Version 3.1

A Randomized, Open-Label, Active-Controlled, Multi-Center Study to Evaluate Serum Testosterone Levels in Patients with Metastatic Castration-Resistant Prostate Cancer on SoluMatrix™ Abiraterone Acetate 500 mg (4 x 125 mg qd) with Methylprednisolone (4 mg bid) as Compared to Zytiga® 1,000 mg (4 x 250 mg qd) with Prednisone (5 mg bid): The STAAR STUDY

PROTOCOL NUMBER:	CHL-AA-201
IND NUMBER:	115577
PROTOCOL DATE:	October 10, 2016
SPONSORED BY:	Churchill Pharmaceuticals LLC 3602 Horizon Drive, Suite 160 King of Prussia, PA 19406
CONTRACT RESEARCH ORGANIZATION:	[redacted]

SIGNATURES OF AGREEMENT FOR PROTOCOL

[redacted]

Investigator

Date

1 INVESTIGATOR APPROVAL STATEMENT

Protocol CHL-AA-201

A Randomized, Open-Label, Active-Controlled, Multi-Center Study to Evaluate the Serum Testosterone Levels in Patients with Metastatic Castration-Resistant Prostate Cancer on SoluMatrix™ Abiraterone Acetate 500 mg (4 x 125 mg qd) with Methylprednisolone (4 mg bid) as Compared to Zytiga® 1,000 mg (4 x 250 mg qd) with Prednisone (5 mg bid): The STAAR Study

[October 10, 2016]

I have read this protocol and agree to conduct this clinical trial as outlined herein. I will ensure that all sub-investigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with Churchill Pharmaceuticals LLC and their representatives during the study. I will adhere to all Food and Drug Administration (FDA), International Conference on Harmonisation (ICH), and other applicable regulations and guidelines regarding clinical trials on a study drug during and after study completion.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

2 PROTOCOL SYNOPSIS

TITLE	A Randomized, Open-Label, Active-Controlled, Multi-Center Study to Evaluate the Serum Testosterone Levels in Patients with Metastatic Castration-Resistant Prostate Cancer on SoluMatrix™ Abiraterone Acetate 500 mg (4 x 125 mg qd) with Methylprednisolone (4 mg bid) as Compared to Zytiga® 1,000 mg (4 x 250 mg qd) with Prednisone (5 mg bid): The STAAR Study
OBJECTIVES	**Primary:** The primary objective of this study is to evaluate serum testosterone levels after treatment with SoluMatrix™ Abiraterone Acetate as compared with Zytiga® in patients with metastatic castration-resistant prostate cancer (mCRPC) on Day 9 and Day 10. **Secondary:** • To evaluate serum testosterone levels after 4, 8 and 12 weeks of treatment with with SoluMatrix™ Abiraterone Acetate as compared with Zytiga® in patients with mCRPC • To evaluate the PSA levels and response rate after four, eight, and 12 weeks of treatment with SoluMatrix™ Abiraterone Acetate as compared with Zytiga® in patients with mCRPC • To determine the steady state pharmacokinetics of SoluMatrix™ Abiraterone Acetate 500 mg (4 x 125 mg) vs. Zytiga® 1,000 mg (4 x 250 mg) when administered to a subgroup of patients 2 hours after consumption of food. • To evaluate the steady state trough concentrations of abiraterone for patients with mCRPC treated with SoluMatrix™ Abiraterone Acetate 500 mg (4 x 125 mg) vs. Zytiga® 1,000 mg (4 x 250 mg) in the full study population (n=50) at study Days 9, 28, 56 and 84. • To evaluate the safety of SoluMatrix™ Abiraterone Acetate 500 mg (4 x 125 mg) and Zytiga® 1,000 mg (4 x 250 mg) in patients with mCRPC
NUMBER OF SUBJECTS	Approximately 50 patients will be enrolled
INVESTIGATIVE SITES	Approximately 20 study sites in the United States
METHODOLOGY	This is a Randomized, Open-Label, Active-Controlled, Multicenter Study to Evaluate the Serum Testosterone levels in Patients on SoluMatrix™ Abiraterone Acetate 500 mg (4 x 125 mg qd) with Methylprednisolone (4 mg bid) compared to Zytiga® 1,000 mg (4 x 250 mg qd) with Prednisone (5 mg bid)in Patients with mCRPC. The study consists of 3 periods: a screening period (approximately 4 weeks), treatment period (approximately 4 weeks), and an extension period (approximately 8 weeks). Following a screening period of 4 weeks, approximately 50 eligible patients will be randomized in a 1:1 allocation ratio to receive in

	parallel design either SoluMatrix™ Abiraterone Acetate with methylprednisolone (n=25) or Zytiga® with prednisone (n=25) for four weeks. • Arm 1: Patients will receive SoluMatrix™ Abiraterone Acetate (500 mg qd) in combination with methylprednisolone (4 mg bid). • Arm 2: Patients will receive Zytiga® (1,000 mg qd) in combination with prednisone (5 mg bid). After 4 weeks, patients in both arms of the study will continue participation in an extension period (additional 8 weeks) with the originally assigned treatment. Serial pharmacokinetic samples will be collected at Day 9 for a subgroup of patients. Safety will be monitored continuously from the time of informed consent signing until the end of the study. Preliminary data analysis will be at the completion of Day 28 which is the end of the treatment period. A secondary data analysis will be conducted at the end of the extension period.
SUBJECT POPULATION	**Inclusion criteria** Patients are eligible for inclusion into the study if the following criteria are met: 1. Written informed consent obtained prior to any study-related procedure being performed 2. Male subjects at least 18 years of age or older at time of consent 3. Pathologically confirmed adenocarcinoma of the prostate 4. Ongoing therapy with a GnRH agonist or antagonist AND serum testosterone level <50 ng/dL at screening 5. Metastatic disease documented by computed tomography (CT)/ magnetic resonance imaging (MRI) or bone scan. Imaging obtained within 42 days prior to the start of study medication will be accepted. 6. Meeting disease progression according to the recommendations of the prostate cancer working group 2 by one of the following criteria: a. Two rises of PSA (taken a minimum of 1 week apart) from a baseline measurement of at least 2 ng/mL, b. Imaging progression (CT/MRI) by RECIST criteria c. Nuclear scan progression by new lesion. 7. Discontinuation of flutamide or nilutamide, and other anti-androgens at least 4 weeks prior to the start of study medication; discontinuation of bicalutamide at least 6 weeks prior to start of study medication.

	8. Discontinuation of Radiotherapy > 4 weeks prior to start of study medication. 9. ECOG performance status of 0-1 at screening 10. Screening blood counts of the following: a. Absolute neutrophil count ≥ 1500/µL b. Platelets ≥ 100,000/µL c. Hemoglobin ≥ 9 g/dL 11. Screening chemistry values of the following: a. ALT and AST ≤ 2.5 x ULN b. Total bilirubin ≤ 1.5 x ULN c. Creatinine≤ 1.5 x ULN d. Albumin > 3.0 g/dL 12. Potassium ≥ 3.5 mmol/L 13. Life expectancy of at least 6 months at screening 14. Subject is willing and able to comply with all protocol requirements assessments 15. Agrees to protocol-defined use of effective contraception. **Exclusion criteria** Patients meeting the following criteria will be excluded from participation in the study: 1. History of impaired pituitary or adrenal gland function (eg., Addison's disease, Cushing's syndrome) 2. Prior therapy with abiraterone acetate, orteronel, ketoconazole or any other CYP17 inhibitor 3. Prior therapy with enzalutamide 4. Prior use of experimental androgen receptor antagonist 5. Previous exposure to Ra-223:Xofigo 6. Previous chemotherapy with the exception of docetaxel (Taxotere, Docefrez) for mCRPC with treatment completed at least 1 year prior to enrollment in this study 7. Initiation of bisphosphonate or denosumab therapy within 30 days prior to the start of study medication. Patients who are on a stable dose of these medications for at least 30 days at the time of starting study drug are eligible. 8. Therapy with estrogen within 30 days prior to the start of study medication 9. Use of systemic glucocorticoids equivalent to ≥ 10 mg of prednisone daily; patients who have discontinued or have reduced dose to < 10 mg prednisone within 14 days prior to the start of study medication will be eligible 10. Prior use of any herbal products that may decrease PSA levels (eg., saw palmetto) within 30 days of start of study medication 11. Known metastases to the brain or CNS involvement 12. History of other malignancy within the previous 2 years (no longer being actively treated), except basal cell carcinoma

	13. Major surgery within 30 days prior to the start of study medication 14. Blood transfusion within 30 days of screening 15. Serious, persistent infection within 14 days of the start of study medication 16. Persistent pain that requires the use of a narcotic analgesic 17. Known gastrointestinal disease or condition that may impair absorption (e.g., Crohn's disease) including history of bariatric surgery 18. Treatment with any investigational drug within 4 weeks prior to Day -1 of the study. 19. Known history of human immunodeficiency virus (HIV) or seropositive test for hepatitis C virus or hepatitis B virus 20. Have poorly controlled diabetes. 21. Uncontrolled hypertension (blood pressure greater than 140 mm Hg systolic or 90 mm Hg diastolic at enrollment) 22. History of New York Heart Association (NYHA) class III or IV heart failure 23. Serious concurrent illness, including psychiatric illness, that would interfere with study participation 24. Inability to swallow tablets whole 25. Known hypersensitivity to abiraterone acetate, methylprednisolone, prednisone or any excipients in study medications 26. Moderate to severe hepatic impairment (Child-Pugh Classes B and C) 27. Prior inclusion into this study (patients may be rescreened upon permission from the medical monitor)
STUDY DRUG	SoluMatrix™ Abiraterone Acetate with methylprednisolone is the experimental treatment. Patients are to take 500 mg (4 x 125 mg tablets) orally once daily. SoluMatrix™ Abiraterone Acetate should be stored at 59 to 86 degrees Fahrenheit (15 to 30 degrees Celsius). No food should be consumed for at least 2 hours before taking the dose or 1 hour after the dose. During the first 9 days of the treatment period, patients in the pharmacokinetic population will be advised to take their SoluMatrix™ Abiraterone Acetate 2 hours after a morning meal. The tablets should be swallowed whole with water. Do not crush or chew tablets. Methylprednisolone (4 mg) should be taken twice daily, orally. Methylprednisolone should be stored at controlled room temperature of 68 to 77 degrees Fahrenheit (20 to 25 degrees Celsius). Patients who develop hepatotoxicity defined as ALT or AST greater than 3X ULN and bilirubin greater than 2X ULN should discontinue treatment and follow early termination procedures.
REFERENCE PRODUCT	Zytiga®with prednisone is the active control. Zytiga® is supplied as 250 mg tablets. Patients are to take 1,000 mg (4 x 250 mg tablets) orally once daily. No food should be consumed for at least 2 hours before taking the dose or 1 hour after the dose. During the first 9 days of the treatment period, patients in the pharmacokinetic population will

	be advised to take their Zytiga® 2 hours after a morning meal. The tablets should be swallowed whole with water. Do not crush or chew tablets. Zytiga® should be stored at 59 to 86 degrees Fahrenheit (15 to 30 degrees Celsius). Prednisone (5 mg) should be taken twice daily, orally. Prednisone should be stored at 59 to 86 degrees Fahrenheit (15 to 30 degrees Celsius). Patients who develop hepatotoxicity defined as ALT or AST greater than 3X ULN and bilirubin greater than 2X ULN should discontinue treatment and follow early termination procedures.
RANDOMIZATION	This is a randomized 1:1 to SoluMatrix™ Abiraterone Acetate with methylprednisolone: Zytiga® with prednisone parallel design
STUDY DURATION	Approximately 4 months including screening **Screening Period (up to 4 weeks)** Patients will be assessed for eligibility through a review of inclusion and exclusion criteria during the Screening Phase, which will last up to 4 weeks. **Treatment Period (4 weeks)** Patients will be randomized to one of the arms for Treatment Period (4 weeks): • Arm 1: Patients will receive SoluMatrix™ Abiraterone Acetate (500 mg once daily) in combination with methylprednisolone (4 mg twice daily). • Arm 2: Patients will receive Zytiga® (1,000 mg once daily) in combination with prednisone (5 mg twice daily). **Extension Treatment Period (8 weeks)** After the initial 4 weeks patients from both arms of the study will continue in an extension study in which all subjects will remain on the originally assigned study treatment for an additional 8 weeks. **Discontinuation Criteria/Termination Rules**: Patients should be discontinued for one or more of the following reasons: 1. Intolerable adverse event(s) 2. Patients who develop an increase in ALT or AST greater than 3 x ULN and bilirubin greater than 2x ULN should be discontinued from the study. 3. Withdrawal of consent or 4. Based on the decision of the Investigator.
CRITERIA FOR EVALUATION	1. **Safety variables**: adverse events (AEs) and serious adverse events (SAEs), vital signs, physical exam findings, ECGs, and laboratory test results. 2. **Testosterone (T), and prostate specific antigen (PSA)** 3. **Pharmacokinetic variables**:

	• For the determination of plasma concentrations of abiraterone, blood samples will be taken during Day 9 under modified fasting conditions at predose (0) and .25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 9, and 24 hours • All patients will have Trough PK drawn at Days 9, 28, 56 and 84.
STATISTICAL METHODS SUMMARY	**Sample size calculation:** This study intends to assess the effects of the test drug of SoluMatrix™ Abiraterone Acetate (SAA) 500 mg on testosterone compared to the reference drug of Zytiga 1,000 mg, based on the bioequivalence approach of 80% to 125% confidence interval of the test-to-reference geometric mean ratio. [redacted] the study needs to randomize approximately 25 subjects per group for a 80% power (two one-sided t-tests at 0.05 level) to conclude bioequivalence of SAA to Zytiga on testosterone. **Analysis populations:** Study participants include all patients who were screened and found eligible for randomization on Day 1. Four analysis populations are defined as follows: • The intent-to-treat (ITT) population: includes all patients who were randomized. • The per-protocol (PP) population will include all of the ITT patients who successfully complete the Treatment Period without a major protocol deviation. The PP population is the secondary population of PD analysis. • Safety population: includes all patients who took at least 1 dose of study test medication. • PK population: includes all patients who received treatment and had blood sample taken on Day 9 of the treatment period with sufficient plasma concentrations for calculating PK parameters of C_{min}, C_{max}, and AUC_{0-24} **Analyses:** <u>Safety Analyses</u> Assessment of safety will be based on the safety population. Incidences of patients reporting treatment-emergent AEs, AEs resulting in discontinuation, and SAEs will be reported by treatment for the primary treatment period and extension treatment period. AE summaries will be provided showing the number and percentage of subjects who experienced at least 1 AE. These summaries will be presented by body system and preferred term. SAEs and AEs resulting in discontinuation will be summarized separately by treatment and period.

	Laboratory data, vital sign and ECG parameters will be summarized using descriptive statistics by treatment and, where applicable, will be compared between two treatments at pre-dose and each post-dose time point, using analysis of variance (ANOVA) with the treatment as the independent variable. Shift tables to summarize change in the referenced abnormality or study-defined abnormality from pre-dose to post-dose time-points will also be presented. Physical exam findings will also be summarized by treatment. <u>PK Analysis</u> 1-way ANOVA will be employed to examine differences between the two treatment regimens for SoluMatrix™ Abiraterone Acetate 500 mg (test) and Zytiga® 1,000 mg (reference) for PK parameters of AUC, C_{max} and C_{min} obtained over Day 9 of the treatment period. A null hypothesis of zero difference in a parameter among the two treatments will be assessed at the 0.05 level, with the alternative hypothesis of non-zero differences. The PK parameters of Tmax, T½ and Kel will be compared for test vs. reference regimens, using the non-parametric Wilcoxon rank sum test. <u>Analyses of T and PSA</u> Analyte assessment will be based on the ITT population. Analyte endpoints and their analyses include the following: **Primary:** The primary analysis will be conducted on the primary endpoint of the T level, defined as the average level of serum testosterone levels obtained on Day 9 and Day 10. The primary endpoint will be summarized using analysis of variance (ANOVA) and compared between two treatments by two approaches. The first approach is a comparative approach, using a 2-way ANOVA model with treatment and site as the independent variables. A null hypothesis of zero difference in a parameter between two treatments will be assessed at the 0.05 level. The second approach is a bio-equivalence (BE) approach, using the same ANOVA model described above. The primary endpoint of the T level will be analyzed on log scale in the BE approach to assess the equivalence effect of SoluMatrix™ Abiraterone Acetate 500 mg (test) vs. Zytiga® 1000 mg (reference). The two one-sided t-test hypotheses will be tested at the 0.05 level by constructing 90% confidence interval (CI) for the ratio of the T level geometric means of test vs. reference treatments. **Secondary:** To compare the safety of SoluMatrix™ Abiraterone Acetate and Zytiga® over 28 days and then at the conclusion of the extension period (Day 84).

	To compare PSA levels at Day 28 in patients on SoluMatrix™ Abiraterone Acetate as compared with Zytiga®, using the same approaches described for the primary endpoint. Durability of testosterone response and PSA response observed over the extension period to SoluMatrix™ Abiraterone Acetate will be assessed. The testosterone response will be defined as a serum testosterone level of less than or equal to the assay's limit of quantification (LOQ), and the PSA response is defined as a 50% reduction or more from baseline (Day 1)

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4 LIST OF ABBREVIATIONS

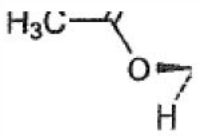
ACTH	adrenal corticotrophic hormone
AE	adverse event
AEPD	adverse events selected for pharmacodynamic evaluation
ALP	alkaline phosphatase, serum
ALT	alanine aminotransferase
ANOVA	analysis of variance
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC_{0-t}	area under the concentration-time curve, from time 0 to time of last sample with a quantifiable concentration
$AUC_{0-\infty}$	area under the concentration-time curve, from time 0 extrapolated to infinity
BID	twice daily
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum measured concentration
CMH	Cochran-Mantel-Haenszel
Cmin	minimum measured concentration
CPK	creatine phosphokinase
CRF	case report form
CT	computed tomography
CTA	clinical trial agreement
CTCAE	Common terminology criteria for adverse events
CYP17	cytochrome p450 enzyme 17α-hydroxylase
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCFR	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
GCP	good clinical practice
GGT	Gamma-glutamyl transferase
IB	Investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IND	investigational new drug
IRB	Institutional review board
ITT	intent-to-treat

IUD	intrauterine device
IWRS	interactive web response system
Kel	apparent elimination rate constant, determined by linear regression of the terminal points of the log linear concentration-time curve
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LHRH	luteinizing hormone release hormone
LOQ	limit of quantification
MAA	marketing authorization application
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	medical dictionary for regulatory activities
NCI	National Cancer Institute
NDA	new drug application
NYHA	New York Heart Association
PCWG	prostate cancer working group
PD	pharmacodynamic
PDF	portable document format
PK	pharmacokinetic
PP	per protocol
PSA	prostate specific antigen
QD	once daily
RECIST	Response Evaluation Criteria in Solid Tumors
SAA	SoluMatrix™ Abiraterone Acetate
SAP	statistical analysis plan
SAE	serious adverse event
SD	standard deviation
TEAE	treatment-emergent AE
T	testosterone
T_{max}	Time to maximum measured concentration
ULN	upper limit of normal
USA	United States of America
WBC	White blood cell count

5 INTRODUCTION

5.1 Background and Rationale

Abiraterone acetate is designated chemically as (3β)17-(3-pyridinyl)androsta-5,16-dien-3-yl acetate and its structure is:



Zytiga® (abiraterone acetate) is a CYP17 inhibitor indicated for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC). Abiraterone is an irreversible inhibitor of 17α-hydroxylase/C17, 20-lyase (CYP17), a key enzyme in the production of androgens in the testes, adrenal glands and within prostatic tumors. CYP17 catalyzes 17α-hydroxylation of C21 steroids and cleavage of the C17, 20 bond of C21 steroids. The 17α-hydroxylation activity is a step in cortisol biosynthesis, whereas the C17, 20 bond cleavage is needed for subsequent biosynthesis of androgens. Therefore, inhibition of the CYP17 enzyme blocks the production of androgens including testosterone.

Currently, Zytiga is approved to treat mCRPC and is co-prescribed with prednisone to manage mineralocorticoid excess that may be caused by CYP17 inhibition. Churchill Pharmaceuticals LLC is developing an alternative treatment to Zytiga, SoluMatrix™ Abiraterone Acetate (SAA). SAA is to be co-prescribed with 4 mg methylprednisolone. A review of the literature indicates that 4 mg of methylprednisolone should be sufficient to manage mineralocorticoid excess.

Retrospective studies have suggested that patients undergoing continuous androgen deprivation (CAD) have superior survival and time to progression if lower castrate levels of testosterone (0.7 nmol/L) are achieved. This study will determine if SAA and Zytiga are equivalent in maintaining the same level of suppression of testosterone.

Previously, it has been shown that a single 500 mg dose of SAA is bioequivalent (BE) to a single 1,000 mg dose of Zytiga administered to healthy, male volunteers in fasted conditions. This study will compare the relative steady state pharmacokinetics of 500 mg dose of SAA qd with 4 mg methylprednisolone bid and 1,000 mg Zytiga with 5 mg of prednisone bid under modified fasting conditions in patients with mCRPC.

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

5.2 Clinical and Nonclinical Experience

The basis of the SoluMatrix fine-particle technology™ is particle size reduction. By reducing the drug particle size, the surface area increases which facilitates faster dissolution compared to large particles. The intrinsic solubility of the compound is the same, the only difference is the time it would take to reach that solubility limit a given quantity of fluid. Note that the molecular structure of the compound is not altered, therefore once the drug is dissolved, it is absorbed and exerts the same physiological effects regardless of the starting particle size.

Abiraterone acetate exhibits dissolution-limited bioavailability. SAA tablets contain fine particles of abiraterone acetate, and have been shown *in-vitro* to have faster dissolution compared to the commercially available Zytiga (abiraterone acetate) Tablets. A Phase 1 clinical trial has shown that SAA tablets have approximately twice the bioavailability compared to Zytiga, such that a 500 mg dose of SAA (4 X 125 mg), is bioequivalent to 1,000 mg of Zytiga (4 X 250 mg), in healthy, male volunteers under fasted conditions.

There have been no animal studies with the novel formulation of abiraterone acetate. Non-clinical studies in the reference product package insert and articles in the published literature are summarized in the Investigator's Brochure for SAA.

[redacted]

Additionally, many clinical studies have been conducted on the commercially available abiraterone acetate, Zytiga. The clinical studies in the reference product package insert and articles in the published literature are summarized in the Investigator's Brochure for SAA.

Although the active pharmaceutical ingredient (drug substance – abiraterone acetate) is a relatively new product, its uptake in to the market has been rapid. Zytiga (abiraterone acetate) was approved by the FDA in 2011, and is currently indicated for use in combination with prednisone for the treatment of patients with mCRPC.

In the USA, Zytiga (abiraterone acetate) is sold in the following formulation:

Zytiga (abiraterone acetate) 250 mg Tablets.

SAA tablets are a novel formulation of abiraterone acetate under development by Churchill Pharmaceuticals. More rapid dissolution of the active ingredient in SAA tablets appears to lead to more complete absorption *in-vivo* which would allow for the use a lower oral dose than the reference drug to achieve the same rate and extent of absorption. Additionally, the effect of food on the pharmacokinetics of abiraterone appears to be greatly reduced for a single 500 mg dose of SAA, i.e., in healthy, male volunteers, Cmax and AUC are increased by a fatty meal by [redacted] respectively compared to a single dose in fasted conditions in comparison to food effect described in the prescribing information for the reference product in which a single 1,000 mg dose of Zytiga in healthy, male volunteers, Cmax and AUC are increased by a fatty meal by approximately 17-fold and 10-fold respectively compared to a single dose in fasted conditions.

5.3 Selection of the Doses Used in the Study

The Reference Drug for abiraterone acetate is the Janssen Biotech distributed formulation of abiraterone acetate, Zytiga. Zytiga is formulated in 250 mg tablets.

A previous study has demonstrated that 500 mg of SAA is bioequivalent to 1,000 mg of Zytigain healthy male volunteers under fasted conditions.

5.4 Summary of Potential Risks and Benefits

The risks of abiraterone acetate have been evaluated in healthy volunteer and patient studies. Abiraterone acetate is a key standard of care in patients with mCRPC. The reference product has been marketed in the US since 2011. The safety experience with abiraterone acetate is described in the prescribing information for Zytiga[1] and is briefly described in section 5.4.1

In order to minimize the potential risks associated with this study, an approved drug, Zytiga, at the approved dose for the indication will be administered with prednisone at the approved dose for this indication. A novel formulation with the same active pharmaceutical ingredient will be given with an alternative corticosteroid molecule, methylprednisolone. The dose of the novel formulation is intended to deliver the same mean rate and extent of systemic exposure to abiraterone as the approved product. Methylprednisolone has been used in the treatment of patients with mCRPC and will be given at a dose that has comparable glucocorticoid effects to the corticosteroid used with the approved product. Thus, it is anticipated that patients will be exposed to abiraterone

and steroids within acceptable levels with well-known description of risks. Patients will be monitored for adverse events including hepatotoxicity and events associated with apparent mineralocorticoid excess. Should unacceptable hepatotoxicity be found, the patient will be discontinued from the study and managed appropriately. Patients with baseline measurements and cardiovascular history or uncontrolled hypertension at screening that could lead to unacceptable risk will be excluded from enrolment into the study.

The presence of any condition that may affect the absorption, metabolism or passage of drugs out of the body, such as sprue, celiac disease, Crohn's disease, colitis, history of bariatric surgery or liver, kidney or thyroid conditions will also exclude the patient from the study.

Patients in the study will benefit by treatment by contributing to increased knowledge of safety, PSA response and T levels following administration of two different formulations of abiraterone acetate.

5.4.1 Potential Risks Associated with Abiraterone Acetate

There have been no multi-dose studies conducted with the experimental treatment, SAA; however, the following has been adapted from the Zytiga prescribing information to describe some of the most serious risks associated with treatment of mCRPC patients with abiraterone acetate:

- Mineralocorticoid excess
- Adrenal insufficiency
- Hepatotoxicity

The following is a list of most common side effects associated with the use of Zytiga, according to the package insert, from multiple dose studies: weakness, joint swelling or pain, swelling in legs or feet, hot flushes, diarrhea, vomiting, cough, high blood pressure, shortness of breath, urinary tract infection, bruising, low red blood cells, low potassium levels, high blood sugar, high blood cholesterol and triglycerides and other abnormal blood tests. More complete information can be found in the Zytiga package insert and the SAA investigator brochure.

Reproductive risks and contraception requirements:

It is not known if the study drug will affect sperm or semen. If a patients' partner is able to become pregnant, the patient should be advised to use a condom plus another reliable form of birth control during the study and for at least 1 week after the last dose of the study drug. Examples of acceptable forms of birth control include a condom and one of the following:

- Oral contraceptives, or implant
- Intra-uterine device (IUD)
- Barrier method (diaphragm with spermicide cervical cap or sponge)

5.4.2 Potential Risks Associated with Corticosteroids (Prednisone and Methylprednisolone)

The following side effects have been associated with the use of corticosteroids: sodium or fluid retention, potassium loss, hypokalemia, hypertension or hypotension, angioedema, muscle weakness, loss of muscle mass, myalgia, arthralgia, osteoporosis, tendon rupture, vertebral compression fractures, fracture of long bones, fatigue, malaise, peptic ulcer, pancreatitis, ulcerative esophagitis, increase in ALT, AST and alkaline phosphatase, negative nitrogen and calcium balance, impaired wound healing, thin fragile skin, facial erythema, suppression of reaction to skin tests, increased sweating, increased intracranial pressure, convulsions, vertigo, headache, development of cushingoid state, secondary adrenocortical and pituitary unresponsiveness, manifestation of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in diabetics, cataracts, increased intraocular pressure, glaucoma, exophthalmos, infection, increased susceptibility to infection, esophageal candidiasis, urticaria or other allergic, anaphylactic or hypersensitivity reaction, rash, pruritis, acne, behavioral changes including depression, anxiety, insomnia, irritability, or mood swings.

6 OBJECTIVE

The primary objective of this study is to evaluate the levels of T in patients after SAA 500 mg (4 x 125 mg qd) with methylprednisolone (4 mg bid) vs Zytiga 1,000 mg (4 x 250 mg qd) with prednisone (5 mg bid) vs in patients with mCRPC.

The secondary objectives are to evaluate the safety and effect on PSA after treatment with SAA as compared with Zytiga in patients with mCRPC, to describe the comparative pharmacokinetics between Zytiga and SAA in a subset of mCRPC patients, and to describe the safety and durability of PSA and T levels and response to Zytiga and SAA to 12 weeks.

7 STUDY DESIGN

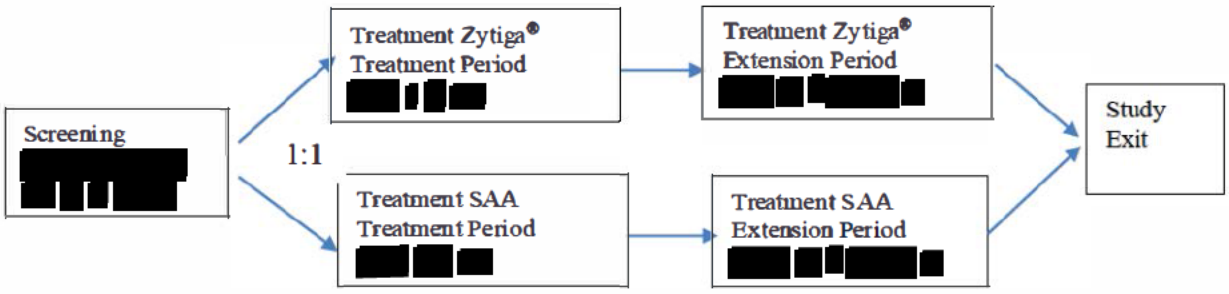
This is a randomized, open-label, multi-center study to evaluate T levels in patients on SAA 500 mg (4 x 125 mg qd) with methylprednisolone (4 mg bid) vs Zytiga 1,000 mg (4 x 250 mg qd) with prednisone (5 mg bid) under modified fasting conditions in patients with mCRPC. Subjects will be screened to determine eligibility for this study. Approximately 50 patients will be randomized in a 1:1 allocation ratio to receive either SAA (500 mg once daily) in combination with methylprednisolone (4 mg twice daily) or Zytiga (1,000 mg once daily) in combination with prednisone (5 mg twice daily) for 4 weeks, starting on Day 1, and an additional 8 weeks of extension treatment with the originally assigned treatment.

Serum testosterone levels and steady-state PK profile of plasma abiraterone concentrations will be determined on Day 9 and Day 10 (+2).

On Day 9, the medication will be taken after an ovemight fast of at least 10 hours and 2 hours after a meal. For patients in the PK population, abiraterone acetate study medication should be taken 2 hours after a moming meal through Day 9 of the study. For the PK population post-Day 9 and for the non-PK population for all study days, patients will be advised that no food should be consumed for at least 2 hours before taking the abiraterone acetate study medication and for at least 1 hour after taking the abiraterone acetate study medication.

There will be 2 parts of this study: Screening and Treatment. During screening, patients will be evaluated for ent y into the study by perfoi ing the assessments listed in the Schedule of Assessments (SOA). Upon completion of the initial treatment period, the patients and investigator will continue in the extension treatment period of the originally assigned study treatment.

Study Schematic



8 PATIENT POPULATION

8.1 Selection of Study Population

A screening log of potential study candidates and an enrollment log of patients must be maintained at the study site. Reasonable pre-screening activities should be performed to eliminate obvious screen failures.

8.1.1 Inclusion Criteria

Patients are eligible for inclusion into the study if all of the inclusion criteria and none of the exclusion criteria are met:

1. Written informed consent obtained prior to any study-related procedure being performed
2. Male subjects at least 18 years of age or older at time of consent
3. Pathologically confirmed adenocarcinoma of the prostate

4. Ongoing therapy with a GnRH agonist or antagonist AND serum testosterone level <50 ng/dL at screening
5. Metastatic disease documented by computed tomography (CT)/ magnetic resonance imaging (MRI) or bone scan. Imaging obtained within 42 days prior to the start of study medication will be accepted.
6. Meeting disease progression according to the recommendations of the prostate cancer working group 2 by one of the following criteria:
   a. Two rises of PSA (taken a minimum of 1 week apart) from a baseline measurement of at least 2 ng/mL,
   b. Imaging progression (CT/MRI) by RECIST criteria
   c. Nuclear scan progression by new lesion.
7. Discontinuation of flutamide or nilutamide, and other anti-androgens at least 4 weeks prior to the start of study medication; discontinuation of bicalutamide at least 6 weeks prior to start of study medication.
8. Discontinuation of Radiotherapy> 4 weeks
9. ECOG performance status of 0-1 at screening
10. Screening blood counts of the following:
    - Absolute neutrophil count $\geq$ 1500/µL
    - Platelets $\geq$ 100,000/µL
    - Hemoglobin $\geq$ 9 g/dL
11. Screening chemistry values of the following:
    a. ALT and AST $\leq$ 2.5 x ULN
    - Total bilirubin $\leq$ 1.5 x ULN
    - Creatinine $\leq$ 1.5 x ULN
    - Albumin > 3.0 g/dL
12. Potassium $\geq$ 3.5 mmol/L
13. Life expectancy of at least 6 months at screening
14. Subject is willing and able to comply with all protocol requirements assessments
15. Agrees to protocol-defined use of effective contraception.

8.1.2 Exclusion criteria

Patients meeting the following criteria will be excluded from participation in the study:

1. History of impaired pituitary or adrenal gland function (eg., Addison's disease, Cushing's syndrome)
2. Prior therapy with abiraterone acetate , orteronel, ketoconazole or any other CYP17 inhibitor
3. Prior therapy with enzalutamide
4. Prior use of experimental androgen receptor antagonist

5. Previous Exposure to Ra-223:Xofigo
6. Previous chemotherapy with the exception of docetaxel (Taxotere, Docefrez) for mCRPC with treatment completed at least 1 year prior to enrollment in this study
7. Initiation of bisphosphonate or denosumab therapy within 30 days prior to the start of study medication. Patients who are on a stable dose of these medications for at least 30 days at the time of starting study drug are eligible.
8. Therapy with estrogen within 30 days prior to the start of study medication
9. Use of systemic glucocorticoids equivalent to > 10 mg prednisone daily. Patients who have discontinued or reduced are eligible within 14 days prior to the start of study medication
10. Prior use of any herbal products that may decrease PSA levels (eg., saw palmetto) within 30 days of start of study medication
11. Known metastases to the brain or CNS involvement
12. History of other malignancy within the previous 2 years (no longer being actively treated), except basal cell carcinoma
13. Major surgery within 30 days prior to the start of study medication
14. Blood transfusion within 30 days of screening
15. Serious, persistent infection within 14 days of the start of study medication
16. Persistent pain that requires the use of a narcotic analgesic
17. Known gastrointestinal disease or condition that may impair absorption (e.g., Crohn's disease) including history of bariatric surgery
18. Treatment with any investigational drug within 4 weeks prior to Day -1 of the study.
19. Known history of human immunodeficiency virus (HIV) or seropositive test for hepatitis C virus or hepatitis B virus
20. Have poorly controlled diabetes.
21. Uncontrolled hypertension (blood pressure greater than 140 mm Hg systolic or 90 mm Hg diastolic at enrollment)
22. History of New York Heart Association (NYHA) class III or IV heart failure
23. Serious concurrent illness, including psychiatric illness, that would interfere with study participation
24. Inability to swallow tablets whole
25. Known hypersensitivity to abiraterone acetate, methylprednisolone, prednisone or any excipients in study medications
26. Moderate to severe hepatic impairment (Child-Pugh Classes B and C)

27. Prior inclusion into this study (patients may be rescreened upon permission from the medical monitor)

8.1.3 Restrictions

Subjects will be questioned at screening and each visit regarding prior involvement or use of the following products, substances and activities, which are restricted during the indicated time limits.

Prohibited medications during the study are described in section 12.4 of this protocol.

Table 1 Study Restrictions through Day 9 of Study for Patients participating in the 24 hour PK study

Restriction	From	To
Consumption of any food or beverage (except water).	10 hrs pre- Day 9 dose (Evening fast to begin around 8:00 pm)	2 hrs pre-dose (Day 9)
Consumption of grapefruit or grapefruit juice.	48 hrs pre-dose (Day 7 through)	Post-dose (Day 10)
Consumption of beverages containing alcohol.	48 hrs pre-dose (Day 7through)	Post-dose (Day 10)
Use of any herbal/vitamin supplement (if not approved by Investigator).	Day 1 through	Post-dose (Day 10)
Use of OTC medications (if not approved by Investigator).	Day 1 through	Post-dose (Day 10)
Use of narcotic analgesics	Screening	Post-dose (Day 10)

8.1.4 Removal of Patients from Therapy or Assessment

All patients are free to withdraw from participation in this study at any time, for any reason, and without prejudice.

Patients who develop a concomitant increase in ALT or AST greater than 3 x ULN and bilirubin greater than 2 x ULN should be discontinued from the study.

The investigator may withdraw a patient from the study at any time for the following reasons:

- adverse event
- protocol violation (reason must be specified, for example, repeated non-compliance with study dmg, use of a prohibited medication, etc.,)

- administrative reasons (e.g., study terminated by the sponsor)
- any other reason that would protect the patient's best interest in the investigator's opinion (must be specified)
- patient withdraws consent (e.g., patient is moving, no longer wishes to participate, etc.)

Data collected up to the time of withdrawal of consent will be reported and analyzed. Any patient that withdraws consent due to an adverse event must be reported as a discontinuation due to adverse event.

For patients who withdraw before completing the study, the reason for withdrawal will be entered in the case report form (CRF). Whenever possible and reasonable, the evaluations which were to be conducted at the completion of the study should be performed at the time of premature discontinuation.

9 STUDY PROCEDURES

The schedule of assessments is summarized in Appendix I. Patients will provide written informed consent before any study-related procedures are performed, including the cessation of prohibited concomitant medications. Standard of care procedures that were performed as part of the diagnosis of mCRPC are not considered study-related procedures.

9.1 Screening[redacted]

All screening assessments should be completed within 28 days of randomization. Adverse events and concomitant medications should be collected and recorded from the time of informed consent in source documents but do not need to be entered into the electronic case report form (eCRF) unless the patient is eligible to enter the study.

9.1.1 Visit 1, Screening

The following procedures will be performed at Screening:

1. Obtain written informed consent.
2. Assign a screening number.
3. Review inclusion/exclusion criteria (including contraception requirements, Section 5.4.1).
4. Record demographics, including patients initials, date of birth, sex, race and ethnicity
5. Collect a complete medical history, including documentation that confirms the diagnosis of metastatic, castration resistant prostate cancer.
6. Evaluate ECOG status
7. Record medications taken within 30 days before Screening.
8. Perform a complete physical examination (including recording height and weight).
9. Record vital signs (blood pressure, pulse, respiratory rate, and oral body temperature) after the patient has been in a sitting position for at least 5 minutes.

10. Perform a 12-lead ECG.
11. Collect blood and urine samples for clinical laboratory tests (hematology, chemistry, hormones, and urinalysis; see Section 11.3 for a complete list of required laboratory tests)
12. Collect a blood sample for serum testosterone and PSA labs.
13. Collect blood sample for HIV, HBsAG, and HCV antibody testing (must be negative or non-reactive).
14. Remind the patient not to use any prohibited concomitant medications and to comply with all study restrictions.

Note: If a patient does not meet entry criteria or has indicated they do not wish to participate in the study, they should be recorded as a screen failure. Patients may be re-screened for eligibility if there is a change in their condition that warrants re-screening.

9.2 Determination of Patient Eligibility, Randomization

All information available from the patient's medical records and screening assessments should be reviewed to determine if the patient qualifies for the study and return to the clinic for the Day 1 visit.

9.2.1 Visit 2, Randomization, [redacted]

1. Review inclusion and exclusion criteria and verify that the patient continues to meet all study entry criteria (recognizing they may still be in a medication washout period).
2. Ensure medical history is current (including adverse events experienced and concomitant medications taken, if applicable, since Visit 1).
3. Collect blood sample for PSA and serum testosterone
4. Perform a complete physical exam
5. Record vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) after the patient has been in a sitting position for at least 5 minutes.
6. Collect blood and urine samples for complete safety labs
7. Evaluate ECOG status
8. Record concomitant medications
9. Record adverse events
10. Dispense study drug
11. Schedule the next study visit
12. Patients in the PK population will be reminded to take their dose of SAA or Zytiga on the morning of Day 8 two hours after a morning meal. The patients in the non-PK population will be reminded to take their dose of SAA or Zytiga on the morning of Day 8 at least one hour before or two hours after a meal.

9.3 Treatment Period

9.3.1 [redacted]

Patients participating in the 24 hour PK subgroup at pre-selected sites will report to the clinic in the evening on [redacted]

1. Subjects will be questioned about timing of last dose of study medication, other medication use, restricted foods and substances, blood donation, and any other changes since last seen at the clinic.
2. Collect blood and urine for complete safety labs
3. Record concomitant medications and adverse events

9.3.2 Visit 3, [redacted]

1. Vital Signs: Pre-dose vital signs (heart rate, blood pressure, respiratory rate and temperature) will be obtained within 90 minutes of scheduled dosing
2. Collect blood sample for serum testosterone (7am – 10am)
3. Collect blood and urine from Patients who are not participating in the 24 hour PK for complete safety labs.
4. Perform drug accountability
5. PK Blood Samples:
    - PK trough sample will be taken for those patients not participating in the 24 hour PK subgroup
    - For those patients who are participating in the 24 hour PK sampling: A morning meal will be provided to be consumed 2 hours before dosing. Blood samples for pre-dose PK profiling will be collected approximately 45 minutes before dosing, i.e. within 60 to 30 minutes prior to dosing. Post-dose blood samples will be collected throughout the day at the times specified in **Table 2**. If more than one event is scheduled for the same time, blood draw times take precedence over all other study activities except dosing, unless otherwise specified.
6. Study Drug Administration for subjects in the 24 hour PK group: Subjects will be dosed orally with one 500 mg dose of SAA or one 1000 mg dose of the reference product, Zytiga. In all cases, the study drug must not be chewed and must be swallowed whole with water. A mouth check will be performed to ensure that the entire dose has been consumed. Subjects will remain sitting upright or ambulatory for 4 hours following dosing.
7. Record adverse events

9.3.3 Visit 4, Day 10

1. Collect blood sample for serum testosterone (7 am 10 am)
2. Collect blood for final PK sample (24 hour draw) for the PK subgroup
3. Dispense study drug for subjects to take home
4. Continue to remind the patient about compliance with study medications and the avoidance of prohibited medications
5. Schedule the next study visit and provide a prescription for the serum chemistry draw

[redacted]

[redacted]

9.3.4 Day 21

1. Patient goes to local lab for serum chemistry draw

9.3.5 Visit 5, [redacted]

This visit marks the end of the Treatment Period. Subjects will be asked to report to the clinic without taking the daily study medication. The following procedures will be performed at this visit:

1. Collect blood sample for PSA, and serum testosterone
   - P[redacted]
2. Perform a complete physical exam
3. Record vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) after the patient has been in a sitting position for at least 5 minutes.
4. Collect blood and urine samples for complete safety labs
5. [redacted]
6. Evaluate ECOG status
7. Record concomitant medications
8. Record adverse events
9. Perform drug accountability
10. Study Drug Dispensing for those who will continue to the Extension part of the study
11. For those continuing on the Extension part of the study provide a prescription for the serum chemistry draw

9.3.6 Early Termination Visit

Patients who terminate the study before 28 Days should have the following assessments performed:

1. Perform a complete physical exam

2. Evaluate ECOG status
3. Record vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) after the patient has been in a sitting position for at least 5 minutes.
4. Collect blood and urine samples for complete safety labs
5. Collect blood samples for PSA and serum testosterone
6. Record concomitant medications
7. Record adverse events
8. Collect study drug and perform final drug accountability

9.4 Extension Period

9.4.1 Day 42

1. Patient goes to local lab for serum chemistry draw

9.4.2 Visit 6, Day 56

1. Perform a complete physical exam
2. Evaluate ECOG status
3. Record vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) after the patient has been in a sitting position for at least 5 minutes.
4. Collect blood samples for PSA, and serum testosterone
   - [redacted]
5. Collect blood and urine samples for complete safety labs
6. Record concomitant medications
7. Record adverse events
8. Drug accountability and Drug dispense

9.4.3 Day 70

1. Patient goes to local lab for serum chemistry draw

9.4.4 Visit 7, Day 84

This visit marks the end of the Extension Period.

1. Perform a complete physical exam
2. Evaluate ECOG status
3. Record vital signs (blood pressure, heart rate, respiratory rate, and oral body temperature) after the patient has been in a sitting position for at least 5 minutes.
4. Collect blood sample for PSA, and serum testosterone

- PK trough sample will be taken for those patients not participating in the 24 hour PK subgroup

5. Collect blood and urine samples for complete safety labs
6. Record concomitant medications
7. Record adverse events
8. Collect study drug and perform final drug accountability

10 EFFICACY ASSESSMENTS

10.1 *PSA and Testosterone Level*

Serum testosterone levels measured at Day 9 and Day 10 will be averaged to get a single testosterone value for each subject, which will be considered as the primary endpoint of pharmacodynamic (PD) assessment. Blood samples for serum testosterone will also be collected at Screening, randomization (Day 1), end of the treatment period (Day 28), and Day 56 and Day 84 of the extension period as well as, where applicable, at early termination visit. In addition, subjects' serum testosterone response of complete suppression will be assessed at end of the treatment period (Day 28) and at Day 56 and Day 84 of the extension period. For a given assessment time point, a testosterone response of complete suppression is defined as a [redacted] For PD analysis of absolute values, serum testosterone levels of less than the assay's LOQ at an assessment time point will be replaced with the assay's LOQ or 1 ng/dL, whichever is greater.

Prostate specific antigen (PSA) level measured at end of the treatment period (Day 28) will be analyzed as the key secondary endpoint of PD assessment. Blood samples for PSA will be collected at Screening, randomization (Day 1), end of the treatment period (Day 28), and Day 56 and Day 84 of the extension period as well as, where applicable, at early termination visit. In addition, subjects' PSA 50 response will be assessed at end of the treatment period (Day 28) and at Day 56 and Day 84 of the extension period. For a given assessment time point, a PSA-50 response is defined as [redacted] For PD analysis of absolute values, PSA levels of less than the assay's LOQ at an assessment time point will be replaced with the assay's LOQ or 1 ng/mL, whichever is greater.

10.2 Pharmacokinetic Variables

[redacted] For all subjects, blood samples will

be collected [redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

11 SAFETY EVALUATIONS

Safety will be evaluated by the incidence of TEAEs, AEPD, changes in physical examination findings, clinical laboratory test results, ECGs, and vital sign measurements.

11.1 Physical Examination

A complete physical examination will be performed at screening, randomization [redacted], end of treatment [redacted]

The examination will include an assessment of the following: general appearance, skin, head and neck (including eyes, ears and throat), thorax, lymph nodes, thyroid, musculoskeletal extremities, cardiovascular, lungs, abdomen and neurological systems. The screening physical exam will also include a measurement of height and weight.

All examinations will be performed by a physician or health professional listed on the Form FDA1572 and licensed to perform physical exams. The investigator will review all physical examination findings for clinical significance.

Except for the screening physical exam, only changes from the previous exam need to be recorded in the source and eCRF.

11.2 Vital Signs

Vital signs (including blood pressure, pulse, respiratory rate, and oral body temperature) will be measured after the patient has been in a sitting position for at least 5 minutes.

Vital signs will be measured at screening, randomization and each post-randomization visit, including the early termination visit.

The investigator will review all vital signs for clinical significance.

11.3 Clinical Laboratory Tests

Clinical labs will be performed according to the Schedule of Assessments. Some visits will require the collection of blood and urine for complete safety labs. See the below list of parameters measured for complete safety labs for Hematology and Serum Chemistry.

All laboratory results should be evaluated by the investigator, and abnormal values assessed for clinical significance. All clinically significant lab values should be reported as an AE or SAE as appropriate.

Table 3 Summary of Blood Volume

Sample	Days of collection	Volume of sample
Serum chemistry, hematology, HIV, Hepatitis B&C	Screening Phase	1 x 10 mL

Serum chemistry, hematology*	Day 1, Day 8 or 9, Day 28, Day 56 and Day 84	5 x (6.5 mL)
Serum Chemistry	Day 21, Day 42 and Day 70	3 x (2 mL)
Testosterone	Screening, Day 1, Day 9, Day 10, Day 28, Day 56, and Day 84	7 x (3.5 mL)
PSA	Screening, Day 1, Day 28, Day 56, and Day 84	5 x (0.6 mL)
PK trough samples **(for non PK subgroup)**	Day 9, Day 28, Day 56 and Day 84	4 x 6 mL
24 hour Pharmacokinetic blood samples	Day 9	1 x (12 x 6 mL)
Expected Total Volume of Blood Collected per Subject not participating in 24 hour PK sub group :		**100mL**
Expected Total Volume of Blood Collected per Subject participating in 24 hour PK sub group		**148mL**

*LFTs are included in Serum Chemistry

Hematology: Hemoglobin, hematocrit, platelet count (or estimate), red blood cell count, white blood cell count, complete blood cell count (including differential)

Serum Chemistry: ALT, AST, total bilirubin, GGT, ALP, creatinine, albumin, BUN, glucose, calcium, sodium, potassium, chloride, bicarbonate, CPK

Urinalysis: pH, color, appearance, specific gravity, glucose, protein, ketones, bilirubin, urobilinogen, blood and microscopic exam

Additional Tests: Testosterone, Total Serum (TTBS)
Prostate specific antigen (PSA)

11.4 12-Lead Electrocardiograms

A 12-lead ECG will be performed at Screening.

The patient should rest in a supine position for at least 5 minutes before the recording is conducted.

If the unconfirmed ECG report from the instrument indicates QT prolongation with QTcF> 450 msec, the investigator should repeat the ECG within 1 hour. If the initial findings are

confirmed, the investigator should exclude/withdraw the patient from study participation. The investigator should review all ECG results for clinical significance.

11.5 Adverse Events

Adverse events will be collected from the time of signing of the ICF through each study visit. Adverse events collected in the source documents for screen failed patients do not need to be entered into the electronic case report form (eCRF); however once a patient is randomized, all AEs should be entered into the eCRF.

11.5.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with the product, whether or not related to the product.

Preexisting diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition.

11.5.2 Definition of Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly
- Is an important medical event

Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent another of the outcomes listed in the definition above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

An elective hospital admission to treat a condition present before exposure to the study drug, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE.

A newly diagnosed pregnancy in a patient who has received a study drug is not considered an SAE unless it is suspected that the study drug interacted with a contraceptive method

and led to the pregnancy. A congenital anomaly in an infant born to a mother who was exposed to the study drug during pregnancy is an SAE.

11.5.3 Adverse Event Intensity Assessment

An assessment of intensity grade will be made using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version v 4.03 which includes the following descriptors:

Grade 1	Mild	No specific medical intervention; asymptomatic laboratory findings only, radiographic findings only, marginal clinical relevance
Grade 2	Moderate	Minimal intervention; local intervention; non-invasive intervention
Grade 3	Severe	Significant symptoms requiring hospitalization or invasive intervention; transfusion, elective interventional radiological procedure; therapeutic endoscopy or operation
Grade 4	Life-threatening or disabling	Complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, and sepsis; life-threatening physiologic consequences; need for intensive care or emergent interventional radiological procedure, therapeutic endoscopy or operation
Grade 5	Death	Death related to the adverse event

For those AEs not directly referenced in CTCAE, the Investigator should use clinical judgment in assessing the intensity of such events using the above categories as a guide. For a continuous episode of an AE with variable intensity, the greatest intensity should be recorded for the AE.

11.5.4 Definition of Start Date and Stop Date

Start date: The date at which the AE is first noted

Stop date: The date at which the AE is known to be resolved. If it has not known to have stopped, then indicate "ongoing."

11.5.5 Action(s) Taken

Action(s) taken may consist of the following (as appropriate):

None: No actions taken.

Discontinued study drug: Study drug was permanently discontinued because of the AE.

Treatment: Specified medication (to be listed on the concomitant medication chart) was used as a countermeasure.

Other: Other actions, such as an operative procedure, were required because of the AE.

11.5.6 Definition of Expectedness

An expected AE is one for which the nature or severity is consistent with the known AE profile of the product. For a study drug, the known information is contained in the IB. For a marketed product, the known information is contained in the current package insert for the product.

An unexpected AE is one for which the specificity or severity is not consistent with the current IB. For example, hepatic necrosis would be unexpected (greater severity) if the IB only listed elevated hepatic enzymes or hepatitis. Likewise, cerebral thromboembolism and cerebral vasculitis would be unexpected (greater specificity) if the IB only listed cerebral vascular accidents.

Furthermore, reports which add significant information on specificity or severity of known, already documented adverse events constitute unexpected events. Examples would be (a) acute renal failure as an expected adverse event with a subsequent new occurrence of interstitial nephritis and (b) hepatitis with a first occurrence of fulminate hepatitis.

11.5.7 Definition of Relationship to Study Drug(s)

The categories for classifying the investigator's opinion regarding the relationship of an AE to study drug(s) are listed below. They are derived from published criteria.

Certain:	An AE occurring in a plausible time relationship to study drug administration and that cannot be explained by a concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) is clinically reasonable.
Probable (likely):	An AE with a reasonable time sequence to administration of the study drug and that is unlikely to be attributed to concurrent disease or other drugs or events. The response to withdrawal of the drug (dechallenge) is clinically reasonable.
Possible:	An AE with a reasonable time sequence to administration of the study drug, but that could also be explained by concurrent disease or other drugs or events. Information on drug withdrawal may be lacking or unclear.
Unlikely:	An AE, including laboratory test abnormality, with a temporal relationship to study drug administration that makes a causal relationship improbable and in which other drugs, events, or underlying disease provide plausible explanations.
Not related:	An AE with sufficient evidence to accept that there is no causal relationship to study drug administration (e.g., no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; another cause was proven; etc.).
Unassessable (unclassifiable):	A report suggesting an adverse event for which the relationship to study drug cannot be judged because information is insufficient or contradictory and which cannot be supplemented or verified.

11.5.8 Definition of Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as:

- Resolved
- Resolved with sequelae
- Ongoing
- Death
- Other
- Unknown

Death should only be selected as an outcome when the AE resulted in death. If more than 1 AE is possibly related to the patient's death, the outcome of death should be indicated for each such AE. Although "death" is usually an event outcome, events such as sudden death or unexplained death should be reported as an SAE.

11.5.9 Documentation of Adverse Events

The investigator will monitor and/or ask about or evaluate AEs using non-leading questions at each visit or evaluation. The occurrence of all AEs will be documented in the CRF with the following information, where appropriate:

- AE name or term
- When the AE first occured (start date)
- When the AE stopped (stop date), or an indication of "ongoing"
- Severity of the AE
- Seriousness
- Actions taken
- Outcome
- Investigator opinion regarding the relationship of AE to the study drug(s)

11.5.10 Follow-up of Patients with an Adverse Event

Any AE will be followed to a satisfactory resolution, until the patient becomes stable, or until the event can be explained by another known cause(s) (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the patient's medical record.

11.5.11 Special Procedures for Managing Serious Adverse Events

The Investigator will notify the Sponsor of a serious adverse event for any subject within 24 hours of learning of its occurrence. Such notification will be made by telephone, or email, as appropriate to the timeframe of learning of its occurrence. Notification by

electronic mail is allowed only between the hours of 8:00 AM and 5:00 PM EST Monday through Friday except holidays.

If AEs occurring in a patient are not tolerable, or if continued administration of study drug is not reasonable in view of the potential benefit to patient, the investigator must decide whether to withdraw the patient from the study and/or provide treatment.

Contact information for the medical monitor is: [redacted]

Mobile:
[redacted]

At the time of first notification of an SAE, the following information should be provided by the study site, if available:

- Patient's study number and initials
- Patient's date of birth
- Patient's gender
- Date of first dose of study drug(s)
- Date of last dose of study drug(s), if applicable
- AE term
- Time (if available) and date of occurrence of the event
- A brief description of the event, outcome to date, and any actions taken
- The seriousness criteria(on) that were met
- Concomitant medication at onset of the event
- Relevant medical history information
- Relevant laboratory test findings
- Investigator's opinion of the relationship to study drug. ("Is there a reasonable possibility that the study drug caused the SAE? Yes or no?").
- Any missing or additional relevant information concerning the serious (or unexpected) AE should be provided in a written follow-up report.

The investigator is required to comply with applicable regulations reg rding the notification of his or her IRB or independent ethics committee.

12 TREATMENTS

12.1 Treatments Administered

12.1.1 Study Drugs

Patients who meet all eligibility criteria will be randomized on Day 1 to receive daily study treatments for the treatment period consisting of 28 Days:

- Arm 1: Four 125 mg SAA tablets to be taken once daily plus one 4 mg methylprednisolone tablet twice daily, spaced approximately 12 hours apart
- Arm 2: Four 250 mg Zytiga (abiraterone acetate) tablets to be taken once daily plus one 5 mg prednisone tablet to be taken twice daily, spaced approximately 12 hours apart

[redacted]

No food should be consumed for at least two hours before the dose of study dmg is taken and for at least one hour after the dose of study drug is taken. Tablets should be swallowed whole with water. Do not crush or chew tablets.

Patients in the PK subgroup will be instructed to take the SAA or Zytiga study dmg 2 hours after a morning meal for Day 1 through Day 9.

[redacted]

After 4 weeks, patients in both arms of the study will continue in an extension period (additional 8 weeks) with the originally assigned treatment.

12.1.2 Discontinuation of Treatment Due to Hepatotoxicity

Patients who develop hepatotoxicity defined as ALT or AST greater than 3 X ULN and bilirubin greater than 2 X ULN will be discontinued from the study.

12.1.3 Storage

SAA tablets, Zytiga (abiraterone acetate) tablets, and prednisone tablets should be stored at 15°C to 30°C (59°F to 86°F). Methylprednisolone tablets should be stored at controlled room temperature of 20°C to 25°C (68°F to 77°F).

12.1.4 Labeling

Each container of SAA will be labeled with study-specific information meeting all the applicable regulatory requirements, including the statement, Caution: New Drug--Limited

by Federal (or United States) law to investigational use. Zytiga, methylprednisolone, and prednisone will be provided in commercially available bottles/packaging.

Zytiga, methylprednisolone, and prednisone will be obtained and provided to the study sites.

12.1.5 Drug Accountability

The investigator must maintain adequate records showing the receipt, dispensing, return, or other disposition of the study drug including the date, quantity, batch or code number, and identification of patients (patient number and initials) who received the study drug. The investigator will not supply the study drug to any person except those named as subinvestigators on the form FDA 1572, designated staff, and patients in this study. The investigator will not dispense the study drug from any sites other than those listed on the form FDA 1572. Study drug(s) may not be relabeled or reassigned for use by other patients.

At the conclusion of the study, each site with patients participating in full pharmacokinetic analysis will retain an adequately identified and properly stored reserve sample of SAA and Zytiga. All remaining unused IMP should be reconciled with dispensing records, documented, and return or destroyed as agreed upon with the sponsor

12.2 Method of Assigning Patients to Treatment Groups

Eligible patients will start study drug on their Day 1 and continue through approximately Day 30 of the study, and then all patients will be evaluated to see if they should continue to the extension treatment period

12.3 Prior and Concomitant Therapy

While the use of narcotic analgesic for persistent pain is an exclusion criteria entering the study. It is not prohibited after Day 10, as subjects should receive the best supportive care in accordance with current standards and guidelines. Refer to the Zytiga package insert prior to prescribing concomitant therapy.

Upon entering the study, each patient will be instructed to report the use of any medications to the investigator. Patients will also be instructed about the importance of discussing any new medications (including over the counter medications) before use, with the investigator whenever possible.

Any concomitant medication or therapy used while the patient is in the study must be recorded in the source documents and eCRF. The medication name, dosage, date and indication for use must be captured. The medical monitor should be notified, in advance, whenever possible, of any instances in which a prohibited medication or therapy is needed. Any changes to ongoing concomitant medications including change of dose of the concomitant mediation and the addition of new medications must be recorded in the source documents and eCRF. If possible, patients taking a concomitant medication acceptable to

the investigator on enrolhnent should continue to take that medication at the same dose for the duration of the clinical trial.

12.4 Prohibited Medications

The following medications/therapy will be prohibited during the study

- Chemotherapy, radiotherapy, or immunotherapy
- Use of any drugs known to induce or inhibit hepatic drug metabolism (Carbamazepine, Dexamethasone, Ethosuximide, Glucocorticoids except prednisone and methylprednisolone provided as study medication, Griseofulvin, Phenytoin, Primidone, Progesterone, Rifabutin, Rifampin, Nafcillin, Nelfinavir, Nevirapine, Oxcarbazepine, Phenobarbital, Phenylbutazone, Rofecoxib, St John's wort, Sulfadimidine, Sulfinpyrazon, Troglitazone)
- Substrate of CYP2D6 with a narrow therapeutic index (e.g.,thioridazine)
- Use of antiandrogens and estrogens
- Herbal supplements that may reduce testosterone levels, such as saw palmetto
- Any investigational treatments/therapy

The investigator should be familiar with all cautions identified in the package insert for Zytiga in relation to the use of concomitant medications.

13 STATISTICAL METHODS

13.1 Statistical Analyses

This section presents a summary of the planned statistical analyses. A statistical analysis plan (SAP) describing in detail the analyses to be conducted will be written before first patient is enrolled.

Categorical variables will be summarized in general using frequencies and percentages, whereas continuous variables will be summarized in general using descriptive statistics of number of observations (n), mean, standard deviation (SD), minimum (Min), median, and maximum (Max).

Hypothesis testing, unless otherwise indicated, will be performed at the 5% significance level. All p-values will be rounded to 4 decimal places; p-values less than 0.0001 will be presented as '<0.0001' in all tables. All group comparisons from analysis of variance (ANOVA) and/or analysis of covariance (ANCOVA) models will be based on Type III sums of squares. For superiority testing, all confidence intervals will be 2-sided with 95% coverage, whereas for bio-equivalence testing, all confidence intervals will be 2-sided with 90% coverage.

For safety and PD data, records with valid data within each visit or assessment time point will be identified for initial and repeat, where applicable. The initial record will be used in statistical analysis, whereas all records will be presented in data listings. All of the scheduled assessments will be performed and every effort will be made to collect the data. Missing data, if any, will be treated as missing for the corresponding visit or time point.

For the analyses of the PD variables, baseline values are defined as the last measurements obtained before the initial dosing with the study drug.

Unless specified otherwise, SAS® Version 9.1.3 or higher will be used to perform the statistical analyses of efficacy and safety measures.

13.1.1 Analysis Populations

Study participants include all patients who were screened and found eligible for randomization on Day 1. Four analysis populations are defined as follows:

- The intent-to-treat (ITT) population: includes all patients who were randomized.
- The per-protocol (PP) population will include all of the ITT patients who successfully complete the Treatment Period without a major protocol deviation. The PP population is the secondary population of PD analysis.
- Safety population: includes all patients who took at least 1 dose of study test medication.
- PK population: includes all patients who received treatment and had blood sample taken on Day 9 of the treatment period with sufficient plasma concentrations for calculating PK parameters of C_{min}, C_{max}, and $AUC_{0\ 24}$

Membership in the analysis populations will be determined before database lock.

13.1.2 Disposition

Descriptive summaries of patient disposition will be presented for the safety population, ITT population, and PP population as well as PK population. A detailed description of individual patient disposition will be provided in a data listing.

13.1.3 Patient Characteristics

Descriptive summaries of patient demographic and baseline characteristics will be presented for the safety population, ITT population, and PP population as well as PK population. Patient characteristics will include a summary of demography, baseline disease characteristics, pre-existing medical conditions, prior therapies for the treatment of prostate cancer, and baseline efficacy measures of ECOG performance status, testosterone and PSA concentrations as well proportions of subjects with serum testosterone of $\leq$LOQ and $\leq$1 ng/dL.

13.1.4 Efficacy

13.1.4.1 Efficacy Analyses

Efficacy analyses will be based on the ITT population.

Primary efficacy analysis

The primary analysis will be conducted on the primary PD endpoint of the testosterone (T) level, which is defined as the average of serum testosterone (absolute) levels obtained on Day 9 and Day 10.

The primary PD endpoint will be analyzed, using analysis of variance (ANOVA) model, and compared between treatments by two approaches. The first approach is a comparative approach, using a 1-way ANOVA model with treatment as the independent variable, and the least-square (LS) means and standard error (SE) of T levels under each treatment and the between-treatment difference in LS means will be reported. A null hypothesis of zero difference in a parameter between two treatments will be assessed at the 0.05 level. The second approach is a bio-equivalence (BE) approach, using the same ANOVA model described above.

The primary PD endpoint of the T level will be analyzed on log scale in the BE approach to assess the equivalence effect of SoluMatrix™ Abiraterone Acetate 500 mg (test) vs. Zytiga® 1000 mg (reference). The two one-sided t-test hypotheses will be tested at the 0.05 level by constructing 90% confidence interval (CI) for the ratio of the T level geometric means of test vs. reference treatments.

Secondary efficacy analysis

A secondary PD endpoint is the PSA (absolute) levels on Day 28, and the other secondary PD endpoints include PSA levels on Day 56 and Day 84, and PSA-50 response on Day 28, Day 56 and Day 84, as well as serum testosterone levels and complete suppression of testosterone on Day 28, Day 56, and Day 84.

The PSA levels on Day 28, Day 56 and Day 84 will be analyzed, respectively, using the same approaches described for the primary PD endpoint of the T level. For a given assessment time point, proportion of subjects with PSA-50 response will be reported by treatment and compared for between-group differences, using a non-parametric Fisher's Exact Test.

The testosterone levels on Day 28, Day 56 and Day 84 will be analyzed, respectively, using the same approaches described for the primary PD endpoint of the T level. For a given assessment time point, proportion of subjects with complete suppression of

testosterone will be reported by treatment and compared for between-group differences, using a non-parametric Fisher's Exact Test.

Durability analysis of testosterone response and PSA response

To assess the durability (or persistence) of PSA-50 response and testosterone complete suppression, the Fisher's Exact Test will be used to examine between-group differences in proportion of subjects with PSA response or testosterone complete suppression at Day 56 and Day 84, respectively, for those subjects who achieved the corresponding response upon entering the extension period (Day 28).

13.1.4.2 Pharmacokinetic (PK) Analysis

The PK variables include the trough concentrations (C_{min}) of abiraterone at steady state, $AUC_{0\ t}$, $AUC_{0\ 24}$, $AUC_{0\ inf}$ and C_{max} as well as T_{max}, $t_{1/2}$ and Kel. These PK parameters are defined as the following:

Variable	Description
$AUC_{0\ t}$	The area under the plasma concentration versus time curve, from time 0 to the time (t) of the last measurable concentration (C_t), as calculated by the linear trapezoidal method.
AUC0-24	The area under the plasma concentration versus time curve, from time 0 to the 24 hours post dose, as calculated by the linear trapezoidal method.
$AUC_{0-\infty}$	Area under the plasma concentration time curve from time 0 to infinity, approximated by linear trapezoidal summation and extrapolated to infinity by addition of C_t/K_{el} (i.e., $AUC_{0\ \infty} = AUC_{0\ t} + C_t/K_{el}$)
C_{max}	Maximum measured plasma concentration.
T_{max}	Time to maximum measured plasma concentration.
K_{el}	Apparent elimination rate constant, determined by linear regression of the terminal points of the log-linear concentration-time curve.
$T_{1/2}$	Apparent terminal half-life, calculated as $\log_e(2)/K_{el}$ or $0.693/K_{el}$

For pharmacokinetic analysis, plasma drug concentrations identified as below the limit of quantification (BLQ or LOQ) will be replaced with zero prior to the first sample ≥ LOQ and treated as missing thereafter. PK parameters will be calculated from the derived plasma drug concentration data. No value of K_{el}, $AUC_{0\ \infty}$ or $T_{½}$ will be reported for cases that do not exhibit terminal log-linearity of the concentration-time profile or if the estimated K_{el} would be physiologically implausible.

Mean plasma concentration-time data will be presented and summarized both graphically (including linear-linear and semilog-linear plots) and in tabulation with descriptive statistics (n, mean, SD, CV%, median, minimum and maximum). Pharmacokinetic data

will be summarized according to nominal (protocol) sampling times. The reported (or actual) times of sample collection will be used in the pharmacokinetic calculations.

A 1-way ANOVA model with treatment as the independent variable will be employed to examine the differences in the rate and extent, as indexed by C_{max} and AUC, of drug absorption between the two treatment regimens for SAA 500 mg (test) and Zytiga 1,000 mg (reference). A null hypothesis of zero difference in a parameter between each test and reference conditions will be assessed at the 0.05 level, with the alternative hypothesis of non-zero differences. The PK parameters of T_{max}, T½ and Kel will be compared for test vs. reference regimens, using the non-parametric Wilcoxon rank sum test.

The results of the PK analysis will be used to assess the comparability of the pharmacokinetics of SAA 500 mg (4 x 125 mg) vs. Zytiga 1,000 mg (4 x 250 mg) in patients when dosed with the test or reference article 1 hour prior to a meal.

In addition to the above analysis which will be conducted on the pharmacokinetic population, patients enrolled in the non-PK arm will have trough concentrations (C_{min}) of abiraterone determined at the pre-dose level of steady-state drug concentrations on [redacted] using the same 1-way ANOVA model described above, to assess the differences between two treatments.

13.1.5 Safety

Safety endpoints include adverse events, vital signs, ECGs, physical examination, and clinical laboratory tests. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) adverse event dictionary.

Frequency of treatment-emergent adverse events (TEAEs) will be calculated for each body system, by preferred term, and by treatment and by study period, for number of patients and proportion reporting the event. The severity of adverse events and the relationship to study medication will be summarized for each body system and preferred term by treatment. Withdrawals due to adverse events will be summarized for each body system and preferred term. Narratives will be presented for all deaths, patients reporting SAEs, and patients withdrawn due to adverse events.

Vital signs will be summarized descriptively by treatment at pre-dose and at each post-dose time point and will be analyzed for each assessment time point, using an ANOVA model with treatment as independent variable.

Laboratory data and ECG parameters will be summarized using descriptive statistics by treatment and change from pre-dose at each post-dose time point will be compared between two treatments using an ANOVA model with treatment as independent variable. Shift tables to summarize change in the referenced abnormality or study-defined abnormality from pre-dose to post-dose time-points will also be presented.

Proportions of patients with the obtained value >3 times of the upper normal limit will be compared between the two treatment groups, respectively, for ALT, AST, and total bilirubin. Abnormal findings of clinical laboratory tests for individual patients will be provided by data listing.

Findings of physical examination will be summarized for screening and will be reported for Day 28 (end of Treatment Period), and Day 84 (end of extension period) using a shift table.

Safety analyses will be conducted for the safety population.

13.1.6 Interim Analysis

No interim analyses of the primary endpoint are planned. For regulatory submission, the study database will be locked and analyzed after all of the subjects have completed the primary treatment period (i.e., Day 28).

13.2 Sample Size

[redacted]

This study intends to assess the effects of the test drug of SAA 500 mg on testosterone compared to the reference drug of Zytiga 1,000 mg, based on the bioequivalence approach of 80% to 125% confidence interval of the test-to-reference geometric mean ratio. Under the assumptions of [redacted], a lower and upper limit of 80% to 125%, and [redacted], the study needs to randomize approximately 25 subjects per group for a 80% power (two one-sided t-tests at 0.05 level) to conclude bioequivalence of SAA to Zytiga on testosterone.

14 DATA SAFETY MONITORING BOARD

A Data Safety Monitoring Board will not be used for this study.

15 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1 Source Documents

Source documents include but are not limited to original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, lab results, patient diaries, data collected in automated instruments, microfilm or magnetic media, and pharmacy records, etc. At a minimum all data required to be collected by the protocol should have supporting source documentation for entries in the eCRF, unless the protocol specifies that data can be recorded directly on/in the eCRF or other device.

15.2 Study Monitoring

A representative of Churchill Pharmaceuticals LLC will meet with the investigator and his/her staff prior to the entrance of the first patient to review study procedures and methods or recording study data. This may take place in the form of a Site Initiation visit, or other form of training.

After enrollment of the first patient, a Churchill Pharmaceuticals LLC representative will be assigned to periodically monitor each site for study progress and to verify that standards for Good Clinical Practice (GCP) were followed. The investigator is expected to prepare for the monitoring visit, ensuring that all source documents, completed eCRFs, signed consent forms and other study related documents are readily available for review.

15.3 Audits and Inspections

The investigator shall permit audits and inspections by the sponsor, its representatives and members of the regulatory agencies. The investigator should immediately notify the sponsor of an upcoming FDA or other regulatory agency inspection.

15.4 Institutional Review Board (IRB)

The investigator shall permit members of the IRB to have direct access to source documents.

15.5 Data Recording and Documentation

All data recordings and source documentation (including electronic health records) must be made available to the sponsor (or designee), FDA and other regulatory agencies that request access to study records, including source documents, for inspection and copying, in keeping with the federal and local regulations.

16 QUALITY CONTROL AND QUALITY ASSURANCE

Steps to assure the accuracy and reliability of data include the selection of qualified principal investigators and appropriate study centers, review of protocol procedures with the principal investigator and associated personnel prior to start of the study and periodic monitoring visits conducted by the sponsor (or designee). Significant and/or repeated non-compliance will be investigated and remedial action instituted when appropriate. Failure to comply with the remedial actions may result in investigator site termination and regulatory authority notification.

The sponsor (or designee) will utilize qualified monitors to review and evaluate activities conducted at the investigator site.

The study will be monitored or audited at intervals to ensure that the clinical study is conducted and data are generated, documented and reported in compliance with the study protocol, ICH guidelines and other applicable regulations. The extent, nature and frequency of monitoring and/or auditing will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity and

enrollment rate. At the conclusion of a program, a compliance statement will be generated by the sponsor (or designee) listing all audit activities performed during the clinical study.

17 DATA HANDLING AND RECORD KEEPING

17.1 Data Collection

Data collection will involve the use of an electronic data capture (EDC) system to which only authorized personnel will have access. The system will be secured to prevent unauthorized access to the data or the system. This will include the requirement for a user identification and password to enter of change data. The level of access to the EDC system will be dependent on the person's role in the study.

Study data will be collected from source documents and entered into an eCRF within the EDC system. The investigator will be responsible for ensuring the eCRFs are completed in a timely manner relative to the patient's visit. In addition to periodic monitoring occurring within the system by the Sponsor monitor or designee, programmatic edit checks will be used to review EDC data for completeness, logic, and adherence to the study protocol. As a result of this monitoring and these checks, queries may be issued electronically to the clinical study sites and closed electronically by the monitor, data management staff or authorized staff at the study site. Additionally, the investigator will review eCRFs, ensuring all data is collected and all corrected data is provided and will sign the eCRF pages with an electronic signature.

An electronic audit trail will be maintained in the EDC system to track all changes made to data entered in the eCRF. Data will be retrievable in such a fashion that all information regarding each individual patient is attributable to that patient. Unless otherwise indicated, all data captured in the eCRF must first be captured in source documents. Data that can be directly recorded in the eCRF will be clearly identified in the section(s) of the protocol that describe the assessment(s).

In addition, any contact with the patient via telephone or other means that provide significant clinical information must be documented in source documents are described above.

17.2 Study Documentation

Upon study completion, the complete eCRF, in portable document format (PDF), will be created from the EDC system. Study sites will be provided with the PDF of the eCRF for their patients.

18 ETHICS

18.1 Ethics Review

Approval by the IRB prior to the start of the study will be the responsibility of the investigator. A copy of approval documentation will be supplied to Churchill along with a roster of IRB members that demonstrates appropriate composition.

The study protocol, the informed consent form, any advertisements, materials being provided to patients and amendments (if any) will be approved by the IRB at each study center in conformance with ICH E6, the Code of Federal Regulations (CFR), Title 21, Part 56 and any other applicable local laws. The investigator is responsible for supplying the IRB with a copy of the current IB, Package Insert or Summary of Product Characteristics (SPC), as well as any updates issued during the study. During the course of the study, the investigator will provide timely and accurate reports to the IRB on the progress of the study, at intervals not to exceed one year, and will notify the IRB of SAEs or other significant safety findings, per the policy of the IRB. At the conclusion of the study, the investigator will submit a final report of close out report to the IRB and provide a copy to Churchill (or designee).

Any amendment to the protocol will be provided to the investigator. No protocol amendment may be implemented before it has been approved by the IRB and the signature page, signed by the investigator, has been received by Churchill (or designee). If the protocol amendment is issued to eliminate immediate risk to study patients, the amendment may be implemented prior to IRB approval. However, the IRB must be notified in a timely manner. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the patient and must be reported immediately to Churchill (or designee).

The investigator is responsible for supplying updated safety and/or study information to patients as it becomes available.

18.2 Ethical Conduct of the Study

This clinical study is designed to comply with the ICH E6, Good Clinical Practice, 21 CFR parts 50, 54, 56 and 312 and the ethical principles that have their origin in the Declaration of Helsinki.

18.3 Patient information and informed consent

The principal investigator will ensure that each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. A patient must also be notified that he is free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

Each patient must voluntarily sign and date the informed consent form prior to the performance of any study-related activity (with the exception of standard of care procedures). The consent form must be approved by both the reviewing IRB and the Sponsor (or designee) prior to use.

The consent form will incorporate wording that complies with the relevant data protection and privacy legislation. Pursuant to this wording, patients will authorize the collection, use and disclosure of their study data by the investigator and by those persons who need that information for the purposes of the study.

The consent form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with the national data legislation. For data verification purposes, authorized representatives of the sponsor, a regulatory authority or an IRB may require direct access to source data relevant to the study, including the patients' medical history.

The consent process shall be recorded in source documents. Signed copies of the fully executed informed consent will be given to the patient and originals will be placed in the investigator study files.

19 INVESTIGATOR OBLIGATIONS

19.1 Regulatory Documents

The investigator is responsible for creating and/or maintaining all study documentation required by 21 CFR parts 50, 54, 56 and 312, ICH, E6, Section 8, as well as any other documentation defined in the protocol of the Investigator Agreement. The investigator must maintain the documentation relating to this study and permit Churchill (or designee), or a member of a regulatory agency access to such records.
The investigator must provide the following key documents to Churchill (or designee) prior to the start of the study:

- A completed and signed Form FDA 1572. If during the course of the study any information reported on the Form FDA 1572 changes, a revised form must be completed and returned to Churchill (or designee) for submission to the FDA.
- A fully executed Clinical Trial Agreement
- The Investigator's Statement page in this protocol, signed and dated by the investigator and any subsequent amendment signature pages.
- The Investigator Brochure acknowledgment of receipt page
- Curricula Vitae for the principal investigator and all sub-investigators listed on the Form FDA 1572, including a copy of current licensure (if applicable)
- A copy of the original IRB approval for conducting the study. Yearly renewals must be submitted if the study is ongoing. Any subsequent amendments must be submitted and approved by the IRB
- A copy of the IRB approved informed consent form
- A list of IRB members of DHHS assurance number
- Laboratory certifications and normal ranges (if local labs are being used)
- A financial disclosure form completed by the investigator and each sub-investigator listed on the FDA Form 1572. Site staff that submitted an initial financial

disclosure form are responsible for informing Churchill (or designee) of any changes to their initial form for up to 1 year following completion of the study

19.2 Delegation of Responsibilities and Adequate Resources

The investigator should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study. The investigator shall delegate tasks only to individuals qualified by education, training and experience to perform the delegated tasks. The investigator shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The investigator is responsible for ensuring all delegated staff has been properly trained on the protocol and their assigned study responsibilities.

19.3 Medical Care of Study Patients

The investigator and/or qualified designee shall be responsible for the patients' medical care. Any unrelated medical condition discovered during the course of the study should be communicated to the patient so that they may seek appropriate medical care. The investigator will report AEs as required by the protocol. The investigator will inform patients of new information regarding the study drug as it becomes available.

19.4 Use of Investigational Materials

The investigator will acknowledge that the study drug supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the investigator or designated sub-investigators listed on FDA Form 1572. Study drug must be stored in a safe and secure location. At the study initiation or first monitoring visit, a representative of Churchill (or designee) will inventory the study drug at the site. The investigator must maintain adequate records documenting the receipt and disposition of all study supplies. Churchill (or designee) will supply forms to document total inventory as well as patient specific accountability forms. The investigator is responsible for monitoring the use of the study drug to ensure compliance with the protocol. All study supplies shall be returned to Churchill (or designee) at completion of the study or intervals appropriate to the design of the study with the exception of retention samples per 21 CFR 320.38 which will be kept at the site under storage conditions for the test and reference product.

19.5 Retention of Records

Federal and local regulations require that the investigator retain a copy of all regulatory documents and records that support the data for this study (e.g., informed consent forms, lab reports, source documents, study drug accountability records) for whichever of the following is the longest period of time:

- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of

an application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation.

Churchill (or designee) will notify investigators once one of the above 2 referenced time frames has been satisfied.

If the investigation does not result in the submission of the data in support or, or as part of, an application for a research or marketing permit, records must be maintained for a period of 2 years following notification by Churchill (or designee) that the entire clinical investigation is complete, terminated, or discontinued or 2 years following withdrawal of the IND/CTA or NDA/MAA.

If the investigator retires, relocates or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibilities outlined above. Churchill (or designee) must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consulting with Churchill (or designee).

19.6 Patient Confidentiality

All patient records submitted to Churchill (or designee) will be identified only by initials and study identification number. Patients' names are not to be transmitted. The investigator will keep a master patient list on which the identification number and the full name, address and telephone number of each patient are listed. It is the investigators responsibility to inform patients that representatives of the sponsor, FDA or other regulatory agency may review all records that support their participation in the study. The investigator will adhere to all privacy laws to which he/she is subject.

20 GENERAL CONSIDERATIONS

20.1 Discontinuation of the Study

Churchill reserves the right to discontinue this study for safety or administrative reasons at any time.

20.2 Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of Churchill. The protocol amendment must be signed by the investigator and approved by the IRB or independent ethics committee before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

20.3 Use of Information and Publication

All information concerning SAA tablets, Churchill operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by Churchill to the investigator and not previously published, is considered confidential and remains the sole property of Churchill. The CRFs also remain the property

of Churchill. The investigator agrees to use this information for purposes of study execution through finalization.

The information developed in this study will be used by Churchill in connection with the continued development of SAA tablets and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

Publication or other public presentation of SAA tablets data resulting from this study requires prior review and written approval of Churchill. Abstracts, manuscripts, and presentation materials should be provided to Churchill for review at least 30 days before the relevant submission deadline.

21 REFERENCES

1 Zytiga® package insert. Janssen Biotech, Inc. Revised May 2016.

22 APPENDIX - SCHEDULE OF ASSESSMENTS