CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1b/2 Study of GS-5829 in Combination with Fulvestrant or Exemestane in Subjects with Advanced Estrogen Receptor Positive, HER2 Negative-Breast Cancer
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City CA, 94404
IND Number:	124032
EudraCT Number:	2016-002365-63
Clinical Trials.gov Identifier:	NCT02983604
Indication:	Estrogen Receptor Positive HER2 Negative Breast Cancer
Protocol ID:	GS-US-350-1937
Clinical Program Manager:	Name: PPD Telephone: PPD Email: PPD
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Protocol Version/Date:	Original: 17 June 2016 Amendment 1: 10 August 2016 Amendment 2: 05 May 2017

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City CA, 94404

Study Title:	A Phase 1b/2 Study of GS-5829 in Combination with Fulvestrant or Exemestane in Subjects with Advanced Estrogen Receptor Positive, HER2 Negative-Breast Cancer
IND Number:	124032
EudraCT Number:	2016-002365-63
Clinical Trials.gov Identifier:	NCT02983604
Study Centers Planned:	Approximately 50 centers in the USA and Europe
Objectives:	**The primary objective:** **Phase 1b Dose Escalation** • To characterize the safety and tolerability of GS-5829 in combination with fulvestrant and exemestane in subjects with advanced estrogen receptor positive, HER2 negative breast cancer (ER+/HER2- BrCa) • To determine the Maximum Tolerated Dose (MTD), or the recommended Phase 2 Dose (RP2D) of GS-5829 in combination with fulvestrant in subjects with advanced ER+/HER2- BrCa **Randomized Phase 2 Dose Expansion** • To evaluate the efficacy of GS-5829 in combination with fulvestrant compared to fulvestrant alone in subjects with advanced ER+/HER2- BrCa as measured by progression-free survival (PFS). **Secondary objectives:** **Phase 1b Dose Escalation** • To evaluate the pharmacokinetics of GS-5829 in combination with fulvestrant in subjects with advanced ER+/HER2- BrCa **Randomized Phase 2 Dose Expansion** • To evaluate the efficacy of GS-5829 in combination with fulvestrant compared to fulvestrant alone in subjects with advanced ER+/HER2- BrCa, as measured by overall response rate (ORR) and

clinical benefit rate (CBR) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1. ORR is defined as the proportion of subjects with response (complete response [CR], or partial response [PR]). CBR is defined as proportion of subjects with CR, PR, or stable disease (SD) that lasts for ≥ 24 weeks

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

Exploratory objectives:

Study Design:

Phase 1b Dose Escalation:

Cohorts of postmenopausal women with advanced ER+/HER2- BrCa, for whom no standard curative therapy exists and who are candidates for exemestane or fulvestrant, will be sequentially enrolled at progressively higher dose levels of oral GS-5829 in combination with standard doses of exemestane or fulvestrant. Up to 30 subjects will be enrolled for the Phase 1b Dose Escalation portion of the study. The starting dose of GS-5829 has been determined to be 4 mg once daily based on safety information, pharmacokinetic and biomarker data from two ongoing GS-5829 studies (GS-US-350-1599, GS-US-350-1604) and the recommendation by the Bayesian Logistic Regression Model (BLRM) of dose-dose limiting toxicity (DLT) relationship (Section 1.3.1).

Eligible subjects will be assigned to either Group A or B based on prior treatment. Group A will initiate with GS-5829 orally once daily on Cycle 1 Day 1 (C1D1) combined with 25 mg of exemestane administered orally once daily (or in accordance with locally approved labeling). The subject may initiate exemestane any time prior to, or on, C1D1.

Due to recent approvals of several CDK4/6 inhibitors in treatment of ER+/Her2- breast cancer, as well as unmet medical needs for subjects

who have progressed from these, a cohort of patients (approximately 60) who have progressed on prior CDK4/6i (plus AI) will be included in phase 2 part of the study. In addition, the main objective of the phase 2 will be on evaluating safety and efficacy of GS-5829 in combination with fulvestrant. Therefore, enrollment in Group A will be stopped after completion of the 4 mg GS-5829 dose level safety assessments. Subjects who were previously enrolled/treated in Group A will continue to be followed and managed according to the protocol as outlined below.

Group B will initiate GS-5829 orally once daily on Cycle 1 Day 1 (C1D1), with fulvestrant administered intramuscularly (in accordance with locally approved labeling) every 28 days (± 3 days). The subject may initiate fulvestrant any time prior to, or on, C1D1. For subjects whom are treatment naïve (in metastatic setting) and for all subjects for whom C1D1 is the subject's first dose of fulvestrant, a one-time additional dose of 500 mg fulvestrant should be administered on Cycle 1 Day 15 (C1D15).

The doses of GS-5829 for each Dose Level are shown in the table below.

Phase 1b Dose Escalation: Combination of GS-5829 with exemestane or fulvestrant in Subjects with Advanced ER+/HER2- Breast Cancer

Dose Level	GS-5829 (once daily)	Group A (GS-5829 + Exemestane)	Group B (GS-5829 + Fulvestrant)
1	3 mg		
2	4 mg*	25 mg orally once daily (or in accordance with locally approved labelling)**	500 mg intramuscularly on day 1, 15***, 29 and then every 28 days (or in accordance with locally approved labeling)
3	6 mg		
4	9 mg		

* The starting dose for the phase 1b was determined to be 4 mg based on safety information, PK and biomarker data from two ongoing GS-5829 studies (GS-US-350-1599, GS-US-350-1604) and the recommendation by the Bayesian Logistic Regression Model (BLRM) of dose-DLT relationship.

** Enrollment in Group A has been stopped after completion of the 4 mg GS-5829 dose level safety assessments.

*** A one-time additional dose of 500 mg fulvestrant should be administered on Cycle 1 Day 15 (C1D15) for subjects initiating fulvestrant on this study at C1D1

Group A and Group B will dose escalate independently of each other. Each dose escalation cohort will consist of 3 newly enrolled subjects who will be treated at the specified dose level. Enrollment in Group A has been stopped after completion of the 4 mg GS-5829 dose level safety assessments. Dose escalation in Group B will continue until identification of the MTD of GS-5829, or until a RP2D is reached (see rationale above).

After all the subjects in each cohort have been followed for at least 28 days after C1D1 of GS-5829 and are evaluable, a dose- DLT model (see Appendix 10) utilizing all available GS-5829 safety data will be built and will provide estimates of DLT rates at all dose levels. The recommended dose from the dose-DLT model for the next cohort will be the one having the highest probability that the DLT rate falls in the target interval (16.7%, 33.3%), and a probability of < 25% that the DLT rate exceeds 33.3%.

The dose escalation decision and the final decision for the RP2D will be made by the Safety Review Team (SRT), following a review of the model recommendation and all relevant data including safety information, pharmacokinetics, biomarkers and clinical data from evaluable subjects.

The recommended dose of GS-5829 to be combined with fulvestrant in the Randomized Phase 2 Dose Expansion part of this study will be determined based on the data available in the Phase 1b Dose Escalation portion of this study and from studies GS-US-350-1599 and GS-US-350-1604. The recommended dose will not exceed the MTD identified by the Phase 1b Dose Escalation from this study. At least 6 subjects should have already been treated and evaluated at that dose level prior to enrolling subjects in the Randomized Phase 2 Dose Expansion.

Dose Limiting Toxicity (DLT) Definition

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

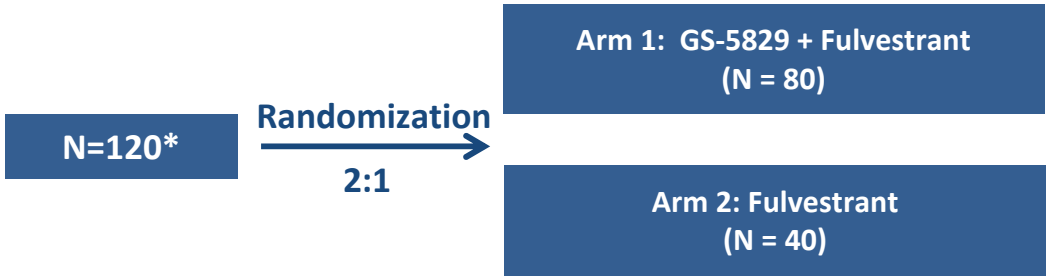
- Grade ≥ 3 or higher non-hematologic toxicity, except:
  - Grade 3 nausea or emesis with maximum duration of 48 hours on adequate medical therapy
  - Grade 3 diarrhea which persists for < 72 hours in the absence of adequate medical therapy
- Grade ≥ 2 non-hematologic treatment-emergent adverse event (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 the Gilead 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. See Section 3.2 for details.

Randomized Phase 2 Dose Expansion:

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

Study Schema: Randomized Phase 2 Dose Expansion:



* Randomization will be stratified by prior CDK4/6 inhibitor plus AI status (naïve vs. progressed). The target number of subjects in each of the 2 strata will be approximately 60 (40 for GS-5829 in combination with fulvestrant and 20 for fulvestrant alone).

Number of Subjects Planned:	Phase 1b Dose Escalation: Up to 30 subjects will be enrolled Randomized Phase 2 Dose Expansion: Approximately 120 subjects will be enrolled
Target Population:	Phase 1b Dose Escalation: Postmenopausal women with histologically or cytologically confirmed ER+/HER2- BrCa who have progressed after treatment with an anti-estrogen or an aromatase inhibitor (AI) therapy and are candidates for fulvestrant or exemestane therapy. Randomized Phase 2 Dose Expansion: Postmenopausal women with histologically or cytologically confirmed ER+/HER2- BrCa who had disease progression during treatment or within 12 months of completion of endocrine therapy (tamoxifen, and/or an AI) in the adjuvant setting, or disease progression during treatment or within 1 month post-treatment with endocrine therapy (tamoxifen, AI or CDK4/6 inhibitor plus AI) for advanced/metastatic disease. Subjects may have had unlimited prior hormonal therapy, but must be naïve to fulvestrant in the metastatic setting. A total of 2 prior chemotherapies are allowed, however, only one for metastatic disease is permitted.
Duration of Treatment:	Subjects may continue receiving GS-5829 once daily until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or death whichever comes first (Section 3.5).
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) ≥18 years of age, female 2) Histologically or cytologically confirmed breast cancer with evidence of metastatic or locally advanced disease not amenable to resection or radiation therapy with curative intent and who have progressed during treatment with at least one prior hormonal therapy a) Phase 1b Dose Escalation - Subjects may have had unlimited prior hormonal therapy and a total of 2 prior chemotherapy regimens (adjuvant chemotherapy is considered 1 regimen). Subjects may have progressed on fulvestrant or exemestane. b) Randomized Phase 2 Dose Expansion - Subjects may have disease progression during treatment or within 12 months of completion of endocrine therapy (tamoxifen, and/or AI) in the adjuvant setting, or disease progression during treatment with endocrine therapy (tamoxifen, AI or CDK4/6 inhibitor plus AI) for advanced/metastatic disease. Subjects may have had

unlimited prior hormonal therapy, but must be naïve to fulvestrant in the metastatic setting. A total of 2 prior chemotherapies are allowed, however, only one for metastatic disease is permitted.

3) Documentation of ER positive breast cancer (≥ 1% positive stained cells by local standards) based on the most recent tumor biopsy, unless bone-only disease
4) Documented HER2-negative tumor based on local testing on most recent tumor biopsy (immunohistochemistry score 0/1+ or negative by in situ hybridization HER2/CP17 ratio < 2 or for single probe assessment HER2 copy number < 4)
5) Post-, pre- or peri-menopausal subjects considered to be in the post-menopausal state as defined by one of the following:
   a. Age ≥ 60 years
   b. Age < 60 years and cessation of regular menses for at least 12 consecutive months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and serum estradiol and follicle-stimulating hormone (FSH) level within the post-menopausal range
   c. Prior bilateral oophorectomy
   d. Pre-/peri-menopausal women can be enrolled if amenable to be treated with the luteinizing-hormone releasing hormone (LHRH) agonist, goserelin. Subjects must have commenced treatment with goserelin or an alternative LHRH agonist at least 4 weeks prior to C1D1. If subjects have received an alternative LHRH agonist prior to study entry, they must switch to goserelin on or before C1D1 for the duration of the study
6) Measurable disease defined per RECIST v. 1.1, or bone-only disease must have a lytic or mixed lytic blastic lesion that can be accurately assessed by computed tomography (CT) or magnetic resonance imaging (MRI). Subjects with bone-only disease and blastic-only metastases are not eligible
7) 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])
8) Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1
9) Life expectancy of ≥ 3 months, in the opinion of the investigator

10) 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

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

12) Negative serum pregnancy test (Appendix 5)

13) Female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 5

14) Females who are nursing must agree to discontinue nursing before C1D1

15) 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 the Gilead 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. Note: if treated and stable at least 6 months prior to enrollment, subject is eligible.

3) Uncontrolled intercurrent illness including, but not limited to, active uncontrolled infection, active or chronic bleeding event within 28 days prior to C1D1 of study drug, uncontrolled cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements as judged by treating physician

4) Myocardial infarction, symptomatic congestive heart failure (New York Heart Association Classification > Class II), unstable angina, or serious uncontrolled cardiac arrhythmia within 6 months of C1D1

5) Major surgery, defined as any surgical procedure that involves

general anesthesia and a significant incision (i.e., larger than what is required for placement of central venous access, percutaneous feeding tube) within 28 days of C1D1

6) 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) V 4.03 Grade > 1

7) 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)

8) 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; adequately treated Stage 1 or 2 cancer currently in complete remission; any other cancer that has been in complete remission for ≥ 5 years

9) Anti-tumor therapy (chemotherapy, chemoradiation, radiation, molecular targeted therapy) within 21 days or 5 half-lives whichever is longer of C1D1 (6 weeks for nitrosoureas, mitomycin C, or molecular agents with $t_{1/2}$ > 10 days); 5 half-lives of any investigational drug. Concurrent use of goserelin for pre-/peri-menopausal breast cancer and exemestane or fulvestrant per the protocol are permitted

10) History of long QT syndrome or whose corrected QT interval (QTc) measured (Fridericia method) at screening is prolonged (> 470 ms). Subjects who screen fail due to this criterion are not eligible to be re-screened

11) Prior exposure to any bromodomain (BET) inhibitors

12) Known hypersensitivity to the study drugs (GS-5829, fulvestrant or exemestane), the metabolites, or formulation excipients

13) Immunotherapy within 6 months of C1D1

14) Evidence of bleeding diathesis or clinically significant bleeding, within 28 days of C1D1 or history of hemoptysis of ≥ 2.5 mL/1 teaspoon within 6 months of C1D1

15) Anticoagulation/antiplatelet therapy within 7 days of C1D1, including acetylsalicylic acid, low molecular weight heparin, or warfarin

16) Known human immunodeficiency virus (HIV) infection

17) Hepatitis B surface Antigen (HBsAg) positive
18) Hepatitis C virus (HCV) antibody positive with HCV RNA positive
19) Use of moderate/strong cytochrome P450 (CYP)3A4 inhibitors or moderate/strong CYP3A4 inducers within 2 weeks prior to C1D1
20) History of high grade esophageal or gastric varices

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 C1D1. Screening procedures will include the following: medical history review, physical exam, vital signs, 12-lead electrocardiogram (ECG), echocardiogram (ECHO), ECOG Performance Status, prior/concomitant medication review, chemistry, hematology and coagulation, hepatitis B and hepatitis C virus (HBV)/(HCV) testing, human immunodeficiency virus (HIV) testing, serum pregnancy β-HCG (serum estradiol and FSH for subjects < 60 years old and who have been amenorrheic for at least 12 consecutive months), and CT or MRI and bone scans. Scans that meet protocol requirements that are obtained as part of standard medical practice up to 28 days prior to C1D1 are acceptable as long as: (1) tests were performed using the method requirements outlined in RECIST v.1.1, (2) the same technique/modality can be used to follow identified lesions throughout the trial for a given subject, and (3) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the subject's source notes. Baseline tumor lesions per RECIST 1.1 will be measured and characterized prior to C1D1 to assess the subject's disease status prior to beginning treatment.

Treatment:

Phase 1b Dose Escalation with Exemestane or Fulvestrant

Subjects who meet eligibility criteria will receive GS-5829 orally once daily combined with either 25 mg of exemestane orally once daily or with fulvestrant intramuscularly on Day 1, 15 (for whom C1D1 is the subject's first dose of fulvestrant), 29 and then every 28 days (± 3 days). Subjects in the Phase 1b Dose Escalation portion may initiate exemestane (Group A) or fulvestrant (Group B) any time prior to, or on, C1D1. 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 pharmacokinetic/pharmacodynamic markers, and biomarkers atapplicable visits), and assessment of AEs. In addition, subjects will

	undergo a computed tomography (CT) scan (or magnetic resonance imaging [MRI]) scan every 8 weeks for the first year, then every 12 weeks. A subject who does not show evidence of disease progression may continue receiving GS-5829 once daily and exemestane (Group A) or fulvestrant (Group B) until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or death whichever comes first. Following treatment discontinuation, subjects will be followed for safety for 30 days from the last dose of study drug. Pharmacokinetic and pharmacodynamic samples for GS-5829 will be collected on Day 1 and Day 15 of Cycle 1 at pre-dose, 0.5, 1, 2, 3, 4, 6, 8 and 24 hours post-dose and anytime on Day 1 of Cycles 2 through 6. **Randomized Phase 2 Dose Expansion** Sparse pharmacokinetics and pharmacodynamic samples will be collected at pre-dose and anytime between 1 to 4 hours post-dose on Day 1 and Day 15 of Cycle 1 and at pre-dose on Day 1 of Cycles 3 and 6. Note: pharmacokinetic samples will only be collected for subjects who are randomized to a GS-5829 in combination with fulvestrant arm (Arm 1). Subjects in the Randomized Phase 2 Dose Expansion portion of the study will also be followed for up to two years for OS.
Test Product, Dose, and Mode of Administration:	GS-5829 will be supplied as round, plain-faced tablets containing 1 mg or 5 mg GS-5829. GS-5829 tablets will be self-administered orally once daily, beginning on C1D1 of the study and thereafter at approximately the same time each day until end of treatment (EOT). For subjects in Group A of the Phase 1b Dose Escalation, 25 mg exemestane tablets will be self-administered orally once daily (or in accordance with locally approved labeling), beginning on C1D1 of the study and thereafter at approximately the same time each day until the EOT. For subjects in Group B of the Phase 1b Dose Escalation or subjects in Arm 2 of the Randomized Phase 2 Dose Expansion, fulvestrant will be administered intramuscularly (in accordance with locally approved labeling) by the clinic staff approximately every 28 days (± 3 days) until the EOT. For subjects in the Phase 1b Dose Escalation or subjects in the Randomized Phase 2 Dose Expansion part of the study for whom are treatment naïve (in metastatic setting) and for all subjects for whom C1D1 is the subject's first dose of fulvestrant, a one-time additional dose of 500mg fulvestrant will be administered on Cycle 1, Day 15 (± 3 days).

Reference Therapy, Dose, and Mode of Administration:	The reference therapy in the Randomized Phase 2 Dose Expansion portion of the study is fulvestrant alone. For subjects in the Randomized Phase 2 Dose Expansion, fulvestrant will be administered intramuscularly (in accordance with locally approved labeling) by the clinic staff approximately every 28 days (±3 days) until the EOT. For subjects in the dose expansion Phase whom are treatment naïve (in metastatic setting) and for all subjects in the dose escalation phase for whom C1D1 is the subject's first dose of fulvestrant, a one-time additional dose of 500 mg fulvestrant will be administered on Cycle 1 Day 15 (± 3 days).
Criteria for Evaluation:	**Phase 1b Dose Escalation and Randomized Phase 2 Dose Expansion**
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:	PFS – defined as the interval from date of randomization to the earlier of the first documented confirmed disease progression or death from any cause ORR – defined as the proportion of subjects who achieve CR or PR, based on RECIST v. 1.1 CBR - defined as the proportion of subjects who achieve a CR or PR or SD that lasts for ≥ 24 weeks based on RECIST v. 1.1 OS - defined as interval from date of randomization to date of death from any cause
Pharmacokinetics:	Phase 1b Dose Escalation: The pharmacokinetic parameters for GS-5829 will be calculated as applicable: [e.g., C_{max}, and AUC_{tau}]
Statistical Methods:	Analysis Methods Phase 1b Dose Escalation: The incidence of DLTs, AEs, serious adverse events (SAEs), and clinically significant laboratory abnormalities in subjects treated with GS-5829 in combination with exemestane or fulvestrant will be evaluated. Randomized Phase 2 Dose Expansion: The Intent-to-Treat (ITT) analysis set includes all subjects who are randomized, regardless of whether subjects receive any study drug(s) or receive a different regimen from the regimen they were randomized to. Treatment assignment will be designated according to randomization. The analysis of PFS based on the ITT analysis set will be considered the primary analysis of the study. PFS will also be analyzed for each of the 2 strata separately.

A Safety Analysis Set for this study consists of all subjects who receive ≥ 1 dose of study drug. Other analysis sets (DLT evaluable analysis set, pharmacokinetics analysis set, and biomarker analysis set) will be used for the corresponding analyses.

Subject characteristics and study results will be described and summarized by dose level, treatment arm and study visit for the relevant analysis sets. Descriptive summaries will be prepared to show sample size, mean, standard deviation (StD), 95% confidence intervals (CIs) on the mean, median, minimum and maximum for continuous variables, and counts, percentages and 95% CIs on the percentage for categorical variables.

Kaplan-Meier estimates and plots will be provided for PFS and OS. The log-rank test will be used to compare PFS and OS between subjects who received GS-5829 + fulvestrant and those who received fulvestrant alone. ORR and CBR will be calculated along with the 95% CIs based on exact method and compared between treatment arms by Fisher's exact test. 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 relevant Analysis Sets, GS-5829 plasma concentrations will be summarized. Pharmacodynamic markers will also be described and summarized. Plasma concentrations of GS-5829 metabolite(s), fulvestrant and exemestane may also be determined.

Sample Size

Up to approximately 30 subjects will be enrolled in the Phase 1b Dose Escalation portion of the study.

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

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

AAG	alpha-1 acid glycoprotein
AE	adverse event
AI	aromatase inhibitor
ALT	alanine transaminase
ANC	absolute neutrophil count
AR	androgen receptor
AST	aspartate transaminase
AUC_{tau}	area under the plasma concentration-time curve
BCRP	breast cancer resistance protein
BET	bromodomain and extra-terminal
BRD	bromodomain
CBC	complete blood count
CBR	Clinical benefit rate
CDK4/6 inhibitor	Cyclin-dependent kinase 4/6 inhibitor
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
CRP	c-reactive protein
CRPC	castrate-resistant prostate cancer
CT	computed tomography
CTC	circulating tumor cells
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
ECHO	echocardiogram
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment

ER	estrogen receptor
eSAE	electronic serious adverse events
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HNSTD	highest non-severely toxic dose
IB	Investigator's brochure
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
MYC	myelocytomatosis viral oncogene homolog
MUGA	multigated acquisition scan
NCI	National Cancer Institute
ORR	overall response rate
OS	overall survival
PD	Progressive Disease
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
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

SD	stable disease
StD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SRT	safety review team
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 2012, Hargreaves 2009}. The tandem bromodomain motifs of BET proteins specifically recognize acetylated histones and, in turn, recruit protein factors that regulate RNAPII {Shi 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 2014}. Transcription of the MYC gene is dependent on BET proteins in many cells {Mertz 2011}. Androgen receptor-dependent transcription of target genes requires BET proteins in prostate cancer cells {Asangani 2014}. Cancer cells addicted to MYC and AR are highly sensitive to BET protein inhibition {Asangani 2014, Delmore 2011, Mertz 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 2014, Barrans 2010, Chesi 2008, Chng 2011, Glitza 2014, Hawksworth 2010, Nesbit 1999, Nupponen 1998, Perry 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 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 {Filippakopoulos 2014, Ghoshal 2016}. Initial evidence of clinical activity at tolerated doses has been reported for the BET inhibitor OTX015 in subjects with refractory hematological cancers {Amorim 2016, Berthon 2016}. 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), estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer (BrCa) (ER+/HER2- BrCa), 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.

1.2. GS-5829

1.2.1. General Information

For further information on the 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-glycoprotein (P-gp) and breast cancer resistance protein (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 single and 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 of GS-5829. 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 (WBC), 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 Experience of GS-5829

As of April 2017, 2 clinical studies have been initiated in which subjects have been dosed with GS-5829: a Phase 1 clinical study (GS-US-350-1599) in subjects with advanced solid tumors and lymphomas (initiated in March 2015) and a Phase 1b/2 clinical study (GS-US-350-1604) in subjects with metastatic castrate-resistant prostate cancer (mCRPC) (initiated in January 2016). The following summary was based on November 11, 2016 data cut unless specified otherwise.

1.2.3.1. Study GS-US-350-1599

Study GS-US-350-1599 is an open label, Phase 1 study that includes subjects with advanced solid tumors, ER+/Her2- breast cancer, and lymphomas. This study is an ongoing, multicenter,

sequential dose-escalation study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of GS-5829 in subjects with advanced solid tumors and lymphomas. This study includes a cohort of subjects with advanced stage breast cancer who receive GS-5829 combined with exemestane or fulvestrant. Doses planned for this study are 0.6, 1.4, 2, 3, 4, 6, 9, and 12 mg once daily.

Based on the data collected so far for GS-350-1599, the most frequently reported AEs, occurring in ≥ 20% of the subjects in either group include abdominal pain, nausea, decreased appetite, fatigue, dehydration, diarrhea, hypotension, and vomiting. The majority of AEs have been ≤ Grade 2. Two out of 24 subjects (8.3%) have discontinued GS-5829 due to AEs.

Two DLTs were reported as of 11 November 2016: a DLT of Grade 3 thrombocytopenia was reported in 1 subject at 3 mg, and a second DLT of adrenal hemorrhage was reported in 1 subject at 4 mg. Following the data-cut-off of 11 November 2016, two dose-limiting toxicities (grade 3 thrombocytopenia, grade 3 AST elevation) occurred in two out of 3 subjects who were dosed at the 6 mg dose level. Therefore, the single agent MTD of GS-5829 from the dose escalation portion of Group 1 of this study was determined to be 4 mg daily.

Additional information for Group 2 subjects with ER+/HER2- breast cancer are as follows: Treatment-emergent AEs were reported for 6 of the 7 subjects in Group 2: 3 in the 2-mg + exemestane group and 3 in the 2-mg + fulvestrant group. Adverse events reported by 2 or more subjects total in Group 2 included nausea (3 subjects), and vomiting, diarrhea, dehydration, and hypotension (2 subjects each). One event of vomiting was considered by the investigator to be Grade 3, and the remainder of the AEs were ≤ Grade 2. All remaining AEs occurred in ≤ 1 subject per treatment group. No TEAE reported in Group 2 has led to study drug discontinuation. Enrollment to this cohort has been stopped when GS-US-350-1937 was being initiated.

1.2.3.2. Study GS-US-350-1604

Study GS-US-350-1604 is an open-label, multicenter, sequential dose-escalation study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of GS-5829 as a single agent and combined with enzalutamide in subjects with mCRPC. The doses planned for this study are 1.4, 2, 3, 4, 6, and 9 mg once daily. One DLT of G3 fatigue, asthenia, and fall has been reported as of 11 November 2016.

Please refer to the current GS-5829 investigator's brochure (IB) for additional details.

1.2.4. Information about Exemestane

Exemestane is an irreversible, steroidal aromatase inactivator, structurally related to the natural substrate androstenedione. It acts as a false substrate for the aromatase enzyme and is processed to an intermediate that binds irreversibly to the active site of the enzyme, causing its inactivation, an effect also known as "suicide inhibition." Exemestane significantly lowers circulating estrogen concentrations in post-menopausal women. In the US, exemestane is approved for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy. For current information about exemestane (Aromasin ®) refer to

the regional prescribing information Appendix 8 or the summary of product characteristics in the pharmacy binder.

1.2.5. Information about Fulvestrant

Fulvestrant is an estrogen receptor antagonist that binds to the estrogen receptor in a competitive manner with affinity comparable to that of estradiol and down-regulates the ER protein in human breast cancer cells. In vitro studies demonstrated that fulvestrant is a reversible inhibitor of the growth of tamoxifen resistant as well as estrogen sensitive human breast cancer cell lines. In vivo tumor studies demonstrated that fulvestrant delayed the establishment of tumors from xenografts of human breast cancer MCF-7 cells in nude mice. Fulvestrant inhibited the growth of established MCF7 xenografts and of tamoxifen resistant breast tumor xenografts. In the US, fulvestrant is approved for the treatment of hormone receptor (HR) positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy.

1.3. Rationale for This Study

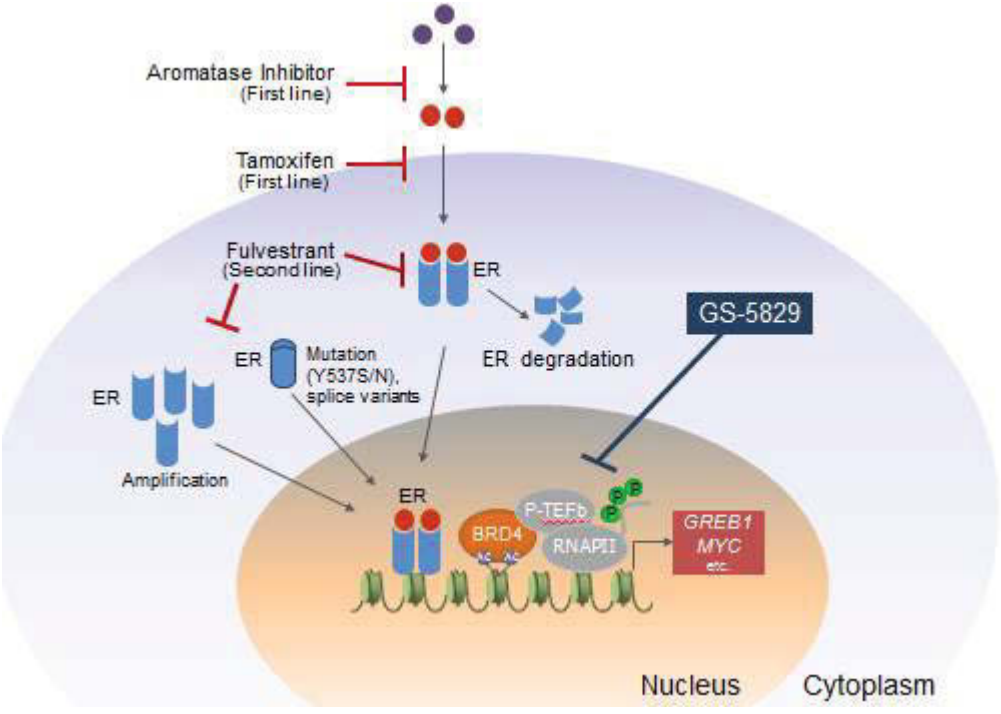
Among all breast cancers, ER+ and HER2- tumors constitute the largest proportion, approximately 65 to 70% {Howell 2010, Tan 2010}. These breast cancer subtypes are characterized by expressing the ER, a nuclear hormone receptor and transcription factor that promotes the expression of genes involved in cell growth and survival {Clark 1984}. Anti-estrogen endocrine therapies, such as aromatase inhibitors (AIs) and tamoxifen are the primary treatments for early stage ER+ BrCa, but many women relapse during or after completing these adjuvant hormonal therapies. In the metastatic setting, single-agent treatment with AIs, tamoxifen, or the selective ER degrader, fulvestrant, has limited benefit. When combined with other targeted therapies such as the cyclin-dependent kinase (CDK) 4/6 inhibitor, palbociclib, the first-line anti-estrogen therapy significantly improves progression-free survival (PFS). Standard of care includes sequential administration of endocrine therapies until hormone resistance occurs, at which time patients have no standard of care options and are usually transitioned to chemotherapy. Therefore, the development of effective therapies that improve response to endocrine therapy and prevent or reverse resistance continues to be of clinical importance.

Resistance to endocrine therapy is mediated by several mechanisms that enable reactivation of ER-driven transcription under conditions of low estrogen (ie, estrogen-independent transcription by the ER). These mechanisms include ER overexpression, activating ER mutations, increased expression of ER co-activators, or increased expression of ER-target genes such as MYC and cyclin D1 {Osborne 2011}. Importantly, BET proteins are required for both estrogen-dependent and estrogen-independent transcription by the ER receptor. BRD4 and BRD3 are recruited to ER target genes, including MYC, where they promote transcription by RNA polymerase II {Nagarajan 2014, Sengupta 2015}. In preclinical studies, the BET inhibitor JQ1 decreased ER-mediated gene transcription and inhibited the growth of ER+ tumors {Alluri 2014, Nagarajan 2014, Sengupta 2015}. In addition, combination of JQ1 with fulvestrant significantly increased time to disease progression in an endocrine-resistant ER+ xenograft mouse breast tumor {Feng 2014}.

The potency of GS-5829 and fulvestrant as single agents and in combination to reduce growth of estrogen-dependent breast cancer cell lines impact on cell growth was evaluated in colony survival assays and the results were summarized in IB Section 3.1.1.1.6. Consistent with the reported activity of BET inhibitors in ER+ BrCa, in cell lines dependent on estrogen for growth, cell viability was reduced with GS-5829 treatment, and the magnitude of the effect was increased with fulvestrant. These data suggest that BET proteins impact ER-dependent cell viability in vitro, and may combine well with fulvestrant in patients failing AI therapy.

We hypothesize that the combination of GS-5829 and an anti-estrogen such as fulvestrant may increase the efficacy of endocrine therapy in patients with advanced ER+ BrCa by targeting orthogonal mechanisms. The combination is expected to lead to overall greater inhibition of ER-dependent transcription by blocking distinct aspects of ER signaling (reduced ligand-dependent ER activation with AI, reduced ER protein stability with fulvestrant, and reduced BET-dependent transcription of ER target genes with GS-5829). By directly inhibiting the transcription of ER target genes such as *MYC*, GS-5829 is hypothesized to block established mechanisms of resistance to endocrine therapy. BET proteins also promote transcription of several ER-independent cell cycle genes, including CDK6, which may additionally contribute to the combination activity in ER+ BrCa cells. Data generated by Gilead have demonstrated that a combination of fulvestrant and GS-5829 inhibits growth of ER+ cell BrCa lines in vitro to a greater extent than either agent alone.

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



Overall, the pre-clinical studies demonstrate that GS-5829 is a potent and selective inhibitor of BET proteins and support the use of GS-5829 to treat solid tumors and hematological cancers.

1.3.1. Rationale for Dose Selection

As of 11 November 2016, a total of 27 subjects have been dosed with single agent GS-5829 once daily in Studies GS-US-350-1599 and GS-US-350-1604 and are evaluable for DLT assessment: 2 subjects at 0.6 mg, 1 subject at 1.4 mg, 5 subjects at 2 mg, 10 subjects at 3 mg, 9 subject at 4 mg. A DLT of thrombocytopenia at the 3 mg dose level and a DLT of adrenal hemorrhage at the 4 mg dose level have been reported. In addition, 6 breast cancer subjects in Group 2 of Study GS-US-350-1599 have been dosed with 2 mg GS-5829 in combination with either exemestane (n=3) or fulvestrant (n=3) and are evaluable for DLT assessment, with no DLT being reported. Based on the BLRM model (see Appendix 10), the probabilities of under-dosing (DLT rate<16.7%), falling in the target interval of DLT rate (between 16.7% and 33.3%) and overdosing (DLT rate>33.3%) will be about 70%, 18% and 12%, respectively, if the starting dose level is at 4.0 mg in the Phase 1b portion of this study. The probabilities will be about 89%, 10%, and 1%, respectively, if the starting dose is at 3.0 mg. This means that there is a high chance (89%) of underdosing at 3.0 mg of GS-5829 in combination with standard of care and a low chance (12%) of overdosing at 4.0 mg of GS-5829 in combination with standard of care. Pharmacokinetics of GS-5829 when administered in combination with fulvestrant appear to be generally similar to that of GS-5829 administered as monotherapy. Based on the clinical safety and pharmacokinetic/pharmacodynamic data collected so far for GS-5829 and the dose-DLT model prediction, the starting dose of GS-5829 was selected to be 4.0 mg in the Phase 1b Dose Escalation.

The recommended dose of GS-5829 to be combined with fulvestrant in the Randomized Phase 2 Dose Expansion part of this study will not exceed the maximum tolerated dose (MTD) identified by the Phase 1b dose escalation. A lower dose may be chosen for the Randomized Phase 2 Dose Expansion study based on emerging safety, pharmacokinetic, pharmacodynamic, and efficacy results from this study and including additional safety data generated from other ongoing Phase 1 and 2 studies with GS-5829.

1.4. 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.

As of November 2016, a total of 40 subjects have been dosed with GS-5829 as monotherapy or in combination with standard of care through two ongoing studies: GS-US-350-1599 and GS-US-350-1604. The drug is generally well tolerated. Assessments for AEs and monitoring for laboratory abnormalities are specified in the protocol and include symptom and AE assessment on Days 1 and 15 of the first two 28 day cycles, Day 1 of the third 28 day cycle, and

then every 28 days until end of treatment (EOT) which will be followed by a 30-day Safety Follow-Up Visit. Physical examinations will occur on Day 1 of each 28-day cycle until EOT which will be 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.

Exemestane and fulvestrant have been approved for treatment of advanced breast cancer in postmenopausal women whose disease has progressed either following tamoxifen or anti-estrogen therapy. The known toxicities for exemestane for this patient population are hot flushes, nausea, fatigue, increase sweating, increased appetite (Appendix 8).The known toxicities for fulvestrant are increased hepatic enzymes (ALT, AST and ALP), injection side pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremity, hot flash, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea and constipation (Appendix 9).

1.5. Potential Benefits

The combination of GS-5829 with fulvestrant is expected to lead to overall greater inhibition of ER-dependent transcription by blocking distinct aspects of ER signaling (reduced ER protein stability with fulvestrant, and reduced BET-dependent transcription of ER target genes with GS-5829). By directly inhibiting the transcription of ER target genes such as MYC, GS-5829 is hypothesized to block established mechanisms of resistance to endocrine therapy. Although Fulvestrant + CDK4/6 inhibitor has been approved as standard of care for second line treatment for metastatic ER+ breast cancer, there is no reported benefit on overall survival comparing to fulvestrant alone. In addition this study will enable patients in countries who don't have access to CDK4/6 inhibitor to participate as well as to explore any clinical activities of GS-5829 in combination with fulvestrant in both CDK4/6 inhibitor progressed and CDK4/6 inhibitor naïve setting.

1.6. Compliance

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

2. OBJECTIVES

The primary objectives:

Phase 1b Dose Escalation

- To characterize the safety and tolerability of GS-5829 in combination with fulvestrant and exemestane in subjects with advanced ER+/HER2- BrCa
- To determine the MTD, or the recommended Phase 2 dose (RP2D) of GS-5829 in combination with fulvestrant in subjects with advanced ER+/HER2- BrCa

Randomized Phase 2 Dose Expansion

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

The secondary objectives:

Phase 1b Dose Escalation

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

Randomized Phase 2 Dose Expansion

- To evaluate the efficacy of GS-5829 in combination with fulvestrant compared to fulvestrant alone in subjects with advanced ER+/HER2- BrCa, as measured by ORR and CBR evaluated according to RECIST v. 1.1 criteria. ORR is defined as the proportion of subjects with response (CR, or PR). CBR is defined as proportion of subjects with CR, PR, or SD that lasts for ≥ 24 weeks
- To evaluate the safety and tolerability of GS-5829 in combination with fulvestrant compared to fulvestrant alone in subjects with advanced ER+/HER2- BrCa
- To evaluate OS in subjects with advanced ER+/HER2- BrCa who receive GS-5829 in combination with fulvestrant compared to fulvestrant alone

The exploratory objectives:

3. STUDY DESIGN

3.1. Endpoints

The endpoints for this study are described in Section 8**.**

3.2. Study Design

Phase 1b Dose Escalation:

Cohorts of postmenopausal women with advanced ER+/HER2- BrCa, for whom no standard curative therapy exists and who are candidates for exemestane or fulvestrant, will be sequentially enrolled at progressively higher dose levels of oral GS-5829 in combination with standard doses of exemestane or fulvestrant. Up to 30 subjects will be enrolled in the Phase 1b Dose Escalation portion of the study. The starting dose of GS-5829 has been determined to be 4 mg once daily based on safety information, pharmacokinetic and biomarker data from two ongoing studies (GS-US-350-1599, GS-US-350-1604) and recommendation by the BLRM model of dose-DLT relationship (Section 1.3.1).

Eligible subjects will be assigned to either Group A or Group B based on prior treatment. Group A will initiate with GS-5829 orally once daily on C1D1 combined with 25 mg of exemestane administered orally once daily (or in accordance with locally approved labeling). The subject may initiate exemestane any time prior to, or on, C1D1.

Due to recent approvals of several CDK4/6 inhibitors in the treatment of ER+/Her2- breast cancers, as well as unmet medical needs for subjects who have progressed from these, a cohort of patients (approximately 60) who have progressed on prior CDK4/6i (plus AI) will be included in phase 2 part of the study. In addition, the main objective of the phase 2 will be on evaluating safety and efficacy of GS-5829 in combination with fulvestrant. Therefore, enrollment in Group A will be stopped after completion of the 4 mg GS-5829 dose level safety assessments. Subjects who were previously enrolled/treated in Group A will continue to be followed and managed according to the protocol as outlined below.

Group B will initiate GS-5829 orally once daily on C1D1 with fulvestrant administered intramuscularly every 28 days (± 3 days) (or in accordance with locally approved labeling). The subject may initiate fulvestrant any time prior to, or on, C1D1. For subjects whom are treatment naïve (in metastatic setting) and for all subjects for whom C1D1 is the subject's first dose of fulvestrant, a one-time additional dose of 500 mg fulvestrant should be administered on Cycle 1 Day 15 (C1D15).

The doses of GS-5829 for each Dose Level are shown in the following table.

Phase 1b Dose Escalation: Combination of GS-5829 with exemestane or fulvestrant in Subjects with Advanced ER+/HER2- Breast Cancer

Dose Level	GS-5829 (once daily)	Group A (GS-5829 + Exemestane)	Group B (GS-5829 + Fulvestrant)
1	3 mg		
2	4 mg*	25 mg orally once daily (or in accordance with locally approved labelling)**	500 mg intramuscularly on day 1, 15***, 29 and then every 28 days (or in accordance with locally approved labeling)
3	6 mg		
4	9 mg		

* The starting dose for the phase 1b was determined to be 4 mg based on safety information, PK and biomarker data from two ongoing GS-5829 studies (GS-US-350-1599, GS-US-350-1604) and the recommendation by the Bayesian Logistic Regression Model (BLRM) of dose-DLT relationship.

** Enrollment in Group A has been stopped after completion of the 4 mg GS-5829 dose level safety assessments.

*** A one-time additional dose of 500 mg fulvestrant should be administered on Cycle 1 Day 15 (C1D15) for subjects initiating fulvestrant on this study at C1D1

Group A and Group B will dose escalate independently of each other. Each dose escalation cohort will consist of 3 newly enrolled subjects who will be treated at the specified dose level. Enrollment in Group A has been stopped after completion of the 4 mg GS-5829 dose level safety assessments. Dose escalation in Group B will continue until identification of the MTD of GS-5829, or until a RP2D is reached (see rationale above).

After all the subjects in each cohort have been followed for at least 28 days after C1D1 of GS-5829 and are evaluable, a dose-DLT model (Bayesian logistic regression model, see Appendix 10) utilizing all available GS-5829 safety data will be built and will provide estimates of DLT rates at all dose levels. The recommended dose from the dose-DLT model for the next cohort will be the one having the highest probability that the DLT rate falls in the target interval (16.7%, 33.3%), and a probability of < 25% that the DLT rate exceeds 33.3%.

The dose escalation decision and the final decision for the RP2D will be made by the SRT, following a review of the model recommendation and all relevant data including safety information, pharmacokinetics, biomarkers and clinical data from evaluable subjects.

The SRT will consist of at least one investigator and the following Gilead Sciences, Inc. (Gilead) study team members: the Gilead medical monitor, representatives from Drug Safety and Public Health (DSPH) and Biostatistics. Others may be invited to participate as members of the SRT if additional expertise is desired. The Gilead medical monitor serves as the chair of the SRT. Investigators whom have enrolled a subject into the cohort the SRT is evaluating is/are required to participate in the dose escalation/expansion decision.

The recommended dose of GS-5829 to be combined with fulvestrant in the Randomized Phase 2 Dose Expansion part of this study will be determined based on the data available in the Phase 1b Dose Escalation portion of this study and from studies GS-US-350-1599 and GS-US-350-1604. The recommended dose will not exceed the MTD identified by the Phase 1b dose escalation

from this study. At least 6 subjects should have already been treated and evaluated at that dose level prior to enrolling subjects in the Randomized Phase 2 Dose Expansion.

Dose Limiting Toxicity (DLT) Definition

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

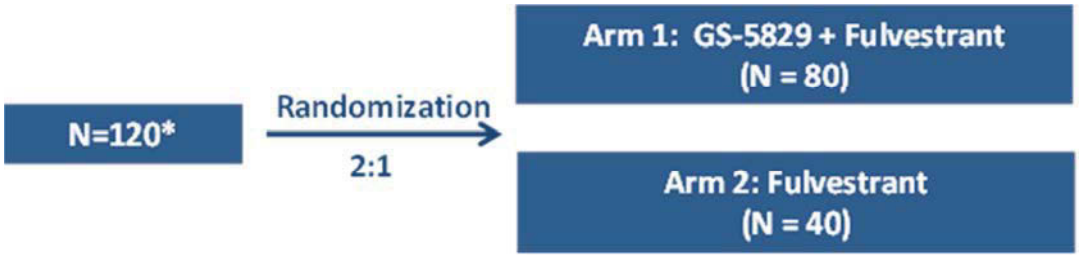
- Grade ≥ 4 neutropenia (absolute neutrophil count [ANC] < 500/mm^3)
- Grade ≥ 3 neutropenia (ANC < 1000/mm^3) with fever (a single temperature of > 38.3°C or a sustained temperature of ≥ 38°C for more than one hour)
- Grade ≥ 3 thrombocytopenia
- Grade ≥ 2 bleeding (e.g. gastrointestinal, respiratory, 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 adequate 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 the Gilead medical monitor may take place to determine if this 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.

Randomized Phase 2 Dose Expansion:

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

Figure 3-1. Randomized Phase 2 Dose Expansion



* Randomization will be stratified by prior CDK4/6 inhibitor plus AI status (naïve vs. progressed). The target number of subjects in each of the 2 strata will be approximately 60 (40 for GS-5829 in combination with fulvestrant and 20 for fulvestrant alone).

3.3. Study Treatments

Subjects who meet eligibility criteria will receive GS-5829 orally once daily combined with either 25 mg of exemestane orally once daily or with fulvestrant intramuscularly on Day 1, 15 (for whom C1D1 is the subject's first dose of fulvestrant), 29 and then every 28 days (± 3 days). Subjects in the Phase 1b Dose Escalation portion may initiate exemestane (Group A) or fulvestrant (Group B) any time prior to, or on, C1D1. 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 pharmacokinetic, pharmacodynamic markers, and biomarkers at applicable visits), and assessment of AEs. In addition, subjects will undergo a CT scan (or MRI) scan every 8 weeks for the first year, then every 12 weeks.

Subjects who do not show evidence of disease progression may continue receiving GS-5829 combined with either exemestane (Group A) or fulvestrant (Group B) until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or death, whichever comes first.

Following treatment discontinuation, subjects will be followed for safety for 30 days from last dose of study drug. Subjects in the Randomized Phase 2 Dose Expansion portion of the study will also be followed for up to two years for OS from the last dose of study drug.

3.4. Duration of Treatment

Subjects may continue receiving GS-5829 once daily until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent or death, whichever comes first. See Section 3.5 for criteria for study drug discontinuation.

3.5. 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
- Pregnancy
- Subject decision
- Lost to follow-up
- Study termination by the sponsor
- Adverse Event

3.6. Criteria for Removal from Study

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

- Documented progression of malignant disease
- Death
- Investigator discretion
- Withdrawal of consent
- Lost to follow-up
- Important protocol deviation
- Pregnancy
- Study termination by the sponsor

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Up to 30 subjects who meet the eligibility criteria will be enrolled in the Phase 1b Dose Escalation portion of the study.

Up to 120 subjects who meet the eligibility criteria will be enrolled in the Randomized 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) ≥18 years of age, female

2) Histologically or cytologically confirmed breast cancer with evidence of metastatic or locally advanced disease not amenable to resection or radiation therapy with curative intent and who have progressed during treatment with at least one prior hormonal therapy

    a) Phase 1b Dose Escalation - Subjects may have had unlimited prior hormonal therapy and a total of 2 prior chemotherapy regimens (adjuvant chemotherapy is considered 1 regimen). Subjects may have progressed on fulvestrant or exemestane

    b) Randomized Phase 2 Dose Expansion - Subjects may have disease progression during treatment or within 12 month of completion of endocrine therapy (tamoxifen, and/or AI) in the adjuvant setting, or disease progression during treatment with endocrine therapy (tamoxifen, AI or CDK4/6 inhibitor plus AI) for advanced/metastatic disease. Subjects may have had unlimited prior hormonal therapy, but must be naïve to fulvestrant in the metastatic setting. A total of 2 prior chemotherapies are allowed, however, only one for metastatic disease is permitted.

3) Documentation of ER positive breast cancer (≥ 1% positive stained cells by local standards) based on the most recent tumor biopsy, unless bone-only disease

4) Documented HER2-negative tumor based on local testing on most recent tumor biopsy (immunohistochemistry score 0/1+ or negative by in situ hybridization HER2/CP17 ratio < 2 or for single probe assessment HER2 copy number < 4)

5) Post, pre or peri-menopausal subjects considered to be in the post-menopausal state as defined by one of the following:

   a) Age ≥ 60 years

   b) Age < 60 years and cessation of regular menses for at least 12 consecutive months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and serum estradiol and follicle-stimulating hormone (FSH) level within the post-menopausal range

   c) Prior bilateral oophorectomy

   d) Pre-/peri-menopausal women can be enrolled if amenable to be treated with the luteinizing-hormone releasing hormone (LHRH) agonist goserelin. Subjects must have commenced treatment with goserelin or an alternative LHRH agonist at least 4 weeks prior to C1D1. If subjects have received an alternative LHRH agonist prior to study entry, they must switch to goserelin on or before C1D1 for the duration of the study

6) Measurable disease defined per RECIST v. 1.1 or bone-only disease must have a lytic or mixed lytic blastic lesion that can be accurately assessed by CT or MRI. Subjects with bone-only disease and blastic-only metastases are not eligible

7) 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])

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

9) Life expectancy of ≥ 3 months, in the opinion of the investigator

10) 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

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

12) Negative serum pregnancy test (Appendix 5)

13) Female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 5

14) Females who are nursing must agree to discontinue nursing before C1D1

15) 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 the Gilead 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. Note: if treated and stable at least 6 months prior to enrollment, subject is eligible.

3) Uncontrolled intercurrent illness including, but not limited to, active uncontrolled infection, active or chronic bleeding event within 28 days prior to C1D1, uncontrolled cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements as judged by treating physician

4) Myocardial infarction, symptomatic congestive heart failure (New York Heart Association Classification > Class II), unstable angina, or serious uncontrolled cardiac arrhythmia within 6 months of C1D1

5) Major surgery, defined as any surgical procedure that involves general anesthesia and a significant incision (i.e., larger than what is required for placement of central venous access, percutaneous feeding tube) within 28 days of C1D1

6) 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 CTCAE Grade > 1

7) 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)

8) 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; adequately treated Stage 1 or 2 cancer currently in complete remission; any other cancer that has been in complete remission for ≥ 5 years

9) Anti-tumor therapy (chemotherapy, chemoradiation, radiation, antibody therapy, molecular targeted therapy) within 21 days or 5 half-lives whichever is longer, of C1D1 (6 weeks for nitrosoureas, mitomycin C, or molecular agents with $t_{1/2}$ > 10 days); 5 half-lives of any investigational drug. Concurrent use of goserelin for pre-/peri-menopausal breast cancer and exemestane or fulvestrant per the protocol are permitted

10) History of long QT syndrome or whose corrected QT interval (QTc) measured (Fridericia method) at screening is prolonged (> 470 ms). Subjects who screen fail due to this criterion are not eligible to be re-screened

11) Prior exposure to any bromodomain (BET) inhibitors

12) Known hypersensitivity to the study drugs (GS-5829, fulvestrant or exemestane), the metabolites, or formulation excipients

13) Immunotherapy within 6 months of C1D1

14) Evidence of bleeding diathesis or clinically significant bleeding, within 28 days of C1D1 or history of hemoptysis of $\geq$ 2.5mL/1 teaspoon within 6 months of C1D1

15) Anticoagulation/antiplatelet therapy within 7 days of C1D1, including acetylsalicylic acid, low molecular weight heparin, or warfarin

16) Known human immunodeficiency virus (HIV) infection

17) Hepatitis B surface Antigen (HBsAg) positive

18) Hepatitis C virus (HCV) antibody positive with HCV RNA positive

19) Use of moderate/strong cytochrome P450 (CYP) 3A4 inhibitors or moderate/strong CYP3A4 inducers within 2 weeks prior to C1D1

20) History of high grade esophageal or gastric varices

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.

Up to 30 subjects will be enrolled in the Phase 1b Dose Escalation portion of the study, each subject will be assigned to either Group A (exemestane +GS-5829) or B (fulvestrant + GS-5829) based on prior treatment. Enrollment in Group A will be stopped after completion of the 4 mg GS-5829 dose level safety assessments. Subjects who were previously enrolled/treated in Group A will continue to be followed and managed according to the protocol as outlined below.

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

A subject will be considered enrolled once they have been registered in the Interactive Web Response System (IxRS).

5.2. Description and Handling of GS-5829

5.2.1. Formulation

GS-5829 will be supplied as round, plain-faced tablets containing 1 mg or 5 mg. The 1 mg tablet is film-coated gray and the 5 mg tablet is film-coated orange.

In addition to the active ingredient, 1 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.

5.2.2. Packaging and Labeling

GS-5829 tablets are provided 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-activated, 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.

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. 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 when handling GS-5829 tablets.

Commercially available product of exemestane and fulvestrant will be used for the study. Further information regarding formulation is available in the Prescribing Information for commercial products.

5.3. Dosage and Administration of GS-5829, Exemestane and Fulvestrant

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. Tablets should be taken whole, they should not be chewed or crushed. 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. Grapefruit juice is prohibited while on study drug.

GS-5829 tablets will be self-administered orally once daily, beginning on C1D1 of the study and thereafter at approximately the same time each day until EOT.

For subjects in Group A (Phase 1b), exemestane 25 mg tablets will be self-administered orally once daily (or in accordance with locally approved labelling), beginning on C1D1 of the study and thereafter at approximately the same time each day until the EOT. Exemestane will be dispensed to subjects at visits on the first day of each cycle.

For subjects in Group B (Phase 1b) and in the Phase 2 Dose Expansion, fulvestrant will be administered intramuscularly (in accordance with locally approved labeling) by the clinic staff approximately every 28 days (± 3 days) until the EOT.

For subjects in the Randomized Phase 2 Dose Expansion phase and for subjects in Group B of the Phase 1b Dose Escalation whom are treatment naïve (in metastatic setting) and for all

subjects for whom C1D1 is the subject's first dose of fulvestrant, a one-time additional dose of 500 mg fulvestrant will be administered on C1D15 (± 3 days).

5.3.1. Dose Adjustment of GS-5829

If at any time in the study, a subject experiences a toxicity consistent with a Grade 4 AE that is deemed to be related to GS-5829, GS-5829 treatment will be discontinued permanently, with the exception of Grade 4 neutropenia, thrombocytopenia, or alopecia. If a subject experiences non-hematologic Grade 3 toxicity consistent with a DLT (See Section 3.2), dosing with GS-5829 will be postponed until the toxicity is resolved to Grade 0 or 1 (as defined by the CTCAE, version 4.03) or returns to the subject's baseline value. If the toxicity resolves to Grade 0 or 1 or returns to the subject's baseline value within 28 days from the start of the event, the subject may resume dosing of GS-5829 at a dose that is at least one dose level lower after discussion with the Gilead medical monitor (See Table 5-1). If a subject has Grade 4 neutropenia, Grade 3 neutropenia with fever, or Grade 3 thrombocytopenia, GS-5829 should be interrupted for up to 28 days and/or until the toxicity resolves to ≤ Grade 1. If the Grade 4 neutropenia or Grade 3 fever and neutropenia resolves within 4 days (7 days for Grade 3 thrombocytopenia), then the subject may resume dosing at the same dose. If the Grade 4 neutropenia or Grade 3 fever and neutropenia takes > 4 days (> 7 days for Grade 3 thrombocytopenia), but within 28 days to recover, then the dose of GS-5829 must be resumed at a lower dose. If the Grade 4 neutropenia, Grade 3 fever and neutropenia or Grade 3 or higher thromboctyopenia takes longer than 28 days to recover then GS-5829 must be permanently discontinued. Grade 4 thrombocytopenia observed at any time must be followed by a dose reduction.

If the recurrent toxicity is hematologic a second dose decrease is allowed (lowest dose allowed is 2 mg) in either total daily dose or by a change in schedule such that the total amount of GS-5829 administered over a 28 day period is decreased by at least 25%.

Table 5-1. Dose Reduction of GS-5829

HEMATOLOGICAL ADVERSE EVENTS	
Neutropenia	
Grade ≤ 3 Neutropenia	Maintain current dose level and schedule.
Grade 4 neutropenia (or occurrence of 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) or infection	Hold dosing with GS-5829 until the toxicity is resolved to ≤ Grade 1. If the toxicity resolves to ≤ Grade 1 within 4 days, the subject may resume dosing of GS-5829 at the same dose. If recovery to Grade ≤ 1 takes > 4 days, but within 28 days, then the subject may resume dosing of GS-5829 at a dose that is at least one dose level lower after discussion with the Gilead medical monitor. Granulocyte colony-stimulating factor (GCSF) is allowed (but not concurrent with GS-5829)

HEMATOLOGICAL ADVERSE EVENTS	
Thrombocytopenia	
Grade ≤ 2 Thrombocytopenia	Maintain current dose level and schedule.
Grade 3 Thrombocytopenia	Hold dosing with GS-5829 until the toxicity is resolved to ≤ Grade 1. If the toxicity resolves within 7 days, the subject may either resume at the same dose or a dose with is one level lower or at an intermittent dosing schedule (at least 25% less GS-5829 in a 28 day dosing period) after discussion with the Gilead medical monitor. If the thrombocytopenia takes 7-28 days to recover then the subject must resume at a dose one level lower or at an intermittent dosing schedule after discussion with the Gilead medical monitor.
Grade 4 Thrombocytopenia	Hold dosing with GS-5829 until the toxicity is resolved to ≤ Grade 1. If the toxicity resolves within 28 days, the subject may either resume at a dose with is at least one level lower, or at intermittent dosing schedule (at least 25% less GS-5829 in a 28 day dosing period) after discussion with the Gilead medical monitor.
NON-HEMATOLOGICAL ADVERSE EVENTS	
Hepatic Adverse Events (elevations in ALT or AST and/or bilirubin)	
Grade 1 (ALT/AST ≤ 3 x ULN) (Bilirubin ≤ 1.5 x ULN)	Maintain current dose level and schedule.
Grade 2 (ALT/AST > 3-5 x ULN) (Bilirubin>1.5 -≤ 3 x ULN)	Maintain current dose level and schedule. Monitor ALT, AST, ALP, and bilirubin at least once a week.
Grade 3	Hold dosing until ≤ Grade 2. Permanently discontinue if any Grade 3 or Grade 4 elevation in AST or ALT associated with a Grade 2 elevation in bilirubin
Grade 4	Permanently discontinue GS-5829
Non-Hepatic, Non-Hematologic Adverse Events	
Grade ≤ 2	No change in dosing required. Dosing may be interrupted until Grade ≤ 1 or baseline
Grade 3	Hold dosing until ≤ Grade 1 and decrease dose by at least one dose level lower or at intermittent dosing schedule (at least 25% less GS-5829 in a 28 day dosing period) after discussion with the Gilead medical monitor.
Grade 4	Permanently discontinue GS-5829

For subjects only enrolled to Phase 2 part of the study: if a subject tolerates a reduced dose for > 4 weeks, GS-5829 dose may be increased to the next higher dose level, at the discretion of the investigator and after discussion with Gilead medical monitor. Successive adjustments to progressively higher dose levels can be made at 4-weeks intervals up to the starting dose level.

If the toxicity does not resolve or return to baseline, or subject experiences a recurrence of the toxicity after restarting study drug at a lower dose or if the toxicity does not resolve within 28 days, study drug(s) GS-5829, exemestane (Group A Phase 1b) or fulvestrant will be permanently discontinued and the subject will return for an EOT and a 30-day Safety Follow-Up visit. If a subject who is randomized to the combination arm discontinues one study drug for any reason, such as toxicity the other study drug will be discontinued as well.

If the subject was not receiving GS-5829 at the time disease progression was documented (e.g., due to reversible toxicity), after discussion with the Gilead medical monitor, GS-5829 may be re-started if the criteria for resuming treatment are met and the investigator feels it is in the subject's best interest to do so.

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 Phase 1b Dose Escalation and at any time in the Randomized Phase 2 Dose Expansion, 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.

Subjects whose dose of exemestane (Group A Phase 1b) or fulvestrant is interrupted for a non-drug related toxicity for up to 28 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 15 or 28 days (exemestane or fulvestrant respectively), or longer than 28 days for GS-5829 in subjects who do not have disease progression may be considered for resumption of study drugs after discussion with the Gilead medical monitor.

No dose reduction of GS-5829 below 3 mg is allowed.

Table 5-2. Dose Reduction of GS-5829

Dose at time of toxicity (mg)	Restarting dose level (mg)
9	6
6	4
4*	3**
3	2

* Dose level 1
** Dose level -1

5.3.2. Dose Adjustment of Exemestane (Group A Phase 1b)

Since there is no anticipated drug-drug interaction between GS-5829 and exemestane, the dose, route and schedule for administration of exemestane in Group A is provided in package insert included in Appendix 8. Dose adjustment for GS-5829 is provided in Section 5.3.1.

5.3.3. Dose Adjustment of Fulvestrant

Since there is no anticipated drug-drug interaction between GS-5829 and fulvestrant, the dose, route and schedule for administration of fulvestrant in the Phase 1 portion and the Phase 2 portion is provided in package insert included in Appendix 9. Dose adjustment for GS-5829 is provided in Section 5.3.1.

5.4. Prior and Concomitant Medications

Pre-/peri-menopausal subjects must have commenced treatment with goserelin or an alternative LHRH agonist at least 4 weeks prior to C1D1. If subjects have received an alternative LHRH agonist prior to study entry, they must switch to goserelin for the duration of the study on or before C1D1.

Subjects enrolling in the Phase 1b Dose Escalation portion of the study may have progressed on fulvestrant or exemestane.

Subjects enrolling in the Randomized Phase 2 Dose Expansion portion of the study may not have received prior fulvestrant.

In vitro data indicates 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 within 2 weeks prior to study drug. 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 (e.g., warfarin), low molecular weight heparin, Factor Xa inhibitors, thrombin inhibitors and aspirin. If anticoagulation/antiplatelet therapy needs to be initiated while on study treatment, the investigator should consult with the Gilead medical monitor to determine if study treatment should be discontinued.

5.5. Accountability for GS-5829, Exemestane and Fulvestrant

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

Study drug (GS-5829 and fulvestrant (only for sites outside of US)) 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, Exemestane (Group A Phase 1b) and Fulvestrant Investigational Medicinal Product Return or Disposal

Study drugs 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. Whenever possible, study drug returned by the subject should be retained for review by the study site monitor prior to destruction.

For additional information about study drug accountability, return and disposal, refer to Section 9.1.7.

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 described in the text that follows. Additional information is provided in the study procedures 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

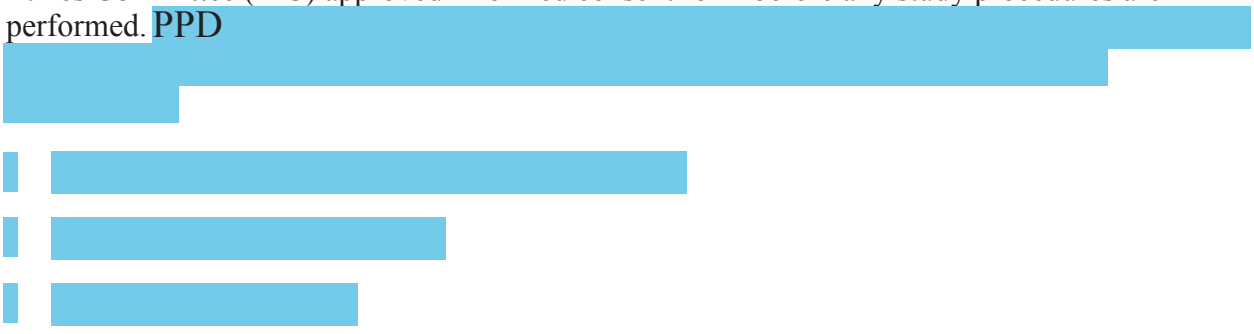
Subjects will be assigned a unique screening number at the time of consent. Subject eligibility will be established at the conclusion of the screening evaluations. Once eligibility is confirmed, subjects will be assigned a unique subject number. The screening number and/or subject ID will be assigned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

6.2.1. Informed Consent

All subjects must sign and date the most recent Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form before any study procedures are performed. PPD



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 at screening and recorded on the eCRF. Medical history will include information on the subject's significant past medical events (e.g., prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent illnesses.

6.2.3. Prior and Concomitant Medications

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 designated time points during the study (Refer to Appendix 2). 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. Screening and End of Treatment (EOT) physical examinations will be complete physical examinations. 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.

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

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

6.2.5. Vital Signs

Vital signs will include blood pressure, respiratory rate, pulse, 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.

C1D1 vital signs will be taken within 15 min pre-GS-5829 dose and 2 and 4 hours post dose (+/- 15 min). At all subsequent visits, vital signs will be taken pre-GS-5829 dose only.

6.2.6. Electrocardiogram

12-lead electrocardiograms (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.

Triplicate ECGs will be collected at any time during the Screening window, C1D1, Day 1 of Cycles 2-6 (at pre-dose), and at EOT. In the Phase 1b Dose Escalation phase of the study, triplicate ECGs will be collected on C1D1 at pre-dose and 1-4 hrs post-dose and on C1D15 at pre-dose, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, and 8 hours post dose (+/- 20 min). In the Randomized Phase 2 Dose Expansion phase of the study, triplicate ECGs will be collected on C1D1 at pre-dose and 1-4 hrs post-dose and on C1D15 at pre-dose, 1 hour, 2 hours, 4 hours, and 6 hours post dose (+/- 20 min).

ECGs should always be collected prior to pharmacokinetics (or any other blood draw) if they are to be collected at the same nominal time point. Subjects should be resting quietly and free of distraction (e.g., television, 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. Echocardiogram

Echocardiograms will be performed at the time points listed in the Study Procedures Table (Appendix 2). Multigated acquisition (MUGA) scans are also acceptable. However, the same modality must be used throughout study participation.

Abnormal echocardiogram findings that are considered clinically significant by the investigator should be reported as AEs and recorded in the AE eCRF if the finding meets the definition of an AE.

6.2.8. ECOG Performance Status

ECOG Performance Status is an investigator assessment of the impact of the disease on the subject's activities of daily living. ECOG assessments will be performed at the time points listed in the Study Procedures Table (Appendix 2). ECOG will be scored using the scale index in Appendix 6.

6.2.9. Adverse Events

Subjects will be assessed for AEs per guidelines in the National Cancer Institute (NCI) CTCAE (version 4.03) at the time points outlined in Appendix 4. 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 4 CTCAE grading criteria.

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

6.2.10. Disease Assessments

6.2.10.1. 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 RECIST 1.1 (refer to Appendix 7). The same assessment methods should be used for the subject throughout all treatment cycles. CT, or MRI scans will be obtained at the applicable study visits per the Study Procedures Table (Appendix 2) and transferred to a central vendor for storage.

In subjects who cannot tolerate iodinated contrast, a CT of the lung without contrast and MRI of the abdomen and pelvis should be performed. Imaging by CT scan (with contrast) or MRI or applicable scan will be performed at Screening (within 28 days before C1D1 if the scan was performed as part of standard medical practice) and every 8 weeks for the first year and then 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 RECIST v. 1.1 (refer to Appendix 7). The same radiographic procedure and specification (e.g., the same contrast agent, slice thickness, etc.) used to define measurable lesions at baseline must be used throughout the study for each subject.

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

6.2.10.2. Bone Scans

All subjects will undergo radionuclide bone scan at Screening (within 12 weeks prior to randomization). Bone scans performed before the signing of informed consent as routine procedures (but within 12 weeks before randomization) do not need to be repeated and may be

used as baseline assessments as long as (1) tests were performed using the method requirements outlined in RECIST v.1.1 (2) appropriately documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes.

Any suspicious abnormalities (i.e., hotspots) identified on the bone scans at baseline and on subsequent bone scans MUST be confirmed by X-ray, CT scan with bone windows or MRI. The same modality must be used throughout the trial for confirmation for a given lesion/patient. Bone lesions identified at baseline will be followed up according to the same assessment schedule and every 8 weeks (±7 days) for the first year and then every 12 weeks (±7 days) from the date of C1D1 during the treatment period. Scans at the EOT visit are not necessary if the prior scan was performed within 4 weeks prior to the EOT visit date. Bone scans will be obtained at the applicable study visits per the Study Procedures Table (Appendix 2) and transferred to a central vendor for storage.

Bone lesions imaging:

- If bone lesions were identified at baseline as the only sites of a subject's disease the following assessment must be performed:
    - CT scan/MRI every 8 weeks (±7 days) for the first year and then every 12 weeks (±7 days) from the date of C1D1 and to confirm CR using the same modality used to confirm the bone lesions at baseline. Areas that have received palliative radiotherapy on study cannot be used to assess response to study treatment.
- If no bone lesions were identified at baseline, or if bone is not the only site of a subject's disease, bone scans will only be repeated as clinically indicated (i.e., subject describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases) but are required to confirm CR. Abnormalities found on subsequent bone scans shall also be confirmed by X-ray, CT or MRI.

6.2.11. Laboratory Assessments

Screening laboratory samples should be obtained within 28 days prior to C1D1 dose (GS-5829). Local laboratory complete blood count (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, and coagulation 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 Study Procedures Table (Appendix 2) 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 pharmacokinetics is collected. 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.

C1D1 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 CRP	White Blood Cell (WBC) Count Hemoglobin Hematocrit Platelet Count Neutrophils (ANC) Lymphocytes Monocytes Basophils Eosinophils **Coagulation** PT/INR[c] aPTT[c]	Serum β-hCG for pregnancy test GS-5829 concentration Concentrations of GS-5829 metabolite(s), fulvestrant, and/or metabolites, as applicable, may be determined PPD Hepatitis B surface antigen[d] Hepatitis C antibody FSH Serum Estradiol Hepatitis C RNA Reflex 26- hydroxyvitamin D HIV Urine pregnancy test

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 Collected at Screening and pre-dose of C1D1, C1D15, C2D1
d HCV RNA Reflex is required

6.2.12. Pregnancy Test for Females of Childbearing Potential

All female subjects of childbearing potential (as defined in Appendix 5) will have serum pregnancy, estradiol and FSH testing throughout the study (refer to Appendix 2). The results must be confirmed as negative for pregnancy prior to continued administration of study drug.

Female subjects of childbearing potential must have commenced treatment with goserelin or an alternative LHRH agonist at least 4 weeks prior to C1D1. Additionally, subjects on goserelin will have serum pregnancy, serum estradiol, and FSH checked on the first day of Cycle 1 to Cycle 3, urine pregnancy test will be performed monthly thereafter.

6.2.13. Vitamin D Assessment

Routine assessment of 25-hydroxy vitamin D levels prior to the start of exemestane (Group A Phase 1b) and fulvestrant treatment should be performed, due to the high prevalence of vitamin D deficiency in women with breast cancer. Women with vitamin D deficiency should receive supplementation with vitamin D.

6.2.14. Pharmacokinetic & Pharmacodynamic Samples

Pharmacokinetic samples will be collected at the time points listed below for each Phase. GS-5829 plasma concentrations will be determined using a validated assay. Plasma concentrations of GS-5829 metabolites and/or exemestane (Group A Phase 1b) and/or fulvestrant metabolites may be determined. Plasma protein binding of analytes may be evaluated. Pharmacodynamics samples may be modified based on the emerging data. The date and clock time of GS-5829 and exemestane dosing (Group A Phase 1b), as applicable, will be collected prior to and on the day of pharmacokinetic sampling. The date and clock time of each fulvestrant dose will be recorded on eCRF, as applicable.

Modulation of the expression of CCR2 and HEXIM1 will be monitored in the pharmacodynamic samples to confirm on target activity of GS-5829.

Phase 1b Dose Escalation

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

Randomized Phase 2 Dose Expansion

Sparse pharmacokinetic and pharmacodynamic samples will be collected at pre-dose and anytime between 1 to 4 hours post-dose on Day 1 and Day 15 of Cycle 1 and at pre-dose on Day 1 of Cycles 3 and 6. Refer to Appendix 3. Note: pharmacokinetic samples will only be collected for subjects who are randomized to GS-5829 combination arm.

6.3. Biomarker Testing

6.3.1. Biomarker Samples to Address the Study Objectives:

PPD

PPD

PPD

PPD

PPD

PPD

6.3.2. Biomarker Samples for Optional Future Research

PPD

PPD

6.3.3. Biomarker Samples for Optional Genomic Research

PPD

6.4. 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. Subjects who do not meet QTc criteria are not allowed to re-screen (see Section 4.3). 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.

Subjects who meet eligibility criteria will receive GS-5829 orally once daily combined with daily orally dosing of exemestane (Group A Phase 1b) or injection of fulvestrant intramuscularly on Day 1, Day 28 and then every 28 days (± 3 days). Subjects initiating fulvestrant on C1D1 should receive a single additional dose at C1D15. Subjects in the Phase 1b Dose Escalation phase of the study may initiate exemestane (Group A) or fulvestrant (Group B) any time prior to, or on, C1D1. 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 pharmacokinetic, pharmacodynamic markers, and biomarkers at applicable visits), and assessment of AEs. In addition, subjects will undergo a CT scan (or MRI) scan every 8 weeks for the first year and then every 12 weeks. Bone scans may be repeated as clinically indicated or to confirm a CR.

A subject who does not show evidence of disease progression may continue receiving GS-5829 once daily and exemestane (Group A Phase 1b) or fulvestrant until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 3.5. If a subject who is randomized to the combination arm discontinues one study drug for any reason, such as toxicity the other study drug will be discontinued as well.

6.6. Post-treatment Assessments

All subjects will complete the 30-Day Safety Follow-Up Visit (±5 days). For Phase 1b Dose Escalation subjects, the 30-Day Safety Follow-Up will be the final study visit. Randomized Phase 2 Dose Expansion subjects will complete the 30-Day Safety Follow-Up Visit and proceed to Long Term Survival Follow-Up (LTFU) (See Section 6.7).

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

6.7. Long-Term Survival Follow-Up

Randomized Phase 2 Dose Expansion subjects will participate in long-term survival follow-up. These subjects will be contacted via phone call every 3 months (+/- 7 days) 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 study drug. 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, ECHO, 12-lead ECG, bone scan and CT or MRI, may be conducted at these visits and recorded on the applicable eCRFs.

6.9. Assessments for Premature Discontinuation from Study

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 6.10, Criteria for Discontinuation of Study Treatment). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.10. Criteria for Discontinuation of Study Treatment

See Section 3.5 for discontinuation criteria.

6.11. Post Study Care

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

Every attempt should be made to keep the subject in the study and continue collecting CT or MRI scans for tumor assessment at every 8 weeks for the first year and then every 12 weeks from the date of C1D1 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 when discontinuing from the study treatment. Randomized 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 study drug.

6.12. Replacement of Subjects

If a subject in the Phase 1b portion of the study 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.

6.13. 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.

6.14. 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. Randomized 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 study drug.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

An 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
- 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 SAE 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 a 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

7.1.2.1. Protocol-Specific Serious Adverse Event Instructions

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

In addition, events that are indicative of the following disease-related SAEs that are assessed as unrelated to study drugs will not be reported as expedited reports by Gilead during the study:

- Progression of disease
- Death related to disease progression

These events will be exempt from global expedited reporting requirements for the duration of the study as they are the primary endpoints of this study. They will be reported as appropriate in the final clinical study report as well as any relevant aggregate safety report.

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 (e.g., clinical chemistry, hematology) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, 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 (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 5.3.1.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified sub-investigator 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 sub-investigator is responsible for assessing the relationship to IMP therapy using clinical judgment and the following considerations:

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

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

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 (e.g., 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, (e.g., venipuncture).

7.2.2. Assessment of Severity

The severity of AEs will be graded using the CTCAE, Version 4.03 (Appendix 4).

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

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 case report form (CRF/eCRF): all SAEs, and AEs related to protocol-mandated procedures.

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30-days after last administration of study IMP 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.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (i.e., signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the CRF/eCRF database and Gilead 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 IMP, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up 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 IMP, 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.

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, i.e., the eCRF database is not functioning, record the SAE on the paper SAE reporting form and submit within 24 hours 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 CRF/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, serious adverse drug reactions (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 the relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. 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.

7.5. Toxicity Management

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead 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 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.

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 and 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

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

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

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.1.2 Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. 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: Email: PPD and Fax: PPD

Refer to Appendix 5 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 IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications does 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 not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Refer to 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 objective:

Phase 1b Dose Escalation

- To characterize the safety and tolerability of GS-5829 in combination with fulvestrant and exemestane in subjects with advanced ER+/HER2- BrCa

- To determine the MTD or RP2D of GS-5829 in combination with fulvestrant in subjects with advanced ER+/HER2- BrCa

Randomized Phase 2 Dose Expansion

- To evaluate the efficacy of GS-5829 in combination with fulvestrant compared to fulvestrant alone in subjects with advanced ER+/HER2- BrCa, as measured by PFS

Secondary objectives:

Phase 1b Dose Escalation

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

Randomized Phase 2 Dose Expansion

- To evaluate the efficacy of GS-5829 in combination with fulvestrant compared to fulvestrant alone in subjects with advanced ER+/HER2- BrCa, as measured by ORR and CBR evaluated according to RECIST v. 1.1. ORR is defined as the proportion of subjects with response (CR or PR). CBR is defined as proportion of subjects with CR, PR, or SD that lasts for ≥ 24 weeks

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

- To evaluate OS for subjects with advanced ER+/HER2- BrCa who received GS-5829 in combination with fulvestrant compared to fulvestrant alone

Exploratory objectives:

8.1.2. Primary Endpoints

Phase 1b Dose Escalation:

- Safety profile and tolerability of the combination of GS-5829 and fulvestrant as assessed by DLTs through Day 28 at each dose level of GS-5829

Randomized Phase 2 Dose Expansion:

- PFS defined as the interval from date of randomization to the earlier of the first documented confirmed disease progression or death from any cause

8.1.3. Secondary Endpoints

Phase 1b Dose Escalation:

- GS-5829 pharmacokinetic parameters (e.g., C_{max}, AUC_{tau})

Randomized Phase 2 Dose Expansion:

- Overall safety profile will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study treatment of any AEs or abnormalities in laboratory tests or ECGs
- ORR, defined as the proportion of subjects who achieve CR or PR, based on RECIST v. 1.1
- CBR, defined as the proportion of subjects who achieve CR, PR or SD that lasts for $\geq$24 weeks based on RECIST v. 1.1
- OS, defined as interval from date of randomization to date of death from any cause

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Intent-to-Treat (ITT) Analysis Set

The ITT analysis set includes all subjects who are randomized in the Randomized Phase 2 Dose Expansion phase of the study regardless of whether subjects receive any study drug(s), or receive a different regimen from the regimen they were randomized to. Treatment assignment will be designated according to randomization.

The analysis of PFS based on the ITT analysis set will be considered the primary analysis of the study. PFS will also be analyzed for each of the 2 strata separately.

This analysis set will be used in the analyses of PFS, ORR, CBR and OS. Subjects in the ITT analysis set who do not have sufficient baseline or on-study tumor status information to be adequately assessed for response status will be included in the denominators in the calculation of ORR and CBR.

8.2.1.2. The Per-Protocol (PP) analysis set

The PP analysis set includes data from subjects in the ITT analysis set who meet the general criteria defining the target population for this study: those who are adherent to the protocol, are compliant with study drug treatment, and are evaluable for relevant efficacy endpoints. Treatment assignment will be designated according to the actual treatment received. The PP analysis set will be used in sensitivity analyses of efficacy endpoints.

8.2.1.3. Safety Analysis Set

The Safety Analysis Set includes subjects who receive ≥ 1 dose of study drug. This analysis set will be used for the analyses of safety endpoints, study treatment administration and study drug compliance.

8.2.1.4. DLT-Evaluable Analysis Set

The DLT-Evaluable Analysis Set includes all Phase 1b Dose Escalation subjects in the Safety Analysis Set who complete all treatment and safety procedures through Day 28, or experienced a DLT prior to Day 28. Subjects who are not evaluable for DLT determination may be replaced.

8.2.1.5. Pharmacokinetics and Pharmacodynamics Analysis Sets

The pharmacokinetics and pharmacodynamics Analysis Sets will consist of all subjects in the Safety Analysis Set who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

8.2.1.6. Biomarker Analysis Set

The Biomarker Analysis Sets include data from subjects in the Safety analysis set who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

8.3. Data Handling Conventions

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), 95% confidence intervals (CIs) on the mean, median, the first and third quartiles, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 95% CIs on the percentage. Unless otherwise indicated, 95% 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 (Phase 1b Dose Escalation), time point and treatment group for the corresponding analysis sets. As appropriate, changes from baseline to each subsequent time point will be described and summarized by dose level and treatment group. Similarly, as appropriate, the best change from baseline during the study will also be described and summarized by dose level and treatment group. Graphical techniques (e.g., 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 (Phase 1b Dose Escalation) and by treatment group for the Safety Analysis Set.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The difference in PFS between the treatment arms will be assessed in the ITT analysis set using the log-rank test. Kaplan-Meier estimates and plots, hazard ratios and corresponding 95% CIs will be presented.

Subjects who withdraw from the study or are lost to follow-up without disease progression or death will be censored on the date of the last visit when lack of disease progression was documented. Subjects who have progression or die after ≥ 2 consecutive missing tumor assessments will be censored at the last time prior to the missing assessments that lack of

definitive progression was objectively documented. Subjects without any adequate post-baseline disease assessment will be censored on the date of first study dose.

8.5.2. Secondary Analyses

The best overall response will be summarized by each response category as CR, PR, SD and PD by treatment arms. Fisher's exact test will be used to compare ORR and CBR between treatment arms. The 2-sided 95% CIs for ORR and CBR will be calculated based on exact method. The difference in OS between the treatment arms will be assessed using the log-rank test. Kaplan-Meier estimates and plots, hazard ratios and corresponding 95% CIs will be presented.

8.6. Safety Analysis

Safety will be evaluated by assessment of clinical laboratory tests, physical examination, 12-lead ECG, vital signs measurements and documented AEs as described in the Study Procedures Table (Appendix 2). 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 (Phase 1b Dose Escalation) and visit where appropriate and by treatment group for subjects in the Safety Analysis Set. AEs occurred in pretreatment will be included in data listings.

8.6.1. Extent of Exposure

A subject's extent of exposure to GS-5829 and fulvestrant will be reported. Exposure data and study drug compliance will be summarized by dose level and treatment group for subjects in the safety analysis set.

GS-5829 compliance will be described in terms of the amount actually taken based on returned pill count relative to the amount that was dispensed (taking into account physician-prescribed reductions and interruptions).

Fulvestrant compliance will be described in terms of the number of doses actually administered relative to the expected number of doses planned.

8.6.2. Adverse Events

The focus of AE summarization will be on treatment-emergent AEs. Treatment-emergent AEs (TEAEs) are events in a given study period that meet one of the following criteria:

- Events with onset dates on or after the start of treatment and up to 30 days after the permanent discontinuation of the study treatment.

- AEs resulting in treatment discontinuation after the start of treatment.

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 study drug will be categorized as related or unrelated. TEAEs will be summarized by dose level (Phase 1b Dose Escalation) and treatment group. Summary tables will be presented to show the number of subjects reporting treatment-emergent AEs by severity grade and corresponding percentages.

Following summaries (number and percentage of subjects) of TEAEs will be provided:

1) All AEs

2) AEs related to study drug

3) AEs that are Grade ≥ 3 in severity

4) AEs leading to study drug modification (interruption/reduction)

5) AEs leading to study drug discontinuation

6) AEs leading to death

7) SAEs

Summaries of TEAEs (by SOC and PT) will be provided by dose level (Phase 1b Dose Escalation) and treatment group. 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.

All AEs will be listed.

8.6.3. Laboratory Evaluations

All central laboratory results will be listed. Selected laboratory data will be summarized using only observed data. Laboratory results and change from baseline at all scheduled time points will be summarized.

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, worsened by ≥ 1 grade in the period from C1D1 to 30 days after the last dose of study drug. If baseline measurement is missing, then any graded abnormality (i.e., an abnormality that is Grade ≥ 1 in severity) will be considered treatment emergent.

Hematology and serum biochemistry will be graded according to CTCAE 4.03 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 whether a laboratory value is below, within, or above the normal range for the subject's age, sex, etc.

Hematology and serum biochemistry test results and their changes from baseline will be summarized by dose level (Phase 1b Dose Escalation), visit and treatment group. Laboratory abnormalities will be summarized 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 (e.g., during the study or from baseline to a particular visit).

Shift tables for hematology and serum biochemistry will be presented by showing change in CTCAE severity grade from baseline to the worst grade post-baseline. Separate listings and summaries will be prepared for laboratory abnormalities that are Grade ≥ 3 in severity.

8.6.4. Other Safety Evaluations

Dose limiting toxicities will be listed for all dose levels.

8.7. Pharmacokinetic Analysis

In the Phase 1b Dose Escalation portion of study, the plasma concentration of GS-5829 will be summarized by nominal sampling time using descriptive statistics by dose cohorts. Pharmacokinetic parameters will be determined using standard non-compartmental methods. Pharmacokinetic parameters (such as C_{max} and, AUC_{tau}), will be listed and summarized using descriptive statistics (e.g., sample size, arithmetic mean, geometric mean, coefficient of variation (%) StD, median, minimum, and maximum) by dose cohorts. Plasma concentrations over time will be plotted in semi-logarithmic and linear formats as mean ± StD, and median (Q1, Q3) if applicable. In the Randomized Phase 2 Dose Expansion portion of study, plasma concentrations will be summarized by nominal sampling time using descriptive statistics by treatment arm.

8.8. Biomarker Analysis

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

PPD

8.9. Sample Size

The sample size of the Phase 1b Dose Escalation portion of the study will be determined based on the number of dose levels evaluated and the emerging drug-related toxicities, and may enroll up to approximately 30 subjects.

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

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 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 sub-investigators 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 sub-investigator's) participation in the study. The investigator and sub-investigator 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/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC 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 any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC 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 or IEC 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 IEC, 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, eCRF, the IMP, 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, IRB or IEC 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, i.e., 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 IMP, 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 (i.e., United States, 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. eCRFs 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 (e.g. 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

Where possible, study drug(s) should be destroyed at the site. At the start of the study, the study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for disposal or return of unused study drug supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead Sciences, the site may destroy used (empty or partially empty) and unused study drug supplies as long as performed in accordance with the site's SOP. This can occur only after the study monitor has performed drug accountability during an on-site monitoring visit.

A copy of the site's study drug disposal SOP or written procedure (signed and dated by the PI or designee) will be obtained for Gilead site files. If the site does not have acceptable procedures in place, arrangements will be made between the site and Gilead Sciences (or Gilead Sciences' representative) for return of unused study drug supplies.

If study drug is destroyed on site, the investigator must maintain accurate records for all study drugs destroyed. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

The study monitor will review study drug supplies and associated records at periodic intervals.

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, IECs, 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 IRB or IEC in accordance with local requirements and receive documented IRB or IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies). 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.

- 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, e.g. 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

GILEAD SCIENCES, INC.
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STUDY ACKNOWLEDGEMENT

A Phase 1b/2 Study of GS-5829 in Combination with Fulvestrant or Exemestane in Subjects with Advanced Estrogen Receptor Positive, HER2 Negative-Breast Cancer

GS-US-350-1937, Amendment 2, 05 May 2017

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

PPD

PPD

PPD
Gilead Sciences, Inc.

May 5, 2017
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

Study Phase	Screening	Treatment Period					End of Treatment	30 Day Safety Follow Up[8]	Long-Term Survival Follow-Up[9]
Cycle Day	Day -28	Cycle 1		Cycle 2		Cycle 3 and every 4 weeks			
		Day 1[7]	Day 15	Day 1	Day 15	Day 1			
Window (days)	-28	+3	±2	+3	±2	+3	±7	±5	±7
Informed Consent	X								
Medical and Medication History[1]	X								
Physical Examination[2]	X	X		X		X	X	X	
ECOG Performance Status[3]	X	X		X			X	X	
Vital Signs[4]	X	X	X	X	X	X	X	X	
Triplicate 12-lead ECG[5]	X	X	X	X		X	X		
Echocardiogram[6]	X			X			X		
Adverse Events/Concomitant Medication[10]	X	X	X	X	X	X	X	X	
GS-5829 and Exemestane (Group A Phase 1b) Accountability and Dispensing[11]		X		X		X	X		

Study Phase	Screening	Treatment Period					End of Treatment	30 Day Safety Follow Up[8]	Long-Term Survival Follow-Up[9]
Cycle Day	Day -28	Cycle 1		Cycle 2		Cycle 3 and every 4 weeks			
		Day 1[7]	Day 15	Day 1	Day 15	Day 1			
Exemestane (Group A Phase 1b) or Fulvestrant Administration[12]		Subjects will self-administer exemestane (Group A Phase 1b) orally once daily starting on or before C1D1. Subjects will receive fulvestrant during visits on C1D1 and then every 28 days (±3 days). For subjects initiating fulvestrant on this study, a single dose of fulvestrant should be administered on C1D15 (± 3 days).							
CBC with Differential[13]	X	X	X	X		X	X	X	
Chemistry[13]	X	X	X	X	X	X	X	X	
Coagulation[14]	X	X	X	X			X		
25-hydroxy vitamin D	X								
Serum Pregnancy Test, Serum Estradiol and FSH (if applicable), Urine Pregnancy Test (if applicable)[15]	X	X[15]		X[15]		X[15]	X		
HBV, HCV, HIV Virology[16]	X								
Archival Tumor Tissue[17]		X							
PPD									
Treatment Response Assessment[18]	X	CT/MRI Performed every 8 weeks (±7 days) for the first year and then every 12 weeks (±7 days) from the date of C1D1.					X		
CT/MRI[19]	X						X		X[21]
Radionuclide Bone Scan[20]	X						X		X[21]

Study Phase	Screening	Treatment Period					End of Treatment	30 Day Safety Follow Up[8]	Long-Term Survival Follow-Up[9]
Cycle Day	Day -28	Cycle 1		Cycle 2		Cycle 3 and every 4 weeks			
		Day 1[7]	Day 15	Day 1	Day 15	Day 1			
Phone Call									X

PPD

1 Medical history includes significant past medical events (e.g., prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies and any concurrent medical illnesses. At screening, all medications taken up to 30 days prior to screening will be documented in the eCRF.
2 Screening and EOT Physical Examinations (PE) will be a complete PE. Beginning at C1D1, a modified physical examination will be performed. Weight (without shoes) should be measured at each PE. Height (without shoes) is measured at Screening only.
3 ECOG will be scored using the scale index in Appendix 6
4 C1D1 Vital Signs will be taken within 15 minutes pre-GS-5829 dose and 2 and 4 hours post dose (+/- 15 min); vital signs will be taken pre-dose only at all subsequent visits.
5 Triplicate ECGs will be collected at any time during Screening window, C1D1, Day 1 of Cycles 2-6 (at pre-dose), and at EOT. In the Phase 1b Dose Escalation phase of the study, triplicate ECGs will be collected on C1D1 at pre-dose and 1-4 hrs post-dose and on C1D15 at pre-dose, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, and 8 hours post dose (± 20 minutes). In the Randomized Phase 2 Dose Expansion phase of the study, triplicate ECGs will be collected on C1D1 at pre-dose and 1-4 hrs post-dose and on C1D15 at pre-dose, 1 hour, 2 hours, 4 hours, and 6 hours post dose (±20 minutes). ECGs should always be collected prior to pharmacokinetics (or any other blood draw) if they are to be collected at the same nominal time point. Subjects should be resting quietly and free of distraction (e.g., TV, conversation) for 10 minutes prior to ECG collection and ECGs should be collected over a 5 minute window at each time point.
6 Multigated acquisition scan (MUGA) is acceptable. The same modality must be used throughout study participation.
7 Day 1 pre-GS-5829 lab samples may be drawn up to two days prior to the Day 1 visit.
8 For Phase 1b Dose Escalation subjects, the 30-Day Safety Follow-Up Visit (±5 days) will be the final study visit. Randomized Phase 2 Dose Expansion subjects will complete the 30-Day Safety Follow-Up Visit (±5 days) and proceed to Long Term Survival Follow-Up.
9 LTFU will begin for subjects participating in the Randomized Phase 2 Dose Expansion phase of the study after the 30 day Safety Follow-Up visit for up to 2 years after the last dose of study drug. A phone call will be made every 3 months (± 7 days) to confirm whether subject has had disease progression.
10 AE reporting period begins once the Informed Consent Form has been signed. AEs will be assessed using NCI CTCAE (v 4.03) criteria at pre- and post-GS-5829 dosing during applicable clinic visits. Subjects will also return to clinic at 30-day post last study drug dose to assess AEs and SAEs.
11 Beginning on C1D1, subjects will receive GS-5829 daily.
12 Subjects assigned to receive exemestane in combination with GS-5829 in the study will self-administer exemestane orally once daily starting on or before on C1D1 and thereafter at approximately the same time each day until the end of treatment. Subjects assigned to receive fulvestrant in combination with GS-5829 in this study will receive fulvestrant 500 mg IM on C1D1 and every 28 days (± 3 days) until the end of treatment. For subjects initiating fulvestrant on this study a single dose of fulvestrant 500 mg should be administered on Cycle 1 Day 15 (± 3 days).

13 C1D1 pre-dose samples may be drawn up to 2 days prior to the visit.
14 Coagulation assessment includes PT/INR, aPTT to be done at Screening and predose of: C1D1, C1D15 and C2D1
15 Subjects who are on goserelin will have serum pregnancy, serum estradiol, and FSH checked first day of Cycle 1 to Cycle 3, and a urine pregnancy test will be performed monthly thereafter starting cycle 4
16 HCV RNA Reflex is required
17 If available, paraffin embedded archival tumor tissue block or freshly sectioned unstained slides will be requested to be shipped to Gilead or designee. These samples will be requested on or after C1D1.
18 Tumor burden as assessed by RECIST v. 1.1 Guidelines (refer to Appendix 7).
19 The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject. CT/MRI to be done at EOT visit if not done within the previous 4 weeks. Subjects who discontinue study treatment for reasons other than disease progression will continue to have tumor assessments performed during the follow up visits every 8 weeks for the first year and then every 12 weeks until disease progression, initiation of new anti-cancer therapy, or discontinuation from the overall study participation (death, subject's request, lost to follow-up) whichever happens first. Every effort should be made to perform a last tumor assessment before starting a new anti-cancer therapy. Additional unscheduled tumor assessments may be performed as clinically indicated at any time.
20 All subjects will also undergo a bone scan during Screening (within 12 weeks prior to randomization). Bone scans performed before the signing of informed consent as routine procedures (but within 12 weeks before randomization) do not need to be repeated and may be used as baseline assessments as long as (1) tests were performed using the method requirements outlined in RECIST v.1.1 (2) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes. Any suspicious abnormalities identified on the bone scans at baseline and on subsequent bone scans MUST be confirmed by X-ray, CT scan with bone windows or MRI. The same modality must be used throughout the trial for confirmation for a given lesion/patient. Bone lesions identified at baseline will be followed up according to the same assessment schedule every 8 weeks (±7 days) for the first year and then every 12 weeks (±7 days) from the date of randomization.
21 Subjects who discontinue study treatment for reasons other than disease progression will continue to have tumor assessments performed during the follow up visits every 8 weeks for the first year and then every 12 weeks until disease progression, initiation of new anti-cancer therapy, or discontinuation from the overall study participation (death, subject's request, lost to follow-up) whichever happens first. Every effort should be made to perform a last tumor assessment before starting a new anticancer therapy. Additional unscheduled tumor assessments may be performed as clinically indicated at any time.

PPD [redacted]

Appendix 3. Pharmacokinetics, Pharmacodynamic Time Point Collection Tables

Phase 1b Dose Escalation[1]

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

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

2 The last pharmacokinetics/pharmacodynamics collection will be at C6D1

Randomized Phase 2 Dose Expansion [1]

Time point in hours from GS-5829 dose[2]	Screening	C1D1	C1D15	C2D1	C2D15	C3D1	C6D1	EOT
Pre-dose		X	X			X	X	
1-4 Post-dose		X	X					

1 Sparse pharmacokinetic and pharmacodynamic samples will be collected at pre-dose and between 1 to 4 hours post-dose on Day 1 and Day 15 of Cycle 1 at pre-dose on Day 1 of Cycles 3 and 6. End pharmacokinetic/pharmacodynamic collection at C6D1

2 Pharmacokinetic samples will only be collected for subjects who are randomized to a GS-5829 combination arm

Appendix 4. Common Terminology Criteria for Adverse Events (CTCAE) v4.03

CTCAE v 4.03 can be assessed from the link below:

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

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

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.

Subjects with breast cancer who are also receiving hormonal therapies, women are considered to be in a postmenopausal state when they are $\geq$ 60 years of age with cessation of previously occurring menses for $\geq$ 12 months without an alternative cause. In addition, women of any age with amenorrhea of $\geq$ 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.

In addition, pre/perimenopausal women are considered in a postmenopausal state due to treatment with the LHRH agonist goserelin. Subjects must have commenced treatment with goserelin or an alternative LHRH agonist at least 4 weeks prior to C1D1, leading to a reduction in luteinizing hormone production and consequent reduction of sex steroid hormones to castration levels by the time of exposure to study drugs.

b. Definition of Male Fertility

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

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

GS-5829 is contraindicated in pregnancy as any potential for human teratogenicity/fetotoxicity in early pregnancy is currently unknown. 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. Please refer to the latest version of the investigator's brochure for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects who are pre/peri-menopausal and treated with goserelin or an alternative LHRH agonist starting at least 4 weeks prior to C1D1 and throughout the duration of the study (per the above definition) of childbearing potential requires the use of highly effective contraceptive measures. They must also not rely on hormone-containing contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Baseline/Day 1 visit prior to initial randomization. Pregnancy tests will be performed at protocol-specified dates thereafter. Female subjects must agree to one of the following from Screening until 30 days following the end of relevant systemic exposure.

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

Or

- Consistent and correct use of 1 of the following methods of birth control listed below.

  — Intrauterine device (IUD) with a failure rate of <1% per year

  — Tubal sterilization

  — Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

Subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after the end of relevant systemic exposure.

3) 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.

4) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects they are 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 6. 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, e.g., 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 7. RECIST 1.1

E.A. Eisenhauer[a, et al.] New response evaluation criteria in solid tumors:

Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228-247.

Appendix 8. Exemestane (Aromasin®) Prescribing Information

http://www.pfizer.com/products/product-detail/aromasin

Appendix 9. Fulvestrant (Faslodex®) Prescribing Information

http://www.faslodexhcp.com/home.html

Appendix 10. Bayesian Logistic Regression Model

Determination of the MTD will be based on the posterior probability of DLT rate estimated by a 2-parameter BLRM with overdose control {Neuenschwander 2008} and calculated using East software {Cytel Inc 2016}.

Let $\pi[d_i]$ be the probability of DLT at dose level d_i of GS-5829. The statistical model describing dose-toxicity relationship will have the following form:

$$\pi[d_i] = \frac{\exp(\log(\alpha) + \beta\log(\frac{d_i}{d^*}))}{1 + \exp(\log(\alpha) + \beta\log(\frac{d_i}{d^*}))}$$

where $\alpha, \beta > 0$ and d^* is the reference dose level. The prior specification of the model parameters is provided below. The estimate of parameters will be updated as data are accumulated and the toxicity probability at each dose level will be calculated based on the posterior distributions of the model parameters. The estimated posterior probability of DLT rate at each dose level will be summarized using the following intervals:

Under dosing: [0.00, 0.167)

Targeted toxicity: [0.167, 0.333]

Excessive toxicity: (0.333, 1.00]

The overdose control criterion is set as the posterior probability of excessive toxicity less than 25%. The dose level recommended for the next cohort will be the dose cohort at which the posterior probability for the target toxicity interval is maximum among all dose candidates satisfying the overdose control criterion.

The trial can be stopped if any one of three criteria is met:

1. The posterior probability of targeted toxicity exceeds 70% and at least 6 subjects have been allocated at a dose level

2. Maximum number of subjects (N=12) has been treated at a dose level

3. Maximum number of subjects (N=30) has been reached

1. Planned Dose Levels

The provisional dose levels for GS-5829 are 3 mg, 4 mg, 6 mg and 9 mg once daily.

2. Prior Specification

The prior distribution for (log(α), log(β)) is assumed to be a bivariate normal distribution. The following non-informative prior is used first:

- The median DLT rate at 3 mg is assumed to be 15%, i.e. mean(log(α))= -1.73.
- A doubling in dose is assumed to double the odds of DLT, i.e. mean(log(β)) = 0
- The StD of log(α) is set to 2 and the StD of log(β) to 1.
- The correlation between log(α) and log(β) is set to be 0.

Then the posterior is calculated based on the data collected from other on-going studies (GS-US-350-1599 and GS-US-350-1604) and will be updated as more data in these studies are collected. The prior for the current study will be based on the posterior calculated based on the data from GS-US-350-1599 and GS-US-350-1604 with inflated variance to discount the information from GS-US-350-1599 and GS-US-350-1604 considering between-trial variations.

Appendix Table 1. DLT data collected in GS-US-350-1599 and GS-US-350-1604 as of 22 July 2016*

QD Dose (mg)	Total number of evaluable subjects	Number of subjects with DLT
0.6	2	0
1.4	1	0
2	5	0
3	10**	1
4	2	1

* Current data were collected only for subjects with GS-5829 monotherapy
** A total of 13 subjects dosed, but 10 were evaluable

Appendix Table 2. Prior for and Posterior from current data collected in GS-US-350-1599 and GS-US-350-1604

Parameter	Means	Variances	Correlation
Prior for (log(α), log(β))	(-1.73, 0)	(4, 1)	0
Posterior for (log(α), log(β)) from data in Appendix Table 1	(-2.13, 0.52)	(0.56, 1.02)	-0.01
Prior for (log(α), log(β)) used to assess operating characteristics by simulation	(-2.13, 0.52)	(1.12, 2.04)	-0.01

Appendix Table 3 shows the posterior probabilities of DLT rate based on current data from GS-US-1599 and GS-1604. Because there is a high chance of under dosing for 2 mg and low chance of overdosing for 3 mg, 3 mg once daily of GS-5829 is planned as the starting dose in the Phase 1b Dose Escalation portion of this study**.** The starting dose level may be either higher or lower than 3 mg once daily, if either a higher or lower dose has been demonstrated to be both safe and tolerable in Studies GS-US-350-1599 and GS-US-250-1604. The new dose level will be selected prior to initiating dosing in this study.

Appendix Table 3. Summary of posterior probabilities of DLT based on data from GS-US-350-1599 and GS-US-350-1604 as of 22 July 2016

	Pr(DLT)	Posterior Probability of		
QD Dose (mg)	Median	Under [0%, 16.7%)	Target [16.7% 33.3%]	Excessive (33.3%, 100%)
2	0.05	0.95	0.05	0.001
3	0.10	0.68	0.30	0.02
4	0.2	0.43	0.35	0.23
6	0.34	0.24	0.26	0.50
9	0.51	0.15	0.20	0.65

3. Operating Characteristics

In order to assess operating characteristics, simulation was performed under 2 hypothetical scenarios using East software {Cytel Inc 2016}. A total of 1000 trials were simulated under each scenario.

Scenario 1: Only the lowest dose level (2 mg) is safe

Scenario 2: The dose level of 4 mg or below are safe

Appendix Table 4. True underlying DLT rates in hypothetical scenarios

	True DLT rate	
QD Dose (mg)	Scenario 1	Scenario 2
2	0.30	0.10
3	0.40	0.20
4	0.50	0.30
6	0.60	0.40
9	0.70	0.50

As shown in Appendix Table 5, the simulations illustrate that the model has reasonable operating characteristics. The probabilities of recommending a correct dose level and stopping the study with declaring all dose levels to be toxic are 27.9% and 53.1%, respectively, in Scenario 1. The probability of recommending a correct dose level in Scenario 2 is 73.8%. The design is not aggressive to assign subjects to high toxic dose levels even with strong prior information based on the safety data from 20 evaluable subjects from other studies as of July 22, 2016.

Appendix Table 5. Simulation results for operating characteristics in hypothetical scenarios

Operating Characteristics	Scenario 1	Scenario 2
Proportion of trials that recommend dose levels with true Pr(DLT) in [0.167, 0.333] (Correct decision)	27.9%	73.8%
Proportion of trials that recommend dose levels with true Pr(DLT)>0.333 (Patient risk)	19.0%	13.7%
Proportion of trials that recommend dose levels with true Pr(DLT)<0.167	0	3.6%
Proportion of trials which stops early because all dose levels are too toxic	53.1%	8.9%
Average number of subjects evaluated	15	20