Protocol GU 115/I6A-MC-CBBD

A Double-Blinded, Placebo-Controlled, Randomized Phase II Study of Enzalutamide With or Without the PI3 Kinase/mTOR Inhibitor LY3023414 in Men with Metastatic Castration Resistant Prostate Cancer

NCT02407054

Approval Date: 25-Feb-2017

SARAH CANNON
Development Innovations

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SARAH CANNON DEVELOPMENT INNOVATIONS, LLC STUDY NUMBER:	GU 115
SPONSOR STUDY NUMBER:	I6A-MC-CBBD
STUDY DRUG(S):	LY3023414
SPONSOR:	Eli Lilly and Company Indianapolis, Indiana, USA 46285
CONTRACT RESEARCH ORGANIZATION:	Sarah Cannon Development Innovations, LLC 3322 West End Avenue , Suite 900 Nashville, TN 37203 1-877-MY-1-SCRI asksarah@sarahcannon.com
STUDY CHAIR:	PPD Dana Farber Cancer Institute Lank Center for Genitourinary Oncology 450 Brookline Ave Boston, MA 02215 PPD
SPONSOR CONTACT :	PPD Eli Lilly and Company Kolblgasse 8-10 A-1030 Vienna, Austria PPD
DATE FINAL:	10 December 2014

AMENDMENT NUMBER:	1	**AMENDMENT DATE:**	27 February 2015
AMENDMENT NUMBER	2	**AMENDMENT DATE**	30 July 2015
AMENDMENT NUMBER	3	**AMENDMENT DATE**	25 January 2017

SARAH CANNON
Development Innovations

Clinical Study Statement of Compliance

A Double-Blinded, Placebo-Controlled, Randomized Phase II Study of Enzalutamide With or Without the PI3 Kinase/mTOR Inhibitor LY3023414 in Men with Metastatic Castration Resistant Prostate Cancer

This clinical study shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Conference on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards**
  - **Title 21CFR Part 312, Investigational New Drug Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the Study Chair and/or Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of my responsibilities to conduct the clinical study in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

As the Contract Research Organization (CRO) Representative, I understand that my signature constitutes agreement and understanding of acceptance of the defined and contracted sponsor responsibilities as defined by the protocol, applicable Clinical Trial Agreements (CTA), and/or business contracts. Additionally, my signature constitutes my understanding and agreement that any changes to the protocol, CTA, or contracts shall be implemented with the Sponsor's review and approval prior to implementation.

As the Sponsor Representative, I understand that my signature constitutes agreement and understanding of acceptance of the defined and contracted Sponsor responsibilities to the CRO and the Principal Investigator as defined by the protocol, applicable Clinical Trial Agreements (CTA), and/or business contracts, but does not in any capacity relieve me of my responsibilities as the Sponsor. Additionally, my signature constitutes my understanding and agreement that any changes to the protocol, CTA, or contracts shall be implemented timely with my review and approval prior to implementation.

Clinical Study Signature Approval Page

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PPD **Study Chair**	**Study Chair Signature**	Feb-21-17 **Date**
PPD Dana Farber Cancer Institute		
PPD **Sponsor Representative** Eli Lilly and Company	**Sponsor Representative Signature**	16-FEB-2017 **Date**
PPD **Sarah Cannon Development**	**Sarah Cannon Development Innovations, LLC Representative Signature**	**Date**
PPD PPD **Biostatistician** Sarah Cannon Development Innovations	**Biostatistician Signature**	**Date**

STUDY DRUG: LY3023414
GU 115/ I6A-MC-CBBD
AMENDMENT 3: 25 January 2017

CONFIDENTIAL
SARAH CANNON DEVELOPMENT INNOVATIONS/SPONSOR STUDY NUMBER(S):

v 4.0

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PPD

Study Chair | Study Chair Signature | Date

PPD

Dana Farber Cancer Institute

PPD

16-FEB-2017

Sponsor Representative
Eli Lilly and Company | **Sponsor Representative Signature** | **Date**

PPD

Sarah Cannon Development Innovations, LLC Representative | **Sarah Cannon Development Innovations, LLC Representative Signature** | **Date**

PPD

Biostatistician
Sarah Cannon Development Innovations | **Biostatistician Signature** | **Date**

Clinical Study Signature Approval Page

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PPD

Study Chair | **Study Chair Signature** | **Date**

PPD

PPD

16-FEB-2017

Sponsor Representative
Eli Lilly and Company | **Sponsor Representative Signature** | **Date**

PPD

02/21/2017
06:49 AM EST

Sarah Cannon Development Innovations, LLC Representative | **Sarah Cannon Development Innovations, LLC Representative Signature** | **Date**

PPD

Biostatistician
Sarah Cannon Development Innovations | **Biostatistician Signature** | **Date**

Clinical Study Signature Approval Page

A Double-Blinded, Placebo-Controlled, Randomized Phase II Study of Enzalutamide With or Without the PI3 Kinase/mTOR Inhibitor LY3023414 in Men with Metastatic Castration Resistant Prostate Cancer

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PPD
Dana Farber Cancer Institute

PPD

16-FEB-2017

Sponsor Representative
Eli Lilly and Company

Sponsor Representative Signature

Date

PPD

PPD

Clinical Study Principal Investigator Signature Form

A Double-Blinded, Placebo-Controlled, Randomized Phase II Study of Enzalutamide With or Without the PI3 Kinase/mTOR Inhibitor LY3023414 in Men with Metastatic Castration Resistant Prostate Cancer

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By signing this protocol acceptance page, I confirm I have read, understand, and agree to conduct the study in accordance with the current protocol.

_____	_____	_____
Principal Investigator Name	**Principal Investigator Signature**	**Date**

Global Change

SCRI Development Innovations was changed to Sarah Cannon Development Innovations throughout the protocol. The address for Sarah Cannon Development Innovations was updated.

Study Duration: The total duration of the study is approximately ***40*** ~~25~~ months which includes ***31*** ~~16~~ months of enrollment and 9 months of expected treatment duration.

Study Centers: This study will be conducted at approximately ***48*** ~~18~~ sites

Section 2.1 Primary Objective

The primary objective of this study is:

To compare progression-free survival (PFS) – PSA, radiographic, or Prostate Cancer Clinical Trials Working Group (PCWG2) symptomatic progression - in men with mCRPC who are receiving enzalutamide plus LY3023414 versus enzalutamide plus placebo using ~~Prostate Cancer Clinical Trials Working Group (~~PCWG2~~)~~ criteria.

Section 3.1 Inclusion Criteria and Synopsis

3. Prostate cancer progression documented by PSA and/or radiographic progression according to PCWG2 criteria (Appendix F). ***PSA levels must have a starting value of at least 2.0 ng/mL that have increased on 3 occasions obtained a minimum of 1 week apart.***

4. Prior abiraterone treatment completed at least 2 weeks prior to Cycle 1 Day 1. ***Patient must have failed prior abiraterone treatment to be eligible.***

8. Adequate hematologic function defined as:

- Absolute neutrophil count (ANC) ≥1500/μL
- Platelets ≥100,000/μL ***(transfusions to obtain this level are not allowed)***
- Hemoglobin ≥8 g/dL

Section 3.2 Exclusion Criteria and Synopsis

6. History of (a) seizure or any condition that may predispose to seizure (prior cortical stroke or significant brain trauma) ***within 12 months prior to Day 1 of Cycle 1***; (b) loss of consciousness or transient ischemic attack within 12 months prior to Day 1 of Cycle 1.

12.Have a history of New York Heart Association (NYHA) Class ≥3 ***congestive heart failure (CHF)***, QTc interval > ~~450~~ ***480*** ms on screening electrocardiogram (ECG) per Friderica's formula at several consecutive days of assessment, unstable angina, or myocardial infarction (MI) in 6 months prior to study drug administration.

Section 5.1.1 LY3023414 or Placebo

Patients should take the morning and evening doses of LY3023414 approximately 12 hours apart (preferably within a 10- to 14-hour range). ~~Patients should not consume food for approximately 1 hour before taking the dose of LY3023414 or matching placebo and should remain in a fasting state for 1 hour post-dose.~~ LY3023414 or matching placebo should be taken with a glass of water at approximately the same time each day. ***LY3023414 or matching placebo can be taken with or without food.*** Patients should swallow the capsules as a whole and should not chew or crush them.

Section 5.1.2 Enzalutamide

Enzalutamide will be self-administered by the patient. Enzalutamide will be taken together with one of the two daily doses of LY3023414 or matching placebo. ~~Therefore, patients should not consume food for approximately 1 hour before taking the dose of enzalutamide and should remain in a fasting state for 1 hour post-dose~~. ***Enzalutamide can be taken with or without food*** Enzalutamide capsules should be swallowed whole. Patients should not chew, dissolve, or crush them.

Section 5.7 Pharmacogenetic (PGx) Assessment

The PGx sample is part of the biomarker sample. Therefore, there is no separate kit for PGx samples. Samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program.

Section 10.2 Sample Size Consideration and Synopsis

PASS14 ~~PASS13~~ Version (copyright ***2015*** ~~2014~~) was used ***to*** calculate sample size.

Two interim analyses were planned at approximately 39% information rate and 82% information rate. Approximately 0% of total type I error and 20% of total type II error were spent at the first interim. The first interim analysis is planned to be conducted when a total of 36 PFS events are observed. Approximately 20% of total type I error and 0% of total type II error were spent at the second interim. The second interim analysis is planned to be conducted when a total of 75 PFS events are observed.

~~The interim analysis is planned at approximately 75% information rate, with approximately 40% of total type I error and 0% of total type II error spent at the interim. The interim analysis will be conducted when a total of 70 PFS events are observed.~~

Section 10.6.1 Final Analysis

The final analysis of the study will be triggered when ***92*** ~~96~~ patients have had an event (disease progression or all cause death).

Section 10.6.2 Planned Interim Analysis

The first interim analysis will be conducted when a total of 36 PFS events are observed for futility assessment. The one sided p-value of 0.774 will be used as the boundary to assess the efficacy of enzalutamide plus LY3023414 versus enzalutamide plus placebo for the first interim analysis. If the P-value is more than 0.774, the study will be terminated for futility.

The second interim analysis will be conducted when a total of 75 PFS events are observed. One-sided p-value of 0.042 will be used as the boundary to assess the efficacy of enzalutamide plus LY3023414 versus enzalutamide plus placebo for the second interim analysis.

One-sided p-value of 0.2 will be used as the boundary to assess the efficacy of enzalutamide plus LY3023414 versus enzalutamide plus placebo in the final analysis.

~~Interim analysis will be conducted when a total of 70 PFS events are observed. One-sided p-value of 0.077 will be used as the boundary to access the efficacy of enzalutamide plus LY3023414 versus enzalutamide plus placebo during the interim analysis. One-sided p-value of 0.195 will be used as the boundary to access the efficacy of enzalutamide plus LY3023414 versus enzalutamide plus placebo in the final analysis.~~

Schedule of Assessments

Footnote f - PT/INR will only need to be repeated if abnormal at baseline or if clinically indicated. ~~Patients requiring the initiation of an anti-coagulation therapy during study treatment should have their coagulation test performed on a weekly basis.~~

Footnote s - The PGx sample should be collected C1D1. If the sample is not able to be collected C1D1, it can be collected anytime during C1 or C2. ***The PGx sample is part of the biomarker sample and does not require a separate kit.***

GU 115/I6A-MC-CBBD PROTOCOL SYNOPSIS

Title of Study:	A Double-Blinded, Placebo-Controlled, Randomized Phase II Study of Enzalutamide With or Without the PI3 Kinase/mTOR Inhibitor LY3023414 in Men with Metastatic Castration Resistant Prostate Cancer	
Sarah Cannon Development Innovations Study Number:	GU 115	
Sponsor Study Number:	I6A-MC-CBBD	
Sponsor:	Eli Lilly and Company, Indianapolis, IN	
Study Duration:	The total duration of the study is approximately 40 months which includes 31 months of enrollment and 9 months of expected treatment duration.	**Phase of Study:** II
Study Centers:	This study will be conducted at approximately 48 sites	
Number of Patients:	Approximately 144 medically or surgically castrated male patients with metastatic, castration resistant prostate cancer (mCRPC) who have shown disease progression on abiraterone will be enrolled. Part A will include approximately 6-12 patients to assess pharmacokinetics (PKs)/safety. Part B will include 132 patients to assess progression-free survival (PFS).	
Objectives:	**Primary Objective** The primary objective of this study is: • To compare progression-free survival (PFS) – PSA, radiographic, or Prostate Cancer Clinical Trials Working Group (PCWG2) symptomatic progression - in men with mCRPC who are receiving enzalutamide plus LY3023414 versus enzalutamide plus placebo using PCWG2 criteria. **Secondary Objectives** The secondary objectives of this study are: • To compare the clinical response rates (RRs) in men with mCRPC who are receiving enzalutamide plus LY3023414 versus enzalutamide plus placebo and who have measurable disease at baseline using Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 (Eisenhauer et al. 2009). • To compare time to clinical (symptomatic or radiographic) and/or PSA progression (TTP) in men with mCRPC who are receiving enzalutamide plus LY3023414 versus enzalutamide plus placebo using PCWG2 criteria. • To compare the maximum decline in PSA that occurs following treatment in men with mCRPC who are receiving enzalutamide plus LY3023414 versus enzalutamide plus placebo. • To demonstrate the safety and tolerability of 200 mg twice daily (BID) oral LY3023414 given in combination with 160 mg once daily (QD) oral dose of enzalutamide. • To evaluate potential pharmacokinetic (PK) drug interactions (i.e. impact of enzalutamide on LY3023414 exposure) and to further characterize LY3023414 PK properties. • To characterize the safety profile of enzalutamide plus LY3023414 as compared to enzalutamide plus placebo in this patient population.	

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Objectives:	**Exploratory Objective** The exploratory objective of this study is: • To collect blood and archival tissue for exploratory studies to identify potential biomarkers predictive of clinical efficacy of study treatment and disease progression in this patient population.
Study Design:	This is a double-blinded, placebo-controlled, randomized Phase II study of the combination of enzalutamide plus LY3023414 versus enzalutamide plus placebo in medically or surgically castrated men with mCRPC who have shown disease progression on abiraterone. Cycles will be 28 days in length. Patients will be treated until disease progression (radiographic or PCWG2 symptomatic progression), or until they develop an unacceptable adverse event (AE) requiring discontinuation of the drug, or patient/physician choice. Patients with PSA progression are allowed and encouraged to continue treatment until clinical (symptomatic or radiographic) progression. **Lead-In (Part A)** A lead-in (Part A) of approximately 6-12 patients will be conducted prior to the randomized Phase II portion of the study to assess safety, tolerability, and available PK data for potential PK interaction. Prior to starting this combination therapy on Cycle 1 Day 1, patients in Part A will be given single agent LY3023414 200 mg every 12 hours (BID) during the initial week (called Week -1) to assess LY3023414 PKs at a steady state (Section 5.6) on Day -1 (last day of that Week -1). **Double-blinded, Placebo-Controlled Randomized Study (Part B)** After dose is established in Part A, a total of 132 patients will be randomized in a 1:1 ratio to enzalutamide 160 mg orally QD in combination with LY3023414 200 mg or matching placebo orally BID (Part B). Randomization will be stratified based on two factors: 1) the presence or absence of visceral disease (i.e. non-lymph node soft tissue disease), and 2) if patients previously received chemotherapy in the hormone-sensitive setting when commencing androgen deprivation therapy (ADT).
Study Drugs, Doses, and Modes of Administration:	Enzalutamide 160 mg will be administered orally QD. LY3023414 200 mg or matching placebo will be administered orally BID.
Inclusion Criteria:	1. Histologically or cytologically confirmed adenocarcinoma of the prostate. 2. Metastatic disease documented by positive bone scan or metastatic lesions on CT, MRI. If lymph node metastasis is the only evidence of metastasis, it must be ≥ 2 cm in diameter. 3. Prostate cancer progression documented by PSA and/or radiographic progression according to PCWG2 (Appendix F). PSA levels must have a starting value of at least 2.0 ng/mL that have increased on 3 occasions obtained a minimum of 1 week apart. 4. Prior abiraterone treatment completed at least 2 weeks prior to Cycle 1 Day 1. Patient must have failed prior abiraterone treatment to be eligible. 5. If patient has previously been treated with RA-223 dichloride, treatment must be completed at least 4 weeks prior to Cycle 1 Day 1 (minimum 4 week wash out period).

Inclusion Criteria, continued:	6. If a patient was treated with abiraterone, but their last treatment prior to enrolment was an anti-androgen other than abiraterone, PSA or symptomatic progression will need to be documented. The minimum washout period for these agents is as follows: • 6 weeksfor long acting agents (nilutamide, bicalutamide) • 4 weeks for short acting agents (flutamide). Patients whose PSA did not decline for 3 or more months in response to an anti-androgen given as a second line or later intervention will require only a 2-week washout prior to Cycle 1 Day 1. 7. Surgically or medically castrated, with testosterone levels of < 50 ng/dL. If the patient is being treated with LHRH agonists (patients who have not undergone orchiectomy), this therapy must be continued throughout the study. 8. Eastern Cooperative Oncology Group (ECOG) Performance status of 0 or 1. 9. Ability to swallow the study drugs whole. 10. Adequate hematologic function defined as: • Absolute neutrophil count (ANC) ≥1500/μL • Platelets ≥100,000/μL (transfusions to obtain this level are not allowed) • Hemoglobin ≥8 g/dL 11. Adequate liver function defined as: • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the upper limit of normal (ULN). If the liver has tumor involvement, AST and ALT equaling ≤5 times ULN are acceptable. • Total bilirubin ≤1.5 x ULN (unless the patient has Grade 1 bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin). 12. Adequate renal function defined as serum creatinine < 1.5 x ULN OR creatinine clearance > 45 mL/min Cockcroft-Gault formula for patients with serum creatinine > 1.5x ULN. 13. Adequate coagulation parameters, defined as International Normalization Ratio (INR) ≤ 2. Patients with history of blood clots may receive anticoagulation with low molecular weight heparin, central line prophylaxis-dose warfarin, or anti-factor Xa agents. 14. Patients who have partners of childbearing potential must be willing to use a method of birth control with adequate barrier protection as determined to be acceptable by the principal investigator and sponsor during the study and for 3 months after last study drug administration. 15. Male, Age ≥ 18 years. 16. Willingness and ability to comply with study and follow-up procedures. 17. Ability to understand the nature of this study and give written informed consent. 18. Availability of tumor tissue (formalin-fixed paraffin-embedded [FFPE] blocks) or unstained slides from any time since diagnosis of prostate cancer disease (i.e., archival tumor samples). If no tumor samples are available the patient might still be eligible following discussion between the investigator and the Medical Monitor.

Exclusion Criteria:	1. Patients that have received the following prior treatments for CRPC Prior cytotoxic chemotherapy. Note: Patients may have received docetaxel in the hormone-sensitive setting. a. PI3K/AKT /mTOR agent (including TORC1 and TORC2 inhibitors) b. Immune checkpoint inhibitors (e.g. inhibitors of CTLA4, PD1, PD1) c. Prior investigational new generation potent anti-androgen therapy (such as ARN 509). d. Prior treatment with enzalutamide. 2. Pathological finding consistent with small cell carcinoma of the prostate. 3. Concurrent use of other investigational agent(s). 4. Prior systemic treatment with an azole drug (fluconazole, itraconazole) within 4 weeks of Cycle 1 Day 1. 5. Known brain metastasis. 6. History of (a) seizure or any condition that may predispose to seizure (prior cortical stroke or significant brain trauma) within 12 months prior to Day 1 of Cycle 1; (b) loss of consciousness or transient ischemic attack within 12 months prior to Day 1 of Cycle 1. 7. Uncontrolled hypertension (systolic blood pressure [BP] ≥ 160 mmHg or diastolic BP ≥ 95 mmHg). Patients with a history of hypertension are allowed, provided blood pressure is controlled by anti-hypertensive treatment. 8. Have serious pre-existing medical conditions (at the discretion of the investigator). 9. Have known acute or chronic leukemia or current hematologic malignancies that, in the judgment of the investigator and sponsor, may affect the interpretation of results. 10. Have insulin-dependent diabetes mellitus. Patients with a type 2 diabetes mellitus are eligible if adequate control of blood glucose level is obtained by oral anti-diabetics as documented by HbA1c <7%. 11. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of oral therapy (e.g. ulcerative disease, uncontrolled nausea, vomiting, Grade ≥2 diarrhea, and malabsorption syndrome). 12. Have a history of New York Heart Association (NYHA) Class ≥3 congestive heart failure (CHF), QTc interval > 480 ms on screening electrocardiogram (ECG) per Friderica's formula, unstable angina, or myocardial infarction (MI) in 6 months prior to study drug administration. 13. Clinically significant electrolyte imbalance ≥ Grade 2. 14. Currently receiving treatment with therapeutic doses of warfarin sodium. Low molecular weight heparin and oral Xa inhibitors are allowed. 15. Have initiated treatment with bisphosphonates or approved RANK ligand (RANK-L) targeted agents (e.g. denosumab) ≤28 days prior to Day 1 of Cycle 1. 16. Concurrent serious infections requiring parenteral antibiotic therapy. 17. Have a second primary malignancy that in the judgment of the investigator and Medical Monitor may affect the interpretation of results. 18. Have an active, known fungal, bacterial, and/or known viral infection including: • human immunodeficiency virus (HIV) (screening not required) • hepatitis A (screening not required) • hepatitis B or C (screening not required). 19. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.

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Correlative Testing:	Blood and archival tumor samples will be collected to evaluate biomarker including but not limited to PI3K pathway components. Tumor and blood samples may be analyzed to explore potential biomarkers (e.g. gene signature[s]) predictive for response to study treatment. Mutational status, copy number variations, and/or protein products of cancer-related genes (including, but not limited to, *PIK3CA, PTEN,* or *RAS* and *AR-V7*) may be analyzed at a laboratory designated by the sponsor.
Statistical Methodology:	Determination of sample size: Sample size considerations for the randomized portion of the study (Part B) are based on the primary endpoint of PFS and one interim analysis of efficacy. The median PFS in the control arm of enzalutamide is estimated to be 4 months (Schrader et al. 2014) and a clinically meaningful hazard ratio (HR) is taken to be 0.7, equating to a median PFS in the enzalutamide plus LY3023414 arm of 5.7 months. Based on a 16-month accrual period (3 months ramp up plus 13 months full recruitment), a minimum of 9 months follow-up after the last patient has been randomized, and a lost to follow-up/non-compliance rate of no more than 10%, a total of 132 patients will be randomized in a 1:1 ratio between the two treatment arms. With a total of 92 events, the study will have at least 80% power to test the primary hypothesis using a one-sided, log rank test at the 0.20 significance level. Two interim analyses were planned at approximately 39% information rate and 82% information rate. Approximately 0% of total type I error and 20% of total type II error were spent at the first interim. The first interim analysis is planned to be conducted when a total of 36 PFS events are observed. Approximately 20% of total type I error and 0% of total type II error were spent at the second interim. The second interim analysis is planned to be conducted when a total of 75 PFS events are observed.

GU 115/I6A-MC-CBBD CONTACT INFORMATION

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Medical Monitor:	PPD Sarah Cannon Development Innovations 1100 Charlotte Ave., Suite 800 Nashville, TN 37203 PPD
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Sarah Cannon Development Innovations Enrollment Phone #:	1-866-346-1062

LIST OF ABBREVIATIONS

ADT	Androgen deprivation therapy
AE	Adverse event
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Adverse reaction
AST (SGOT)	Aspartate aminotransferase
BID	Twice daily
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CMP	Comprehensive metabolic profile
CR	Complete remission
CRPC	Castration Resistant Prostate Cancer
CT	Computerized tomography
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IP	Investigational product
IRB	Institutional Review Board
LHRH	Luteinizing hormone-releasing hormone
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OR	Objective response
ORR	Overall response rate
OS	Overall survival
PCWG2	Prostate Cancer Clinical Trials Working Group
PD	Progressive disease
PDx	Pharmacodynamic
PGx	Pharmacogenomics
PHI	Protected health information
PI3K	Phosphatidylinositol-3-kinase
PFS	Progression-free survival

LIST OF ABBREVIATIONS (continued)

PK	Pharmacokinetic
PR	Partial response
PSA	Prostate specific antigen
PTEN	Phosphatase and tensin homolog (gene)
QA	Quality assurance
QD	Once daily
RANK-L	Receptor activator of nuclear factor kappa-B ligand
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response rate
SAE	Serious adverse event
SAR	Suspected adverse reaction
SD	Stable disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
TTP	Time to progression
UAE	Unexpected adverse event
ULN	Upper limit of normal

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1. INTRODUCTION

1.1 Background

Prostate cancer is the most commonly diagnosed cancer in men with an estimated 233,000 new cases in the United States in 2014 and is the second-leading cause of cancer death in men with an estimated 29,480 deaths in 2014 (American Cancer Society 2014). The majority of patients are diagnosed with and treated for localized disease. However, a percentage of patients do present with metastatic disease at diagnosis, and others develop metastatic disease after completing definitive treatment. Androgen deprivation therapy (ADT) is the cornerstone of treatment for metastatic prostate cancer; the goal of this line of therapy is primarily palliative and for prolongation of survival, but not as a cure. Initial androgen deprivation is typically achieved with bilateral orchiectomy (surgical castration) or luteinizing hormone-releasing hormone (LHRH) therapy.

In 2014, it was shown that use of docetaxel at the time of ADT for metastatic hormone-sensitive prostate cancer prolonged overall survival (OS) by 13 months (Sweeney et al. 2014). Patients treated with androgen deprivation (medical or surgical castration) who develop disease progression in the presence of adequately depressed serum testosterone are considered to have castration-resistant prostate cancer (CRPC). Approved therapeutic options for the management of patients with CRPC include cytotoxic therapies (mitoxantrone, docetaxel and cabazitaxel), immunotherapy (sipuleucel T), an alpha particle emitting radioactive therapeutic agent (radium RA 223 dichloride), and second generation hormonal therapies (abiraterone and enzalutamide). The goal of treatment with these agents is to prolong survival, improve quality of life, and/or slow progression of the disease (Bennett et al. 2014).

1.2 Treatment for Prostate Cancer

Enzalutamide (Xtandi®, Astellas Pharma US, Inc.) is a second-generation androgen antagonist that targets multiple steps in the androgen signaling pathway with no reported agonistic effects (Sementas et al. 2013, El-Amm et al. 2013). The drug was originally approved by the Food and Drug Administration (FDA) in August 2012 for the treatment of patients with mCRPC who have previously received docetaxel (Ning et al. 2013). This approval was based on the results of a double-blind, placebo-controlled, randomized phase III trial that compared enzalutamide 160 mg orally daily with placebo (Scher et al. 2012). The study was stopped prematurely at the time of an interim analysis based on the significant improvement in OS that was observed with enzalutamide compared to placebo (18.4 vs. 13.6 months; hazard ratio (HR) 0.63; $p < 0.001$). The secondary endpoints of prostate-specific antigen (PSA) response rate (RR) (54% vs. 2%) and soft-tissue RR (29% vs. 4%) also favored the enzalutamide arm.

In September 2014, the FDA subsequently approved enzalutamide for patients with mCRPC regardless of prior docetaxel exposure based on data from the PREVAIL trial. These data demonstrated the efficacy of enzalutamide in prolonging OS in men with chemotherapy-naïve mCRPC who have failed to respond following ADT and have few or no symptoms (Beer et al. 2014). Men receiving enzalutamide experienced a statistically significant OS benefit compared to those receiving placebo (HR 0.71; 95% confidence interval (CI): 0.60-0.84, $p < 0.001$).

Radiographic progression-free survival (PFS) was also prolonged and there was a 17 month delay in the time to initiation of chemotherapy in men receiving enzalutamide. The RR in men with soft tissue metastatic disease was 59% in men receiving enzalutamide compared to 5% of patients receiving placebo; the median time to PSA progression was prolonged from 2.8 to 11.2 months with treatment. In addition, the percentage of men with PSA decline from baseline of >90% was 47% in the abiraterone-naïve population. Data has shown that a larger decline in PSA is associated with improvements in survival (Kelley et al. 1993).

There have not been large randomized trials to evaluate the efficacy of newer generation androgen antagonists after previous exposure to another newer generation androgen antagonist. Multiple smaller trials have evaluated the activity of enzalutamide in patients that have previously received abiraterone and vice versa. These data suggest the response rates and time to progression are vastly diminished when receiving enzalutamide after abiraterone exposure (Noonan et al. 2013, Loriot et al. 2013, Smith et al. 2014, Schrader et al. 2014, Badrising et al. 2014, Cheng et al. 2014). This is not surprising seeing as both agents target the androgen receptor. Specifically, Schrader, et al, studied enzalutamide in 35 patients with castrate-resistant prostate cancer previously treated with docetaxel and abiraterone and found a median time to progression on enzalutamide of 4.0 months which will serve as the benchmark for this trial (Schrader et al. 2014).

1.3 LY3023414

The phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway is one of the most frequently dysregulated pathways in cancer, and loss of phosphatase and tensin homolog (gene) (PTEN) leading to constitutive activation of the PI3K pathway, is common in advanced prostate cancer (Tang et al. 2014, Edlind et al. 2014, Hong et al. 2014, Bitting et al. 2013). Furthermore, preclinical studies demonstrate an association between the PI3K-AKT-mTOR and androgen receptor signaling axes that is potentiated as prostate cancer cells develop resistance to ADT and vice versa (Bitting et al. 2013, Carver et al. 2011). Similar crosstalk has been demonstrated between the estrogen receptor signaling pathway and the PI3K/AKT/mTOR pathway in breast cancer. Everolimus, an oral mTOR inhibitor, was recently approved in combination with exemestane for the treatment of women with advanced hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer after failure of treatment with letrozole or anastozole after demonstrating prolonged PFS in this setting (Baselga J. et al. 2012).

LY3023414 is an orally available, small molecule dual kinase inhibitor of class I PI3K isoforms and mTOR with good solubility across a wide pH range. *In vitro* kinase studies have shown that LY3023414 binds to the adenosine triphosphate (ATP) active site of PI3K to competitively inhibit phosphorylation of phosphatidylinositol-4, 5-bisphosphate (PIP2) at low nanomolar concentrations. In nonclinical studies, LY3023414 has demonstrated potent *in vivo* target inhibition that was linked to potent antitumor efficacy. The nonclinical toxicology profile of LY3023414 has enabled a safe clinical starting dose, and a benefit-risk profile acceptable for cancer treatment with the toxicities observed in animal species that are manageable, monitorable, and likely reversible. Clinical experience with LY3023414 is discussed in Section 1.3.3.

1.3.1 Safety Pharmacology

1.3.1.1 Nonclinical Toxicology

LY3023414 was evaluated in nonclinical toxicology studies up to 1 month in duration using daily oral dosing in rats and dogs to characterize the toxicity. Based on results from nonclinical studies in the rat and the dog, toxicities patients may experience include (but are not limited to) gastrointestinal toxicity, bone marrow and lymphoid organ toxicity (decreases in lymphocytes), and sores/scabbing of the skin. Pharmacologic effects of PI3K/mTOR inhibition related to glucose metabolism have also been observed, including hyperinsulinemia, hyperglycemia, and QT interval prolongation in nonclinical studies. In a rat embryo-fetal developmental pilot study of LY3023414, embryo-fetal lethality was seen along with an increase in fetal and litter incidence of external, visceral, and skeletal malformations.

For additional details on nonclinical toxicology data, see Section 5.2.1 of the Investigator's Brochure (IB).

1.3.1.2 Nonclinical Efficacy Pharmacology Summary

LY3023414 is a potent selective inhibitor of the class I PI3K isoforms mTOR and DNA-PK, with selectivity in kinase enzyme assays as an ATP competitive inhibitor of PI3K α (inhibition binding constant [Ki] of 8.5nM). LY3023414 demonstrated inhibitory activity against PI3K/mTOR pathway targets *in vitro* and *in vivo* as measured by phosphoprotein levels from cultured cells and tumor xenografts. LY3023414 showed antiproliferative and cell-cycle arresting effects in cultured cancer cells, and anti-angiogenesis activity via inhibition of in vitro vascular cord formation. LY3023414 has excellent solubility and oral bioavailability across a wide pH range, allowing for simple suspension formulations to be used for oral administration in nude mice. In xenograft tumor models, LY3023414 demonstrated dose-and time-dependent target inhibition, as well as antitumor efficacy in a wide range of tumor models (including renal cancer and non-small cell lung carcinoma [NSCLC]). The mouse pharmacokinetic (PK)/pharmacodynamics (PDx) model indicates a direct inhibition of downstream target phosphoproteins (such as, phospho Akt [pAkt], phospho 70S6K [p70S6K]). LY3023414 has potential for combination with standard of care agents to produce synergistic effects in cell culture and *in vivo* xenograft models.

1.3.2 Nonclinical Pharmacokinetics/Pharmacodynamics

Bioavailability of LY3023414 was 66% in dogs, and the clearance was less than hepatic blood flow. No accumulation of LY3023414 was noted following repeated dosing to rats and dogs. Also, no consistent gender differences in toxicokinetic parameters were observed in rats or dogs throughout the 1-month study. *In vivo* metabolism data showed that LY3023414 is metabolized predominantly via oxidation in rats and via oxidation and glucuronidation in dogs. In both species, LY3023414 was the largest circulating entity in plasma. Overall, clearance of LY3023414 in rats was primarily via metabolism while clearance in dogs involved metabolism as well as elimination via feces and urine. Fecal excretion was the major route of elimination for LY3023414-related radioactivity in both species.

1.3.3 Clinical Experience with LY3023414

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1.4 Rationale for the Study

The PI3K and AR signaling pathways regulate each other through complex reciprocal feedback mechanisms; upregulation of the AR pathway seems to counter the effect of small-molecule inhibitors of the PI3K/Akt pathway when administered as single agents (Wen et al. 2000, Lin et al. 2001, Carver et al. 2011). Like the AR signaling pathway in prostate cancer, there is evidence in breast cancer that the estrogen receptor signaling pathway interacts with the PI3K pathway in a similar fashion. In a phase 3 study of women with breast cancer who had progressed on an aromatase inhibitor, adding the mTOR inhibitor everolimus to exemestane produced a 6-month increase in progression-free survival (Baselga J. et al. 2012). This trial provided rationale for the study of combined targeting of the AR and PI3K pathways with enzalutamide and the PI3K inhibitor BEZ235 in PTEN-deficient prostate cell lines; this combination treatment resulted in a marked increase in apoptosis, while only modest cytostatic activity was seen with each individual agent (Carver et al. 2011). The Akt inhibitor AZD5363 in combination with enzalutamide showed similar synergistic activity in another preclinical study (Thomas et al. 2013), providing further support for clinical evaluation of a combination targeting the PI3K/Akt/mTOR pathway and the androgen-receptor axis in patients with prostate cancer. As enzalutamide is approved for patients with mCRPC in this setting and the PI3K pathway is frequently dysregulated in patients with prostate cancer, adding LY3023414 to enzalutamide is an attractive strategy for improving outcomes over enzalutamide alone.

This double-blinded, placebo-controlled, randomized Phase II study will evaluate PFS in men with mCRPC treated with enzalutamide with or without the PI3K/mTOR inhibitor LY3023414, who have shown disease progression on the adrenal inhibitor, abiraterone. Since a formal Phase Ib study has not been conducted with the combination regimen of LY3023414 and enzalutamide,

there will be a lead-in (Part A) of approximately 6-12 patients to assess safety, tolerability, and potential PK interaction. Prior to starting this combination therapy on Cycle 1 Day 1, patients in Part A will be given single agent LY3023414 every 12 hours (BID) during the initial week (called Week -1) to assess LY3023414 PKs at a steady state (Section 5.6) on Day -1 (last day of that Week -1). Once Part A is completed and the combination regimen is shown to be tolerated, all subsequent patients will be randomized to receive enzalutamide in combination with LY3023414 or in combination with a matching placebo (Part B).

In numerous clinical trials evaluating AR antagonists, some patients never have a PSA decline on abiraterone (after enzalutamide) or enzalutamide (after abiraterone), suggesting primary resistance to AR-targeted agents (Noonan et al. 2013, Loriot et al. 2013, Smith et al. 2014, Schrader et al. 2014, Badrising et al. 2014, Cheng et al. 2014). The mechanisms of resistance are multifactorial and a better understanding is needed. A recent report of constitutive AR splice variants (AR-Vs) may represent a potential resistance mechanism and AR-V7 may be the most important one. Recently, a prospective biomarker study showed that presence of AR-V7 in circulating tumor cells (CTC) of CRPC men on abiraterone or enzalutamide resulted in decreased progression-free survival (PSA, clinical, and radiographic) as compared to men whose CTCs were AR-V7 negative. Furthermore, some AR-V7 negative patients became positive during treatment, suggesting acquired resistance (Antonarakis et al. 2014). To explore potential mechanism of resistance to AR therapy, this study may evaluate the impact of variants of the androgen receptor and other biomarkers (including, but not limited to, PIK3CA, PTEN, RAS, or AR-V7) in blood and tissue.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- To compare progression-free survival (PFS) – PSA, radiographic, or Prostate Cancer Clinical Trials Working Group (PCWG2) symptomatic progression - in men with mCRPC who are receiving enzalutamide plus LY3023414 versus enzalutamide plus placebo using PCWG2 criteria.

2.2 Secondary Objectives

The secondary objectives of this study are:

- To compare the clinical response rates (RRs) in men with mCRPC who are receiving enzalutamide plus LY3023414 versus enzalutamide plus placebo who have measurable disease at baseline using Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1(Eisenhauer et al. 2009).
- To compare time to clinical (symptomatic or radiographic) and/or PSA progression (TTP) in men with mCRPC who are receiving enzalutamide plus LY3023414 versus enzalutamide plus placebo using PCWG2 criteria.

- To compare the maximum decline in PSA that occurs following treatment in men with mCRPC who are receiving enzalutamide plus LY3023414 versus enzalutamide plus placebo.
- To demonstrate the safety and tolerability of 200 mg twice daily (BID) oral LY3023414given in combination with 160 mg once daily (QD) oral dose of enzalutamide.
- To evaluate potential pharmacokinetic (PK) drug interactions (i.e. impact of enzalutamide on LY3023414 exposure) and to further characterize LY3023414 PK properties.
- To characterize the safety profile of enzalutamide plus LY3023414 as compared to enzalutamide plus placebo in this patient population.

2.3 Exploratory Objective

The exploratory objective of this study is:

- To collect blood and archival tissue for exploratory studies to identify potential biomarkers predictive of clinical efficacy of study treatment and disease progression in this patient population.

3. STUDY PATIENT POPULATION AND DISCONTINUATION

3.1 Inclusion Criteria

Patients must meet all of the following criteria in order to be included in the research study:

1. Histologically or cytologically confirmed diagno sis of adenocarcinoma of the prostate.
2. Metastatic disease documented by positive bone scan or metastatic lesions on CT, MRI. If lymph node metastasis is the only evidence of metastasis, it must be ≥ 2 cm in diameter.
3. Prostate cancer progression documented by PSA and/or radiographic progression according to PCWG2 criteria (Appendix F). PSA values must have a starting value of at least 2.0 ng/mL that have increased on 3 occasions obtained a minimum of 1 week apart.
4. Prior abiraterone treatment completed at least 2 weeks prior to Cycle 1 Day 1. Patient must have failed prior abiraterone treatment to be eligible.
5. If patient has previously been treated with RA-223 dichloride, treatment must be completed at least 4 weeks prior to Cycle 1 Day 1 (minimum 4 week wash out period).
6. If a patient was treated with abiraterone, but their last treatment prior to enrolment was an anti-androgen as last treatment prior to enrolment, PSA or symptomatic progression will need to be documented. The minimum washout period for these agents is as follows:
    - 6 weeks for long acting agents (nilutamide, bicalutamide)
    - 4 weeks for short acting agents (flutamide).

Patients whose PSA did not decline for 3 or more months in response to an anti-androgen given as a second line or later intervention will require only a 2-week washout prior to Cycle 1 Day 1.

7. Surgically or medically castrated, with testosterone levels of < 50 ng/dL. If the patient is being treated with LHRH agonists (patients who have not undergone orchiectomy), this therapy must be continued throughout the study.
8. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (Appendix A).
9. Able to swallow the study drugs whole.
10. Adequate hematologic function defined as:
    - Absolute neutrophil count (ANC) ≥1500/μL
    - Platelets ≥100,000/μL (transfusions to obtain this level are not allowed)
    - Hemoglobin ≥8 g/dL
11. Adequate liver function defined as:
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the upper limit of normal (ULN). If the liver has tumor involvement, AST and ALT equaling ≤5 times ULN are acceptable.
    - Total bilirubin ≤1.5 x ULN (unless the patient has Grade 1 bilirubin elevation due to Gilbert's disease or a similar syndrome involving slow conjugation of bilirubin)
12. Adequate renal function defined as serum creatinine < 1.5 x ULN OR creatinine clearance > 45 mL/min by Cockcroft-Gault formula for patients with serum creatinine > 1.5x ULN.
13. Adequate coagulation parameters, defined as International Normalization Ratio (INR) ≤ 2. Patients with history of blood clot may receive anticoagulation with low molecular weight heparin, central line prophylaxis-dose warfarin, or anti-factor Xa agents.
14. Patients who have partners of childbearing potential must be willing to use a method of birth control with adequate barrier protection as determined to be acceptable by the principal investigator and sponsor during the study and for 3 months after last study drug administration.
15. Male, Age ≥ 18 years.
16. Willingness and ability to comply with study and follow-up procedures.
17. Ability to understand the nature of this study and give written informed consent.
18. Availability of tumor tissue (formalin-fixed paraffin-embedded [FFPE] blocks) or unstained slides from any time since diagnosis of prostate cancer disease (i.e., archival tumor samples). If no tumor samples are available the patient might still be eligible following discussion between the investigator and the Medical Monitor.

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Patients that have received the following prior treatments for CRPC
    a. Prior cytotoxic chemotherapy Note: Patients may have received docetaxel in the hormone-sensitive setting.
    b. PI3K/AKT /mTOR agent (including TORC1 and TORC2 inhibitors) for the treatment of CRPC.
    c. Immune checkpoint inhibitors (e.g. inhibitors of CTLA4, PD1, PDL1)
    d. Prior investigational new generation potent anti-androgen therapy (such as ARN 509).
    e. Prior treatment with enzalutamide.
2. Pathological finding consistent with small cell carcinoma of the prostate.
3. Concurrent use of another investigational agent(s).
4. Prior systemic treatment with an azole drug (fluconazole, itraconazole) within 4 weeks of Cycle 1 Day 1.
5. Known brain metastasis.
6. History of (a) seizure or any condition that may predispose to seizure (prior cortical stroke or significant brain trauma) within 12 months prior to Day 1 of Cycle 1 ; (b) loss of consciousness or transient ischemic attack within 12 months prior to Day 1 of Cycle 1.
7. Uncontrolled hypertension (systolic blood pressure [BP] ≥ 160 mmHg or diastolic BP ≥ 95 mmHg). Patients with a history of hypertension are allowed, provided blood pressure is controlled by anti-hypertensive treatment.
8. Have serious pre-existing medical conditions (at the discretion of the investigator).
9. Have known acute or chronic leukemia or current hematologic malignancies that, in the judgment of the investigator and Medical Monitor, may affect the interpretation of results.
10. Have insulin-dependent diabetes mellitus. Patients with a type 2 diabetes mellitus are eligible if adequate control of blood glucose level is obtained by oral anti-diabetics as documented by HbA1c <7%.
11. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of oral therapy (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea Grade ≥2, and malabsorption syndrome).

12. Have a history of New York Heart Association (NYHA) Class ≥3 congestive heart failure (CHF), QTc interval > 480 ms on screening electrocardiogram (ECG) per Friderica's formula, unstable angina, or myocardial infarction (MI) in 6 months prior to study drug administration.
13. Clinically significant electrolyte imbalance ≥ Grade 2.
14. Currently receiving treatment with therapeutic doses of warfarin sodium. Low molecular weight heparin and oral Xa inhibitors are allowed.
15. Have initiated treatment with bisphosphonates or approved RANK ligand (RANK-L) targeted agents (e.g. denosumab) ≤28 days prior to Day 1 of Cycle 1.
16. Concurrent serious infections requiring parenteral antibiotic therapy.
17. Have a second primary malignancy that in the judgment of the investigator and sponsor may affect the interpretation of results.
18. Have an active, known fungal, bacterial, and/or known viral infection including:
    - human immunodeficiency virus (HIV) (screening not required)
    - hepatitis A (screening not required)
    - hepatitis B or C (screening not required).
19. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.

3.3 Discontinuation from Study Treatment

Patients will be discontinued from study treatment for any of the following reasons:

- Disease progression (except PSA progression)
- Irreversible or intolerable AE thought to be related to study drugs
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (this will be at the investigator's discretion)
- Inability of the patient to comply with study requirements or lost to follow-up
- Patient requests to discontinue treatment
- Patient withdraws consent from the study
- Investigator or Sponsor team, for any ethical, medical, or scientific reason, while considering the rights, safety, and well-being of the patient(s), stops the study or stops the patient participation in the study.
- Any patient requiring an AE-related dose delay of more than 21 days due to a study drug related AE must be discontinued from the study, unless discussed with the Medical Monitor.

After discontinuation from protocol treatment, patients must be followed for AEs for a minimum of 30 days, after their last dose of study drugs. All new AEs possibly related to the study drugs

occurring during this 30 day period must be reported and followed until resolution, unless, in the opinion of the investigator, these values are not likely to improve, because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patients' medical records and as a comment in the electronic Case Report Form (eCRF).

All patients who have Grade 3 or 4 laboratory abnormalities (per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.03) (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf), at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the investigator, not likely that these values are to improve. In this case, the investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment on the CRF.

4. STUDY REGISTRATION

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks, and discomforts. Institutional Review Board (IRB) approval of this protocol and consent form is required. Eligible patients who wish to participate in the study will be enrolled into the study.

Registration must occur prior to the initiation of protocol therapy. Patient registration will be performed by Sarah Cannon Development Innovations and will be outlined in the Study Reference Manual.

In Part B, patients who agree to participate in the study and meet eligibility criteria will be randomly assigned treatment (1:1) to LY3023414 plus enzalutamide or placebo plus enzalutamide stratified by visceral disease status (present or absent) and prior chemotherapy in the hormone-sensitive setting when commencing ADT (yes or no). Randomization will be performed using an IWRS (see Study Manual).

5. STUDY DESIGN

This is a double-blinded, placebo-controlled, randomized Phase II study of the combination of enzalutamide plus LY3023414 versus enzalutamide plus placebo in patients with mCRPC who have shown disease progression on abiraterone.

Lead-In (Part A)

Since a formal Phase Ib study has not been conducted with the combination regimen of LY3023414 and enzalutamide, there will be a lead-in (Part A) of approximately 6-12 patients to assess safety, tolerability, and available PK data for potential PK interaction.

Prior to starting this combination therapy on Cycle 1 Day 1, patients in Part A will be given single agent LY3023414 every 12 hours (BID) during the initial week (called Week -1) to assess LY3023414 PKs at a steady state (Section 5.6) on Day -1 (last day of that Week -1). Thereafter, patients will receive 200 mg of LY3023414 BID in combination with 160 mg of enzalutamide QD beginning Cycle 1 Day 1. A treatment cycle will be defined as 28 days. LY3023414 PK

will be again evaluated during the combination therapy dosing (in Cycle 1) to explore any potential intra-patient PK interactions with enzalutamide. If no safety signals are reported and the PK profile is acceptable then this combination regimen (LY3023414 200 mg BID + enzalutamide 160 mg QD) will be the regimen to be studied in the randomized part of the study (Part B) which will commence without the single agent dosing Week -1.

After at least 6 patients have been treated for a full cycle in Part A, a Safety Internal Monitoring Committee (SIMC) will conduct a review of the safety and available PK data prior to the initiation of the randomized part (Part B) of the study. If 2 (or more) of 3 or 2 (or more) of 6 patients in Part A experience DLTs as defined in Section 5, 3 to 6 additional patients will be treated at the next lower dose of LY3203414 defined in Table 3 (150 mg PO BID) and assessed for DLTs prior to initiation of the randomized Part B portion of the study. If there is a PK interaction deemed to be clinically significant by the SIMC, the SIMC may recommend enrollment of approximately 6 additional patients to further evaluate the safety of the combination, or explore other doses of LY3023414 in combination with enzalutamide. In the case of unacceptable and/or unmanageable toxicity of the combination the SIMC may decide to discontinue the study upon completion of Part A or proceed with a lower LY3023414 dose level tolerated in combination with enzalutamide. All outcomes from these safety reviews will be communicated in a timely manner to the participating investigators so that they may notify their IRBs. No amendment will be needed to proceed with an adjusted dose level of LY3023414.

The SIMC will, at a minimum, be composed of a Sponsor-Assigned Clinical Research Physician, Study Chair, Medical Monitor, Safety Scientist, and Biostatistician.

A toxicity will be considered dose-limiting if it occurs within the first cycle of treatment (28 days) to Part A patients and is deemed at least possibly related to study drug. Dose-limiting toxicities will be defined as any one of the following AEs:

- Grade 4 thrombocytopenia; Grade 4 neutropenia ≥7 days; Grade ≥3 febrile neutropenia; and Grade ≥3 thrombocytopenia with Grade ≥2 hemorrhage;
- Grade ≥ 3 non-hematologic toxicity despite maximal medical management with the exception of:
    - Diarrhea, nausea, or vomiting that resolves to ≤ Grade 2 within 48 hours
    - ALT/AST elevation that resolves to ≤ Grade 2 within 7 days
    - Grade 3 mucositis that resolves to ≤ Grade 2 within 7 days. Grade 4 mucositis of any duration will be considered a DLT.
    - Grade 3 fasting hyperglycemia that resolves to ≤ Grade 2 within 7 days. Grade 4 hyperglycemia of any duration that results in intensive care unit admission will be considered a DLT.
    - Grade 3 fatigue that resolves to ≤ Grade 2 within 5 days.
    - Grade 3 hypertension controlled with medical therapy.
    - Any lab abnormalities that are not clinically significant and resolve in 72 hours.
- Hy's law: Hepatocellular injury defined as ALT (or AST) > 3X ULN and total bilirubin > 2X ULN with no significant cholestasis (ALP< 2X ULN) and no other cause which explains the abnormality in liver tests.
- Treatment delay of ≥14 days due to unresolved AE
- Any other study drug related AE that is clinically significant, does not respond to supportive care, or is judged to be an unacceptable and/or unmanageable study drug related AE by the investigator in collaboration with the Medical Monitor.

Determination of Dose-Limiting Toxicities

The patient population used for determination of DLTs will consist of patients who have met the minimum safety evaluation requirements of the study, and/or who have experienced a DLT. Minimum safety requirements will be met if, during Cycle 1 of treatment, the patient receives at least 75% of study drug regimen (LY3023414 and enzalutamide) and is observed for at least 28 days following the first dose of study drugs.

Double-blinded, Placebo-Controlled Randomized Study (Part B)

Once Part A has been evaluated by the SIMC and the dose and schedule of LY3023414 in combination with enzalutamide is selected to move forward, the double-blinded, placebo-controlled randomized portion (Part B) will be initiated.

Approximately 132 patients will be enrolled in Part B and they will be randomized (1:1) to one of two treatment groups:

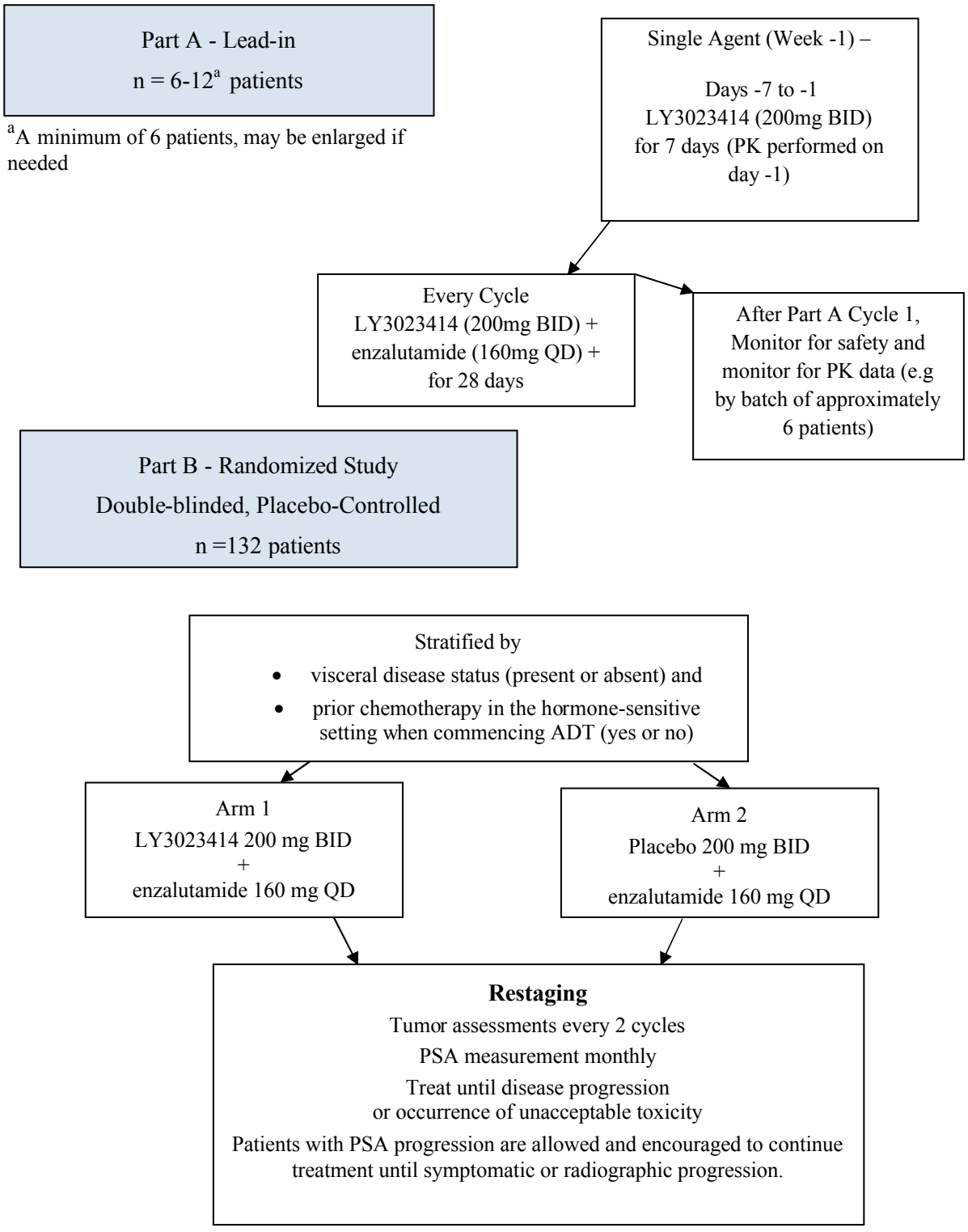
- Arm 1 (experimental group) enzalutamide plus LY3023414
- Arm 2 (control group) enzalutamide plus matching placebo

LY3023414 (200 mg BID) or matching placebo will be administered orally BID. All patients will receive enzalutamide 160 mg QD.

A treatment cycle will be defined as 28 days. Response to treatment will be evaluated every 2 cycles using RECIST v 1.1 (Appendix E) and per PCWG2 criteria for patients with bone disease (see Appendix E) and monthly by PSA. Patients will be treated until disease progression (radiographic or PCWG2 symptomatic progression), death, toxicity requiring cessation of treatment, or withdrawal of consent. Patients that discontinue on the study will not be replaced. Patients with PSA progression are allowed and encouraged to continue treatment until clinical (symptomatic or radiographic) progression.

The Study Schema is presented in Figure 1.

Figure 1 Study Schema



5.1 Treatment Plan

Patients will self-administer LY3023414 or matching placebo and enzalutamide daily by oral administration. The order in which these drugs and/or placebo are taken is not relevant to this study.

On the PK days (see Section 5.6), patients will be asked hold study drugs administration until the pre-dose PK sample at the investigating site has been collected.

5.1.1 LY3023414 or Placebo

LY3023414 or matching placebo will be self-administered by the patient BID on continuous daily dosing.

Patients should take the morning and evening doses of LY3023414 approximately 12 hours apart (preferably within a 10- to 14-hour range). LY3023414 or matching placebo should be taken with a glass of water at approximately the same time each day. LY3023414 or matching placebo can be taken with or without food. Patients should swallow the capsules as a whole and should not chew or crush them.

If the patient misses a dose of LY3023414 or matching placebo, the patient should take the dose as soon as possible, but not less than 6 hours before the next dose is due for twice daily dosing. If the next dose is due in less than 6 hours, the patient should skip the missed dose and take the next dose as scheduled.

If vomiting occurs after taking LY3023414 or matching placebo, the patient should be instructed not to retake the dose. Patients should take the next scheduled dose of LY3023414 or matching placebo. If vomiting persists the patient should contact the investigator.

LY3023414 or matching placebo compliance will be assessed by pill counts on Day 1 of each cycle. The research staff will count and document the amount of LY3023414 or matching placebo taken and returned by the patient.

5.1.2 Enzalutamide

All patients will receive a standard regimen of enzalutamide 160 mg (four 40 mg capsules) QD for continuous daily dosing.

Enzalutamide will be self-administered by the patient. Enzalutamide will be taken together with one of the two daily doses of LY3023414 or matching placebo. Enzalutamide can be taken with or without food. Enzalutamide capsules should be swallowed whole. Patients should not chew, dissolve, or crush them.

If a dose of enzalutamide is missed, the patient should take it as soon as they remember. If the patient forgets to take his dose before 6:00 pm, then the dose should be withheld that day and the enzalutamide should be restarted the following day. However, patients that experience fatigue while taking enzalutamide may take it at night after Cycle 1 of treatment. The Medical Monitor should be consulted for PK logistics post Cycle 1 for patients who require dosing at night. Enzalutamide achieves steady state by day 28 of treatment.

At each new cycle, patients will be prescribed sufficient supplies until the next visit.

Enzalutamide drug compliance will be assessed at the beginning of a new cycle.

5.2 Treatment Duration

The end of the study is defined as the last visit of the last patient on the study.

Patients will be evaluated for toxicity and symptomatic progression at the start of each cycle. PSA will be measured at the beginning of each 28 day cycle. Prior to Cycle 3 and after every 2 cycles, restaging will occur with imaging and PSA as defined in Appendix D (Schedule of Assessments).

Patients will be allowed to continue on therapy as long as they do not meet the discontinuation criteria listed in Section 3.3, and are considered, by the investigator, to still be receiving clinical benefit (patients may continue on therapy after progression criteria have been met only if they are considered to be receiving clinical benefit after consulting with the study Medical Monitor and depending upon availability of study drug).

5.3 Treatment Assignment Unblinding Procedures

It is very important for all study personnel to respect the blinded nature of the study; there is no intention to routinely unblind individual patients at any time prior to the conclusion of the study. In the event of an emergency unblinding thought to be related to LY3023414 (or matching placebo) or a medication error, a request for urgent safety unblinding should be made to the Medical Monitor. Emergency unblinding will be allowed only when approved by the Medical Monitor. The investigator may hold administration of LY3023414 or matching placebo while waiting for a decision on unblinding to be made. All unblinding must be documented by the site.

Examples of emergencies requiring unblinding include:

- A life-threatening, unexpected AE that is thought to be related to LY3023414 and for which unblinding would change or influence treatment decisions.
- Medication error, such as an accidental overdose, that would warrant unblinding in order to more effectively manage toxicity.

For additional information regarding unblinding procedures please refer to the Study Reference Manual.

5.4 Concomitant Medications

Patients will be instructed not to take any additional medications except those listed in Section 5.4.1 below during the course of the study without prior approval of the investigator and Sponsor. At each visit, the patient will be asked about any new medications he is taking or has taken after the start of the study drug.

5.4.1 Permitted Concomitant Medications

Premedication with anti-emetics is allowed according to standard practice guidelines.

Medications may be administered for maintenance of existing conditions prior to study enrollment or for a new condition that develops while on study, including but not limited to the following:

- Bisphosphonate use, as recommended according to practice guidelines
- Receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor use, as recommended according to practice guidelines
- Anticoagulation with coumadin -derivatives will not be permitted. However, a maximum daily dose of 1 mg will be permitted for port line patency. Should a thrombotic event occur while the patient is receiving treatment the patient may continue, but low molecular weight heparin (LMWH) will be the preferred treatment.
- Patients who develop hyperglycemia during the study should be treated according to the American Diabetes Association guidelines. It is recommended to start treatment with metformin.

Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the investigator with the exception of those listed in Section 5.4.2.

5.4.2 Prohibited Concomitant Medications

The following treatments are prohibited while in this study:

- No other investigational therapy should be given to patients. No anticancer agents other than the study medications should be given to patients. If such agents are required for a patient, then the patient must first be withdrawn from the study.

5.4.3 Concomitant Medications to be avoided

The following treatments should be avoided while in this study:

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer (see Appendix I).

- Avoid strong of CYP2C8 inhibitors, as they can increase the plasma exposure to enzalutamide (Appendix I). If co-administration is necessary, consider reducing the dose of enzalutamide.
- Avoid strong or moderate CYP3A4 or CYP2C8 inducers as they can alter the plasma exposure of enzalutamide (Appendix I).
- Avoid CYP3A4, CYP2C9 and CYP2C19 substrates with a narrow therapeutic index, as enzalutamide may decrease the plasma exposures of these drugs. If enzalutamide is co-administered with warfarin (CYP2C9 substrate), conduct additional INR monitoring.

LY3023414 is a weak inhibitor of CYP3A4 and from *in vitro* data the major cytochrome P450 involved in the clearance of LY3023414 was identified as CYP3A (~80%):

- Avoid strong inhibitors of CYP3A4 and strong and moderate inducers of CYP3A4 (other than enzalutamide)
- Drugs causing QTc interval prolongations should be avoided (Appendix H)

Approximately 20% of LY3023414 is metabolized by CYP1A2. Therefore,

- Particular attention should be paid in recording CYP1A2 inducers/inhibitor in the concomitant medication (Appendix I).
- Smoking should be avoided and for all patients smoking habit should be recorded.

Patients receiving these agents should be treated with other equivalent medications if possible:

- Patients should avoid grapefruit, Seville oranges, or Star fruit.
- Herbal preparations/medications should be avoided throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.

5.5 Correlative Studies

Biological samples (i.e., blood and fresh or archival tissue samples, primary or metastatic lesions) will be requested and may be analyzed to identify potential biomarkers predictive of clinical efficacy of the study drugs and disease progression in this patient population. The time points for the collection of samples for correlative testing are specified in Appendix D.

Tumor biopsy specimens from the primary site or from metastatic lesions from all patients with available archived tissue will be collected. Tumor and blood specimens may be tested for biomarkers including, but not limited to, mutation and expression of *PIK3CA*, *PTEN*, or *RAS* and others. Samples may be assessed by targeted exome sequencing or other techniques as scientifically appropriate. The status of these biomarkers will be analyzed in an attempt to correlate to the clinical patient outcome (e.g. RR and PFS). Blood samples drawn from the patients at baseline, Day 1 of Cycle 1, and every 2 cycles thereafter, and at end of treatment visit may be assessed to explore potential gene signature(s) for clinical benefit to study treatment, such as *PIK3CA*, *PTEN*, or *RAS* and *AR-V7*.

Information regarding shipment, handling, and length of retention time, etc. of tissue and blood will be provided in the Laboratory Manual.

5.5.1 Samples for Pharmacogenetics and/or Tailoring Biomarkers

Collection of samples for biomarker research is also part of this study. Blood and Tissue samples will be collected.

Samples for biomarker research to be collected from all patients in this study are the follow ing:

- blood
- tumor tissue (if available; archival or fresh, primary or metastatic lesions)

Samples may be tested to identify biomarkers predictive of clinical efficacy and disease progression in this patient population.

Samples will be stored and analysis may be performed on biomarker variants thought to play a role in PI3K pathways, including, but not limited to, *PIK3CA*, *PTEN*, or *RAS* and *AR-V7*, to evaluate their association with observed clinical outcomes to study treatment.

In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic biomarker samples may be genotyped and analysis may be performed to evaluate a genetic association with response to LY3023414 and enzalutamide. These investigations may be limited to a focused candidate gene study or, if appropriate, genome wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic biomarker samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis. The samples will be coded with the patient number and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the LY3023414.

Samples will be destroyed according to a process consistent with local regulation.

5.6 Pharmacokinetic Assessments

LY3023414 mean half-life (t1/2) is approximately 2 hours ranging from 1 to 5 hours hence a 12 hour period post dose is suitable to investigate LY3023414 exposure. More information about LY3023414 PK is available in Section 1.3.3 and in the LY3023414 IB.

CCI

As stated in Section 1.3.3, LY3023414 is a weak inhibitor of CYP3A4. In addition, the in-vitro data indicate that LY3023414 is NOT an inducer or an inhibitor of CYP2C8, the major metabolic enzyme for enzalutamide. Consequently, formal, within patients, comparison of enzalutamide AUC after administration of enzalutamide alone and in combination with LY3023414 will NOT be done in this CBBD study because it is not anticipated that LY3023414 will significantly increase (i.e. > 1.5 fold change) enzalutamide exposure.

LY3023414 is possibly a CYP3A4 substrate, and as enzalutamide is a strong CYP3A4 inducer, enzalutamide may impact LY3023414 AUC.

For all the reasons outlined above, LY3023414 exposure will be investigated in all Part A patients (i.e. in at least 6 and up to 12 patients) at steady state after single-agent LY3023414 monotherapy for 7 days and after combination therapy with enzalutamide for at least 15 days (see Table 1 and Appendix J). The enzalutamide mean half-life (t1/2) is approximately 140 hours and therefore steady state following daily administration can be considered to be almost reached (at least 80 %) after 15 days. These data will enable, formal, within patients, comparison of LY3023414 AUC after administration of LY3023414 alone and in combination with enzalutamide.

Based on the limited intra-patient variability in LY3023414 exposure (~25%) in study CBBA, the sample size of 6 to 12 patients is adequate to investigate the impact of enzalutamide on LY3023414 exposure. Enzalutamide is anticipated to decrease LY3023414 exposure. A decrease of 30 % of LY3023414 exposure in the presence of enzalutamide should be detected with a sample of 6 to 12 patients. The 90% confidence interval around a mean value of 1.5 for the ratio LY3023414 AUC alone: LY3023414 AUC in the presence of enzalutamide should be 1.2 to 1.8 for a sample size of 10 patients.

Furthermore, the plan includes investigation of enzalutamide PK to determine enzalutamide AUC at steady state (on day 15) when administered in combination with LY3023414 in all Part A patients (i.e. in at least 6 and up to 12 patients). Enzalutamide exposure will be compared to historical data following enzalutamide single agent therapy. Additionally, the PK parameters of the active N-desmethyl enzalutamide metabolite may be determined.

LY3023414 concentration will be characterized in whole blood (per the schedule presented in Table 1). Venous blood will be drawn at each time point using a micro sampling technique (dried blood spot [DBS] sampling) for quantifying LY3023414 concentration. A hematocrit value (which can be obtained from a complete blood count [CBC]) is required within +/- 2 days of sampling for PK. In Part A, classical plasma samples will also be drawn to compare LY3023414 concentrations. Detailed instructions and supplies for the collection, handling, and shipping of blood and plasma samples will be provided by either the sponsor or Sarah Cannon Development Innovations. LY3023414 will be assayed using a validated DBS or plasma liquid chromatography (LC)-mass spectrometry (MS)/MS method.

Pharmacokinetic studies will be done during Part A to determine plasma levels of enzalutamide following concurrent administration of enzalutamide with LY3023414. Additionally, concentrations of the active N-desmethyl enzalutamide metabolite may be quantified. The schedule for collection of whole blood specimens is presented in Table 1. Detailed instructions and supplies for the collection, handling, and shipping of plasma samples will be provided by either the Sponsor or Sarah Cannon Development Innovations. Enzalutamide will be assayed using a validated LC-MS/MS method.

Table 1 Pharmacokinetic Sample Collection Times – Part A Patients only

Study Visit	Collection Time (± 15 minutes)	LY3023414 PK-DBS/Plasma Sample	Enzalutamide PK Plasma Sample
Week -1, Day -1[a]	Pre-dose 1.5, 3, and 6 hours post LY3023414 dose	✓	
Cycle 1, Day 1 [a]	Pre-dose of LY3023414 and enzalutamide	✓	
Cycle 1, Day X (Day 15 –Day 28)[b, c, d]	Pre-dose of LY3023414 and enzalutamide 1.5, 3, and 6 hours post LY3023414 dose	✓	✓
Cycle 1, Day X + 1[b, c, d]	Pre-dose of LY3023414 and enzalutamide	✓	✓
Cycle 2, Day 1 [b, c]	Pre-dose of LY3023414 and enzalutamide 1.5 hours post LY3023414 and enzalutamide dose	✓	✓
Cycle 3, Day 1 [b, c]	Pre-dose of LY3023414 and enzalutamide 1.5 hours post LY3023414 and enzalutamide dose	✓	✓

a: On Day -1, last day of Week -1, the morning LY3023414 dose is given and PK samples taken to estimate the exposure of LY3023414 as monotherapy. On Day 1, a pre-dose sample is taken prior to initiation of the combination treatment LY3023414 + enzalutamide (this sample is about 12 hours post the Day-1 evening LY3023414 dose)

b: It is planned that the morning dose of LY3023414/placebo will be taken together/concomitantly with the daily dose of enzalutamide.

c: On PK days, pre-dose measurements and dose administration will be done in a fasted state. Patients should remain fasted for 1 hour post- dose.

d: Day X of Cycle 1 is any day between Day 15 and Day 28.

In addition, limited blood sample collection is planned in Part B of the study to assess LY3023414 steady state concentrations in a larger patient population as presented in Table 2.

Table 2 Pharmacokinetic Sample Collection Times – Part B Patients only

Study Visit	Collection Time (± 15 minutes)	LY3023414 PK-DBS Sample
Cycle 2, Day 1	Pre-dose of LY3023414/placebo and enzalutamide 1.5 hours post LY3023414/placebo dose [a, b]	✓
Cycle 3, Day 1	Pre-dose of LY3023414/placebo and enzalutamide 1.5 hours post LY3023414/placebo dose [a, b]	✓

a: It is planned that the morning dose of LY3023414/placebo will be taken together/ concomitantly with the daily dose of enzalutamide.

b: On PK days, pre-dose measurements and dose administration will be done in a fasted state. Patients should remain fasted for 1 hour post- dose.

On the days when PK samples are collected, patients will not take their LY3023414/ placebo and enzalutamide dose until after the pre-dose specimen is obtained.

On the PK days the date and time and amount of the LY3023414/placebo doses associated with the LY3023414 PK samples must be recorded in the eCRF.

For Part A, on the PK days of combination therapy, the date and time and amount of the enzalutamide doses associated with the enzalutamide PK samples must be recorded in the eCRF.

The date and time of samples collection will be recorded in the requisition form.

Samples for Drug Concentration Measurements Pharmacokinetics

A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and Study team.

Bioanalytical samples collected to measure LY3023414 and enzalutamide concentrations will be retained for a maximum of 1 year following last patient visit for the study.

5.7 Pharmacogenomic (PGx) Assessement

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology, and/or the molecular subtype of the disease being treated.

In the event of an unexpected AE, the samples may be genotyped and analysis may be performed to evaluate a genetic association with response to LY3023414. These investigations may be limited to targeted exome sequencing approach of known targets involved in drug metabolism or, if appropriate, genome-wide association studies may be performed to identify regions of the genome associated with the variability observed in drug response.

The PGx sample is part of the biomarker sample. Therefore, there is no separate kit for PGx samples. Samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad

exploratory unspecified disease or population genetic analysis. Samples will be identified by the patient number (coded) and stored for up to 15 years after the last patient visit for the study at a facility selected by the sponsor. The sample and any data generated from it can only be linked back to the patient by investigator site personnel.

6. DOSE MODIFICATIONS

If an AE occurs, the AE will be graded utilizing the NCI CTCAE v 4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf), and appropriate supportive care treatment will be administered as needed to decrease the signs and symptoms thereof. Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity.

Doses of LY3023414 will be modified based on hematologic and non-hematologic toxicity. If dose reductions are necessary, they will be permanent for the remainder of the treatment. No dose reductions due to study drug related toxicities of LY3023414 or enzalutamide are permitted in Part A during Cycle 1.

During Part B and after Cycle 1 in Part A, dose reductions for enzalutamide and LY3023414 may be adjusted according to Table 3. If the responsible study drug can be identified, it may be adjusted according to the dose modification table and the patient may continue with the other study drug, as appropriate. If the patient is receiving the lowest allowable dose and experiences an AE requiring a dose reduction, the offending study drug should be discontinued. If the offending study drug is discontinued, the patient may continue single-agent treatment.

If any AE occurs, it should resolve to a level that, in the opinion of the investigator, is reasonable to allow for continuation of treatment taking into consideration the recommendations below.

If a patient experiences a Grade 3 drug-related AE or an intolerable Grade 2 AE:

- LY3023414 dosing should be withheld until symptoms improve to ≤ Grade 1 or baseline then may be resumed at a reduced dose according to Table 3. In part B only, re-escalation of LY3023414 may be considered if clinically warranted, following discussion and approval by the medical monitor.
- Enzalutamide dosing must be withheld for one week or until symptoms improve to ≤ Grade 2 then may be resumed per the package insert at the same or reduced dose according to Table 3.

Permanently discontinue study drugs for Grade 4 adverse events. Re-challenge of patients with dose-reduced study drug(s) following recovery from Grade 4 AEs may be considered on a case-by-case basis in consultation with the medical monitor.

Grade 3 or 4 laboratory changes that are not clinically significant and which can be corrected within 48 hours may not require dose modification.

If the AE is clearly attributable to one drug, then dose reduction of only that drug is necessary. For toxicities possibly caused by both drugs, the dose levels of both should be reduced.

Any patient requiring an AE-related dose delay of more than 21 days from the intended day of the next scheduled dose due to a study drug related AE must be discontinued from the study, unless discussed with the Medical Monitor.

Dose delays within a cycle do not alter the start of the next scheduled cycle. Assessments for any missed visit will be done when the patient returns to the clinic. These would need to be entered into the EDC as unscheduled.

A maximum of two dose reductions per drug are allowed in this study. If more than two dose reductions of study drug(s) are necessary for a patient, the responsible agent will be discontinued.

Table 3 Dose Level Modifications

Dose Level	LY3023414 or Placebo	Enzalutamide
Starting Dose	200 mg PO BID	160 mg PO QD
Dose Level -1	150 mg PO BID	120 mg PO QD
Dose Level -2	100 mg PO BID	80 mg PO QD

7. STUDY ASSESSMENTS AND EVALUATIONS

7.1 Overview

All patients should visit the study center on the days specified within this protocol. The complete Schedule of Assessments for this study is shown in Appendix D. The baseline physical examination, medical history, ECOG performance status, CBC, Comprehensive Metabolic Profile (CMP), urinalysis, prothrombin time (PT)/INR, and blood for biomarker analysis should be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1, they do not have to be repeated on Day 1. Scans, ECG, testosterone levels, and PSA must be performed ≤4 weeks prior to initiation of treatment.

7.2 Baseline Study Assessments

The following information will be collected and procedures will be performed for each patient at screening:

- Written informed consent prior to any other study-related procedures (≤28 days prior to initiation of treatment)
- Medical history
- Physical examination, measurements of height (first visit), weight
- Vital signs (resting heart rate, blood pressure [BP], and oral temperature)
- ECOG performance status (Appendix A)
- Electrocardiogram (ECG) performed locally (repeat if clinically indicated)
- Concomitant medication review

- CBC with 3-part differential and platelets
- Fasting CMP to include: glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, calcium, carbon dioxide (CO_2), alkaline phosphatase (ALP), AST, ALT, total bilirubin, total protein albumin, phosphorus, and lactate dehydrogenase (LDH).
- PT/INR (repeat if clinically indicated)
- Blood for biomarker analysis
- Blood for testosterone level
- HbA_{1c} blood sample
- Urine dipstick
- PSA blood sample
- CT scan of chest
- CT scan of the abdomen and pelvis
- Bone scan- technetium only
- Archived or fresh tumor tissue (see Section 5.5)

7.3 Study Treatment Assessments

7.3.1 Single Agent LY3023414 Day -7 (Part A only, Week -1)

- Physical examination including measurement of weight
- Vital signs (unless collected within the previous 72 hours)
- ECOG PS (unless collected within the previous 72 hours [see Appendix A])
- AE assessment
- Concomitant medication review
- CBC, including 3-part differential and platelets (unless collected within the previous 72 hours)
- Fasting CMP plus LDH (unless collected within the previous 72 hours)
- PT/INR (repeat only if abnormal at baseline or if clinically indicated)
- Urine dipstick (unless collected within the previous 72 hours)
- PK blood samples (**Day -1**, pre-dose,1.5 , 3, and 6 hours post LY3023414 dose ± 15 minutes [see Table 1])
- PSA blood sample (unless collected within the previous 72 hours)
- Dispense LY3023414 and patient diary

7.3.2 Cycle 1 – Day 1

- Physical examination including measurement of weight (Part B patients only)
- Vital signs (unless collected within the previous 72 hours)
- ECOG PS (unless collected within the previous 72 hours [see Appendix A])
- ECG- predose
- AE assessment
- Concomitant medication review
- CBC, including 3-part differential and platelets (unless collected within the previous 72 hours)
- Fasting CMP plus LDH (unless collected within the previous 72 hours)
- PT/INR (repeat only if abnormal at baseline or if clinically indicated)
- PK blood sample – **Part A patients only** (pre-dose of LY3023414 and enzalutamide ± 15 minutes [see Table 1])
- PGx blood sample (If the sample is not collected C1D1, it can be collected anytime during C1 or C2)
- Biomarker blood sample (pre-dose)
- PSA blood sample (unless collected within the previous 72 hours)
- Urine dipstick (unless collected within the previous 72 hours)
- Dispense LY3023414 or matching placebo and patient diary (Part A patients will not receive a placebo)
- Dispense enzalutamide

7.3.3 Cycle 1 – Day 15 (Part A patients only)

- Vital signs
- ECOG PS (see Appendix A)
- AE assessment
- Concomitant medication review
- Study drug compliance assessment
- CBC, including 3-part differential and platelets
- Fasting CMP plus LDH
- PK blood sample (any day [day X] between Day 15 and Day 28, pre-dose of LY3023414 and enzalutamide, 1.5 , 3, and 6 hours post LY3023414 dose ± 15 minutes [see Table 1]).

A hematocrit value (which can be obtained from a CBC) is required within +/- 2 days of sampling for PK.

- PK blood sample (on day X+1 between Day 16 and Day 29, pre-dose of LY3023414 and enzalutamide ± 15 minutes [see Table 1]). A hematocrit value (which can be obtained from a CBC) is required within +/- 2 days of sampling for PK.
- Urine dipstick

7.3.4 Cycle 2 and all Subsequent Cycles, Day 1 (±72 hours)

- Physical examination including measurement of weight
- Vital signs
- ECOG PS (see Appendix A)
- ECG predose (Cycles 2, 3, and 4 only)
- AE assessment
- Concomitant medication review
- Study drug compliance assessment
- CBC, including 3-part differential and platelets
- Fasting CMP plus LDH
- PT/INR (repeat only if abnormal at baseline or if clinically indicated)
- PK blood sample, (see Table 1 and Table 2)
- Blood collected for biomarker analysis (pre-dose of Day 1 Cycle 3 and Day 1 of every 2 cycles thereafter)
- HbA_{1c} blood sample (starting with Cycle 3 Day 1 and every 2 cycles thereafter)
- Urine dipstick
- PSA blood sample
- Dispense LY3023414 or matching placebo (Part A patients will not receive a placebo) and patient diary
- Dispense enzalutamide

7.4 Response Assessment – Prior to Cycle 3 and After Every 2 Cycles

Patients will be radiographically evaluated for response to treatment prior to Cycle 3 and after every 2 cycles of treatment (i.e. Cycle 5, Cycle 7, etc.). The following assessments will be performed in addition to determination of PSA levels (which are taken on Day 1 of each cycle):

- CT scans of chest (repeat only if abnormal at baseline)
- CT of the abdomen and pelvis
- Bone scan- technetium only

Lymph nodes and bone lesions should be evaluated using PCWG2 criteria (Appendix F) not RECIST v 1.1. Patients with progressive disease or unacceptable toxicity should be discontinued from the study; patients with stable disease or response to therapy w ill continue treatment.

7.5 PSA Progression

PSA progression is defined as ≥25% increase and ≥2 ng/mL increase above the nadir or baseline value for patients who had a PSA decrease on treatment which is confirmed by a second value 3 or more weeks later.

For patients without a decrease on treatment, PSA progression is defined as ≥25% increase and an absolute increase of ≥2 ng/mL after 12 weeks.

PSA progressions must be confirmed at the next study visit 4 weeks later. PSA will be collected at screening and on Day 1 of each treatment cycle.

Patients with PSA progression are allowed and encouraged to continue treatment until symptomatic or radiographic progression.

7.6 End of Treatment Visit

The follow-up evaluations required after treatment ends due to completion of the planned study treatment period, disease progression, or once the patient is discontinued due to unacceptable toxicity or decision t o discontinue treatment by the patient or the study physician are specified in Appendix D.

After withdrawal from or completion of protocol treatment, patients must be followed for AEs for at least 30 (+3) calendar days after the last dose of study drug. The following assessments will be performed.

- Physical examination including measurement of weight
- Vital signs
- ECOG PS (see Appendix A)
- ECG
- AE assessment
- Concomitant medication review
- Study drug compliance assessment
- CBC, including 3-part differential and platelets
- Fasting CMP plus LDH
- Blood sample for biomarker analysis
- HbA_{1c} blood sample
- Urine dipstick

- PSA (does not have to be repeated if done within 4 weeks of End of Study Treatment visit)
- CT scan chest (repeat only if abnormal at baseline; does not have to be repeated if done within 8 weeks of End of Study Treatment visit)
- CT of the abdomen and pelvis (does not have to be repeated if done within 8 weeks of End of Study Treatment visit)
- Bone scan- technetium only (does not have to be repeated if done within 8 weeks of End of Study Treatment visit).

7.7 Follow-up

7.7.1 Follow-up for Patients Who Discontinue Prior to Disease Progression

Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 2 months (±2 weeks) from the date of last dose of study drug until disease progression or for up to 3 years whichever comes first. Assessments at these visits will be performed as described in Appendix D.

8. DRUG FORMULATION, AVAILABILITY, ADMINISTRATION, AND TOXICITY INFORMATION

8.1 LY3023414 or Placebo

Investigational Product	Dosage Form and Strength	Manufacturer
LY3023414 or Placebo	25mg, 100mg, and 200mg capsules	Eli Lilly and Company

8.1.1 Labeling, Packaging, and Supply

LY3023414 and the matching placebo will be supplied as capsules by Eli Lilly and Company.

At each visit, patients will be dispensed sufficient supplies until the next visit. Study drug compliance will be assessed at each patient visit. The research staff will count and document the amount of LY3023414 and the matching placebo taken and returned by the patient.

The immediate packaging will contain a statement that administration is limited to investigational use only.

LY3023414 and matching placebo must be kept in a secure place under appropriate storage conditions. Storage conditions for LY3023414 are included on the investigational product label.

The Sponsor or its representatives must be granted access on reasonable request to check LY3023414 and matching placebo storage, dispensing procedures, and accountability records.

If another formulation of LY3023414 and the accompanying matching placebo becomes available at a later point in time (e.g. tablets), that might be used instead of capsules for this study.

8.1.2 Precautions and Risks Associated with LY3023414

Precautions and risks are located in the LY3023414 IB.

8.2 Enzalutamide

Investigational Product	Dosage Form and Strength	Manufacturer
Enzalutamide	40 mg capsules	Astellas Pharma US, Inc.

Enzalutamide will be administered orally as capsules.

Additional information can be found in the Enzalutamide US Package Insert (PI) https://www.astellas.us/docs/us/12A005-ENZ-WPI.pdf.

8.2.1 Labeling, Packaging, and Supply

At each visit, patients will be prescribed sufficient enzalutamide until the next visit. Study drug compliance will be assessed at each patient visit.

Enzalutamide must be kept in a secure place under appropriate storage conditions. Storage conditions for enzalutamide are included in the USPI https://www.astellas.us/docs/us/12A005-ENZ-WPI.pdf.

8.2.2 Precautions and Risks Associated with Enzalutamide

Please refer to the enzalutamide USPI https://www.astellas.us/docs/us/12A005-ENZ-WPI.pdf for detailed information on the risks associated with the use of enzalutamide.

8.3 Accountability for All Study drugs

The Principal Investigator (or designee) is responsible for accountability of all used and unused LY3023414 and matching placebo supplies at the site.

All LY3023414 and matching placebo inventories must be made available for inspection by the monitor, Sponsor, or representatives of the aforementioned and regulatory agency inspectors upon request.

At the end of the study, all Sarah Cannon Development Innovations Drug Accountability Record Form(s) for LY3023414 and matching placebo will be completed by the site and sent to the Sarah Cannon Development Innovations Regulatory Department. Study drug supplies must not be destroyed unless prior approval has been granted by the Sponsor or its representative. Please contact Sarah Cannon Development Innovations regarding disposal of any study drug.

No drug accountability will be done for enzalutamide.

9. RESPONSE EVALUATIONS AND MEASUREMENTS

Response and progression will be evaluated in this study using the PCWG2 criteria (Appendix F). These criteria will be followed for determining the change in PSA levels. PSA levels will be measured monthly throughout the study. Evaluation of PSA levels will be the primary evaluation for efficacy outcomes in men with no measurable disease at baseline.

Men with measureable disease at baseline will be evaluated using the RECIST v 1.1 (see Appendix E). Tumors will be assessed at screening, after every 2 cycles, and at follow-up visits. Reassessment of tumor will be done by the same methods used to establish baseline tumor measurements. All responding patients (CR and PR) must have their response confirmed no less than 4 weeks after the first documentation of response. For SD, measurements must meet the SD criteria at least 6 weeks after study entry.

For patients evaluated using both PSA changes and RECIST v 1.1, the earliest determined date of progression will be used to derive progression-based efficacy outcomes.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Design

This is a double-blinded, placebo-controlled, randomized Phase II study of the combination of enzalutamide plus LY3023414 versus enzalutamide plus placebo in men with mCRPC who have shown disease progression on abiraterone.

The primary, secondary and exploratory objectives are found in Section 2.

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10.3 Analysis Population

The following analysis populations will be used:

- All patients who have signed the informed consent form (i.e. screening failures plus patients enrolled) will comprise the All Patients Set (APS). The All Patients Set will be used to describe the patient disposition.
- All enrolled patients randomized to treatment arms will comprise the Full Analysis Set (FAS). Information using this population will be tabulated by treatment arm, as randomized (Intent to Treat) according to the IWRS, unless otherwise indicated. This population will be used for the primary analyses of the efficacy endpoints.
- All randomized patients having no major protocol deviations will comprise the Per Protocol Analysis Set (PPAS). Those protocol deviations that are deemed to have an important impact on the analysis of study endpoints and leading to the exclusion of a patient will be listed in the Statistical Analysis Plan (SAP) prior to database lock. This analysis set will be used for sensitivity analyses of efficacy endpoints.
- All patients who have received at least one dose of study treatment will comprise the Safety Analysis Set (SAF). Patients will be allocated as treated.

10.4 Data Analysis

Descriptive statistics, including mean, median, standard deviations, minimum and maximum for all continuous measures will be tabulated and reported. Percentages and frequencies for all categorical measures will also be presented. A SAP outlining methods for analysis and data display will be developed and approved prior to unblinding. Any deviation(s) from the approved plan or ad-hoc evaluations or analyses will be properly documented in the clinical study report.

10.4.1 Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized by treatment group. Data to be tabulated will include demographic features such as age, sex and race, as well as stratification factors and disease-specific characteristics.

The number and percentages of patients screened, randomized, treated, completed the treatment/study and withdrawn from treatment/study for any reasons will be presented overall and also by treatment group.

10.4.2 Efficacy Analysis

All efficacy analyses will be performed using the FAS. Sensitivity analyses may be performed using the PPAS.

Measurement of PSA levels, bone scans and CT scans will be performed for all patients at screening, after every 2 cycles (PSA will be measured monthly), and at follow-up visits before a subsequent anti-cancer therapy or death.

Tumor reassessment will be done by the same method used to establish baseline tumor measurements for each patient. For a response of stable disease (SD), measurements must meet the SD criteria at least 6 weeks after study entry.

10.4.2.1 Primary Endpoint

Progression–free survival (PFS)

PFS will be the primary endpoint for this study. PFS is defined as the time from randomization until the date of disease progression per PCWG2 or death by any cause regardless of whether the patient withdraws from study drug or receives a subsequent anti-cancer therapy (as determined by the investigator). Patients who have not progressed or died at the time of assessment will be censored at the time of the last date of assessment (tumor evaluation or PSA level). Patients who are randomized but do not receive treatment and patients who have no evaluable visits will be censored on day 0 unless they die within two visits of baseline. In the event patients demonstrate progression based on RECIST v 1.1, PSA levels, and/or bone scans at differing points, the earliest date of documented progression will be used to calculate PFS.

PFS will be derived based on relevant scan or lab dates, and not associated visit dates. In the event that RECIST v 1.1 assessments are conducted across multiple days, the date of progression will be based on the earliest of the dates of the component that triggered the progression. When censoring, the patient will be censored at the latest of the dates contributing to the particular visit assessment.

Treatment group differences will be tested using an unstratified log rank test. The stratified analysis using the stratification factors defined as part of the randomization process will be performed as sensitivity analysis.

The Kaplan-Meier (Kaplan E and Meier P 1958) product limit method will be used to estimate the median PFS and the associated 95% CI for the two treatment arms. Progression-free survival will additionally be analyzed using a Cox Proportional Hazards Model, and will be used to estimate the HR of PFS in the enzalutamide plus LY3023414 arm relative to the enzalutamide plus placebo arm and the associated 95% CI.

10.4.2.2 Secondary Endpoints

Overall Response Rate (ORR)

The ORR based on each patient's best objective response will be determined for all patients evaluable via the RECIST v 1.1 criteria. The ORR (%) will be calculated as the number of patients with best objective response of CR or PR divided by the number of patients with measurable disease at baseline. The best objective response for a given patient will be based on objective responses determined from data obtained up to: progression, the last evaluable assessment in the absence of progression, or initiation of subsequent anticancer therapy. Patients for whom an objective response cannot be determined or for who the best objective response is 'not evaluable' (NE) will be considered non-responders. The ORR will be summarized along with the 95% Clopper Pearson CI for each treatment arm.

Treatment group comparisons in ORR will be evaluated using Chi-square test and Cochran-Mantel Haenszel test adjusted by stratification factors.

Percent change from baseline in PSA levels

The percent change from baseline in PSA levels after 12 weeks on study and the maximum percent change from baseline will be summarized using box-whisker plots for each treatment

arm. For patients who discontinue on or before the 12 week assessment or for whom the 12 week assessment is missing, the last observation prior to the week12 assessment will be utilized. Patients with no post-baseline PSA data will be excluded from the summaries.

Time to Disease Progression (TTP)

TTP will be calculated as the time from randomization to objective disease progression. The date of progression will be determined as described above for PFS. Patients who die for any reason prior to disease progression will be censored at the time of death. Treatment group differences will be tested using a stratified log rank test as for PFS.

TTP will be analyzed in the same manner as those in PFS.

Study Drug Interactions

As specified in Sections 5.6 and 10.4.4, collection of PK samples is planned to be able to compare, within patient, the steady state LY3023414 AUC, C_{max}, and C_{trough} (C_{min}) following LY3023414 administration as a single agent and in combination with enzalutamide. These data will enable to determine whether enzalutamide impacts LY3023414 exposure.

As specified in Sections 5.6 and 10.4.4, collection of PK samples is planned to determine in a limited number of patients (Part A, Lead-In), the steady state exposure of enzalutamide. These results will be compared to historical enzalutamide data. This population to population comparison of enzalutamide exposure is believed to be adequate given that it is not anticipate that LY3023414 would impact enzalutamide clearance.

10.4.2.3 Exploratory Endpoints

The number and proportion of patients having an alteration in pre-specified markers at baseline, including but not limited to PIK3CA, PTEN, RAS, and AR-V7, may be presented if deemed relevant. The relationship between clinical outcomes and the presence of alterations in each marker may also be summarized using methods appropriate for each specific clinical outcome as specified in the SAP.

10.4.2.4 Subgroup Analyses

For exploratory purposes, efficacy sub-group analyses may also be performed if applicable, using the FAS/PPAS. The details of these analyses and selection of the prognostic factors and/or baseline characteristics will be specified in the SAP.

10.4.3 Safety Analysis

The NCI CTCAE v 4.03 will be used to grade all AEs (severity grade). A copy of the CTCAE scoring system may be downloaded from:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

Duration and treatment of toxicities will be recorded. The safety measures will be assessed on an ongoing basis. The safety variables will be assessed by body system. Any AEs that are considered probably or possibly study drug-related will be monitored until resolution or stabilization.

Toxicity profile data will include AEs and laboratory parameters. Safety data will be tabulated for all patients who receive any amount of study medication , overall and by part and treatment

group. Adverse terms recorded on the eCRFs will be standardized using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs (TEAEs), defined as events that start or worsen after the first dose of study treatment, will be summarized and tabulated in accordance with system organ class (SOC) and preferred term by overall incidence, severity, and relationship to study treatment. The tabulation of laboratory parameters will indicate the normal range of each parameter. Each value will be classified according to CTCAE v 4.03 where applicable.

Other safety endpoints, including laboratory results, vital signs and ECG findings, will be summarized for all patients in the Safety Analysis Set, overall and by part and treatment group.

Concomitant medications will be coded using the World Health Organization-Drug Dictionary and they will be listed and summarized by treatment group.

10.4.4 Pharmacokinetics/Pharmacodynamics

Pharmacokinetic analyses will be conducted on patients who have received at least 1 dose of the study drug and have had sufficient post-dose samples collected to allow estimation of PK parameters. Blood and plasma (Part A only) concentrations of LY3023414 and plasma concentration for enzalutamide will be used to calculate LY3023414 and enzalutamide PK parameters, respectively. The PK parameters will be calculated by standard noncompartmental methods.

The primary parameters for analysis will be maximum concentration (C_{max}) and area under the concentration-time curve (AUC) of LY3023414 and Enzalutamide following multiple doses. Other noncompartmental parameters, such as t1/2, CLss/F, and Vss/F may be reported. These parameters will be listed by individual patient and summarized by descriptive statistics (means, medians, ranges, standard deviations and coefficient of variation and, as appropriate.

For Part A the ratio of LY3023414 AUCs when administered concomitantly with enzalutamide over single agent will be computed to quantify the possible impact of enzalutamide on LY3023414 exposure (LY3023414 AUC ratio = $AUC_{\tau,ss,alone} : AUC_{\tau,ss,presENZ}$; with τ the dosing interval for LY3023414 that is 12 h, ss meaning that the PK assessment is done at steady state ; alone and presENZ meaning that LY3023414 was administered either alone or with enzalutamide). The result will be summarized by descriptive statistics (mean, median, range, standard deviations and coefficient of variation) and the 90% confidence interval for this ratio will be computed.

Additional exploratory analyses will be performed if warranted by data and other validated PK software programs may be used if appropriate and approved by Global Pharmacokinetic management. It is planned that LY3023414 PK data will be analyzed using the nonlinear mixed effect modeling (NLME) techniques. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

Further details on the PK/PD analysis will be documented in a separate PK/PD analysis plan.

10.5 Handling of Missing Data

Except where noted above, missing data will not be estimated or imputed.

10.6 Analysis Time Point

10.6.1 Final Analysis

The final analysis of the study will be triggered when 92 patients have had an event (disease progression or all cause death).

10.6.2 Planned Interim Analysis

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The results from the interim analyses will be examined by a Lilly internal assessment committee that will be established prior to the inclusion of the first patient in the trial. The Lilly internal assessment committee will consist of at least a Lilly medical director, a Lilly clinical research physician/clinical research scientist, and a Lilly statistician and will make recommendations about the trial. The outcome of the interim analyses will be documented, and a written letter will be submitted to the IRB(s) and the investigators for documentation purposes. Enrollment will continue while the interim analysis is being performed.

10.6.3 Safety Review

After at least 6 patients have been treated for a full cycle, a SIMC will review the safety and PK data prior to the initiation of the randomized phase of the study. If 2 (or more) of 3 or 2 (or more) of 6 patients in Part A experience DLTs as defined in Section 5, 3 to 6 additional patients will be treated at the next lower dose of LY3203414 defined in Table 3 (150 mg PO BID) and assessed for DLTs prior to initiation of the randomized Part B portion of the study. If there is significant PK interaction seen, the SIMC may recommend enrolling approximately 6 additional patients to further evaluate the safety of the combination, or explore other dose combinations to assure safety at a maximal exposure of study drug. In the case of unacceptable and/or unmanageable toxicity of the combination the SIMC may decide to discontinue the study upon completion of Part A or proceed with a lower LY3023414 dose level tolerated in combination with enzalutamide. Any outcome of these safety reviews will be communicated in a timely manner to the participating investigators so that they may notify their IRBs. No amendment will be needed to proceed with an adjusted dose level of LY3023414.

For Part B of the study, safety will continue to be monitored as defined by the medical monitoring plan. The safety profile will be reviewed by the Medical Monitor and Sponsor Designees.

The SIMC will, at a minimum, be composed of a Sponsor-Assigned Clinical Research Physician, Study Chair, Medical Monitor, Safety Scientist, and Biostatistician.

The criteria for assessing safety in these patients are found in Section 5.

10.6.4 Unblinding Patients

There is no intention to routinely unblind individual patients at any time. Individual requests for urgent safety unblinding require the approval of the Medical Monitor.

There also may be instances where unblinding of a patient(s) may be required for a safety review at the request of the Sarah Cannon Development Innovations Medical Monitor or SIMC or for Regulatory Authority reporting requirements.

After all patients have completed protocol treatment and the database has been locked, the trial will be unblinded for analysis of the safety and efficacy outcomes.

11. SAFETY REPORTING AND ANALYSES

Investigators are responsible for monitoring the safety of patients who have entered into this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient. The investigator is responsible for the appropriate medical care of the patient during the study.

The investigator remains responsible for following, through an appropriate health care option, all AEs that are serious or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Frequency of AE and SAE follow-up evaluation is left to the discretion of the investigator.

Investigators or their designees must document their review of each laboratory report.

11.1 Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Any clinically significant findings from labs, ECGs, vital sign measurements, and so on, that occur should also be reported to Lilly or its designee as an AE using the same guidelines and schedules as those for AEs. Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish drug effect.

The investigator, monitor, and sponsor will review the collected data regularly for evidence of AEs. All patients will be assessed routinely for AEs as outlined in the study schedule. All AEs observed will be graded using CTCAE Version 4.03.

The CTCAE Version 4.03 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. For AEs without matching terminology within the CTCAE Version 4.03 criteria, the investigator will be responsible for selecting the appropriate SOC and assessing severity grade based on the intensity of the event. Note that both CTCAE term (actual or coded) and severity grade must be selected by study site personnel and collected on the CRF. This collection is in addition to verbatim text used to describe the AE.

Minor updates to the CTCAE Version 4.03 from the National Cancer Institute (NCI) will not necessitate a protocol amendment and the use of updated CTCAE Version 4.0 will not be considered a protocol violation.

In addition to collecting the AE verbatim, the CTCAE term, and the CTCAE severity grade, AE verbatim text will also be mapped by the sponsor or designee to corresponding terminology within MedDRA.

Cases of pregnancy that occur during paternal exposures to study drug should be reported. Data on fetal outcome and breastfeeding should be collected, if feasible, for regulatory reporting and drug safety evaluation.

For all enrolled patients, study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. While the patient is on study, site personnel will record any change in these preexisting condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures are reported to Lilly or designee.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee the circumstances and data leading to any such dosage reduction or discontinuation of treatment. This information must also be documented in the eCRF.

The investigator decides whether he or she interprets the observed safety signals as either related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies.

To assess the relationship of the AE to the study drug, the following terminologies are defined:

- **Probably related**: a direct cause and effect relationship between the study treatment and the AE is likely.
- **Possibly related**: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible.
- **Does not know:** the investigator cannot determine.
- **Not related**: without question, the AE is definitely not associated with the study treatment.

As per Lilly's standard operating procedures, all "probably related," "possibly related," or "does not know" AEs and SAEs will be defined as related to study drug.

11.2 Serious Adverse Events

Previously planned (that is, prior to signing the informed consent form [ICF]) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs.

An SAE is any AE during this study that results in 1 of the following outcomes:

- death
- initial or prolonged inpatient hospitalization (except for study drug administration)
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.

Serious AEs due to disease progression, including death, should not be reported unless the investigator deems them to be possibly related to the study drug.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

If an investigator becomes aware of SAEs occurring after the patient's participation in the study has ended, and the investigator believes that the SAE is related to a protocol procedure or study drug, the investigator should report the SAEs to the sponsor, and the SAEs will be entered in the Lilly Safety System.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the study may be found in the IB.

11.2.1 Adverse Event and Serious Adverse Event Reporting

Prior to Administration of Study Drug(s)
During screening, all AEs and SAEs (regardless of relatedness to protocol procedures) are collected after the patient has signed the informed consent document. For patients who do not enroll in the study (that is, receive at least 1 dose of study drug), only AEs and SAEs related to protocol procedures are required to be collected.

On Study
All AEs and SAEs, regardless of relatedness to study drug, or protocol procedures, occurring while the patient is receiving study drug(s) must be reported to Lilly or its designee. A patient is considered to be receiving study drug from the time he/she receives the first dose of study drug(s) to when he/she receives the last dose of study drug(s).

Follow-Up Visit
All AEs and SAEs, regardless of relatedness to study drug, or protocol procedures, occurring during the Follow-Up Visit must be reported to Lilly or its designee. The Follow-Up Visit starts the day after the last dose of study drug. At the end of the Follow-Up Visit, the patient will be required to have specific safety assessments according to the Study Schedule (Appendix D). The timing of these safety assessments is 30 days ± 3 days after the last dose of study drug.

Following the safety assessments, which mark the end of the Follow-Up Visit, the patient will be discontinued from the study, unless there is an ongoing AE or SAE that is possibly related to study drug. In this instance, the patient should be seen for subsequent follow-up visits until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up.

After the Follow-Up Visit, only new AEs or SAEs that are considered possibly related to study drug or protocol procedures should be reported to Lilly or their designee.

To report an SAE, the Lilly SAE Report Form should be completed with the necessary information.

The SAE report should be sent to Lilly via fax using the following contact information (during both business and non-business hours):

Lilly Safety Department

Safety Dept. Fax #: 1- 866-644-1697

Transmission of the SAE report should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to Lilly as soon as it is available; these reports should be submitted using the Lilly SAE Report Form. The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the Study Reference Manual.

Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of the responsible IRB.

11.3 Complaint Handling

Lilly collects product complaints on study drugs and drug delivery systems used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Complaints related to unblinded concomitant drugs are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

For blinded studies, all product complaints associated with material packaged, labeled, and released by Lilly or delegate will be reported.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Monitoring

Site monitoring shall be conducted to ensure that patient protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet Sponsor, GCP/ICH and, when appropriate, regulatory guidelines.

12.2 Audits and Inspections

The investigator will permit study-related quality audits and inspections by the Sponsor or its representative(s), government regulatory authorities, and the IRB of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The investigator will ensure the capability for review of applicable study-related facilities. The investigator will ensure that the auditor or inspector or any other compliance or QA reviewer is given access to all study-related documents and study-related facilities.

Participation as an investigator in this study implies the acceptance of potential inspection by government regulatory authorities, the IRB, the Sponsor or its representative(s).

13. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This research study will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

13.1 Institutional Review Board Approval

The clinical study protocol, ICF, IB, available safety information, patient documents (e.g., study diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., Principal Investigator payments) and compensation available to the patients and documentation evidencing the Principal Investigator's qualifications should be submitted to the IRB for ethical review and approval if required by local regulations, prior to the study start.

The Principal Investigator/Sponsor and/or designee will follow all necessary regulations to ensure appropriate, initial, and on-going, IRB study review. The Principal Investigator/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by the Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

Safety updates for LY3023414, will be prepared by the Sponsor or its representative as required, for distribution to the investigator(s) and submission to the relevant IRB.

13.2 Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation. If required, the Sponsor will also ensure that the implementation of substantial amendments to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

13.3 Informed Consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.

The informed consent form will be submitted for approval to the IRB that is responsible for review and approval of the study. Each consent form must include all of the relevant elements currently required by the relevant regulatory authorities, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the research study. Once the essential information has been provided to the prospective candidate, and the investigator is sure that the individual candidate understands the implications of participating in this research study, the candidate will be asked to give consent to participate in the study by signing an informed consent form. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the informed consent form, to include the patient's signature, will be provided by the investigator to the patient.

If an amendment to the protocol substantially alters the study design or the potential risks to the patients, the patient's consent to continue participation in the study should be obtained.

13.3.1 Confidentiality

13.3.1.1 Patient Confidentiality

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization form for the study that he or she has been informed of following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws
- The information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study
- Whether the authorization contains an expiration date
- The rights of a research patient to revoke his or her authorization

In the event that a patient revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the investigator and institution permit authorized representatives of Sponsor, the regulatory authorities and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

Measures to protect confidentiality include: only a unique study number and initials will identify patients in the eCRF or other documents submitted to the Sponsor. This information, together with the patient's date of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF database system. No material bearing a patient's name will be kept on file by Sponsor. Patients will be informed of their rights within the ICF.

13.3.1.2 Investigator and Staff Information

Personal data of the investigators and sub-investigators may be included in the Sponsor or the Sarah Cannon Development Innovations database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the investigator or sub investigator, the Sponsor and/or Sarah Cannon Development Innovations

shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

13.4 Financial Information

The finances for this clinical study will be subject to a separate written agreement between the Sponsor and applicable parties. Any Investigator financial disclosures as applicable to 21CFR Part 54 shall be appropriately provided and retained.

14. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

14.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor or its representative. All amendments require review and approval of the Sponsor and the Principal Investigator supporting the study. The written amendment must be reviewed and approved by the Sponsor, and submitted to the IRB at the investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to patient, increase to dosing or exposure, patient number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB of record for the Investigator's facility.

The amendment will be submitted formally to the relevant regulatory authorities by the Sponsor as applicable, and IRB approved obtained specifically when an increase to dosing or patient exposure and/or patient number has been proposed; or, when the addition or removal of an Investigator is necessitated.

Items requiring a protocol amendment with IRB and if necessary other relevant regulatory authorities approval may include but are not limited to, the following:

- Change to study design
- Risk to patient
- Increase to dose or patient exposure to drug
- Patient number increase
- Addition or removal of tests and / or procedures
- Addition/removal of a Study Chair

It should be further noted that, if an amendment to the protocol substantially alters the study design or the potential risks to the patients, their consent to continue participation in the study should be obtained.

14.2 Documentation Required to Initiate the Study

Before the study may begin in the United States (US) certain documentation required by FDA regulations and ICH GCP must be provided by the Investigator. The required documentation should be submitted to:

Sarah Cannon Development Innovations
1100 Charlotte Ave., Suite 800
Nashville, TN 37203

Documents at a minimum required to begin a study in the US include, but are not limited to, the following:

- A signature-authorized protocol and contract
- A copy of the official IRB approval of the study and the IRB members list
- Current Curricula Vitae for the principal investigator and any associate investigator(s) who will be involved in the study
- Indication of appropriate accreditation for any laboratories to be used in the study and a copy of the normal ranges for tests to be performed by that laboratory
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed
- A copy of the IRB -approved consent form containing permission for audit by representatives of Sarah Cannon Development Innovations, the Sponsor, the IRB, and the FDA
- Financial disclosure forms for all investigators listed on Form FDA 1572 (if applicable, i.e., for covered trials)
- Site qualification reports, where applicable
- Verification of Principal Investigator acceptability from local and/or national debarment list(s)

14.3 Study Documentation and Storage

The Principal Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the CRFs are to be included on this document. All entries in the patient's CRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the patient's CRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The Principal Investigator and each study staff member is responsible for maintaining a comprehensive and centralized filing system (e.g., regulatory binder or investigator study file [ISF]) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, copies of completed CRFs, IRB approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain Principal Investigator name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the CRF must be maintained and be readily available.

The Sponsor shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

The IRB shall maintain adequate documentation / records of IRB activities as per 21CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment / delivery of the drug for investigational use is discontinued and FDA has been notified that the investigation has been discontinued.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records e.g., eCRFs and medical records), all original, signed informed consent forms, and copies of all eCRFs, records, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). Sponsor or its representatives will notify the investigator(s)/institutions(s) when the study-related records are no longer required.

If the investigator relocates, retires, or for any reason withdraws from the study, both the Sponsor and its representative should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor. The investigator must obtain the Sponsor's written permission before disposing of any records, even

if retention requirements have been met. All study files will be maintained by the Sponsor or its representative throughout the study. If study files are maintained by a representative of the Sponsor, the study files will be transferred to the Sponsor at the conclusion of the study.

14.4 Data Collection

The study CRF is the primary data collection instrument for the study. Case report forms will be completed using the English language and should be kept current to enable the Sponsor to review the patients' status throughout the course of the study.

In order to maintain confidentiality, only study number, patient number, initials and date of birth will identify the patient in the eCRF. If the patient's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to Sarah Cannon Development Innovations and replaced instead with the patient number and patient's initials. The investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested by the eCRF must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or "Unknown." For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The investigator will electronically sign and date the patient CRF casebook indicating that the data in the CRF has been assessed. Each completed CRF will be signed and dated by the Principal Investigator, once all data for that patient is final.

14.5 Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the study. Results from the study may be published and/or presented as per the Sponsor's disclosure process.

Inclusion of the investigator in the authorship of any multi-center publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the study. The investigator acknowledges that the study is part of a multi-center study and agrees that any publication by the investigator of the results of the study conducted at research site shall not be made before the first multi-center publication. In the event there is no multi-center publication within fifteen (15) months after the study has been completed or terminated at all study sites, and all data has been received, the investigator shall have the right to publish its results from the study, subject to the notice requirements described herein and subject to acknowledgement of the Sponsor as appropriate. Investigator shall provide the Sponsor thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the study for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the

Sponsor requests in writing, the investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit the Sponsor to seek patent protection and to remove any Sarah Cannon Development Innovations Confidential Information from all publications.

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16. APPENDICES

Appendix A: ECOG Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death no imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead	0	Dead


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Appendix C: Guidelines for Fertile Male Patients

Fertile male patients, defined as all males physiologically capable of conceiving offspring, with female partners of childbearing potential must use condoms plus spermicidal agent during the study treatment period and for 3months after the last dose of study drug, and should not father a child during this period.

Male patients must also refrain from donating sperm during their participation in the study.

Pregnancies

Pregnancy outcomes must be collected for the female partners of any males who took study drug(s) in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Appendix D: Schedule of Assessments and Study Plan

Assessments	Screening	Study Treatment					Response Assessments Prior to Cycle 3 & every 2nd Cycle thereafter (i.e. 5,7, etc.)	Off-Treatment	Follow-Up
		Single Agent Week -1 LY302414 (Part A only)		Cycle 1		Cycle 2 & All Subsequent Cycles (±72 hrs)			
	Baseline[a]	D -7	D -1	D1	D15[p]	D1		End of Study Treatment[q]	Off Treatment Prior to Progression[r]
TESTS AND OBSERVATIONS									
Informed consent	X								
Medical history	X								
Physical exam[b]	X	X		X		X		X	X
Vital Signs[c]	X	X		X	X	X		X	X
ECOG PS	X	X		X	X	X		X	X
12-lead ECG[d]	X			X		X[d]		X	
Adverse event evaluation		X		X	X	X		X	
Concomitant medication review	X	X		X	X	X		X	
Study drug compliance assessment					X	X		X	
STUDY TREATMENT (Continuous Dosing)									
LY3023414 or matching placebo BID[j]		X[n]	X[n,o]	X	X	X			
Enzalutamide 160 mg[j] QD				X	X	X			
LABORATORY EVALUATIONS									
CBC, 3-part differential, and platelets	X	X		X	X	X		X	
Fasting CMP[e] plus LDH	X	X		X	X	X		X	
PT/INR[f]	X	X[f]		X[f]		X[f]			
Urine dipstick	X	X		X	X	X		X	
Biomarker blood sample[g]	X[g]			X[g]		X[g]		X	
Testosterone blood sample	X								
HbA_{1c} blood sample[h]	X					X[h]		X[h]	
PK blood sample[i,j]			X[i,j]	X[i,j]	X[i,j]	X[i,j]			
PGx blood sample				X[s]					

Appendix D: Schedule of Assessments (continued)

Assessments	Screening	Study Treatment					Response Assessments Prior to Cycle 3 & every 2nd Cycle thereafter (i.e. 5, 7, etc)	Off-Treatment	Follow-Up
		Single Agent Week -1 LY302414 (Part A only)		Cycle 1		Cycle 2 & All Subsequent Cycles (±72 hrs)		End of Study Treatment[q]	Off Treatment Prior to Progression[r]
	Baseline[a]	D -7	D -1	D1	D15[p]	D1			
LABORATORY EVALUATIONS									
Archived or fresh tumor tissue (optional)	X								
STAGING									
PSA[l]	X	X[l]		X		X[l]		X[l]	X[l]
Bone scan[m]	X						X[k,m]	X[k,m]	X[k,m]
CT scan of chest, abdomen and pelvis[n]	X						X[k,n]	X[k,n]	X[k,n]

a The physical examination, medical history, concomitant medications recorded ≤7 days prior to study entry, ECOG PS, CBC including differential and platelets, CMP, urinalysis, and PT/INR should be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours prior to the initiation of treatment they do not have to be repeated. Scans to document evaluable disease (i.e., tumor measurement), 12-lead ECG, testosterone levels, and PSA should be performed ≤4 weeks prior to initiation of treatment.

b Physical examination will include measurements of height and weight at the baseline visit. Physical examinations (PE) done at all other times during the study will include only weight. Only Part B patients will need a physical exam on Cycle 1 Day 1.

c Vital signs include resting heart rate, blood pressure, oral temperature

d ECG performed locally at baseline, predose on Cycles 1 -4, and at the End of Treatment visit. Repeat if clinically indicated.

e Fasting CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO2, ALP, AST, ALT, total bilirubin, total protein, albumin, phosphorus, and LDH.

f PT/INR will only need to be repeated if abnormal at baseline or if clinically indicated.

g Biomarker blood samples will be taken at baseline and pre-dose on Day 1 of Cycles 1, and 3 and every 2 cycles thereafter, and at the End of Treatment visit.

h HbA_{1c} blood sample will be taken at baseline, Cycle 3 and every 2 cycles thereafter, and at the End of Treatment visit.

Appendix D: Schedule of Assessments (continued)

i PK blood samples will have a window of ± 15 minutes. PK blood samples for patients who are participating in Part A will be **Day -1**, pre-dose, 1.5, 3, and 6 hours post LY3023414 dose; **Cycle 1 Day 1** pre-dose of LY3023414 and enzalutamide; **Cycle 1 Day X** - any day between Day 15 and Day 28, pre-dose of LY3023414 and enzalutamide, 1.5, 3, and 6 hours post LY3023414 dose; and **Cycle 1 Day X + 1**- between Day 16 and Day 29, pre-dose of LY3023414 and enzalutamide (see Table 1). PK blood samples for all patients will be taken pre-dose of LY3023414/placebo and enzalutamide and 1.5 hours post LY3023414/placebo dose on Cycle 2 Day 1 and Cycle 3 Day 1 (see Table 2). A hematocrit value (which can be obtained from a CBC) is required within +/- 2 days of collection of sampling for PK

j On PK days, pre-dose measurements and dose administration will be done in a fasted state. Patients should remain fasted for 1 hour post- dose.

k Patients will be restaged prior to Cycle 3 and after every 2 cycles of treatment thereafter (every 8 weeks). Patients with progressive disease or unacceptable toxicity should be discontinued from treatment; patients with stable disease or response to therapy will continue treatment.

l PSA blood samples will be taken ≤4 weeks prior to initiation of treatment, on Week -1 Day -7 for Part A patients, Cycle 1 Day 1 (unless collected within the previous 72 hours) Day 1 of every cycle, and at the End of Study visit if not taken in the previous 4 weeks. Patients with PSA progression are allowed and encouraged to continue treatment until symptomatic or radiographic progression.

m Bone scans- technetium only - ≤4 weeks prior to initiation of treatment, prior to Cycle 3 and after every 2 cycle s of treatment thereafter, and at the End of Study visit if scans were not taken in the previous 8 weeks. Bone lesions should be evaluated using PCWG2 criteria and not RECIST v 1.1.

n CT scans of the chest, abdomen and pelvis ≤4 weeks prior to initiation of treatment. CT scan of the chest should be repeated only if abnormal at baseline. CT scans of the abdomen and pelvis should be taken prior to Cycle 3 and after every 2 cycles of treatment thereafter, and at the End of Study visit (if scans were not taken in the previous 8 weeks). Lymph nodes should be evaluated using PCWG2 criteria and not RECIST v 1.1.

o Part A patients do not receive a placebo.

p Only Part A patients come in on Cycle 1 Day 15.

q After patients complete therapy or are discontinued from treatment they will visit the study center 30 days (+3) after finishing treatment for end of treatment assessments. Patients must be followed for AEs for 30 calendar days after the last dose of study drug.

r Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 2 months (±2 weeks) from the date of last dose of study drug until disease progression or for up to 3 years whichever comes first.

s The PGx sample should be collected C1D1. If the sample is not able to be collected C1D1, it can be collected anytime during C1 or C2. The PGx sample is part of the Biomarker sample and does not require a separate kit.


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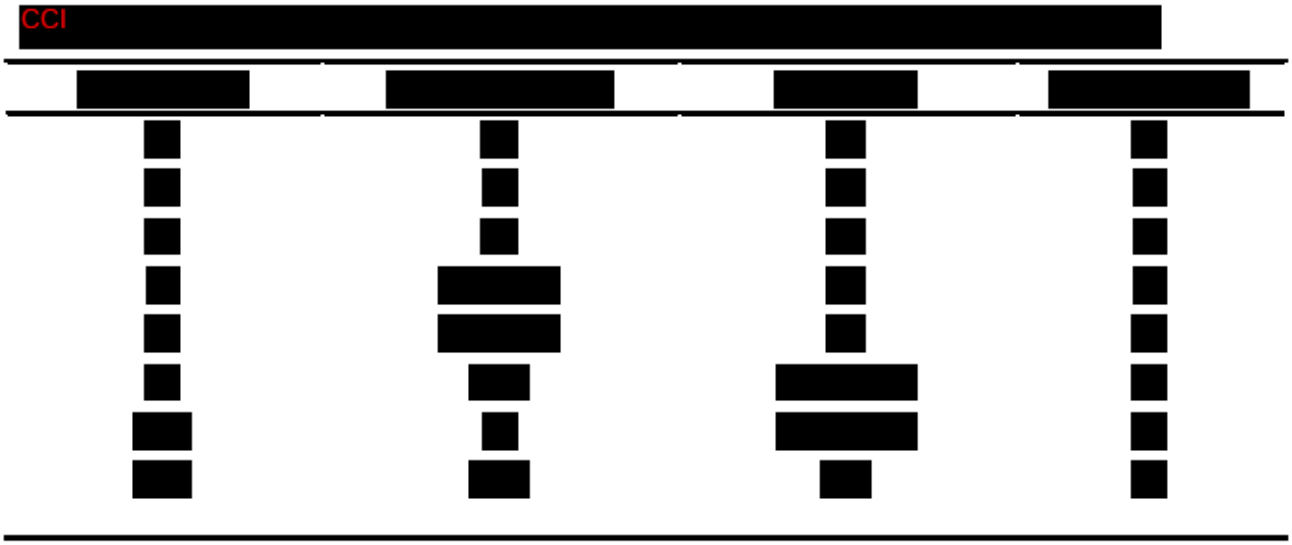

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Appendix G: Drugs That Prolong QT Interval and/or Induce Torsades de Pointes

All QT-prolonging drugs listed below should be avoided for all patients from screening through permanent discontinuation of study treatment.

Drug	QT risk(*)	Comment
Amiodarone	Known risk for TdP	Females>Males,TdP risk regarded as low
Arsenic trioxide	Known risk for TdP	
Astemizole	Known risk for TdP	No Longer available in U.S.
Bepridil	Known risk for TdP	Females>Males
Chloroquine	Known risk for TdP	
Chlorpromazine	Known risk for TdP	
Cisapride	Known risk for TdP	Restricted availability; Females>Males.
Disopyramide	Known risk for TdP	Females>Males
Dofetilide	Known risk for TdP	
Domperidone	Known risk for TdP	Not available in the U.S.
Droperidol	Known risk for TdP	
Halofantrine	Known risk for TdP	Females>Males
Haloperidol	Known risk for TdP	When given intravenously or at higher-than-recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	Known risk for TdP	Females>Males
Levomethadyl	Known risk for TdP	
Mesoridazine	Known risk for TdP	
Methadone	Known risk for TdP	Females>Males
Pentamidine	Known risk for TdP	Females>Males
Pimozide	Known risk for TdP	Females>Males
Probucol	Known risk for TdP	No longer available in U.S.
Procainamide	Known risk for TdP	
Quetiapine	Possible risk for TdP	This drug is a sensitive 3A4 substrate
Quinidine	Known risk for TdP	Females>Males
Sotalol	Known risk for TdP	Females>Males
Sparfloxacin	Known risk for TdP	
Tacrolimus	Possible risk for TdP	This drug is a sensitive 3A4 sibstrate with narrow TI
Terfenadine	Known risk for TdP	No longer available in U.S.
Thioridazine	Known risk for TdP	
Vardenafil	Possible risk for TdP	This drug is a sensitive 3A4 substrate
(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.		

Appendix H: List of QT Prolonging Drugs to be Used with Caution

Below is a list of drugs with a known risk for Torsades de Pointes (TdP).

Drug	QT risk	Comment
Alfuzosin	possible risk for Torsades de Pointes	
Amantadine	possible risk for Torsades de Pointes	
Amitriptyline	conditional risk for Torsades de Pointes	
Azithromycin	possible risk for Torsades de Pointes	
Chloral hydrate	possible risk for Torsades de Pointes	
Citalopram	conditional risk for Torsades de Pointes	
Clomipramine	conditional risk for Torsades de Pointes	
Clozapine	possible risk for Torsades de Pointes	
Desipramine	conditional risk for Torsades de Pointes	
Diphenhydramine	conditional risk for Torsades de Pointes	
Dolasetron	possible risk for Torsades de Pointes	
Doxepin	conditional risk for Torsades de Pointes	
Dronedarone	possible risk for Torsades de Pointes	
Felbamate	possible risk for Torsades de Pointes	
Flecainide	possible risk for Torsades de Pointes	
Fluoxetine	conditional risk for Torsades de Pointes	
Foscarnet	possible risk for Torsades de Pointes	
Fosphenytoin	possible risk for Torsades de Pointes	
Galantamine	conditional risk for Torsades de Pointes	
Gatifloxacin	possible risk for Torsades de Pointes	
Gemifloxacin	possible risk for Torsades de Pointes	
Granisetron	possible risk for Torsades de Pointes	
Imipramine	conditional risk for Torsades de Pointes	
Indapamide	possible risk for Torsades de Pointes	
Isradipine	possible risk for Torsades de Pointes	
Levofloxacin	possible risk for Torsades de Pointes	
Lithium	possible risk for Torsades de Pointes	
Mexiletine	conditional risk for Torsades de Pointes	
Moexipril/HCTZ	possible risk for Torsades de Pointes	
Moxifloxacin	possible risk for Torsades de Pointes	
Nicardipine	possible risk for Torsades de Pointes	
Nortriptyline	conditional risk for Torsades de Pointes	
Octreotide	possible risk for Torsades de Pointes	
Ofloxacin	possible risk for Torsades de Pointes	

Appendix H: List of QT Prolonging Drugs to be Used with Caution (continued)

Drug	QT risk	Comment
Ondansetron	possible risk for Torsades de Pointes	
Oxytocin	possible risk for Torsades de Pointes	
Paliperidone	possible risk for Torsades de Pointes	
Paroxetine	conditional risk for Torsades de Pointes	
Perflutren lipid microspheres	possible risk for Torsades de Pointes	
Protriptyline	conditional risk for Torsades de Pointes	
Ranolazine	possible risk for Torsades de Pointes	
Risperidone	possible risk for Torsades de Pointes	
Roxithromycin*	possible risk for Torsades de Pointes	*not available in the United States
Sertindole	possible risk for Torsades de Pointes	
Sertraline	conditional risk for Torsades de Pointes	
Solifenacin	conditional risk for Torsades de Pointes	
Tizanidine	possible risk for Torsades de Pointes	
Trazodone	conditional risk for Torsades de Pointes	
Trimethoprim-Sulfa	conditional risk for Torsades de Pointes	
Trimipramine	conditional risk for Torsades de Pointes	
Venlafaxine	possible risk for Torsades de Pointes	
Ziprasidone	possible risk for Torsades de Pointes	
(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT		

Appendix I: Common CYP1A2 Inducers, CYP2C9 and CYP2C19 Inducers and Substrates, Substrates for CYP3A4, CYP2C8 Inducers, CYP3A Inducers and Inhibitors, and P-gp/CYP3A Dual Inhibitors

The following list describes medications and foods which are common inhibitors, inducers and substrates of CYP2C9 and CYP2C19, substrates of CYP34A, inducers of CYP2C8, inducers and inhibitors of CYP3A, and dual inhibitors of PgP and CYP3A.

This list should not be considered all-inclusive.

<table>
<tr><th colspan="2">CYP1A2 Inducers</th></tr>
<tr><td>Moderate Inducers
50-80% decrease in AUC:
montelukast
phenytoin</td><td>Weak Inducers
20-50% decrease in AUC:
moricizine
omeprazole
phenobarbital</td></tr>
<tr><th>CYP2C9 Substrates with Narrow Therapeutic Range</th><th>CYP2C9 Inducers</th></tr>
<tr><td>Phenytoin
Warfarin (s)</td><td>Moderate:
Carbamazepine
Rifampin</td></tr>
<tr><th>CYP2C19 Substrates with Narrow Therapeutic Range</th><th>CYP2C19 Inducer</th></tr>
<tr><td>S-mephenytoin</td><td>Moderate:
Rifampin</td></tr>
<tr><th>CYP3A4 Substrates with Narrow Therapeutic Range</th><th>CYP2C8 Inhibitor</th></tr>
<tr><td>Alfentanil
Astemizole
Cisapride
Cyclosporine
Dihydroergotamine
Ergotamine
Fentanyl
Pimozide
Quinidine
Sirolimus
Tacrolimus
Terfenadine</td><td>Strong:
Gemfibrozil</td></tr>
</table>

Appendix I: Common CYP1A2 Inducers, CYP2C9 and CYP2C19 Inducers and Substrates, Substrates for CYP3A4, CYP2C8 Inducers, CYP3A Inducers and Inhibitors, and P-gp/CYP3A Dual Inhibitors (continued)

CYP3A4 Substrates (Oral Administration)	CYP3A/P-gp Dual Inhibitors
• Midazolam • Buspirone	Strong: • Clarithromycin • Conivaptan • Diltiazem • Dronedarone • Indinavir/ritonavir • Itraconazole • Ketoconazole • Lopinavir/ritonavir • Ritonavir Moderate: • Diltiazem • Dronedarone • Erythromycin • Verapamil

Appendix I: Common CYP1A2 Inducers, CYP2C9 and CYP2C19 Inducers and Substrates, Substrates for CYP3A4, CYP2C8 Inducers, CYP3A Inducers and Inhibitors, and P-gp/CYP3A Dual Inhibitors (continued)

CYP3A Inducers	CYP3A Inhibitors
Strong: • Avasimibe • Carbamazepine • Phenytoin • Rifampin (rifampicin) • St. John's wort (hypericum perforatum)	Strong: • Boceprevir • Clarithromycin • Conivaptan • Grapefruit juice • Indinavir • Itraconazole • Ketoconazole • Lopinavir/ritonavir • Mibefradil • Nefazodone • Nelfinavir • Posaconazole • Ritonavir • Saquinavir • Telaprevir • Telithromycin • Voriconazole Moderate: • Amprenavir • Aprepitant • Atazanavir • Ciprofloxacin • Cyclosporine • Darunavir/ritonavir • Diltiazem • Erythromycin • Fluconazole • Fosamprenavir • Grapefruit juice (citrus parasidi fruit juice) • Imatinib • Verapamil

Source: FDA's Drug Development and Drug Interactions: Table of Substrates, Inhibitors and the University of Washington's Drug Interaction Database.
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Appendix J: Schematic to Represent the PK Sampling