynamics
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PSA	prostate-specific antigen
QD	every day
QTc	corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RNAPII	RNA polymerase II
SADR	serious adverse drug reaction
SAE	serious adverse event
StD	standard deviation
SOC	system organ class
SOP	standard operating procedure
STD	severely toxic dose
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	terminal phase half-life
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
WBC	white blood cell

1. INTRODUCTION

1.1. Background

GS-5829 is a small-molecule inhibitor of the highly conserved bromodomain pockets of the bromodomain and extraterminal (BET) proteins. Bromodomain and extraterminal proteins regulate specific gene expression by enhancing ribonucleic acid (RNA) polymerase II (RNAPII)-mediated transcription. Signal transduction pathways recruit BET proteins to target genes through posttranslational modification of histone proteins in the form of lysine acetylation {Belkina et al 2012, Hargreaves et al 2009}. The tandem bromodomain motifs of BET proteins specifically recognize acetylated histones and, in turn, recruit protein factors that regulate RNAPII {Shi et al 2014}. The BET family includes bromodomain-containing proteins 2, 3, 4, and T (BRD2, 3, 4, and T). BRD2, 3 and 4 are widely expressed and regulate gene transcription in diverse cell types, including malignant cells, whereas BRDT expression is restricted to the testes.

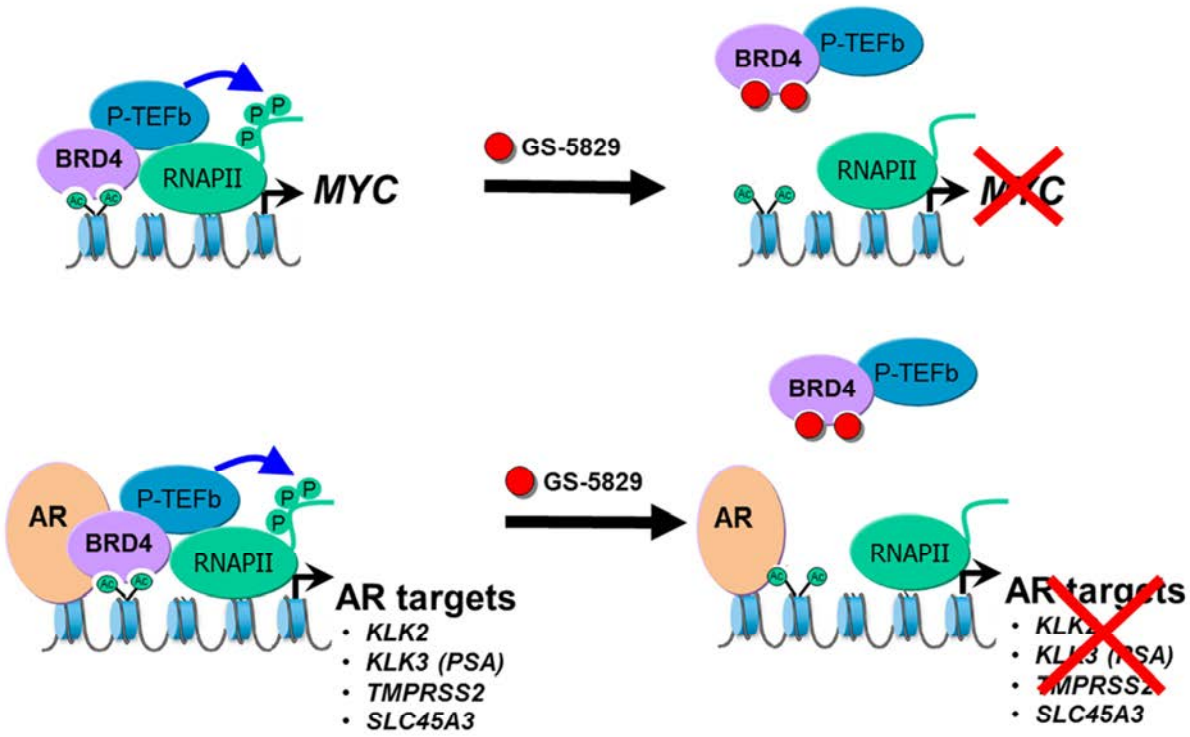
BRD2, 3, 4 are essential regulators of the expression or activity of several key oncogenic transcription factors, including v-myc avian myelocytomatosis viral oncogene homolog (MYC) and the androgen receptor (AR) {Shi et al 2014}. Transcription of the MYC gene is dependent on BET proteins in many cells {Mertz et al 2011} (Figure 1-1). Androgen receptor-dependent transcription of target genes requires BET proteins in prostate cancer cells {Asangani et al 2014}. Cancer cells addicted to MYC and AR are highly sensitive to BET protein inhibition {Asangani et al 2014, Delmore et al 2011, Mertz et al 2011}, which provides the basic therapeutic rationale for BET inhibition with GS-5829 for the treatment of cancer.

MYC promotes cell proliferation, cell survival, and metabolic adaptation and is frequently overexpressed in human cancers {Dang 2012}. Data generated at Gilead demonstrated MYC overexpression to be prevalent in 76% of prostate cancer (n = 60), 67% of diffuse large B-cell lymphoma (DLBCL) (n = 98), 65% of multiple myeloma (MM, n=30), 73% of colorectal cancer (n = 60), and 80% of ovarian cancer (n = 60) cases examined (PC-350-2083). These data are consistent with literature that reports a high incidence of MYC expression in these and other cancers {Affer et al 2014, Barrans et al 2010, Chesi et al 2008, Chng et al 2011, Glitza et al 2014, Hawksworth et al 2010, Nesbit et al 1999, Nupponen et al 1998, Perry et al 2014}. The AR is a nuclear hormone receptor that is nearly ubiquitously expressed in prostate cancer (PC-350-2083) and activates growth and survival signals both by binding to androgen, its natural ligand, and through androgen-independent mechanisms {Yuan et al 2014}.

A number of orally administered, BET-directed compounds (TEN-010, CPI-0610, OTX015, ZEN-3365, and GSK525762) are currently in early-stage clinical development for the treatment of solid tumors or hematologic cancers. Initial evidence of clinical activity at tolerated doses has been reported for the BET inhibitor OTX015 in patients with refractory hematological cancers {Herait et al 2014}. GS-5829 is an orally available small-molecule inhibitor of BET proteins that is being developed by Gilead Sciences, Inc. for the treatment of solid tumors, including castrate-resistant prostate cancer (CRPC), and hematologic malignancies. In nonclinical studies, GS-5829 inhibited cell growth and induced apoptosis of solid tumor and hematological cancer cells by inhibiting BET protein-dependent transcription of MYC and other oncogenic pathways, including transcription mediated by the AR in prostate cancer cells.

Additionally, enzalutamide-resistant LNCaP-AR and VACP tumors in murine xenograft models displayed significantly higher AR expression and signaling relative to controls yet maintained sensitivity to BET inhibitors. The AR-v7 splice variant of CRPC, which has been reported to be associated with resistance to anti-androgen treatments, was elevated in enzalutamide-resistant cells and was markedly repressed by BET inhibitors particularly when combined with continued exposure to enzalutamide {Asangani et al 2016}.

Figure 1-1. Mechanism of Action of GS-5829 to Reduce Transcription of MYC and AR Target Genes in Cancer Cells



Bromodomain and extraterminal proteins, including BRD4, are recruited to the MYC promoter and enhancer elements through an interaction between the tandem bromodomains and acetylated histone proteins in chromatin (top panel). BRD4 recruits the positive transcription elongation factor b (pTEFb) complex to the MYC gene, which phosphorylates RNAPII to increase transcription of the MYC gene. GS-5829 binds to the bromodomains of BET proteins, thereby blocking the interaction with acetylated histone proteins and leading to a reduction of MYC transcription. GS-5829 similarly functions to inhibit the transcription of AR target genes in prostate cancer cells, including the kallikrein-related peptidase 3 (KLK3) gene that encodes prostate specific antigen (bottom panel).

1.2. GS-5829

1.2.1. General Information

For further information on GS-5829, refer to the current investigator's brochure for GS-5829.

1.2.2. Preclinical Pharmacology and Toxicology

1.2.2.1. Absorption, Distribution, Metabolism, and Elimination

GS-5829 shows moderate plasma protein binding and volumes of distribution in nonclinical species that are similar to or slightly higher than total body water. Systemic clearance in nonclinical species is generally well predicted from the rates of metabolism by hepatocytes. Since GS-5829 has high metabolic stability with human hepatic material in vitro, it is likely to show low clearance in humans. The major route of metabolism of GS-5829 involves hydroxylation of the 5-methyl moiety on the 3,4-dimethly isoxazole ring catalyzed primarily by CYP3A4 and CYP3A5 enzymes in humans.

Consistent with the moderate to high bioavailability seen in nonclinical species, GS-5829 shows high forward permeability across Caco-2 monolayers, and low efflux, but GS-5829 is a substrate of human P-p and BCRP.

GS-5829 has relatively high unbound fraction in cell culture medium containing fetal bovine serum. Competitive dialysis between cell culture median and human, dog and mouse plasma yielded a ratio of unbound fractions of 5.7, 15.2 and 13.2 respectively.

GS-5829 is unlikely to cause clinical interaction through inhibition of CYP1A2, CYP2C9, CYP2C19, or CYP2D6, CYP2B6, CYP2C8, CYP3A or UGT1A1, so the potential for causing drug interactions through inhibition of those enzymes is low. GS-5829 is also a weak inhibitor of the human efflux transporters, P-gp and BCRP, and the uptake transporters, OATP1B1 and OATP1B3.

1.2.2.2. Nonclinical Toxicology

Nonclinical safety pharmacology and toxicology studies have characterized the safety of GS-5829 through repeat dose toxicology studies. All pivotal toxicology studies were conducted in full compliance with Good Laboratory Practice regulations (21 CFR 58). The scope of the nonclinical safety evaluation is consistent with the guidance issued by the International Conference on Harmonisation (ICH).

In nonclinical pharmacology studies, GS-5829 showed no significant adverse effects on central nervous, respiratory or cardiovascular system functioning at the projected exposure and human target dose of 25 mg once daily.

The following target organs/systems were identified in the nonclinical toxicology studies: hematopoietic and male reproductive system (mice and dogs), the adrenal and skin (mice), and the gastrointestinal tract, respiratory and cardiac (dogs). With the exception of the adrenals in the mouse and the respiratory and cardiac hemorrhages observed in dogs, target organs are as expected based on the known pharmacology. The dog was the more sensitive species, with the no-observed-adverse-effect levels in the mouse and dog being 10 and 0.03 mg/kg/day respectively. The severely toxic dose in 10% of mice and the highest non-severely toxic dose (HNSTD) in dogs were 25 and 0.1 mg/kg/day, respectively.

Hematopoietic effects include decreases in white blood cells, lymphocytes, platelets and reticulocyte counts as well as mild reduced cellularity in the marrow in mice at doses of ≥ 10 mg/kg/day. Minimal to marked decrease in bone marrow cellularity, decrease in lymphocytes in the lymphoid tissues (spleen, thymus, lymph nodes and gastrointestinal associated lymphoid tissue), decrease in neutrophils and platelets were observed at 0.3 mg/kg/day in dogs. Elevated fibrinogen was also noted at 0.3 mg/kg/day in dogs.

Mild to moderate alveolar (lung) hemorrhage was observed at ≥ 0.1 mg/kg/day in dogs. Mild hemorrhage in the left atrioventricular valve of the heart was seen at 0.3 mg/kg/day in 1 of 6 dogs. The mechanism for the hemorrhage is not known. Prothrombin time and partial thromboplastin time measurements were normal. The anatomic pattern of the hemorrhage in the lung field and microscopy was considered potentially consistent with pneumonia, however bacteria were not identified.

In the male reproductive system, decreased testes weight with oligospermia/aspermia were observed in both mouse and dog studies at 25 and 0.3 mg/kg/day respectively. Minimal to moderate vacuolation of the seminiferous tubules occurred at ≥ 0.1 mg/kg/day in the dog. These changes are consistent with the known effects of a bromodomain inhibitor on the testes.

The gastrointestinal findings in the dog included minimal to mild mucosal atrophy, mucosal hemorrhage and crypt hyperplasia in the stomach or intestines at ≥ 0.1 mg/kg/day. Adrenal gland weight decreases were noted at 25 mg/kg/day and cytoplasmic vacuolation at ≥ 10 mg/kg/day in the mouse studies, of unknown cause. QT prolongation is not expected based on hERG, rodent and dog studies.

1.2.3. Clinical Trials of GS-5829

As of 02 June 2016, two clinical studies evaluating GS-5829 have been initiated (including this ongoing study). One study (Protocol GS-US-350-1599) includes subjects with advanced solid tumors, ER+Her2- breast cancer, and lymphomas. This study is an ongoing open-label, multicenter, sequential dose-escalation study to evaluate the safety, tolerability, pharmacokinetics (PK), and PD of GS-5829 in subjects with advanced solid tumors and lymphomas. This study includes a cohort of subjects with advanced stage breast cancer who will receive GS-5829 combined with exemestane and fulvestrant. Doses planned for this study are 0.6, 1.4, 2, 3, 4, 6, 9, and 12 mg once daily. Pharmacokinetic data are available from 4 dose levels of the single agent GS-5829 in Study GS-US-350-1599 (0.6, 1.4, 2 mg, and 3 mg once daily). GS-5829 is well-absorbed with higher than predicted plasma exposures in humans. No clinically detectable trend in laboratory abnormalities in relationship to dose has been observed. A Grade 3 thrombocytopenia that was considered a DLT was observed in 1 of 6 subjects at 3.0 mg.

Please refer to the current GS-5829 Investigator's Brochure for additional details.

1.2.4. Information about Enzalutamide

Enzalutamide is an androgen receptor inhibitor that acts on different steps in the androgen receptor signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors and inhibit androgen receptor nuclear translocation and interaction

with DNA. A major metabolite, N-desmethyl enzalutamide, exhibited similar *in vitro* activity to enzalutamide. Enzalutamide decreased proliferation and induced cell death of prostate cancer cells *in vitro* and decreased tumor volume in a mouse prostate cancer xenograft model. In the US, enzalutamide is approved as a single agent for mCRPC. For current information about enzalutamide (XTANDI®) {Astellas Pharma US Inc. 2014}, refer to the regional prescribing information (Appendix 9) or the summary of product characteristics in the pharmacy binder.

1.3. Rationale for This Study

In 2014, it was estimated that 233,000 new cases of prostate cancer and 29,480 deaths due to prostate cancer would occur in the US {National Cancer Institute 2014}. The majority of men (approximately 90%) are diagnosed with loco-regional disease that is treated surgically and/or with radiation therapy; 5-year survival approaches 100% for these patients. However, despite the availability of a variety of therapies, including pharmacological inhibitors of AR activity, immunotherapy, radiation, and chemotherapy, metastatic prostate cancer has a 5-year survival of only 30%, with most patients dying from prostate cancer.

In patients with advanced prostate cancer who have progressed while receiving therapy with chemical or surgical castration, the androgen/androgen receptor (AR) axis remains the target of current standard of care agents, abiraterone {Janssen Biotech Inc. 2015} and enzalutamide. Primary and acquired resistance to such agents occurs when the AR is activated in an androgen-independent manner, most notably through the expression of the constitutively active AR splice variant 7 (AR-V7) {Antonarakis et al 2014, Guo et al 2009}. In nonclinical studies, GS-5829 inhibited growth and induced apoptosis in prostate cancer cell lines by inhibiting MYC expression and AR-target gene expression in both AR- and AR-V7-expressing prostate cancer cell lines.

Although GS-5829 has the potential for activity in mCRPC at all points of treatment, first line therapies with enzalutamide and abiraterone are relatively well tolerated and demonstrated improvements in PFS and OS compared with placebo. Abiraterone is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with mCRPC who are chemotherapy-naïve based on demonstrating an improvement in OS from 30.1 to 35.3 months compared with placebo (Hazard Ratio [HR] 0.782 [95% confidence interval (CI); 0.655, 0.956]). Enzalutamide is an androgen receptor inhibitor indicated for the treatment of patients with mCRPC who are chemotherapy-naïve based on demonstrating an improvement in OS from 30.3 to 32.4 months compared with placebo (HR 0.71 [95% CI; 0.60, 0.84]) {Astellas Pharma US Inc. 2014}.

Based on limited data, once a patient has received abiraterone or enzalutamide, the response to the other agent is in the range of 10-26% and median radiographic/clinical progression is 3.6 to 6.6 months {Azad et al 2015, Brasso et al 2014, Noonan et al 2013}. One mechanism of resistance which may explain part of this cross-resistance has been identification of the AR-V7 splice variant, which is estimated to occur in 30-40% of patients who have received abiraterone and/or enzalutamide {Antonarakis et al 2014}. Due to its downstream inhibition of AR-V7 transcription, however, pre-clinical models suggest tumors cells with the AR-V7 splice variant are still sensitive to BET inhibition.

In addition, preclinical data has demonstrated that the combination of GS-5829 and enzalutamide increases the inhibition of AR-mediated transcription and growth of prostate cancer cell lines compared to either agent alone. These results suggests an additive effect of the two agents, which may provide a beneficial option for patients who have failed abiraterone and would otherwise have soon proceeded to chemotherapy.

Chemotherapy (docetaxel, cabazitaxel) is the systemic treatment option after failure of abiraterone and enzalutamide, but it does not offer a potential for cure and use is limited due to its cumulative toxicity in this relatively elderly patient population. One of the greatest unmet needs for patients with mCRPC is to prolong the time from the development of mCRPC to the initiation of chemotherapy.

This is a phase 1b/2 dose escalation and dose expansion study designed to evaluate the single agent safety and activity of GS-5829 in subjects who have progressive disease despite receiving abiraterone and/or enzalutamide. A second group of subjects will evaluate the safety and activity of the combination of GS-5829 and enzalutamide in subjects who have failed abiraterone. A third group of subjects will evaluate the safety and activity of adding GS-5829 to enzalutamide in subjects who have progressed by PSA criteria alone while receiving enzalutamide.

1.3.1. Rationale for the Dose Selection

The starting dose of GS-5829 in this study will be a dose that has been demonstrated to be safe and tolerable in the ongoing Phase 1 study (GS-US-350-1599) in patients with solid tumors and lymphomas. Based on the systemic concentrations of GS-5829 measured in the repeat dose toxicity studies in mice and dogs, the margins of exposure at the severely toxic dose in 10% of rodents (STD10) in mice and highest non-severely toxic dose (HNSTD) in dog are approximately 6.3- and 1-fold, respectively, at a plasma exposure (AUC_{tau}) of 2.5 h.µg/mL which is anticipated to provide clinical efficacy based on in vivo preclinical data and anticipated target inhibition. Preliminary PK data from a limited number of patients in the ongoing Phase 1 study (GS-US-350-1599) indicate plasma exposures are higher than predicted; observed $\mathbf{AUC_{tau}}$ at 0.6 and 1.8 h.ug/mL respectively. Thus, it is anticipated that a clinically efficacious exposure will be achieved at a lower dose than previously predicted and the dose escalation plan has been modified to reflect this emerging data.

For the single agent dose escalation, PK and PD results from the 28 day continuous dosing will be evaluated to explore the dose/exposure-response relationship. Continuation of the study, according to the proposed dose escalation Phase 1b, will require that available data supports the potential to achieve an effective dose of GS-5829 in humans which will be safe and tolerable.

Due to the narrow therapeutic index observed in dogs, the percentage dose increment sequentially decreases at each dose level.

The combination dose escalation 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. Subjects who have mCRPC and have progressive disease despite treatment with abiraterone will be enrolled to receive GS-5829 and enzalutamide.

Enzalutamide is a strong CYP3A4 inducer, which has been demonstrated to decrease the AUC of a CYP3A4 substrate (midazolam) by 86%; therefore further dose escalation of the combination therapy will be performed in these subjects prior to initiation Phase 2 Dose Expansion. As the concern is for decreased GS-5829 exposure, the initial dose level of the combination therapy will be 160 mg of enzalutamide combined with a starting dose of GS-5829 that has been determined to be safe and tolerable in the single agent dose escalation. Enzalutamide dosing will begin approximately 2 weeks prior to GS-5829 dosing to achieve near maximal CYP3A4 induction to reduce changes in GS-5829 exposure over the first cycle. PK evaluations will be performed and if indicated and supported by PK, safety and tolerability, additional cohorts with higher doses and/or more frequent dosing (ie, twice daily) of GS-5829 in combination with enzalutamide may be tested. The total daily dose will not increase by more than 100% in the next cohort.

1.4. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

1.5. Risk/Benefit Assessment for the Study

Based on the systemic concentrations of GS-5829 measured in the repeat dose toxicity studies in mice and dogs, the margins of exposure at the severely toxic dose in 10% of rodents (STD10) in mice and HNSTD in dog are approximately 6.3- and 1-fold, respectively, at the anticipated clinically efficacious exposure. Another bromodomain inhibitor in development has identified thrombocytopenia as the earliest signs of toxicity in human studies, a toxicity which may be easily monitored.

Target organs identified in the repeat-dose toxicity studies included the hematopoietic and male reproductive systems (mice and dogs), the adrenal glands (mice), and the GI tract and respiratory system (dogs). With the exception of the adrenal glands in the mouse and the respiratory system in dogs, all other target organs are expected based on the known pharmacology of GS-5829 to inhibit BET proteins. The effects on the hematopoietic system, male reproductive tract, adrenal glands, and GI tract were considered reversible and can be monitored in the clinic.

As of 17 June 2016, the 3 mg dose level has been found to be safe and tolerable as single agent dosing in the First-In-Human Study GS-US-350-1599 and the 2 mg dose level has been found to be safe and tolerable in the prostate cancer Study GS-US-350-1604, respectively. Two subjects in the First-In-Human Study (GS-US-350-1599) experienced 3 serious adverse events (SAEs) which were considered by the investigator to be Grade 3 and not related to study drug (cholangitis and sepsis in 1 subject at 0.6 mg and thrombocytopenia in 1 subject at 1.4 mg). The following AEs were considered related to study drug: fatigue (1 subject, 0.6-mg group and 1 subject, 1.4-mg group), nausea (1 subject, 0.6-mg group and 1 subject, 1.4-mg group), splenomegaly (1 subject, 1.4-mg group), and dizziness (1 subject, 1.4-mg group). No AEs led to discontinuation of study drug. After the most recent data cut (12 October 2015), a DLT of adrenal hemorrhage was reported in a subject receiving 4 mg of GS-5829. The subject had normal coagulation parameters and a platelet count higher than normal at baseline which did not change at the time of the event. An additional DLT of Grade 3 thrombocytopenia was reported in

a subject receiving 3 mg of GS-5829. To minimize the risk of excessive toxicity, the dose escalation of GS-5829 in this protocol will increase at a proportionally smaller percentage at each subsequent dose level.

Assessments for AEs and monitoring for laboratory abnormalities are specified in the protocol and include symptom and AE assessment on Days 1, 8, 15, 22 of the first 28 day cycle and then every 28 days, until end of treatment followed by a 30 day Safety Follow-Up visit. Physical examinations will occur on Day 1of each 28-day cycle, until end of treatment followed by a 30-day safety follow-up visit.

The safety monitoring frequency is considered sufficient to identify potential AEs as they emerge. In addition, mitigation strategies are incorporated into the study design. The inclusion and exclusion criteria are designed to ensure subjects have acceptable organ function to be eligible for this study such that confounding significant co-morbidities are excluded. Study medications will continue until disease progression, unacceptable toxicity, consent withdrawal, or subject's refusal of treatment.

Enzalutamide is an approved drug for prostate cancer and has known toxicities of seizure, fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flushes, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decrease, headache, hypertension and dizziness/vertigo. Subjects with a history of seizure will be excluded from receiving enzalutamide.

Potential Benefits

The primary potential benefit of BET inhibition alone or combined with androgen inhibition is that therapy may delay progression or improve overall survival over the current standard of care which is either enzalutamide alone or chemotherapy. Participants are informed that their involvement in the study may offer benefits to other current or future patients with metastatic prostate cancer by enhancing knowledge relating to the disease course and treatment of prostate cancer.

2. OBJECTIVES

The primary objectives of this study are 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 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 (subjects **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 (**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 abiraterone as measured by prostate specific antigen (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]

3. STUDY DESIGN

3.1. Endpoints

The endpoints for this study are described in Section 8.

3.2. Study Design

Phase 1b Dose Escalation: This is an open-label, multicenter, sequential dose-escalation study to evaluate the safety, tolerability, PK, and PD of GS-5829 as a single agent and in combination with enzalutamide in subjects with 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 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 (GS-US-350-1599) in patients with solid tumors and lymphomas. Subjects will return to the clinic for frequent evaluation and monitoring as per the Study Procedures Table found in Appendix 2 and Appendix 3.

The doses for each monotherapy dose level are shown in the table below.

Table 3-1. Dose Escalation

Dose Level	GS -5829 (once daily)
1*	1.4 mg
2	2 mg
3	3 mg
4	4 mg
5	6mg
6	9 mg

* The initial dose level may be higher than dose level 1, depending on results in Study GS-US-350-1599

Dose levels may be modified based on emerging safety, PK, PD, and efficacy results.

If a DLT occurs within 28 days at the first dose level, this level will be expanded to enroll 2-3 additional subjects (6 subjects total). If ≥ 2 DLTs occur in the first dose level tested, then one dose level lower will be opened to enroll 3-4 additional subjects. If no DLT occurs in 3-4 subjects or < 2 DLTs occur in up to 6 subjects at the lower dose level, then this dose level will be the MTD of single agent GS-5829.

The safety and tolerability of each dose level will be assessed by a Safety Review Team (SRT) after all subjects in the cohort have been followed for at least 28 days after the first dose of GS-5829. If no DLTs occur in 3-4 subjects or < 2 DLTs occur in up to 6 subjects on the first dose level after 28 days on treatment, the second cohort will open. Each subsequent cohort will open if the dose level preceding has no DLTs in 3-4 subjects or < 2 DLTs in up to 6 subjects.

The SRT will consist of at least one investigator and the following:
Gilead Sciences, Inc. (Gilead) study team members: the Medical Monitor, representatives from Drug Safety and Public Health (DSPH), Clinical Operations and Biostatistics. Others may be invited to participate as members of the SRT if additional expertise is desired. The Medical Monitor serves as the chair of the SRT.

If a subject is enrolled in a cohort but does not complete the PK or PD analysis in the first 28 days of dosing, they may continue on study but an additional subject may be enrolled at that dose level.

The MTD of monotherapy is the highest dose level with a subject incidence of 0 DLTs in 3-4 subjects or < 2 DLTs in 6 subjects during the first 28 days of study drug dosing. A minimum of 3 subjects need to be treated in a cohort before this dose level is deemed as the MTD. If we do not determine the MTD of single agent GS-5829, the dose selected for expansion phase will be the highest administered monotherapy dose. If the lowest dose evaluated is deemed the MTD, then the lower dose cohort may be enrolled to explore the relationship between exposure and efficacy and safety.

The combination dose escalation 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.

Dose Escalation of GS-5829 and enzalutamide

The first 3-4 subjects to enroll will receive GS-5829 at a dose level less than or equal to the previously determined 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 more than 100% in the next cohort.

Similar to the single agent dose escalation, the available safety, tolerability and PK data for each combination therapy cohort will be assessed by an SRT after all subjects in the cohort have been followed for at least 28 days after the first dose of GS-5829. If no DLTs occur in 3-4 subjects or

< 2 DLTs occur in up to 6 subjects on the first dose level after 28 days on treatment (C1D28), the second dose level will open. Each subsequent dose level will open if the dose level preceding has no DLTs in 3-4 subjects or < 2 DLTs in up to 6 subjects. The dose escalation intended is similar to that of the single agent GS-5829 (see Table 3-1). Depending on the exposure observed, the data (including PK, tolerability, safety and PSA response) will be evaluated to determine the appropriate GS-5829 dose in combination with enzalutamide. The dose of GS-5829 for the next combination therapy cohort will be communicated to the sites by administrative letter.

If a subject is enrolled in a cohort but does not complete the PK or PD analysis in the first 28 days of GS-5829 dosing, they may continue on study but an additional subject may be enrolled at that dose level.

The MTD of the combination therapy is the highest dose level with a subject incidence of 0 DLTs in 3-4 subjects or < 2 DLTs in 6 subjects during the first 28 days of study drug dosing. A minimum of 3 subjects need to be treated at a dose level before this dose level can be deemed as the MTD. Based on tolerability, PK, PD, efficacy and emerging data from other studies using GS-5829, dose escalation may be discontinued prior to reaching the MTD.

Dose Limiting Toxicity Definition

A DLT is a toxicity defined below, considered possibly related to GS-5829, occurring during the DLT assessment window (Day 1 through Day 28) in each cohort:

- Grade ≥ 4 neutropenia (absolute neutrophil count [ANC] < 500/mm^3)
- Grade ≥ 3 neutropenia (ANC < 1000/mm^3) with fever (a single temperature of > 38.3°C or a sustained temperature of ≥ 38°C for more than one hour)
- Grade ≥ 3 thrombocytopenia
- Grade ≥ 2 bleeding (e.g. gastrointestinal, respiratory, epistaxis, purpura)
- Grade ≥ 3 or higher non-hematologic toxicity, except:
  - Grade 3 nausea or emesis with maximum duration of 48 hours on adequate medical therapy
  - Grade 3 diarrhea which persists for < 72 hours in the absence of maximal medical therapy
- Grade ≥ 2 non-hematologic treatment-emergent adverse event (TEAE) that in the opinion of the investigator is of potential clinical significance such that further dose escalation would expose subjects to unacceptable risk
- Treatment interruption of ≥ 7 days due to unresolved toxicity

For certain toxicities, such as laboratory assessments without a clear clinical correlate, a discussion between the investigator and medical monitor may take place to determine if this adverse event (AE) should be assessed as a DLT necessitating dose reduction. However, any Grade 3 or Grade 4 elevation in AST or ALT associated with a Grade 2 elevation in bilirubin that is at least possibly related to study drug will be considered a DLT.

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 the 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 the 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.

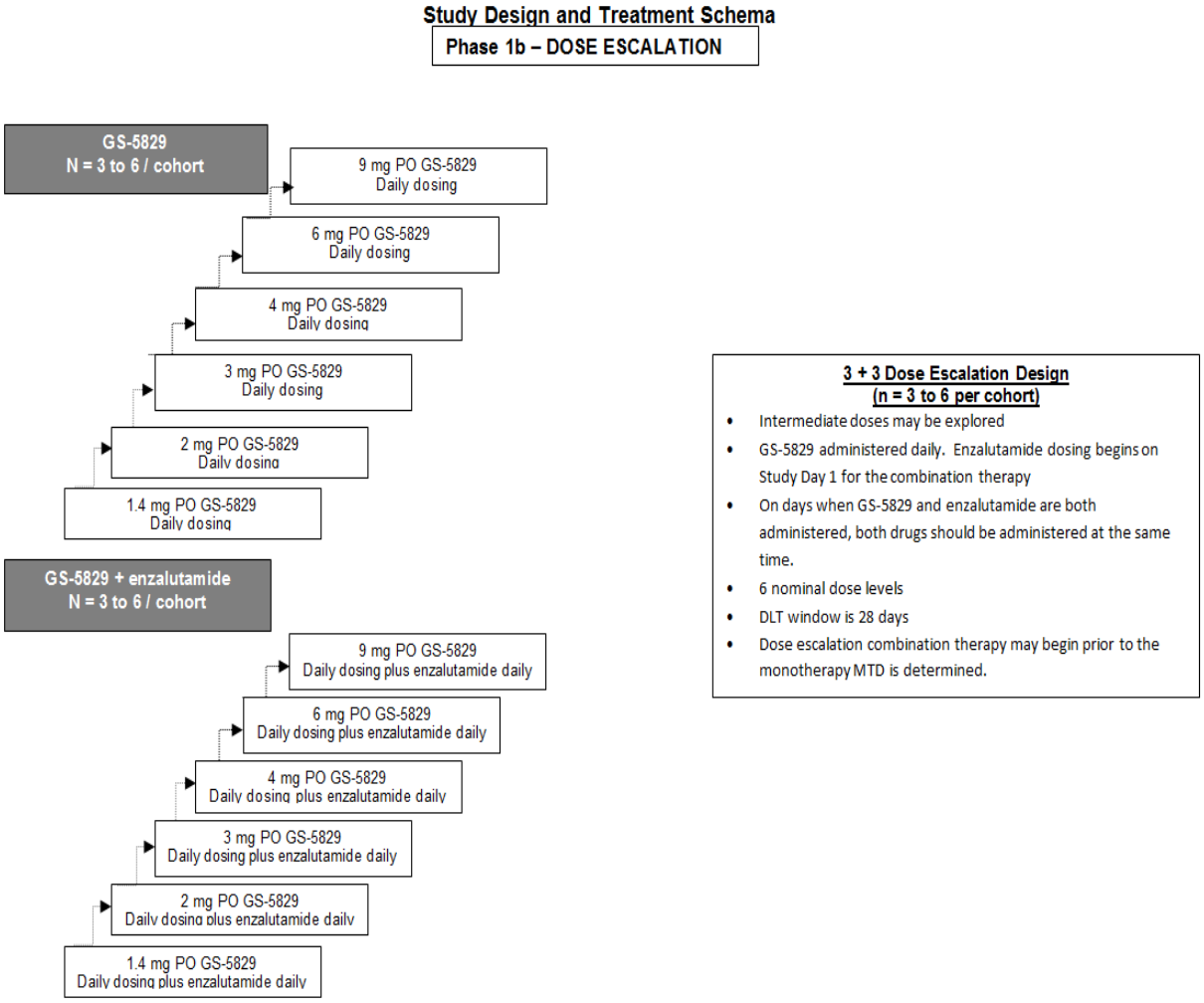
Group 3: A dose equivalent to the dose chosen for Group 2 will be chosen for an expansion phase. A maximum of 20 subjects with mCRPC who have had PSA only progression, but not radiographic progression, despite adequate testosterone suppression and treatment with enzalutamide will be enrolled. These subjects **may** have received prior abiraterone (similar to Group 1). These subjects will continue on 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) 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.

3.2.1. Study Schema

Figure 3-1 provides the study schema

Figure 3-1. Study Design and Treatment Schema



Phase 2 – DOSE EXPANSION

- Dose expansion will begin after completion of the corresponding dose-escalation phase treatment
  - Group 1: GS-5829
  - Group 2: GS-5829 + enzalutamide
  - Group 3: GS-5829 + enzalutamide
- Dose level based upon results from the dose-escalation phase
- Up to 20 additional subjects in each arm

3.3. Study Treatments

Subjects who meet eligibility criteria will receive GS-5829 as a single agent or combined with enzalutamide orally once daily. Each cycle will consist of 28 days. Safety and efficacy assessments will occur on an outpatient basis including assessment of tumor response, physical exam, vitals, electrocardiogram (ECG), collection of blood samples (for routine safety labs, GS-5829 PK, PD markers, and biomarkers at applicable visits), and assessment of AEs. In addition, subjects will undergo a bone scan and CT (or MRI) every 12 weeks.

A subject who does not show evidence of disease progression may continue receiving GS-5829 as a single agent or combined with enzalutamide once daily until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 3.4. Subjects who have progressive disease by PSA measurements alone may continue study drug.

Following treatment, subjects will be followed for safety for 30 days and for survival.

3.4. Criteria for Discontinuation of Study Drug

Study medication may be discontinued in the following instances:

- Documented progression of malignant disease
- Death
- Investigator discretion
- Non-compliance with study drug
- Important protocol deviation

- Subject decision
- Lost to follow-up
- Study termination by the sponsor
- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Unacceptable toxicity, as defined in the toxicity management section of the protocol, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest

3.5. Criteria for Removal from Study

Subjects may be removed from the study for the following reasons:

- Documented progression of malignant disease
- Death
- Investigator discretion
- Non-compliance with study drug
- Subject never dosed with study drug
- Important protocol deviation
- Withdrawal of consent
- Lost to follow-up
- Study termination by the sponsor
- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Unacceptable toxicity, as defined in the toxicity management section of the protocol, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Up to 72 subjects who meet the eligibility criteria will be enrolled in the phase 1b dose escalation portion of the study.

Up to 60 subjects who meet the eligibility criteria will be enrolled in the phase 2 dose expansion portion of the study.

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

1) Male ≥18 years of age

2) Histologically or cytologically confirmed prostate cancer (subjects with primary neuroendocrine carcinoma of prostate are excluded)

   - Phase 1b Monotherapy Escalation: Subjects must have documented progressive disease by meeting at least one of the PCWG2 criteria (Appendix 4) despite treatment with abiraterone and/or enzalutamide

   - Phase 1b Combination Therapy Dose Escalation **and** Phase 2 Combination Dose Expansion (Group 2): Subjects must have documented progressive disease by meeting at least one of the PCWG2 criteria, despite treatment with abiraterone. They may **not** have received prior enzalutamide or chemotherapy for mCRPC

   - Phase 2 Monotherapy Dose Expansion (Group 1): Subjects must have documented progressive disease by meeting at least one of the PCWG2 criteria, despite treatment with enzalutamide. They may have received prior abiraterone, but not prior chemotherapy, for mCRPC

   - Phase 2 Combination Therapy Dose Expansion (Group 3): Subjects must have documented progressive disease by meeting the PCWG2 criteria for PSA progression, but not radiographic progression, despite treatment with enzalutamide. They may have received prior abiraterone, but not prior chemotherapy, for mCRPC (similar to Group 1); however, they must also have been on continuous enzalutamide therapy for at least 12 weeks days prior to Cycle 1, Day 1.

3) Castration-resistant disease defined as ongoing androgen deprivation therapy with GnRH analogue or bilateral orchiectomy and serum testosterone level ≤ 1.73 nmol/L (50 ng/dL) at screening visit. Subjects who have not had a bilateral orchiectomy must have a plan to maintain effective GnRH-analogue therapy for the duration of the trial.

4) Metastatic disease documented by bone lesions on bone scan or by measurable soft tissue disease by CT/MRI. Patients whose disease spread is limited to regional pelvic lymph nodes are not eligible

5) All acute toxic effects of any prior antitumor therapy resolved to Grade ≤ 1 before the start of study drug dosing (with the exception of alopecia [Grade 1 or 2 permitted] and neurotoxicity [Grade 1 or 2 permitted])

6) Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1

7) Life expectancy of ≥ 3 months, in the opinion of the Investigator

8) Adequate organ function defined as follows:

   a) Hematologic: Platelets ≥ 100 x 10^9/L; Hemoglobin ≥ 9.0 g/dL; ANC ≥ 1.5 x 10^9/L (without platelet transfusion or any growth factors within previous 7 days of the hematologic laboratory values obtained at screening visit)

   b) Hepatic: Aspartate transaminase (AST) / Alanine transaminase (ALT) ≤ 2.5 x upper limit of normal (ULN) (if liver metastases are present, ≤ 5 x ULN); total or conjugated bilirubin ≤ 1.5 x ULN

   c) Renal: Serum Creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 60 mL/min as calculated by the Cockroft-Gault method

9) Coagulation: International Normalized Ratio (INR) ≤ 1.2

10) Male subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 7 and refrain from sperm donation for at least 90 days

11) Able and willing to provide written informed consent to participate in the study

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1) History or evidence of clinically significant disorder, condition, or disease that, in the opinion of the Investigator or Medical Monitor would pose a risk to subject safety or interfere with the study evaluations, procedures, or completion

2) Known brain metastasis or leptomeningeal disease

3) Uncontrolled intercurrent illness including, but not limited to, active uncontrolled infection, active or chronic bleeding event within 28 days prior to first dose of study drug, uncontrolled cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements as judged by treating physician

4) History of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the past 12 months, cerebral vascular accident and brain arteriovenous malformation are excluded from combination therapy with enzalutamide.

5) Myocardial infarction, symptomatic congestive heart failure (New York Heart Association Classification > Class II), unstable angina, or serious uncontrolled cardiac arrhythmia within the last 6 months of Cycle 1 Day 1

6) Major surgery, defined as any surgical procedure that involves general anesthesia and a significant incision (ie, larger than what is required for placement of central venous access, percutaneous feeding tube, or biopsy) within 28 days of the first dose of study drug

7) Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of GS-5829, including any unresolved nausea, vomiting, or diarrhea that is Common Terminology Criteria for Adverse Events (CTCAE) Grade > 1

8) Minor surgical procedure(s) within 7 days of enrollment, or not yet recovered from prior surgery (placement of central venous access device, fine needle aspiration, or endoscopic biliary stent ≥ 1 day before enrollment is acceptable)

9) Anti-tumor therapy (chemotherapy, antibody therapy, molecular targeted therapy) within 21 days or 5 half-lives, whichever is longer, of study drug dosing (6 weeks for nitrosoureas, mitomycin C, or molecular agents with $t_{1/2}$ > 10 days); concurrent use of an LHRH agonist is permitted for all subjects and ongoing enzalutamide is required in Group 3.

10) History of a concurrent or second malignancy, except for: adequately treated local basal cell or squamous cell carcinoma of the skin; cervical carcinoma in situ; superficial bladder cancer; breast carcinoma in situ; adequately treated Stage 1 or 2 cancer currently in complete remission; any other cancer that has been in complete remission for ≥ 5 years

11) History of long QT syndrome or whose corrected QT interval (QTc) measured (Fridericia method) at screening is prolonged (> 450 ms). Subjects who screen fail due to this criterion are not eligible to be re-screened

12) Prior exposure to bromodomain (BET) inhibitors

13) Clinically significant bleeding within 28 days of Cycle 1 Day 1

14) Known human immunodeficiency virus (HIV) infection

15) HBsAg positive

16) HCV antibody positive

17) Use of moderate/strong cytochrome P450 (CYP)3A4 inhibitors or moderate/strong CYP3A4 inducers within 2 weeks prior to the first dose of study drug (with the exception of enzalutamide in the combination arms)

18) Evidence of bleeding diathesis

19) History of hemoptysis of ≥ 2.5 mL/1 teaspoon within 6 months of Cycle 1 Day 1

20) History of high grade esophageal or gastric varices

21) Anticoagulation/antiplatelet therapy within 7 days of Cycle 1 Day 1, including low molecular weight heparin, or warfarin.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Enrollment

This is an open-label study. All baseline tests and procedures must be completed prior to the administration of the first dose of study drug on Day 1. It is the responsibility of the Investigator to ensure that subjects are eligible for the study prior to enrollment. A subject will be considered enrolled once he or she has started treatment.

5.2. Description and Handling of GS-5829 and Enzalutamide

5.2.1. Formulation

GS-5829 will be supplied as GS-5829-02 (phosphate salt form of GS-5829) and is available as round, plain-faced tablets containing 1, 5, or 10 mg GS-5829. The 1, and 10 mg tablets are film-coated gray and the 5 mg tablets are film-coated orange.

In addition to the active ingredient, 1, and 10 mg tablets contain the following commonly used excipients: microcrystalline cellulose, lactose monohydrate, crospovidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide black.

In addition to the active ingredient, 5 mg GS-5829 tablets contain the following commonly used excipients: microcrystalline cellulose, lactose monohydrate, crospovidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, FD&C yellow #6, and iron oxide yellow. Refer to the enzalutamide package insert Appendix 9 for the enzalutamide formulation.

5.2.2. Packaging and Labeling

GS-5829 tablets are in white, high density polyethylene bottles with desiccant and polyester packing material. Each bottle contains 30 tablets and is enclosed with a white, continuous thread, child-resistant screw cap with an induction-sealed, aluminum-faced liner.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations.

Refer to Appendix 9 for the enzalutamide packaging information.

5.2.3. Storage and Handling

GS-5829 tablets should be stored at controlled room temperature until required for administration. Controlled room temperature is defined as 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label.

Until dispensed to the subjects, all bottles of study drug should be stored in a securely locked area, accessible only to authorized site personnel. The study center will be required to maintain a log of daily temperature readings in the storage area for the duration of the study. To ensure the stability and proper identification, the drug product should not be stored in a container other than the container in which it was supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure through inhalation when handling GS-5829 tablets.

Refer to Appendix 9 for enzalutamide storage and handling information.

5.3. Dosage and Administration of GS-5829 and Enzalutamide

GS-5829 tablets will be provided by Gilead Sciences, Inc. and will be taken orally. Initiation of treatment with the study drug will take place after enrollment and cohort assignment. Subjects will take their dose of study drug at approximately 24-hour intervals. To reduce inter-subject variability on efficacy and safety, subjects will be instructed to take GS-5829 approximately 1 hour before or 2 hours after a meal, unless otherwise specified by protocol. Grapefruit juice is prohibited while on study drug. In one or more monotherapy dose levels or in the monotherapy expansion (Group 1), on Day 1 of Cycle 2, approximately 10 subjects may be asked to administer GS-5829 in fed state with a standardized meal (~500 to 600 calories and ~30% of calories from fat). If evaluation of food effect cannot be performed on Cycle 2, Day 1, it may be performed at a visit after Cycle 2, Day 1 (where subject has taken at least 7 consecutive days of GS-5829), if necessary.

XTANDI® (enzalutamide) will be supplied as 40 mg capsules for oral administration. Subjects assigned to receive enzalutamide in combination with GS-5829 in this study will orally self-administer 4 capsules of enzalutamide (160 mg total daily dose) once daily at approximately 24-hour intervals beginning on Study Day 1 and GS-5829 will start, at the assigned dose, 14 days (± 3 day window) later on Cycle 1 Day 1. Subjects enrolled into Group 3 should be on at least 12 weeks of continuous enzalutamide treatment prior to starting Cycle 1 Day 1. Capsules should be swallowed whole and may be taken with or without food. Refer to Appendix 9 for further details.

If the subject misses a dose, he should be instructed to take the study drug as soon as he remembers, unless more than 8 hours have elapsed since the scheduled time of the missed dose. In this case, the subject should be instructed to wait and take the next dose at the regularly scheduled time. Subjects should not take more than 1 dose of study drug at a time.

If a subject vomits within 5 minutes of dosing and the tablet is visible, the subject should be instructed to re-dose. If a subject vomits more than 5 minutes after dosing or if the tablet is not visible, the subject should be instructed to wait and take the next dose at the regularly scheduled time.

5.3.1. Dose Adjustment of GS-5829

In the event of a Grade 3 or 4 hematologic or any non-hematologic toxicity that the investigator considers related to GS-5829 and is clinically significant, GS-5289 will be interrupted for a maximum of 28 days until the toxicity resolves to ≤ Grade 1 or returns to baseline level. Following resolution of the toxicity or the toxicity returns to baseline level, treatment may be restarted at a reduced dose as per Table 5-1. If the toxicity does not resolve or return to baseline, study drug(s) GS-5829 and enzalutamide will be permanently discontinued and the subject will return for an End of Treatment and a 30 day Safety Follow-Up visit.

No dose reduction of GS-5829 below 1.0 mg is allowed.

Table 5-1. Dose Reduction of GS-5829

Dose at time of toxicity (mg)	Restarting dose level (mg)
6	5
5	4
4	3
3	2
2	1.0

If a subject develops a recurrence of the same Grade 3 or 4 hematologic or any non-hematologic toxicity that the investigator considers related to GS-5829 and is clinically significant at the lower dose, then the subject should be permanently discontinued from all study drug(s).

After the 28 day DLT period in the Dose Escalation Phase and at any time in the Dose Expansion Phase, in the event of a Grade 2 hematologic or non-hematologic toxicity the investigator considers related to GS-5829, GS-5829 may be interrupted per the investigator's discretion for a maximum of 28 days and resumed at either the same or a lower dose per Table 5-1.

Subjects who dose interrupt for a non-drug related toxicity for up to 28 days, and are deemed by the investigator to be clinically benefiting from GS-5829 prior to dose interruption, may resume GS-5829 treatment. Non-drug related dose interruptions for longer than 28 days in subjects who do not have disease progression may be considered for resumption of GS-5829 after discussion with the Medical Monitor.

5.3.2. Dose Adjustment in Group 2: Combination of Enzalutamide and GS-5829

Due to the CYP3A4 interaction of the two study drugs, discontinuing enzalutamide for more than 2 weeks may lead to a clinically significant increase in GS-5829 exposure. Therefore, in the event of any hematologic or non-hematologic toxicity in the combination arm, even if the toxicity is attributed by the investigator only to enzalutamide, both enzalutamide and GS-5829 may need to be interrupted or discontinued according to Table 5-2.

Table 5-2. Dose Reduction in Group 2: Combination of Enzalutamide and GS-5829

	Considered related to enzalutamide	Considered related to GS-5829	Considered potentially related to both enzalutamide and GS-5829 or unknown relationship
Grade 4 toxicity	Interrupt dosing of enzalutamide for at least 7 days and not longer than 17 days until symptoms improve to ≤ Grade 2, then resume at 120 mg. If subject is already at 120 mg, or it takes longer than 17 days to improve ≤ Grade 2, then permanently discontinue both enzalutamide and GS-5829.	Permanently discontinue both enzalutamide and GS-5829	Permanently discontinue both enzalutamide and GS-5829
Grade 3 toxicity	Interrupt dosing of enzalutamide for at least 7 days and a maximum of 17 days until symptoms improve to ≤ Grade 2, then resume at 120 mg. If subject is already at 120 mg, or it takes longer than 17 days to improve ≤ Grade 2, then permanently discontinue both enzalutamide and GS-5829.	Interrupt GS-5289 for a maximum of 28 days until the toxicity resolves to ≤ Grade 1 or returns to baseline level. Following resolution of the toxicity or the toxicity returns to baseline level, treatment may be restarted at a reduced dose as per Table 5-1. Enzalutamide dosing does not need to be interrupted or dose reduced.	Interrupt both enzalutamide and GS-5829 for at least 7 days and a maximum of 17 days until symptoms improve to ≤ Grade 1 or return to baseline level at which time subjects may resume enzalutamide at either 120 mg or 160 mg and resume GS-5829 at a reduced dose per Table 5-1. If a subject is already at 120 mg of enzalutamide, they must discontinue.
Intolerable Grade 2 Toxicity	Interrupt dosing a maximum of 17 days until symptoms improve to ≤ Grade 2, then resume at either 160 mg or 120 mg. If subject is already at 120 mg, or it takes longer than 17 days to improve ≤ to Grade 1 then permanently discontinue.	Interrupt GS-5829 for a maximum of 28 days until the toxicity resolves to ≤ Grade 1 or returns to baseline level. Following resolution of the toxicity or the toxicity returns to baseline level, treatment may be restarted at either the same dose or a reduced dose as per Table 5-1.	Interrupt both enzalutamide and GS-5829 for a maximum of 17 days until symptoms improve to ≤ Grade 1 or return to baseline level, at which time subjects may resume enzalutamide at either 120 mg or 160 mg and GS-5829 at the same dose or a reduced dose per Table 5-1. A subject may not dose reduce enzalutamide to less than 120 mg once daily

If a subject develops a recurrence of the same Grade 3 or 4 hematologic or non-hematologic toxicity that the investigator considers related to GS-5829 and is clinically significant at the lower dose of GS-5829, then the subject should be permanently discontinued from all study drug(s).

Subjects whose dose of enzalutamide is interrupted for a non-drug related toxicity for up to 17 days, or whose dose of GS-5829 is interrupted for up to 28 days and are deemed by the investigator to be clinically benefiting from the combination treatment prior to dose interruption, may resume combination treatment. Non-drug related dose interruptions for longer than 17 days (enzalutamide) or 28 (GS-5829) days in patients who do not have disease progression may be considered for resumption of study drugs after discussion with the Medical Monitor.

5.4. Prior and Concomitant Medications

Subjects who have not had a bilateral orchiectomy must be receiving androgen deprivation therapy with a GnRH analogue prior to enrollment and must continue on GnRH-analogue therapy for the duration of the study.

Abiraterone and chemotherapy are prohibited while on study drug.

Phase 1b Monotherapy: Subjects must have previously received abiraterone and/or enzalutamide.

Phase 2 Monotherapy Dose Expansion (Group 1): Subjects must have previously received enzalutamide. Subjects must not have previously received chemotherapy for mCRPC.

Phase 1b Combination Therapy Dose Escalation and Phase 2 Combination Dose Expansion (Group 2): Subjects must have previously received abiraterone, but must not have previously received enzalutamide or chemotherapy for mCRPC.

Phase 2 Combination Therapy Dose Expansion (Group 3): Subjects must have previously received enzalutamide and have been on continuous enzalutamide for the 12 weeks prior to Cycle 1, Day 1. Subjects must not have previously received chemotherapy for mCRPC. Subjects must not have previously received chemotherapy for mCRPC.

In vitro data indicate GS-5829 is a substrate of CYP3A4. Co-administration of CYP3A4 inhibitors may increase GS-5829 exposure. As such, co-administration of moderate and strong CYP3A4 inhibitors with study drug is prohibited in this study.

Co-administration of CYP3A4 inducers may decrease GS-5829 exposure. As such, moderate and potent CYP3A4 inducers are prohibited while subject is on study drug and ≥ 2 weeks prior to study drug administration except for subjects in Group 2 who may receive enzalutamide as described in the protocol. Examples of moderate and strong CYP3A4 inhibitors and inducers are provided in the table below.

Table 5-3. Examples of Concomitant Medications Prohibited in this Study

	Moderate	Strong
CYP3A4 Inhibitor	Aprepitant, ciprofloxacin, crizotinib, diltiazem, erythromycin, fluconazole, imatinib, verapamil	Clarithromycin, conivaptan, grapefruit juice, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, voriconazole
CYP3A4 Inducer	bosentan, modafinil, nafcillin	carbamazepine, phenytoin, rifampin, St. John's wort

Toxicology data from dogs demonstrated minimal to moderate gastrointestinal, pulmonary, muscular and intracardiac bleeding. The mechanism for the bleeding is not understood. Anticoagulant medications are prohibited on study; this includes vitamin K antagonists (eg, warfarin), low molecular weight heparin, Factor Xa inhibitors, thrombin inhibitors and aspirin. If anticoagulation therapy needs to be initiated while on study treatment, the Investigator should consult with the Medical Monitor to determine if study treatment should be discontinued.

For subjects receiving enzalutamide, CYP3A4, CYP2C9, and CYP2C19 substrates with a narrow therapeutic index should be avoided with the exception of study drug, as enzalutamide may decrease the plasma exposures of these drugs. Additional INR monitoring should be conducted in subjects receiving warfarin and enzalutamide. Strong or moderate CYP3A4 or CYP2C8 inducers and strong CYP2C8 inhibitors should be avoided. Refer to the prescribing information for XTANDI® for more information regarding potential drug interactions.

5.5. Accountability for GS-5829 and Enzalutamide

The investigator is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgement of receipt of each shipment of study drug (quantity and condition). All used and unused study drug dispensed to subjects must be returned to the site.

Accountability records will be provided to each study site to:

- Record the date received and quantity of study drug kits
- Record the date, subject number, subject initials, the study drug kit number dispensed
- Record the date, quantity of used and unused study drug returned, along with the initials of the person recording the information.

5.5.1. GS-5829 and Enzalutamide Return or Disposal

Study drug should be retrieved from each subject at the end of each dispensing interval. The quantity of study drug and the date returned by the subject should be recorded in the study drug accountability records. All study drug returned by the subject should be retained for review by the study site monitor prior to destruction.

Please see Section 9.1.7 for more information.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and Appendix 3 and described in the text below. Additional information is provided in the study manual.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

Safety and tolerability assessments will include regular monitoring of AEs, changes from baseline in laboratory variables, physical examinations, vital signs, and special safety assessments like ECGs.

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all serious adverse events (SAEs), as well as any non-serious AEs related to protocol-mandated procedures on the AEs electronic case report form (eCRF). All other untoward medical occurrences observed during the Screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7 for additional details.

6.1. Subject Enrollment and Treatment Assignment

Subjects will be assigned a unique screening number at the time of consent. Subject eligibility will be established at the conclusion of the screening evaluations. Once eligibility is confirmed, subjects will be assigned a unique subject number. The screening number and/or subject ID will be assigned for that individual subject by Gilead. The investigator will submit an enrollment form to Gilead for review and approval prior to enrollment of the subject.

It is the responsibility of the investigator to ensure that each subject is eligible for the study before start of treatment.

6.2. Study Procedure Descriptions

The sections below describe the individual study procedures outlined in the subsequent sections and the Study Procedures Table. During the treatment period, all visits may be performed within the specified window for that study visit.

6.2.1. Informed Consent

All subjects must sign and date the most recent IRB/IEC-approved informed consent form before any study procedures are performed. CCI

[redacted]

Subjects who screen fail must re-sign the informed consent, in the event any screening procedures will be performed outside of the 28-day screening window from the time of the first informed consent.

6.2.2. Medical History

A complete medical history will be obtained by the Investigator or qualified designee prior to enrollment and recorded on the eCRF.

6.2.3. Prior and Concomitant Medications

At Screening, all medications taken up to 30 days prior to the screening visit will be recorded on the eCRF. In addition, supportive therapies given during the course of the study (e.g. blood transfusion, growth factor) should be collected and recorded on the eCRF.

At each study visit, the site will capture any and all medications taken by the subject since the last visit or during the visit (as applicable). Concomitant medications include prescription and non-prescription medications, pre-infusion medications (e.g. anti-emetics), and vitamins and minerals.

6.2.4. Physical Examination

The Investigator or qualified designee will perform a complete physical examination at Screening and at the End of Treatment visit. Pre-dose abnormal findings will be reported on the medical history page of the eCRF. Any changes from the pre-dose baseline physical examination that represent a clinically significant deterioration will be documented on the AE page of the eCRF.

Weight (without shoes) should be measured with each physical examination.

Height (without shoes) should be measured at Screening only.

Beginning at C1D1, a modified physical examination will be performed to monitor for any changes, and will also include weight and assessment of disease-related clinical signs and symptoms.

6.2.5. Vital Signs

Vital signs will include blood pressure, respiratory rate, pulse, oxygen saturation and temperature. All measurements will be recorded on the appropriate eCRF page with appropriate source documentation. Any abnormal measurements may be repeated and reported as AEs if appropriate. All measures of blood pressure will be performed using standard sphygmomanometry. Measurements of blood pressure should be taken per institutional guidelines.

6.2.6. Electrocardiogram

Triplicate 12-lead ECGs reporting ventricular rate, PR, QRS, QT, and QTc intervals will be obtained at the applicable study visits and transferred to a central vendor for storage. 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 (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.

The Investigator or qualified designee will review all ECGs. The ECG tracings will be maintained in the source documentation of each subject and the appropriate data reported on the eCRF.

6.2.7. ECOG Performance Status

The Eastern Cooperative Oncology Group (ECOG) Performance Status is an investigator assessment of the impact of the disease on the subject's activities of daily living. ECOG will be scored using the scale index in Appendix 8.

6.2.8. Adverse Events

Subjects will be assessed for adverse events (AEs) per guidelines in the National Cancer Institute (NCI) CTCAE (version 4.03) at the time points outlined in Appendix 2 and Appendix 3. Any AEs reported after informed consent is obtained and throughout the study will be recorded on the eCRF with appropriate source documentation. The subject will be assessed for AEs approximately 30 days after the last dose of study drug. Please refer to Appendix 6 for CTCAE grading criteria.

Please refer to Section 7 for additional information on AE reporting.

6.2.9. Disease Assessments

6.2.9.1. Bone Scans

Subjects will undergo radionuclide bone scan at Screening [within 8 weeks before Cycle 1 Day 1 (or Study Day 1 if in the combination therapy) if the scan was performed as part of standard medical practice] and every 12 weeks during the treatment period. Scans at the End of Treatment visit are not necessary if the prior scan was performed within 4 weeks prior to the EOT visit date.

6.2.9.2. CT or MRI

Subjects will be assessed by CT scan with contrast (or MRI, if unable to tolerate CT contrast) of the chest, abdomen and pelvis to document metastatic disease, identify target lesions and to assess response as per PCWG2 guidelines.

In subjects who cannot tolerate iodinated contrast, a CT of the lung without contrast and MRI of the abdomen should be performed. Imaging by CT scan (with contrast) or MRI or applicable scan will be performed at Screening (within 8 weeks before Cycle 1 Day 1 if the scan was performed as part of standard medical practice) and every 12 weeks during the treatment period regardless of cycle number or dose interruption. During the treatment, scans may be performed at time points other than 12 weeks, as clinically indicated, to assess tumor progression.

Tumor burden will be characterized at baseline and subsequent response assessments will be carried out according to the PCWG2 Criteria. The same radiographic procedure and specification (eg, the same contrast agent, slice thickness, etc.) used to define measurable lesions at baseline must be used throughout the study for each subject.

Please refer to Appendix 5 for additional information on PCWG2 study progression criteria.

6.2.10. Laboratory Assessments

Screening laboratory samples should be obtained within 28 days prior to Study Day 1/Cycle 1 Day 1 dose (GS-5829). Local laboratory CBC assessments may be collected as required for dose adjustments throughout the study. Local laboratory assessments resulting in a dose change will be reported on the eCRF.

The central laboratory will be responsible for chemistry, hematology, coagulation, and urinalysis testing per Table 6-1 and storage of other study samples. If central laboratory results are not available, local laboratories may be used for dosing decision. Other tests listed in Table 6-1 will be performed by Gilead or a designated laboratory. Any sample collected per the Schedule of Assessments (Appendix 2 and Appendix 3) may be analyzed for any tests necessary to ensure subject safety. Specific instructions for processing, labeling, and shipping samples will be provided in the central laboratory manual. The date and time of sample collection will be recorded in the subject's source documentation and reported to the central laboratory.

The date and time of previous GS-5829 dose will be recorded in the subject's source documentation on days where PK is collected. White blood cell (WBC) differentials will be reported as absolute counts. All laboratory tests must be reviewed for clinical significance by the Investigator or qualified designee. Eligibility will be based on central laboratory assessments and will be collected within 7 days of Study Day 1/C1D1.

Study Day 1 and/or Cycle 1 Day 1 pre-dose samples may be drawn up to 2 days prior to the visit.

The analytes listed in Table 6-1 will be tested.

Table 6-1. Analytes

Serum Chemistry	Hematology	Other
Sodium Potassium Chloride Glucose BUN Creatinine Creatinine Clearance[a] ALT AST Alkaline phosphatase Total bilirubin[b] Total protein Albumin Calcium Magnesium Phosphate AAG	White Blood Cell (WBC) Count Hemoglobin Hematocrit Platelet Count Neutrophils (ANC) Lymphocytes Monocytes Basophils Eosinophils	GS-5829 concentration Concentrations of GS-5829 metabolite(s), enzalutamide and enzalutamide metabolites, as applicable, may be determined Serum and Plasma CCI Hepatitis B surface antigen Hepatitis C antibody PSA Total testosterone
	Coagulation	
	PT/INR aPTT Fibrinogen Factor VII Fibrinogen Depredation Products	
	Urine	
	Urinalysis	

a Cockcroft-Gault using Actual Body Weight: CRCL (mL/min) = [(140-age(years)) * weight(kg)] / (serum creatinine (mg/dL)*72)
b Includes direct bilirubin
c At Screening only

6.2.11. Pharmacokinetic & Pharmacodynamic Samples

PK samples will be collected at the timepoints listed below. GS-5829 plasma concentrations will be determined using a validated assay. Plasma concentrations of GS-5829 metabolites and/or enzalutamide and/or enzalutamide metabolites may be determined. Plasma protein binding of analytes may be evaluated. PD samples may be modified based on the emerging data.

Phase 1b Dose Escalation:

Monotherapy Dose Escalation

PK and PD samples for GS-5829 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 may 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 after GS-5829 has been administered in the fed state. If evaluation of food effect cannot be performed on Cycle 2, Day 1, it may be performed at a visit after Cycle 2, Day 1, if necessary.

Dose Escalation with Enzalutamide

PK and PD 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.

Phase 2 Dose Expansion:

Group 1

PK and PD samples will be collected on Day 8 of Cycle 1 at pre-dose and 1, 2, 4, and 6 hours post-dose. Sparse PK and PD 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. PK samples may be collected on Day 1 of Cycle 2 at pre-dose and 1, 2, 4, and 6 hours post-dose after GS-5829 has been administered in the fed state. If evaluation of food effect cannot be performed on Cycle 2, Day 1, it may be performed at a visit after Cycle 2, Day 1 if necessary.

Group 2

PK and PD samples will be collected on Cycle 2, Day 1 at pre-dose and 1, 2, 4, and 6 hours post-dose. Sparse PK and PD 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 3 through 6.

Group 3

PK and PD samples will be collected on Cycle 2, Day 1 at pre-dose and 1, 2, 4, and 6 hours post-dose. Sparse PK and PD 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 3 through 6.

6.3. Biomarker Testing

6.3.1. Biomarker Samples to Address the Study Objectives

Biological specimens detailed below will be collected in this study and will be used to evaluate the association of exploratory systemic and/or tissue specific biomarkers with study drug response, including efficacy and/or adverse events and to increase knowledge and understanding of the biology of disease and/or the validation of a companion diagnostic for GS-5829. The specific analyses will include, but will not be limited to, the biomarkers and assays listed below. Since biomarker science is a rapidly evolving area of investigation, and adverse events in particular are difficult to predict, it is not possible to specify prospectively all tests that will be done on the specimens provided. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests relevant to the study objectives based upon the growing state of art knowledge.

Whole blood, plasma and serum biomarkers will be collected in this study as detailed in Section 6.3.1.2 and will be used to evaluate the association of exploratory systemic and/or tissue specific biomarkers with study drug response, including efficacy and/or AEs and to increase knowledge and understanding of the biology of prostate cancer or related diseases.

Biomarker specimens will be collected from all subjects. In addition, sampling time points may be eliminated based upon emerging data.

The biomarker samples will be destroyed no later than 10 years after the end of study CCI [redacted]

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

6.3.1.1. Archival Tumor Tissue

Paraffin embedded blocks from archival tumor tissue or freshly cut unstained slides will be requested for all subjects who have tissue available. This is not an optional part of the study and samples should be collected from all participating subjects with available tissue. Efforts to acquire a tissue sample should begin on Day 1. The samples will be used to evaluate the association of exploratory biomarkers with study drug response and may include protein, somatic (tumor-specific) DNA and gene expression analysis.

6.3.1.2. Serum, Plasma and Whole Blood Biomarkers

Whole blood for PD biomarkers will be collected at the time points listed in Appendix 2 and Appendix 3. Serum collected for PSA will also be assessed. Whole blood and plasma for Circulating Tumor Cells (CTCs), exosome, circulating proteins and circulating tumor DNA may also be collected to evaluate for the presence of AR-V7 variant and for other exploratory biomarker analysis. In addition, any remaining plasma samples obtained to measure GS-5829 levels may also be used to measure the exploratory PD biomarkers described above.

CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

CCI [redacted]

6.4. Pretreatment Assessments

6.4.1. Screening Visit

The screening date will be defined as the date the subject signs the informed consent. Subjects will be screened within 28 days of enrollment to determine eligibility for participation in the study. Screening laboratory results for chemistry, hematology, coagulation and urinalysis should be obtained from central laboratory. Subjects must meet all eligibility criteria in order to be enrolled. Subjects who do not enroll within the 28 day screening window will be screen failed. Re-screening is allowed (see Section 6.2.1).

The following will be performed and documented during Screening:

- Obtain written informed consent
- Obtain medical history, including prior/concomitant medication review
- Complete physical examination including body weight and height
- Vital Signs
- Triplicate 12-lead ECG
- ECOG Performance Status

- Laboratory assessments
  - Chemistry
  - Complete blood count (CBC) with differential
  - Total testosterone
  - Coagulation
  - Urinalysis
- Bone Scan
- CT scan with contrast or MRI (scans taken as part of standard medical practice up to 8 weeks prior to C1D1 are acceptable)
- [redacted]
- Record any adverse events (occurring after signing of the consent form)
- Complete subject/visit information on enrollment form

Subjects meeting all of the inclusion criteria and none of the exclusion criteria, as approved by Gilead, will return to the clinic within 28 days after screening for enrollment into the study.

From the time of obtaining informed consent through the Cycle 1 Day 1 dose, record all serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.4.2. Re-Screening Criteria

Subjects who do not enroll within 28 days of screening will be screen failed.

Re-screening may be allowed. Subjects who are re-screened will be re-consented with new screening number, and will repeat the screening assessments. Gilead is to be informed prior to a subject re-screening.

6.5. Treatment Assessments

Each on-study visit will be scheduled relative to C1D1. Visits will follow the schedule of assessments in Appendix 2 and Appendix 3.

6.5.1. Study Day 1

Only subjects enrolled into a combination therapy and who have met all eligibility criteria will return to the clinic on Study Day 1 to perform baseline assessments.

The following baseline assessments will be conducted prior to the first dose of enzalutamide:

- Physical examination, including weight
- Vital signs, within 15 minutes prior to the enzalutamide dose
- ECOG performance status
- Laboratory assessments and blood sampling (refer to Table 6-1)
  - Chemistry
  - CBC with differential
  - Urinalysis
  - Coagulation
- Record any adverse events
- Concomitant medications review
- IP accountability and dispensing of Enzalutamide and Dosing Diary.

6.5.2. Baseline Visit / Cycle 1 Day 1 (C1D1)

Subjects in a monotherapy treatment who have met all eligibility criteria will return to the clinic on C1D1 to perform baseline assessments. C1D1 is defined as the date of the first dose of GS-5829, and may occur within 3 days following enrollment.

The following baseline assessments will be conducted prior to the first dose of GS-5829:

- Physical examination, including weight
- Vital signs, within 15 minutes prior to the GS-5829 dose
- Triplicate 12-lead ECG
- ECOG performance status

- Laboratory assessments and blood sampling (refer to Table 6-1)
  - Chemistry
  - CBC with differential
  - Coagulation
  - CCI [redacted]
  - Request archival tumor tissue specimen: Efforts to acquire tissue sample should begin on C1D1 for all subjects
  - Urinalysis
  - GS-5829 PK (see Appendix 2 and Appendix 3)
  - Pharmacodynamics (see Appendix 2 and Appendix 3)
  - PSA
- Record any adverse events
- Concomitant medications review
- IP accountability and dispensing of IP and Dosing Diary.

The site will train the subject on the dosing schedule for the IP and the Dosing Diary at the time of dispensing.

The following assessments will be conducted after the first dose of GS-5829:

- Triplicate ECG (see Appendix 2 and Appendix 3)
- Vital signs (2 and 4 hours post GS-5829 dose [±15 minutes])
- GS-5829 PK (see Appendix 2 and Appendix 3)
- Pharmacodynamics (see Appendix 2 and Appendix 3)

6.5.3. Cycle 1 Day 8, Day 15 and Day 22 (C1D8, C1D15, and C1D22)

The following assessments will be conducted:

- Physical exam, including weight
- Vital signs

- ECOG Performance Status (Days 8 and 22 only)
- Laboratory assessments and blood sampling (refer to Table 6-1, Appendix 2 and Appendix 3)
  - Chemistry
  - CBC with differential
  - Coagulation (D8 only)
  - GS-5829 PK (see Appendix 2 and Appendix 3)
  - Pharmacodynamics (C1D8 and C1D15)
  - Urinalysis (C1D8 only)
- Triplicate 12-lead ECG (see Appendix 2 and Appendix 3)
- Record any adverse events
- Concomitant medications review

6.5.4. Cycle 2 Day 1 (C2D1) and Day 1 of Subsequent Cycles

On-study visits during the treatment period may be completed within a window of ± 7 days. The following procedures will be completed on Day 1 of each subsequent cycle:

- Physical examination, including weight
- Vital signs
- Triplicate 12-lead ECG
- ECOG Performance Status
- Laboratory assessments and blood sampling (refer to Table 6-1)
  - Chemistry
  - CBC with differential
  - GS-5829 PK (see Appendix 2 and Appendix 3)
  - Pharmacodynamics (see Appendix 2 and Appendix 3)
  - Urinalysis
  - CCI [redacted]
  - PSA

- Record any adverse events
- Concomitant medications review
- IP accountability and dispensing of IP and Dosing Diary

6.5.5. End of Treatment (EOT) Visit

The following procedures will be conducted when a subject discontinues GS-5829, with a window of ± 7 days, and prior to initiating a new anti-cancer regimen:

- Complete Physical examination, including weight
- Vital signs (pre-dose only)
- Triplicate 12-lead ECG
- ECOG performance status
- Laboratory assessments and blood sampling
  - Chemistry
  - CBC with differential
  - Coagulation
  - Urinalysis
  - PSA
  - CCI [redacted]
- Bone scan (not necessary if restaging scan was performed within the prior 4 weeks)
- CT with contrast or MRI (not necessary if restaging scan was performed within the prior 4 weeks)
- Record any adverse events
- Concomitant medications review
- IP/Dosing Diary accountability

6.6. Post-Treatment 30-Day Safety Follow-up Visit

All subjects will complete the 30-Day Safety Follow-Up visit. 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.

The following procedures will be completed 30 days after the subject's last dose of IP, within a window of ± 7 days:

- Physical examination, including weight
- Vital signs
- ECOG performance status
- Laboratory assessments
  - Chemistry
  - CBC with differential
  - Urinalysis
- Concomitant medications review
- Record any adverse events (30 days post last dose of IP)

For subjects who come off study treatment for reasons other than disease progression, the Investigator should also obtain information on the subject's post-study anti-cancer therapies, surgeries, and date of definitive disease progression (if known).

6.7. Long Term Survival Follow-Up

Phase 2 Dose Expansion subjects will participate in long term survival follow-up. These subjects will be contacted via phone call every 3 months for determination of long term survival status and record of any other anti-cancer therapy for up to 2 years after the last dose of IP. For subjects who discontinued the study for reasons other than disease progression, the Investigator should obtain information on the subject's post-study anti-cancer therapies, surgeries, and date of definitive disease progression (if known).

Subjects who are alive at the time the sponsor has made the determination the study will be ended will receive a final follow-up phone call to assess survival status and communicate the sponsor's decision. These subjects will be censored on the date the subject was last contacted.

The investigator will make every effort to contact the subject or a close relative or caretaker by phone to collect survival information. The investigator should show due diligence by documenting in the source documents steps taken to contact the subject i.e., dates of phone calls, registered letters, etc.

6.8. Unscheduled Visits

Unscheduled procedures may occur at any time during the study. Vital Signs, ECOG, 12-lead ECG, bone scan and CT or MRI, may be conducted at these visits and recorded on the applicable eCRFs.

6.9. Criteria for Discontinuation of Study Treatment

See Section 3.4 for discontinuation criteria.

6.10. Post Study Care

If a subject has discontinued the study treatment due to toxicity, he/she should not have withdrawal of consent recorded as the reason for discontinuation. Instead, the reason for discontinuation must be recorded as due to adverse event.

Every attempt should be made to keep the subject in the study and continue collecting CT or MRI scans for tumor assessment at every 12 weeks until disease progression or initiation of systemic anti-tumor therapy other than treatment per protocol. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study. The subject will be asked to attend the post-treatment follow-up assessment visit above when discontinuing from the study treatment.

6.11. Replacement of Subjects

If a subject is withdrawn from the study for any reason other than a DLT prior to completion of the DLT assessment window, a replacement subject will be enrolled at the same dose level as the replaced subject. To be evaluable for the DLT observation, a subject must receive at least 21 doses of GS-5829, complete all safety procedures through Day 28, or experience a DLT prior to Day 28.

6.12. Protocol Deviations

Gilead's policy prohibits exemptions from protocol inclusion/exclusion criteria. In the event of a significant deviation related to gross non-compliance from the protocol or incidences that impose significant risk to subject safety, the investigator or designee must notify the sponsor and/or its designee immediately. The site will be required to document deviations in accordance with Gilead's procedures and in accordance with the site's procedures and processes.

6.13. End of Study

End of study for a subject is defined as the date of the last study-related procedure or the date of death for an on-study subject.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.6.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

A **serious adverse event** (SAE) or serious adverse drug reaction (SADR) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)

- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an AE in itself
- An SAE may occur even if the subject was not on study drug at the time of occurrence of the event. Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is a SAE
- "In-patient hospitalization" means the subject is formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department
- The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms

7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- **Yes**: There is reasonable possibility that the event may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.

- **Yes:** The AE occurred as a result of protocol procedures, (eg, venipuncture)

7.2.2. Assessment of Severity

The severity of AEs will be graded using the CTCAE, Version 4.03 (Appendix 6).

For each episode, the highest severity grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 7-1.

Table 7-1. Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the subject's overall health and well-being, does not interfere with the subject's usual function, and is not likely to require medical attention.
Grade 2	Moderate	Sign or symptom causes interference with usual activity or affect clinical status, and may require medical intervention.
Grade 3	Severe	Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow-up.
Grade 4	Life-threatening	Sign or symptom results in a potential threat to life.
Grade 5	Fatal	Sign or symptom results in death.

The distinction between the seriousness and the severity of an AE should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in Section 7.1.2.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

7.3.1. Requirements for Collection Prior to Study Drug Initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the eCRF: all SAEs and AEs related to protocol-mandated procedures.

7.3.2. Adverse Events

Following the initiation of study medication, all AEs (regardless of cause or relationship) until 30 days after last administration of study drug, must be reported to the eCRF database as instructed.

All AEs should be followed up until resolution or until the AE is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship that occur after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported in the eCRF database and to Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30 days of the last dose of study drug, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the 30-day period. However, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of study drug, he/she should promptly document and report the event to Gilead DSPH.

All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

7.3.4. Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper SAE reporting form and submit within 24 hours of the investigator's knowledge of the event to:

  Gilead DSPH: Fax: PPD
  Email: PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, SADRs, or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.4.1. Reporting of Adverse Events Relating to the Primary Endpoint and Other Anticipated Medical Events in the Study Population

Given the endpoints of the study, in order to maintain the integrity of the study, the following events that are assessed as unrelated to study drug will not be considered SAEs:

- Progression of underlying disease (mCRPC)

- Death related to progression of underlying disease (mCRPC)

Disease progression and death from disease progression should be reported as SAEs by the investigator only if it is assessed that the study drug caused or contributed to the disease progression (ie, by a means other than lack of effect). Unrelated disease progression should be captured on the eCRF.

7.5. Toxicity Management

Treatment-emergent toxicities will be noted by the Investigator and brought to the attention of the Gilead Sciences Medical Monitor or designee. Whether or not considered treatment-related, all subjects experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Grade 3 or 4 clinically significant laboratory abnormalities should be confirmed by repeat testing as soon as practical to do so, and preferably within 3 calendar days after receipt of the original test results. Any questions regarding toxicity management should be directed to the Gilead Sciences Medical Monitor or designee.

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of AEs associated with product complaints, and pregnancy reports regardless of an associated AE. Reports of adverse reactions in infants following exposure from breastfeeding, and reports of adverse reactions associated with product complaints and reports arising from occupational exposure are also considered special situation reports.

- A pregnancy report is used to report any pregnancy in female partners of male subjects on study

- Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer

- Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject

- Misuse is defined as any intentional or inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information

- An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s)

- Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must be reported and relevant information should be submitted to Gilead DSPH using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH.

Gilead DSPH contact information is as follows:

Fax: PPD
Email: PPD

Refer to Appendix 7 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.6.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study drug and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications do not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should be appropriately documented as a protocol deviation.

Refer to the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objectives of this study are:

Phase 1b Dose Escalation

- To characterize the safety and tolerability of GS-5829 as a single agent an in combination with enzalutamide in subjects with 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 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 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:

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, PFS and 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:

[redacted]

8.1.2. Primary Endpoint

Primary endpoints of this study are:

Phase 1b Dose Escalation:

The primary endpoint of this study is incidence of DLT as defined in Section 3.2.

Phase 2 Dose Expansion:

The primary endpoint is efficacy assessed as non-progression/progression rate at Week 24 according to PCWG2 Criteria.

8.1.3. Secondary Endpoint

Secondary endpoints of this study are:

Phase 1b Dose Escalation:

- Dose escalation subjects: PK parameters (C_{max}, C_{tau}, AUC_{last}, AUC_{tau}, and T_{max}) for GS-5829

Phase 1b Dose Escalation and Phase 2 Dose Expansion:

- PSA response: ≥ 30% decline in PSA from baseline at 12 weeks for Groups 1, 2 and 3
- Progression free survival (PFS) defined as the interval from first dose date of study drug to the earlier of the first documentation of definitive disease progression (assessed per PCWG2) or death from any cause.

Phase 2 Dose Expansion:

- Overall survival (OS) defined as the interval from first dose date of study drug to death from any cause.

8.1.4. Exploratory Endpoints

CCI [redacted]

[redacted]

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Full Analysis Set (FAS)

The FAS includes all subjects who receive ≥ 1 dose of study drug. This analysis set will be used for subject characteristics and efficacy endpoints.

8.2.1.2. Safety Analysis Set

The Safety Analysis Set for this study will be the same as FAS since this study is a non-randomized study. This analysis set will be used for safety endpoints, study treatment administration and post-study therapy.

8.2.1.3. DLT-Evaluable Analysis Set

The DLT-Evaluable Analysis Set includes all subjects in the Safety Analysis Set who complete all treatment and safety procedures through Day 29, or experienced a DLT prior to Day 29. Determination of the MTD will be in DLT-Evaluable Analysis Set.

8.2.1.4. Pharmacodynamic and Pharmacokinetic Analysis Sets

The PD and PK Analysis Sets consist of all subjects in the FAS who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

8.3. Data Handling Conventions

By-subject listings will be created for important variables from each eCRF module. Summary tables for continuous variables will contain the following statistics: N (number in population), n (number with data), mean, standard deviation (StD), 90% confidence intervals (CIs) on the mean, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 90% CIs on the percentage. Unless otherwise indicated, 90% CIs for binary variables will be calculated using the binomial distribution (exact method) and will be 2-sided. Data will be described and summarized by relevant dose level, analysis set, and time point. As appropriate, changes from baseline to each subsequent time point will be described and summarized by dose level. Similarly, as appropriate, the best change from baseline during the study will also be described and summarized by dose level. Graphical techniques (eg, waterfall plots, Kaplan-Meier curves, line plots) may be used when such methods are appropriate and informative.

The baseline value will be the last (most recent) pre-treatment value. Data from all sites will be pooled for all analyses. Analyses will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.

8.4. Demographic Data and Baseline Characteristics

Subject demographic and baseline characteristics will be listed and summarized by dose level for the Safety Analysis Set.

8.5. Efficacy Analysis

Estimates of progression/non-progression rate at Week 12 will be present with 90% exact CIs. PFS and OS will be visualized using Kaplan-Meier plot, and median survival time estimate will be listed.

8.6. Safety Analysis

All safety data collected on or after the date that study drug was first dispensed up to the date of last dose of study drug plus 30 days will be summarized by dose level. Data for the pretreatment will be included in data listings.

8.6.1. Extent of Exposure

Descriptive information will be provided by dose level regarding the number of doses of study drug prescribed, the total number of doses taken, the percent of expected doses taken, the number of days of study drug, and the number and timing of prescribed dose modification and interruptions.

Compliance will be described by dose level in terms of the proportion of study drug actually taken based on returned pill count relative to the amount that was dispensed (taking into account physician-prescribed modification and interruptions).

8.6.2. Adverse Events

All AEs will be listed. The focus of AE summarization will be on treatment-emergent AEs. A treatment-emergent AE is defined as an AE that occurs or worsens in the period from the first dose of study drug to 30 days after the last dose of study drug.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA http://www.meddramsso.com) with descriptions by System Organ Class (SOC), High-Level Group Term, High-Level Term, Preferred Term, and Lower-Level Term. The severity of AEs will be graded by the investigator according to the CTCAE, Version 4.03, whenever possible. If a CTCAE criterion does not exist for a specific type of AE, the grade corresponding to the appropriate adjective will be used by the investigator to describe the maximum intensity of the AE: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). The relationship of the AE to the IP will be categorized as related or unrelated.

TEAEs will be summarized by dose level. Summary tables will be presented to show the number of subjects reporting treatment-emergent AEs by severity grade and corresponding percentages. A subject who reports multiple treatment-emergent AEs within the same Preferred Term (or SOC) is counted only once for that Preferred Term (or SOC) using the worst severity grade. AE descriptions will be presented by decreasing frequency for a given SOC and Preferred Term. Separate listings and summaries will be prepared for the following types of treatment emergent AEs:

- Study-drug-related AEs
- AEs that are Grade ≥ 3 in severity
- AEs leading to study drug interruption and/or dose modification
- AEs leading to study drug discontinuation
- SAEs

8.6.3. Laboratory Evaluations

All laboratory data will be listed. Summaries of laboratory data will be based on observed data. The focus of laboratory data summarization will be on treatment-emergent laboratory abnormalities. A treatment-emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsens by ≥ 1 grade in the period from the first dose of study drug to 30 days after the last dose of study drug. If baseline data are missing, then any graded abnormality (ie, an abnormality that is Grade ≥ 1 in severity) will be considered treatment emergent.

Hematological, serum biochemistry, and urine data will be programmatically graded according to CTCAE severity grade, when applicable. For parameters for which a CTCAE scale does not exist, reference ranges from the central laboratory will be used to determine programmatically if

a laboratory parameter is below, within, or above the normal range for the subject's age, sex, etc. Hematological and serum biochemistry and their changes from baseline will be summarized by dose level, by visit. Summary tables will be presented for each relevant assay to show the number of subjects by CTCAE severity grade with corresponding percentages. For parameters for which a CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges will be summarized. Subjects will be characterized only once for a given assay, based on their worst severity grade observed during a period of interest (eg, during the study or from baseline to a particular visit).

Shift tables for hematology and serum biochemistry will also be presented by showing change in CTCAE severity grade from baseline to the worst grade post-baseline. For parameters for which a CTCAE scale does not exist, shift tables will be presented showing change in results from baseline to the worst grade post baseline. Separate listings and summaries will be prepared for laboratory abnormalities that are Grade ≥ 3 in severity.

8.7. Pharmacokinetic Analysis

The plasma concentration of GS-5829 will be summarized by nominal sampling time using descriptive statistics. PK parameters (C_{max}, C_{tau}, AUC_{last}, AUC_{tau}, and T_{max}, as applicable), will be listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, coefficient of variation (%) StD, median, minimum, and maximum). Plasma concentrations over time will be plotted in semi-logarithmic and linear formats as mean ± StD, and median (Q1, Q3) if applicable.

8.8. Biomarker Analysis

Descriptive statistics of baseline and change in biomarkers will be provided at each sampling time for all subjects, and by dose.

CCI [redacted]

8.9. Sample Size

The study will consist of up to 132 subjects. The sample size of the phase 1b part of the study will be determined based on the number of dose levels evaluated and the emerging GS-5829-related toxicities, and will be up to 72 subjects.

In patients who have progressed on abiraterone the expected PSA response rate to enzalutamide is approximately 10%-26% and median radiographic/clinical progression is 4.6 to 6.6 months {Azad et al 2015, Brasso et al 2014}. Similarly, although data is limited, patients who have progressed on enzalutamide have a low PSA response to abiraterone (approximately 10%) and short median time to progression of approximately 15 weeks {Noonan et al 2013}.

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 us that lower bound of the 90% confidence interval of the estimated rate will be larger than 30%.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), ICH guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice (GCP) Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of GCP, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB. The investigator will not begin any study subject activities until approval from the IRB has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC on any modifications made to the protocol or any accompanying material to be provided to the subject after initial approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by local requirements. The consent form will inform subjects about genomic testing and sample retention, and their right to receive clinically relevant genomic analysis results.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the sponsor, IRB, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, CRF/eCRF, the study drug, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender)
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date, and including causality and severity)
- Concomitant medication (including start and end date, dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. Electronic CRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

Gilead recommends that used and unused study drug supplies be destroyed at sites if they have applicable standard operating procedure (SOP) to do so. The study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for destruction of unused study drug supplies, as needed. If the site has an appropriate SOP for drug destruction as determined by Gilead Clinical Operations or designee (per SOP-CR-23035), the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files. If the site does not have an acceptable SOP to destroy, or cannot due to other regulatory reasons, Gilead will provide instruction for the return if the study drug for disposal/destruction.

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRBs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the in accordance with local requirements and receive documented approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, eg, attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

The monitor is responsible for routine review of the eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

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FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

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

GS-US-350-1604, Protocol Amendment 2, 30 June 2016

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

Name (Printed)
Author

PPD

Signature

5 - July - 2016

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. 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	
Chemistry[21]	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				

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	
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		
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 preferably 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.
21. AAG will be collected at Screening, pre-dose on C1D1 and C1D8 only.

Appendix 3. 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 Accountability and/or Dispensing			X				X		X		
Enzalutamide Accountability and/or Dispensing[6]		X	X				X		X		
Dosing Diary Accountability and/or Dispensing			X				X		X		
Enrollment	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**	
CBC with Differential	X[8]	X	X	X	X	X	X		X	X	
Chemistry[5]	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		
Radionuclide Bone Scan[17]	X							X	X		
Treatment Response Assessment[19]								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**	
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 preferablyu 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. AAG will be collected at Screening, pre-dose on C1D1 and C1D8 only
6. Subjects in phase 1b dose escalation with enzalutamide and Phase 2 Group 2 or Group 3 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. In Phase 2 dose expansion Group 3: PK samples will be collected on Cycle 2, Day 1 at pre-dose and 1, 2, 4, and 6 hours post-dose. Sparse PK and PD 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 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. In Phase 2 dose expansion Group 3: PD samples will be collected on Cycle 2, Day 1 at pre-dose and 1, 2, 4, and 6 hours post-dose. Sparse PK and PD 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 3 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.

Appendix 4. Criteria of Progression for Trial Eligibility by Disease Manifestation (PCWG2, JCO 2008)

Variable	Criteria
PSA	Obtain sequence of rising values at a minimum of 1-week intervals 2.0 ng/mL minimum starting value • Estimate pre-therapy PSA-Doubling Time if 3 or more values available 4 or more weeks apart
Target lesions	Nodal or visceral progression sufficient for trial entry independent of PSA RECIST to record soft-tissue (nodal and visceral) lesions as target or non-target Only lymph nodes ≥ 2 cm in diameter should be used to asses for a change in size
Prostate	*Directed pelvic imaging (CT, MRI, PET/CT, endorectal MRI, transrectal ultrasound) to document presence of absence of disease*
Bone	Progression = appearance of 2 or more new lesions Confirm ambiguous results by other imaging modalities (eg, CT or MRI)
Other sites	Patients with treated epidural lesions and no other epidural progression are eligible

Appendix 5. On Study Outcome/Efficacy Criteria (PCWG2, JCO 2008)

Variable	Criteria
PSA	Ignore early rises (prior to 12 weeks) in determining PSA response For control/relieve/eliminate endpoints: • Percent change from baseline at 12 weeks and maximal change at any time using a waterfall plot. For progression endpoints: • Decline from baseline: record start of therapy to first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir and confirmed by a second value 3 or more weeks later. • No decline from baseline: PSA progression ≥ 25% and ≥ 2 ng/mL after 12 weeks
Soft tissue	Use RECIST with caveats: • Only report changes in lymph nodes that were ≥ 2 cm in diameter at baseline • Record changes in nodal and visceral soft tissue sites separately • Record complete elimination of disease at any site separately • Confirm favorable change with second scan
Bone	The appearance of ≥ 2 new lesions, and, for the first reassessment only, a confirmatory scan performed ≥ 6 weeks later that shows ≥ 2 additional new lesions The date of progression is the date of the first scan that shows the change

Appendix 6. Common Terminology Criteria for Adverse Events (CTCAE) v4.03

CTCAE v 4.03 can be accessed from the link below:

http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf

Appendix 7. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1. Pregnancy and Contraception Requirements for Males and Females of Childbearing Potential

The risks of treatment with GS-5829 during pregnancy have not been evaluated. Enzalutamide treatment of pregnant mice resulted in an increased incidence of embryo-fetal deaths and external and skeletal changes, and is contraindicated in pregnant women and women of child-bearing potential. Females will not be enrolled in this study.

1) Definitions

a Definition of Childbearing Potential pertaining to Female Partners of Male Study Subjects

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b Definition of Male Fertility

For the purposes of this study, a male born subject is considered to be fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

c Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment and until 90 days after the end of relevant systemic exposure. Additional contraception recommendations should also be considered if the female partner is not pregnant.

GS-5829 has insufficient data to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy; therefore, contraceptive steroids are not recommended as a contraceptive method either solely or as a part of a contraceptive regimen.

Male subjects must also refrain from sperm donation during treatment and until at least 90 days after the end of relevant systemic exposure.

2) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

3) Procedures to be Followed in the Event of Pregnancy

Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.2.1.

Appendix 8. Performance Status Scoring System (ECOG)

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 9. Enzalutamide (Xtandi®) Prescribing Information

http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203415lbl.pdf