

**Version 1.1**

**An Open-Label, Single-Arm, Multiple Center Extension study to Evaluate One Year of Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer with YONSA™ 500 mg (4 x 125 mg qd) with Methylprednisolone (4 mg bid): The STAAR- E Study**

PROTOCOL NUMBER: CHL-AA-202

IND NUMBER: 115577

PROTOCOL DATE: June 2, 2017

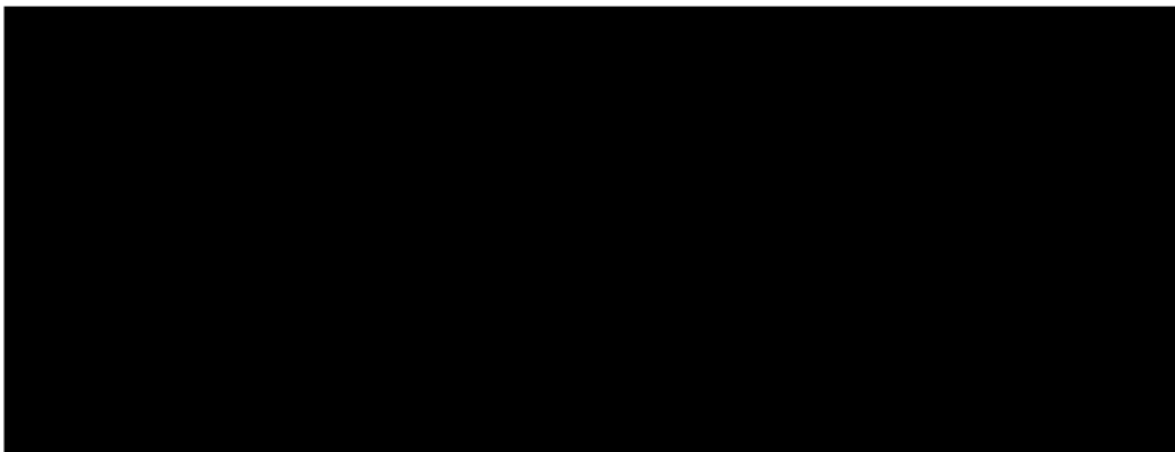
SPONSORED BY: Churchill Pharmaceuticals LLC  
3602 Horizon Drive, Suite 160  
King of Prussia, PA 19406

CONTRACT  
RESEARCH  
ORGANIZATION:



Information contained in this protocol is confidential in nature and may not be used, divulged, published, or otherwise disclosed to others except to the extent necessary to obtain approval of the Institutional Review Board or Ethics Committee or as required by law. Persons to whom this information is disclosed should be informed that this information is confidential and may not be further disclosed without the express permission of Churchill Pharmaceuticals LLC.

**SIGNATURES OF AGREEMENT FOR PROTOCOL**



## INVESTIGATOR APPROVAL STATEMENT

### Protocol CHL-AA-202

#### **An Open-Label, Single-Arm, Multiple Center Extension Study to Evaluate One Year of Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer with YONSA™ 500 mg (4 x 125 mg qd) with Methylprednisolone (4 mg bid)**

[June 2, 2017]

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: \_\_\_\_\_

## 1 PROTOCOL SYNOPSIS

TITLE	An Open-Label, Single-Arm, Multiple Center Extension Study to Evaluate One Year of Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer with YONSA™ 500 mg (4 x 125 mg qd) with Methylprednisolone (4 mg bid): The STARR-E Study
OBJECTIVES	<p><b>Primary:</b> The primary objective of this study is to evaluate safety of one year of treatment with YONSA in patients with mCRPC who have completed three months of treatment with either YONSA or Zytiga® in a previous clinical trial.</p> <p><b>Secondary:</b></p> <ul style="list-style-type: none"> <li>• To evaluate disease progression over the study period</li> <li>• To evaluate serum testosterone levels after 6 months and 1 year of treatment with YONSA compared to baseline testosterone levels in patients with mCRPC</li> <li>• To evaluate the PSA levels and response rate at 6 months and 1 year of treatment with YONSA compared to baseline</li> </ul>
NUMBER OF SUBJECTS	Approximately 25 patients will be enrolled
INVESTIGATIVE SITES	Approximately 20 study sites in the United States
METHODOLOGY	<p>This is An Open-Label, Single-Arm, Multiple Center Extension Study to Evaluate One Year Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer with YONSA 500 mg (4 x 125 mg qd) with Methylprednisolone (4 mg bid).</p> <p>The study consists of One Year of treatment of YONSA 500 mg (4 x 125 mg qd) with Methylprednisolone (4 mg bid)</p> <p>Screening for study entry is based on successful completion of a previous 84 day trial comparing YONSA and Zytiga®. Baseline assessments for this trial will be information collected at Day 84 of the previous trial.</p>
SUBJECT POPULATION	<p><b>Inclusion criteria</b></p> <p>Patients are eligible for inclusion into the study if the following criteria are met:</p> <ol style="list-style-type: none"> <li>1. Successful completion of 84 days of treatment with YONSA in Churchill Pharmaceuticals clinical trial, CHL-AA-201</li> <li>2. Last dose of YONSA or Zytiga within 45 days prior to treatment in this study</li> <li>3. Written informed consent obtained prior to any study-related procedure being performed</li> <li>4. Has in the investigator's opinion, the potential to gain clinical benefit with YONSA treatment</li> </ol>

	<ol style="list-style-type: none"> <li>5. Ongoing therapy with a GnRH agonist or antagonist AND serum testosterone level &lt;50 ng/dL at screening</li> <li>6. Life expectancy of at least 9 months at screening</li> <li>7. Subject is willing and able to comply with all protocol requirements assessments</li> <li>8. Agrees to protocol-defined use of effective contraception.</li> </ol> <p><b>Exclusion criteria</b></p> <p>Patients meeting the following criteria will be excluded from participation in the study:</p> <ol style="list-style-type: none"> <li>1. Serious concurrent illness, including psychiatric illness, that would interfere with study participation</li> <li>2. Inability to swallow tablets whole</li> <li>3. Known hypersensitivity to YONSA, methylprednisolone, or any excipients in study medications</li> <li>4. Moderate to severe hepatic impairment (Child-Pugh Classes B and C)</li> </ol>
STUDY DRUG	<p>YONSA (abiraterone acetate) tablets with methylprednisolone is the experimental treatment. Patients are to take 500 mg (4 x 125 mg tablets) orally once daily. YONSA 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. 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).</p> <p>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.</p>
RANDOMIZATION	<p>This is an open-label, single-arm extension study. No randomization is needed.</p>
STUDY DURATION	<p>Approximately One Year</p> <p><b><u>Discontinuation Criteria/Termination Rules:</u></b></p> <p>Patients should be discontinued for one or more of the following reasons:</p> <ol style="list-style-type: none"> <li>1. Intolerable adverse event(s)</li> <li>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.</li> <li>3. Withdrawal of consent or</li> <li>4. Based on the decision of the Investigator.</li> </ol>
CRITERIA FOR EVALUATION	<ol style="list-style-type: none"> <li>1. <b>Safety variables:</b> adverse events (AEs) and serious adverse events (SAEs), vital signs, and laboratory test results.</li> </ol>

	<ol style="list-style-type: none"><li>2. <b>Disease progression:</b> PCWG2-defined study progression from baseline.</li><li>3. Serum testosterone and PSA levels at 6 months and 1 year.</li></ol>
STATISTICAL METHODS SUMMARY	<p><b>Sample size calculation:</b> This study intends to enroll patients who have successfully completed a previous 84 day study with YONSA or Zytiga and would benefit from a further 360 days of treatment with YONSA.</p> <p><b>Analysis populations:</b> Study participants include all patients who are screened and found eligible on Day 1. Study population is defined as follows:</p> <ul style="list-style-type: none"><li>• Safety population: includes all patients who took at least 1 dose of study medication.</li></ul> <p><b>Analyses:</b> Descriptive safety data, pharmacodynamical parameters of testosterone and PSA levels, and disease progression information will be summarized.</p>

## 2 TABLE OF CONTENTS

1	PROTOCOL SYNOPSIS.....	4
2	TABLE OF CONTENTS.....	7
3	LIST OF ABBREVIATIONS.....	10
4	INTRODUCTION .....	12
4.1	Background and Rationale .....	12
4.2	Clinical and Nonclinical Experience.....	13
4.3	Selection of the Doses Used in the Study .....	14
4.4	Summary of Potential Risks and Benefits.....	14
4.4.1	Potential Risks Associated with YONSA.....	15
4.4.2	Potential Risks Associated with Corticosteroids (Methylprednisolone).....	15
5	OBJECTIVE .....	16
6	STUDY DESIGN.....	16
7	PATIENT POPULATION.....	16
7.1	Selection of Study Population.....	16
7.1.1	Inclusion Criteria .....	16
7.1.2	Exclusion criteria.....	17
7.1.3	Removal of Patients from Therapy or Assessment .....	17
8	STUDY PROCEDURES .....	18
8.1	Visit 1, Determination of Patient Eligibility, Day 1.....	18
8.2	Visit 2, Day 90 .....	18
8.3	Visit 3, Day 180 .....	18
8.4	Visit 4, Day 270 .....	19
8.5	Visit 5, Day 360 – END OF TREATMENT.....	19
8.6	Early Termination Visit.....	20
9	EFFICACY ASSESSMENTS .....	20
10	SAFETY EVALUATIONS .....	20
10.1	Clinical Laboratory Tests .....	20
10.2	Adverse Events.....	21
10.2.1	Definition of Adverse Events .....	21
10.2.2	Definition of Serious Adverse Events .....	21
10.2.3	Adverse Event Intensity Assessment.....	22
10.2.4	Definition of Start Date and Stop Date.....	23
10.2.5	Action(s) Taken .....	23
10.2.6	Definition of Expectedness.....	24

10.2.7	Definition of Relationship to Study Drug(s)	24
10.2.8	Definition of Outcome at the Time of Last Observation	25
10.2.9	Documentation of Adverse Events	25
10.2.10	Follow-up of Patients with an Adverse Event	25
10.2.11	Special Procedures for Managing Serious Unexpected Suspected Adverse Events	25
11	TREATMENTS	27
11.1	Treatments Administered	27
11.1.1	Study Drugs	27
11.1.2	Storage	27
11.1.3	Labeling	27
11.1.4	Drug Accountability	27
11.2	Prohibited Medications	27
12	STATISTICAL METHODS	28
12.1	Statistical Analyses	28
12.1.1	Analysis Populations	28
12.1.2	Disposition	28
12.1.3	Efficacy	28
12.1.4	Safety	29
13	DIRECT ACCESS TO SOURCE DATA/DOCUMENTS	29
13.1	Source Documents	29
13.2	Study Monitoring	29
13.3	Audits and Inspections	30
13.4	Institutional Review Board (IRB)	30
13.5	Data Recording and Documentation	30
14	QUALITY CONTROL AND QUALITY ASSURANCE	30
15	DATA HANDLING AND RECORD KEEPING	30
15.1	Data Collection	30
15.2	Study Documentation	31
16	ETHICS	31
16.1	Ethics Review	31
16.2	Ethical Conduct of the Study	31
16.3	Patient information and informed consent	31
17	INVESTIGATOR OBLIGATIONS	32
17.1	Regulatory Documents	32
17.2	Delegation of Responsibilities and Adequate Resources	33
17.3	Medical Care of Study Patients	33



17.4	Use of Investigational Materials .....	33
17.5	Retention of Records .....	33
17.6	Patient Confidentiality .....	34
18	GENERAL CONSIDERATIONS .....	34
18.1	Discontinuation of the Study .....	34
18.2	Changes to the Protocol .....	34
18.3	Use of Information and Publication .....	35
19	REFERENCES .....	36
20	APPENDIX - SCHEDULE OF ASSESSMENTS .....	37

### 3 LIST OF ABBREVIATIONS

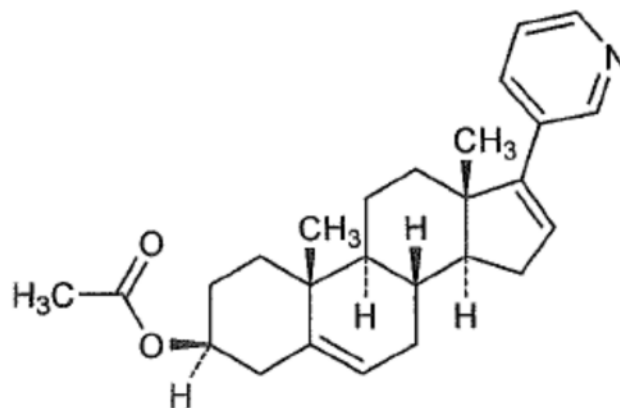
AE	adverse event
ALP	alkaline phosphatase, serum
ALT	alanine aminotransferase
ANOVA	analysis of variance
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC <sub>0-t</sub>	area under the concentration-time curve, from time 0 to time of last sample with a quantifiable concentration
AUC <sub>0-∞</sub>	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 <sub>max</sub>	maximum measured concentration
CMH	Cochran-Mantel-Haenszel
C <sub>min</sub>	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 17 $\alpha$ -hydroxylase
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

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
PCWG	prostate cancer working group
PD	pharmacodynamic
PDF	portable document format
PK	pharmacokinetic
PSA	prostate specific antigen
QD	once daily
SAP	statistical analysis plan
SAE	serious adverse event
SD	standard deviation
TEAE	treatment-emergent AE
T	testosterone
T <sub>max</sub>	Time to maximum measured concentration
ULN	upper limit of normal
USA	United States of America
WBC	White blood cell count

## 4 INTRODUCTION

### 4.1 Background and Rationale

Abiraterone acetate is designated chemically as (3 $\beta$ )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 17 $\alpha$ -hydroxylase/C17, 20-lyase (CYP17), a key enzyme in the production of androgens in the testes, adrenal glands and within prostatic tumors. CYP17 catalyzes 17 $\alpha$ -hydroxylation of C21 steroids and cleavage of the C17, 20 bond of C21 steroids. The 17 $\alpha$ -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 YONSA as an alternative treatment to Zytiga. YONSA utilizes SoluMatrix fine-particle technology™ to provide comparable absorption of abiraterone and comparable effect at a lower dose. YONSA 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 additional treatment for approximately one year with YONSA after an initial three months of YONSA or Zytiga in a previous study is tolerated and if underlying disease progresses during this additional one year.

Previously, it has been shown that a single 500 mg dose of YONSA is bioequivalent (BE) to a single 1,000 mg dose of Zytiga administered to healthy, male volunteers in fasted

conditions. Over a period of approximately one year, this study will evaluate the 500 mg dose of YONSA qd with 4 mg methylprednisolone bid in patients with mCRPC who have previously received three months of YONSA or Zytiga in a randomized clinical trial.

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

#### 4.2 Clinical and Nonclinical Experience

Abiraterone acetate is a highly lipophilic, poorly water soluble compound and exhibits dissolution rate limited oral bioavailability. SoluMatrix Fine Particle Technology™ is used to substantially reduce the abiraterone acetate particle size. By reducing the drug particle size, the ratio of surface area to mass increases which facilitates faster *in-vivo* dissolution compared to large particles. YONSA tablets contain fine particles of abiraterone acetate, and have been shown to have faster *in-vitro* dissolution compared to the commercially available Zytiga (abiraterone acetate) Tablets. A Phase 1 clinical trial has shown that YONSA tablets have approximately twice the bioavailability compared to Zytiga, such that a 500 mg dose of YONSA (4 x 125 mg) is bioequivalent to 1,000 mg of Zytiga (4 x 250 mg), in healthy male volunteers under fasted conditions. The improved oral bioavailability of YONSA relative to Zytiga is attributed to the differences in *in-vivo* dissolution rates between the two drug products.

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 YONSA

[REDACTED]

A fifth clinical study comparing YONSA to Zytiga over an 84 day period is being conducted. The patients in the current study will have successfully completed the 84-day treatment of either YONSA or Zytiga in that study.

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 YONSA.

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) 500 mg film-coated Tablets

Zytiga (abiraterone acetate) 250 mg film-coated Tablets.

Zytiga (abiraterone acetate) 250 mg Tablets.

#### *4.3 Selection of the Doses Used in the Study*

A previous study has demonstrated that a single dose 500 mg of YONSA is bioequivalent to a single dose 1,000 mg of Zytiga in healthy male volunteers under fasted conditions.

#### *4.4 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<sup>1</sup> and is briefly described in section 5.4.1

In this study, a novel formulation with the same active pharmaceutical ingredient as Zytiga 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 as well as disease progression, testosterone, and PSA levels. 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.



Patients in the study will benefit by treatment by contributing to increased knowledge of safety and disease progression following administration of a novel formulation of abiraterone acetate.

#### **4.4.1 Potential Risks Associated with YONSA**

A single multi-dose study is being conducted in mCRPC patients with the experimental treatment, YONSA; 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 Study Drug investigator brochure.

Reproductive risks and contraception requirements:

It is not known if the study drug will affect sperm or semen. If a patient's 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)

#### **4.4.2 Potential Risks Associated with Corticosteroids (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.

## **5 OBJECTIVE**

The primary objective of this study is to evaluate the safety of YONSA 500 mg (4 x 125 mg qd) with methylprednisolone (4 mg bid) in patients with mCRPC over the course of approximately one year following an initial 84 day treatment with abiraterone acetate in a previous study.

The secondary objectives are:

- To evaluate disease progression over the study period
- To evaluate serum testosterone levels after 6 months and 1 year of treatment with YONSA compared to baseline testosterone levels in patients with mCRPC
- To evaluate the PSA levels and response rate at 6 months and 1 year of treatment with YONSA compared to baseline PSA levels in patients with mCRPC

## **6 STUDY DESIGN**

This is an open-label, single-arm, multi-center extension study to evaluate safety in patients with mCRPC of YONSA 500 mg (4 x 125 mg qd) with methylprednisolone (4 mg bid). Patients will have successfully completed an 84-day treatment with abiraterone acetate in a previous trial. Results from the final visit of the previous study will be used to determine patient's eligibility for this study. Patients in this study will be eligible to receive open-label YONSA with methylprednisolone for up to 12 months.

Pharmacodynamic parameters of serum testosterone and PSA levels will be monitored. Disease progression will be assessed by PCWG2 criteria.

## **7 PATIENT POPULATION**

### *7.1 Selection of Study Population*

Successful completion of a previous study, CHL-AA-201, with treatment for 84 days with abiraterone acetate and a reasonable expectation that the patient will benefit from additional treatment with YONSA will be the basis for selection of patients for this study. Day 84 results of the previous study will be used as the screening values for enrollment into this study.

#### **7.1.1 Inclusion Criteria**

Patients are eligible for inclusion into the study if the following criteria are met:



1. Successful completion of 84 days of treatment with abiraterone acetate in Churchill Pharmaceuticals clinical trial, CHL-AA-201 and who would benefit in the investigator's opinion with one year of treatment with YONSA
2. Written informed consent obtained prior to any study-related procedure being performed
3. Ongoing therapy with a GnRH agonist or antagonist AND serum testosterone level <50 ng/dL at screening
4. Life expectancy of at least 9 months at screening
5. Subject is willing and able to comply with all protocol requirements assessments
6. Agrees to protocol-defined use of effective contraception.

### **7.1.2 Exclusion criteria**

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

1. Serious concurrent illness, including psychiatric illness, that would interfere with study participation
2. Inability to swallow tablets whole
3. Known hypersensitivity to abiraterone acetate, methylprednisolone, or any excipients in study medications
4. Moderate to severe hepatic impairment (Child-Pugh Classes B and C)

### **7.1.3 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 drug, 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.

## **8 STUDY PROCEDURES**

The schedule of assessments is summarized in Appendix I. Patients will provide written informed consent before any study-related procedures are performed.

### *8.1 Visit 1, Determination of Patient Eligibility, Day 1*

A patient who is determined to be eligible for study should be provided with YONSA and methylprednisolone that should last until next study visit. The following procedures will be performed:

1. Obtain written informed consent.
2. Review inclusion/exclusion criteria (including contraception requirements, Section 5.4.1).
3. Review results of Day 84 assessments from previous study, CHL-AA-201, including Physical Exam, ECOG status, vital signs, testosterone, PSA levels, and clinical laboratory tests
4. Assessment of Disease Progression
5. Remind the patient not to use any prohibited concomitant medications and to comply with all study restrictions.

### *8.2 Visit 2, Day 90*

1. Review blood test results from Day 30 and Day 60
2. Perform a Physical Exam
3. Evaluate ECOG status
4. Vital Signs
5. Collect blood
6. Perform assessment of disease progression
7. Perform drug accountability
8. Dispense YONSA and methylprednisolone for next 90 days
9. Record adverse events

### *8.3 Visit 3, Day 180*

1. Review blood test results from Day 120, and Day 150
2. Perform a Physical Exam

3. Evaluate ECOG status
4. Vital Signs
5. Collect blood for Central Laboratory (Chemistry, Hematology, testosterone, and PSA)
6. Perform assessment of disease progression.
7. Perform drug accountability.
8. Dispense YONSA and methylprednisolone for next 90 days.
9. Record adverse events.

*8.4 Visit 4, Day 270*

1. Review blood test results from Day 210 and Day 240
2. Perform a Physical Exam
3. Evaluate ECOG status
4. Vital Signs
5. Collect blood
6. Perform assessment of disease progression.
7. Perform drug accountability.
8. Dispense YONSA and methylprednisolone for next 90 days.
9. Record adverse events.

*8.5 Visit 5, Day 360 – END OF TREATMENT*

1. Review blood test results from Day 300, and Day 330
2. Perform a Physical Exam
3. Evaluate ECOG status
4. Vital Signs
5. Collect blood for Central Laboratory (Chemistry, Hematology, testosterone, and PSA)
6. Perform assessment of disease progression.
7. Perform drug accountability
8. Record adverse events.

### 8.6 Early Termination Visit

Patients who terminate the study before 360 Days should have the same assessments performed as for Visit 5

## 9 EFFICACY ASSESSMENTS

Disease progression should be assessed over the duration of the study by PCWG2 criteria per the standard and frequency of the investigator. Pharmacodynamic (PD) parameters of testosterone and PSA levels will be monitored at 6 months and 1 year.

## 10 SAFETY EVALUATIONS

Safety will be evaluated by the incidence of TEAEs, , clinical laboratory test results, and vital sign measurements.

### 10.1 Clinical Laboratory Tests

Clinical labs will be performed according to the label of Zytiga, e.g. since patients will have completed a prior study with 12 weeks of treatment with abiraterone acetate, serum transaminases and bilirubin should be measured monthly for the duration of this study.

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 1 Summary of Blood Volume**

Sample	Days of collection	Volume of sample
Serum chemistry, hematology*	6 Month (180 Days) and 1 Year (360 Days)	2 x (6.5 mL)
Serum Chemistry	Days 30, 60, 90, 120, 150, 210, 240, 270, 300, 330	10 x (2 mL)
Testosterone	6 Month and 1 Year	2 x (3.5 mL)
PSA	6 Month and 1 Year	2x (0.6 mL)
<b>Expected Total Volume of Blood Collected per Subject</b>		<b>41.2 mL</b>

\*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, ALP, creatinine, albumin, BUN, glucose, calcium, sodium, potassium, chloride
Additional Tests:	Testosterone, Total Serum (TTBS) Prostate specific antigen (PSA)

## *10.2 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 case report form (eCRF); however once a patient is randomized, all AEs should be entered into the eCRF.

### **10.2.1 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.

### **10.2.2 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.

### **10.2.3 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.

#### **10.2.4 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.”

#### **10.2.5 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.

### 10.2.6 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.

### 10.2.7 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.



### **10.2.8 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.

### **10.2.9 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 occurred (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)

### **10.2.10 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.

### **10.2.11 Special Procedures for Managing Serious Unexpected Suspected 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 non-urgent protocol and medical inquiries:

Investigative site users will log into [REDACTED]  
[REDACTED]

and complete the steps to submit protocol inquiries to the Project Manager (PM) or Clinical Team Manager (CTM).

For urgent medical inquiries:

[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 regarding the notification of his or her IRB or independent ethics committee.

## **11 TREATMENTS**

### *11.1 Treatments Administered*

#### **11.1.1 Study Drugs**

Patients who meet all eligibility criteria will be receive YONSA on Day 1 and then every 90 day intervals.

- Four 125 mg YONSA tablets to be taken once daily plus one 4 mg methylprednisolone tablet twice daily, spaced approximately 12 hours apart

Patients will be instructed to take study drug at least 1 hour before or 2 hours after a meal.

#### **11.1.2 Storage**

YONSA 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).

#### **11.1.3 Labeling**

Each container of YONSA and methylprednisolone 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.

#### **11.1.4 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, all remaining unused study drug should be reconciled with dispensing records, documented, and return or destroyed.

### *11.2 Prohibited Medications*

The following medications/therapy will be prohibited during the study

- Use of any drugs known to induce or inhibit hepatic drug metabolism (Carbamazepine, Dexamethasone, Ethosuximide, Glucocorticoids except methylprednisolone provided as study medication, Griseofulvin, Phenytoin, Primidone, Progesterone, Rifabutin, Rifampin, Nafcillin, Nelfinavir, Nevirapine, Oxcarbazepine, Phenobarbital, Phenylbutazone, Rofecoxib, St John's wort, Sulfadimidine, Sulfipyrazon, Troglitazone)

- Substrate of CYP2D6 with a narrow therapeutic index (e.g., thioridazine)
- Use of antiandrogens and estrogens
- Any investigational treatments/therapy other than YONSA.

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

## **12 STATISTICAL METHODS**

### *12.1 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 database lock.

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).

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 in the current study.

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

#### **12.1.1 Analysis Populations**

Study participants include all patients who were screened and found eligible for treatment on Day 1. The analysis population is defined as follows:

- Safety population: includes all patients who took at least 1 dose of study medication.

#### **12.1.2 Disposition**

Descriptive summaries of patient disposition will be presented for the safety population. A detailed description of individual patient disposition will be provided in a data listing.

#### **12.1.3 Efficacy**

Disease progression status, testosterone level and response rate, and PSA levels and response rate will be summarized descriptively for baseline and following visits, where



applicable. Changes from baseline in testosterone and PSA levels at follow-up visits of 6 months and 1 year will be reported and tested using one-sample t-test. Time-to-disease progression will be reported descriptively over the 1-year treatment period.

#### **12.1.4 Safety**

Safety endpoints include adverse events, vital signs, 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, 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. 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.

Laboratory data will be summarized using descriptive statistics by treatment and change from pre-dose at each follow-up visit.

Safety analyses will be conducted for the safety population.

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

### **13 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

#### *13.1 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 CRF, unless the protocol specifies that data can be recorded directly on/in the eCRF or other device.

#### *13.2 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.

### *13.3 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.

### *13.4 Institutional Review Board (IRB)*

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

### *13.5 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.

## **14 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.

## **15 DATA HANDLING AND RECORD KEEPING**

### *15.1 Data Collection*

Data collection that will involve the use of any contact with the patient via telephone or other means that provides significant clinical information must be documented in source documents as described above.

## *15.2 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.

# **16 ETHICS**

## *16.1 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.

## *16.2 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.

## *16.3 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 histories.

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.

## **17 INVESTIGATOR OBLIGATIONS**

### *17.1 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

#### *17.2 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.

#### *17.3 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.

#### *17.4 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.

#### *17.5 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 of, 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).

#### *17.6 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.

## **18 GENERAL CONSIDERATIONS**

### *18.1 Discontinuation of the Study*

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

### *18.2 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.

### *18.3 Use of Information and Publication*

All information concerning YONSA 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 YONSA tablets and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

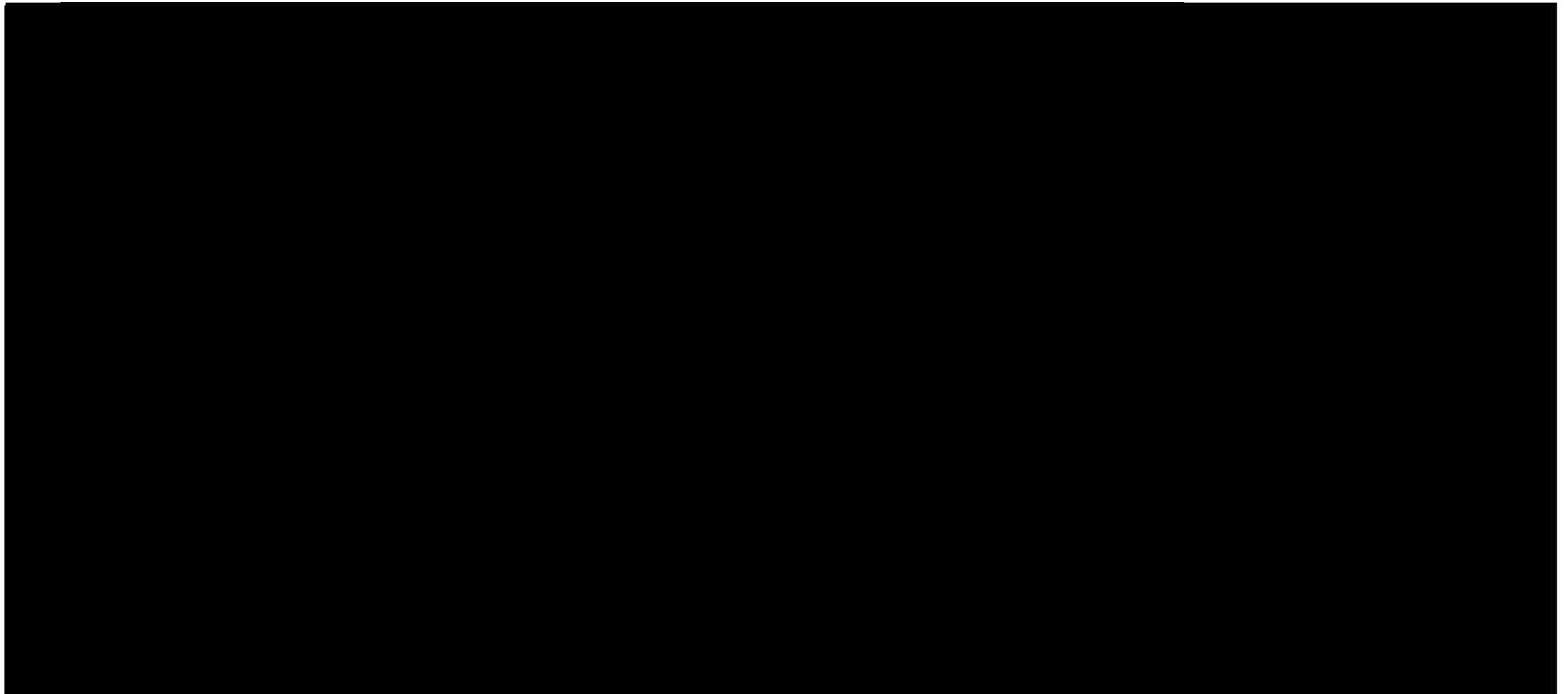
Publication or other public presentation of YONSA tablets data resulting from this study requires prior review and written approval of Churchill. Abstracts, manuscripts, and presentation materials should be provided to Churchill for review at least 30 days before the relevant submission deadline.

## **19 REFERENCES**

- 1 Zytiga® package insert. Janssen Biotech, Inc. Revised April 2017.

## **20 APPENDIX - SCHEDULE OF ASSESSMENTS**

[REDACTED]



### **16.1.9 Documentation of Statistical Methods**

This section contains the following document:

[Statistical analysis plan version 1.0 dated 25 Jun 2017](#)

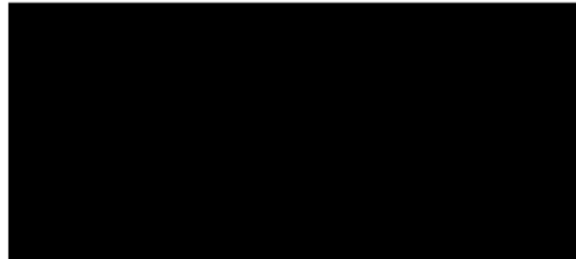
## STATISTICAL ANALYSIS PLAN

---

**Protocol No.** CHL-AA-202  
**Title** An Open-Label, Single-Arm, Multi-Center Extension Study to Evaluate One Year of Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer With YONSA™ 500 mg (4 x 125 mg qd) with Methylprednisolone (4 mg bid): The STAAR-E Study

**Sponsor** Churchill Pharmaceuticals LLC  
3602 Horizon Drive, Suite 160  
King of Prussia, PA 19406

**Prepared By**



**Version** Final (1.0)  
**Date** June 25, 2017

---

**Approved By** Paul Nemeth, Ph.D.  
**Title** Senior Vice President, Clinical Development & Regulatory Affairs  
Churchill Pharmaceuticals LLC

**Signature** *Paul Nemeth*  
**Date** 23 Feb 2018

---

### CONFIDENTIAL MATERIAL

This material is the property of Churchill Pharmaceutical LLC and it must not be disclosed or used without written authorization from Churchill Pharmaceutical LLC.

Version: Final (1.0)



## STATISTICAL ANALYSIS PLAN

<b>ABBREVIATIONS AND DEFINITIONS .....</b>	<b>4</b>
<b>1 INTRODUCTION .....</b>	<b>5</b>
1.1 Trial Objectives .....	5
1.2 Background Information .....	5
<b>2 STUDY DESIGN .....</b>	<b>6</b>
2.1 Rationale .....	6
2.2 Description of Trial Design .....	6
2.3 Schedule of Assessments .....	6
2.4 Treatment Randomization .....	8
2.5 Sample Size Estimation .....	8
2.6 Efficacy and Safety Measurements .....	8
2.6.1 Efficacy measure .....	8
2.6.2 Safety measures .....	9
2.6.3 Other measures .....	9
2.7 Drug Concentration and PK Measurements .....	9
2.8 Handling of Missing, Incomplete, and Repeat Data .....	9
2.9 Statistical Methods .....	10
2.9.1 Efficacy or PD analysis .....	10
2.9.2 Other efficacy analysis .....	11
2.9.3 Safety analysis .....	11
<b>3 STUDY POPULATION .....</b>	<b>12</b>
3.1 Definition of Subject Populations .....	12
3.2 Screening and Enrollment .....	13
3.3 Demography and Baseline Characteristics .....	13
3.4 Disease Diagnosis and Prior Therapy .....	13
3.5 Disposition of Study Participants .....	13
3.6 Protocol Deviations and Violations .....	13
<b>4 EFFICACY EVALUATION .....</b>	<b>14</b>
4.1 Datasets Analyzed .....	14
4.2 Treatment Compliance .....	14
4.3 Missing Data and Imputation .....	14
4.4 Baseline Measures .....	14
4.5 Efficacy or PD Results and Tabulations .....	14
4.5.1 Results of PD analysis .....	14
4.5.2 Results of other efficacy analyses .....	14
<b>5 SAFETY EVALUATION .....</b>	<b>14</b>
5.1 Extent of Drug Exposure .....	14
5.2 Early Termination .....	15
5.3 Adverse Events .....	15
5.4 Vital Signs .....	15
5.5 Physical Examination .....	15
5.6 Clinical Laboratory Evaluation .....	15
5.7 Prior and Concomitant Medication .....	16
5.8 ECOG Performance Status .....	16



<b>6</b>	<b>REFERENCE .....</b>	<b>16</b>
<b>7</b>	<b>LIST OF STATISTICAL TABLE SHELLS .....</b>	<b>17</b>
<b>8</b>	<b>LIST OF KEY LISTING SHELLS .....</b>	<b>19</b>
<b>9</b>	<b>LIST OF FIGURES .....</b>	<b>20</b>
<b>10</b>	<b>LIST OF CRF DATA TABULATIONS.....</b>	<b>20</b>

## ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
CI	Confidence Interval
CRF	Case Report Form
eCRF	Electronic Case Report Form
ECOG	The Eastern Cooperative Oncology Group
ET	Early Termination
ITT	Intent-to-Treat Population
IVRS	Interactive Voice Response System
IWRS	Interactive Web-Based Response System
LOQ	Limit of Qualification
LS	Least Square
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
PD	Pharmacodynamic
PSA	Prostate Specific Antigen
SAA	SoluMatrix Abiraterone Acetate
SAE	Serious Adverse Event
SE	Standard Error
SD	Standard Deviation
T	Testosterone
TEAE	Treatment Emergent Adverse Event

## 1 INTRODUCTION

### 1.1 Trial Objectives

The primary objective of this study is:

- To evaluate the safety of one year of treatment with YONSA in patients with metastatic castration-resistant prostate cancer (mCRPC) who have previously completed three months of treatment with either YONSA or Zytiga in Protocol No. CHL-AA-201.

The secondary objectives of this study are:

- To evaluate disease progression over the study period
- To evaluate serum testosterone levels after 6 months and 1 year of treatment with YONSA compared to baseline testosterone levels in patients with mCRPC.
- To evaluate the prostate specific antigen (PSA) levels and response rate after 6 months and 1 year of treatment with YONSA compared to baseline.

### 1.2 Background Information

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 17 $\alpha$ -hydroxylase/C17, 20-lyase (CYP17), a key enzyme in the production of androgens in the testes, adrenal glands and within prostatic tumors. CYP17 catalyzes 17 $\alpha$ -hydroxylation of C21 steroids and cleavage of the C17, 20 bond of C21 steroids. The 17 $\alpha$ -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) or YONSA. YONSA is a 125 mg tablet with a daily dosage of 500 mg (4 x 125 mg) for the treatment of patients with mCRPC, and is to be co-prescribed with 4 mg methylprednisolone. A review of the literature indicates that 4 mg of methylprednisolone taken twice daily should be sufficient to manage mineralocorticoid excess.

Four clinical trials were conducted to evaluate the safety and pharmacokinetics of YONSA in healthy subjects. A fifth clinical study comparing the safety and efficacy of YONSA to Zytiga in patients with mCRPC over an 84 day period was recently completed. This study will be an extension of the previous 84-day study and will enroll those subjects who have successfully completed the 84-day treatment of either YONSA or Zytiga in that study to continue or start the treatment of YONSA of 500 mg daily combined with 4 mg methylprednisolone taken twice daily.

## **2 STUDY DESIGN**

### **2.1 Rationale**

The rationale for this study is to evaluate the safety and efficacy of YONSA 500 mg taken once daily combined with 4 mg methylprednisolone taken twice daily administration on the levels of testosterone and PSA after 6 and 12 months of treatment in patients with mCRPC.

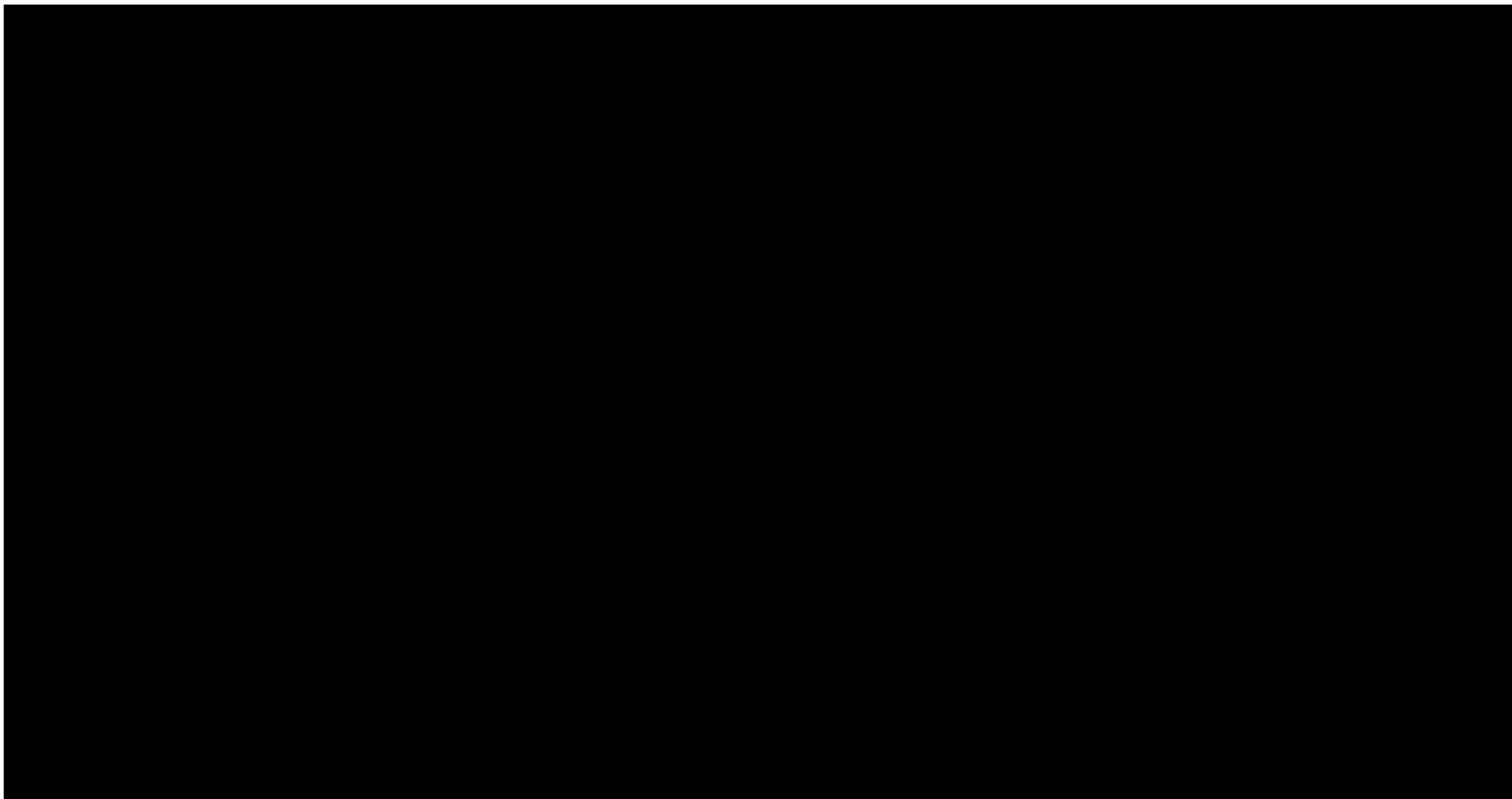
### **2.2 Description of Trial Design**

This is an open-label, single-arm, multi-center study of one year treatment of YONSA 500 mg taken once daily combined with 4 mg methylprednisolone taken twice daily. It is an extension of a previous study of the 84-day treatment of either YONSA or Zytiga. Subjects who have completed successfully the 84-day treatment study will be eligible to enroll into this study, with the exit visit of that study being considered the subjects' eligibility (or screening) visit for this study. Eligible subjects will be asked to receive the treatment of YONSA for one year. The study will have 4 office visits, including Days 90, 180, 270, and 360 from enrollment, and an early termination visit for those who will discontinue from the study prior to Day 360. In addition, clinical labs will be collected monthly over the course of the study for safety evaluation.

Restricted Food Conditions: In general, subjects will be advised, throughout the treatment period, that no food should be consumed for at least 2 hours before taking YONSA or 1 hour after YONSA.

### **2.3 Schedule of Assessments**

The complete schedule of assessments for this study is shown in table below.





## **2.4 Treatment Randomization**

Not applicable.

## **2.5 Sample Size Estimation**

Not applicable.

## **2.6 Efficacy and Safety Measurements**

In this study, efficacy will be assessed during the entire study, using serum testosterone and PSA and disease progression.

Safety will be assessed through subject early terminations, adverse events, vital signs, physical examination, clinical safety lab (hematology, chemistry, and urinalysis), serum chemistry (AST, ALT and total bilirubin) as well as concomitant medications.

### **2.6.1 Efficacy**

This study utilizes the subjects' serum testosterone levels, PSA levels, disease progression status and time for efficacy evaluation.

Subjects' disease progression status will be assessed at the eligibility visit and at Days 90, 180, 270, and 360 or at early termination visit.

Over the study period, blood samples for serum testosterone and PSA will be collected at Days 180 and 360 or, where applicable, at early termination visit. For efficacy analysis of absolute values, serum testosterone levels of less than the assay's limit of quantification (LOQ) at an assessment time point will be replaced with the assay's LOQ or 1 ng/dL, whichever is greater; whereas, 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.

Other efficacy endpoints include subjects' testosterone response of complete suppression and subjects' PSA-50 response. For a given assessment time point, a testosterone response of complete suppression is defined as a serum testosterone level that is less than or equal to the limit of quantification (LOQ) of the assay or 1 ng/dL, whichever is greater, whereas a PSA-50 response is defined as a decrease of  $\geq 50\%$  in PSA levels from the baseline of the previous 84-day study.

Subjects' serum testosterone levels and PSA levels observed at the exit visit of the previous 84-day study will be transferred into the database of the current study as the current baseline visit, and subject's serum testosterone levels and PSA levels observed at the baseline visit of the previous 84-day study will also be transferred into the database of this current study as the 'PRIOR' baseline measurements.

The serum testosterone assay used in this study is an ultra-sensitive assay from Covance Central Lab Services and the assay's LOQ is 0.10 ng/dL, which is much lower compared to the 1.0 ng/dL of an standard testosterone assay. For consistency with the efficacy analysis of the testosterone levels, the testosterone response of complete suppression using this ultra-sensitive testosterone assay will be defined as  $\leq 1.0$  ng/dL.

### **2.6.2 Safety measures**

Adverse events are recorded at each study visit, beginning with the start of the enrollment visit and will end at study completion (End-of-Study or Early Termination). Subjects who discontinue because of an adverse event before study completion will be followed up until the event is resolved or further evaluation is not warranted.

Vital signs (blood pressure, pulse, respiratory rate, oral body temperature) will be measured after the subject has been in a sitting position for at least 5 minutes at enrollment (i.e., the exit visit of the previous study), and each post-enrollment visit as well as ET visit.

Complete clinical laboratory tests, including serum chemistry, hematology, and urinalysis, are conducted at screening, Day 180, and Day 360 as well as ET visit. The laboratory will provide the reference values for their laboratory tests to determine the upper and lower limit of normal. Clinical significance of any abnormal/out of range values will be assessed and any clinically significant abnormality will be documented, marked, and entered into the eCRF, and will be reported as adverse events for safety analysis.

A complete physical examination will be performed at screening, Day 90, Day 180, Day 270 and Day 360, as well as ET visit. The complete exam will involve gross examination of general appearance; skin, head and neck (including ears, eyes, nose and throat); thorax; lymph nodes; thyroid; extremities; cardiovascular; lungs; abdomen; and neurological systems. Body weight will be measured at screening.

### **2.6.3 Other measures**

Prior treatment for mCRPC and concomitant medications taken over the course of the study will be recorded during the study.

The ECOG performance status will be assessed at screening, Day 90, Day 180, Day 270, and Day 360 as well as ET visit.

## **2.7 Drug Concentration and PK Measurements**

No blood samples of drug concentration are collected in this study.

## **2.8 Handling of Missing, Incomplete, and Repeat Data**

Efforts will be made to collect all of the data as completely as possible. Missing or incomplete efficacy data at screening or baseline, or post-baseline visits due to either early study termination or unavailability will remain as missing, unless otherwise specified. The efficacy measures include the testosterone levels and PSA levels.

For the analyses of efficacy variables, CURRENT baseline values of a variable are defined as the measurements obtained at the screening visit, which is the exit visit of the previous study; whereas PRIOR baseline values of a variable are defined as the measurements obtained at the baseline visit of the previous study.

For safety parameters, missing or invalid data will be treated as missing for the corresponding assessment. In analysis of safety data, reported adverse events with missing start and stop dates will be treated as treatment-emergent adverse events, whereas concomitant medications used in this study with missing start date will be treated as pre-study concomitant medications.

For each data domain, all data records with valid data are identified for initial and repeat within each study visit and/or assessment time point. Should repeated data records exist within a study visit and/or assessment time point, the initial data record will be utilized for any statistical analyses of the corresponding study visit and/or assessment time point. All existing data records including the repeat data records in the study database will be presented in data listings and CRF data tabulations. Any resultant incomplete or missing data will be treated as missing in the statistical analyses involving these parameters.

## 2.9 Statistical Methods

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

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).

In both data listings and CRF domain data tabulations, subject ID will consist of site number plus the assigned subject number.

Hypothesis testing, unless otherwise indicated, will be performed at the 5% significance level. All p-values will be rounded to four 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 two-sided with 95% coverage, whereas for bio-equivalence testing, all confidence intervals will be 2-sided with 90% coverage.

For statistical analyses, study participants in this extension study will be grouped into two groups by subjects' **PRECEDING TREATMENT** of either YONSA or Zytiga received in the previous study of Protocol CHL-AA-201.

All of the analyses will be conducted on the safety population defined in Section 3.1.

### 2.9.1 Efficacy analysis

The efficacy endpoints, testosterone and PSA levels, will be reported at screening (i.e., current baseline), Day 180 and Day 360 for preceding treatment group and for the all subjects. Changes from the PRIOR baseline in testosterone and PSA levels will be tested for Day 180 and Day 360, using one-sample t-test, for preceding treatment group and for the all subjects.

Proportion of subjects with identified disease progression will be reported by preceding treatment group and compared for between-group differences, using a non-parametric Fisher's Exact Test, for a given assessment time point.



### **2.9.2 Other efficacy analysis**

Other PD endpoints include: 1) complete suppression of testosterone on Day 180 and Day 360; and, 2) PSA-50 response on Day 180 and Day 360.

Proportion of subjects with complete suppression of testosterone and PSA-50 response will be reported by preceding treatment group and compared for between-group differences, using a non-parametric Fisher's Exact Test, for a given assessment time point.

### **2.9.3 Safety analysis**

Safety endpoints include adverse events, vital signs, physical examination, clinical laboratory tests. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) adverse event dictionary. The baseline for safety analysis is the screening visit.

#### Drug Exposure

Drug exposure will be calculated based on the duration study drug administered by preceding treatment group. The duration of drug exposure will be categorized as the following: 1-2, 3-4, 5-6, 7-8, 9-10, and 11-12 months.

#### Early Termination

Subjects' disposition will be summarized by preceding treatment group. A listing will be provided for all early terminations. This listing will include a subject's demographic variables, preceding treatment, duration of treatment, and the primary reason for early termination.

#### Adverse Events

All adverse events will be coded for preferred terminologies using MedDRA. AEs will be grouped into pre-treatment AEs and treatment-emergent AEs (TEAEs) based upon the starting date, if available, of both the events and the 1<sup>st</sup> dose of study drug in this study. An AE that occurs on the 1<sup>st</sup> dose date or later will be defined as a TEAE. An AE that has no valid start date and no valid stop date or stop date being after the first dose date will be considered as a TEAE.

TEAEs will be analyzed by preceding treatment group for the entire study period. Frequency of TEAEs will be calculated for each body system, by preferred term, and by preceding treatment, for number of subjects 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.

Withdrawals due to adverse events will be summarized for each body system and preferred term. Serious adverse events (SAEs) (including adverse events with an outcome of death) will be listed.

Narratives will be provided for all deaths, non-fatal serious adverse events, and subjects withdrawn due to adverse events.

#### Vital Signs

Vital signs will be summarized descriptively by preceding treatment group at baseline and at each post-baseline visit, including Days 90, 180, 270 and 360.

#### Clinical Laboratory Assessments

Clinical laboratory tests of hematology, chemistry, and urinalysis (specific gravity and pH) will be summarized descriptively at baseline, Days 90, 180, 270 and 360 by preceding treatment group. Changes in clinical laboratory tests from baseline will be analyzed, using an one-sample t-test. Qualitative changes in clinical laboratory tests at post-baseline visits from baseline, using shift tables, will be presented by preceding treatment group for each laboratory test based on three reference categories of abnormal low, normal and abnormal high. Any abnormal laboratory test will be listed by subjects by preceding treatment group.

Proportions of subjects with the obtained value >3 times of the upper normal limit will be compared between the two preceding treatment groups, respectively, for ALT, AST, and total bilirubin. Abnormal findings of clinical laboratory tests for individual subjects will be provided by data listing. Clinically significant lab tests will be reported as adverse events.

#### Physical Examination

Findings of physical examination will be summarized for baseline and will be reported, using a shift table, for Day 180 and Day 360, respectively.

#### Prior and Concomitant Medication

Recorded prior and concomitant medications will be grouped into those taken pre-baseline and those taken post-baseline, based upon the starting dates of both medication and screening.

Number and percent of subjects who take pre-baseline medications and who take post-baseline medications will be reported by preceding treatment group, respectively.

#### ECOG Performance Status

The score of ECOG performance status ranges from fully active (0) to dead (5). For reporting, the raw score will be tabulated. Number and percent of subjects in each category will be reported by treatment for Days 90, 180, 270, and 360, respectively.

### **3 STUDY POPULATION**

#### **3.1 Definition of Subject Populations**

All subjects who are eligible and enrolled into this study will be considered study participants, i.e., the enrolled population. Study populations are defined in the following sections to assess the safety and efficacy of YONSA.

#### Safety Population

The safety population is defined as all subjects who are enrolled and who receive at least 1 dose of study medications of YONSA. The safety population will be utilized for safety and



efficacy analyses among preceding treatment groups. The safety population will be identified and finalized before the database is locked.

### **3.2 Screening and Enrollment**

An enrollment summary including the number of subjects enrolled (i.e., study participants) and treated (i.e., safety population) (Table 1.1.1). Study participants include all individuals who have all required baseline assessments/procedures completed on screening visit. The number of subjects by site will be summarized for each preceding treatment group and overall in Table 1.1.2. The number of subjects terminating from study will be summarized in Table 1.1.3.

### **3.3 Demography and Baseline Characteristics**

For the safety population, descriptive summaries of demography and baseline characteristics will be presented for each preceding treatment group and overall to establish baseline comparability (Table 1.2.1).

Demography includes age in years (continuous and categorical 18 to 49, 50 to 64, 65 to 74, and 75+), gender, race, ethnicity, weight, height and BMI. Demography will also be listed for all subjects enrolled (Listing 1).

### **3.4 Disease Diagnosis and Prior Therapy**

For the safety population, descriptive summaries will be presented for each preceding treatment group and overall to establish baseline comparability for ECOG performance status, and baseline testosterone and PSA levels and proportion of subjects' testosterone of  $\leq 1$  ng/dL (Table 1.3.1).

### **3.5 Disposition of Study Participants**

Subject disposition including completion and discontinuation along with CRF-based termination reason will be summarized for the safety population (Table 1.5.1). Subjects' early termination details will be listed for all subjects enrolled (Listing 3).

Subjects' treatment and date will be listed for all subjects enrolled (Listing 4).

### **3.6 Protocol Deviations and Violations**

All major and minor deviations/violations will be recorded and categorized in the CRF or eCRF, using a protocol deviation log, and confirmed prior to database lock and unbinding. A major protocol deviation/violation should be considered if the event could potentially affect the efficacy or safety conclusions of the study (e.g., subject had prohibited concomitant medications); otherwise, a minor protocol deviation/violation should be considered (e.g., visit was outside the window that deviates from the protocol specification but do not affect the efficacy or safety conclusions of the study).

A summary of protocol deviation and violations will be provided (Table 1.6.1). Major protocol violations and deviations that lead to exclusion from the PP population are as follows:

- The subject is terminated from study by the CRF completion status;
- The subject has major protocol deviation/violation(s) identified in the CRF/eCRF protocol deviation log;

- The subject's average weekly treatment compliance during the treatment period as defined in Section 4.2 is less than 80% or greater than 120%.

Subjects may have more than one major protocol violation or deviation.

## **4 EFFICACY EVALUATION**

### **4.1 Datasets Analyzed**

The safety population is defined for both efficacy and safety analyses. The definition of the safety population is provided in Section 3.1.

### **4.2 Treatment Compliance**

For this study, the treatment compliance rate will be summarized by preceding treatment group and demographic parameters for the safety population in Table 1.6.2. The compliance rate, expressed as percent, is calculated by dividing total number of capsules taken by total number of capsules prescribed multiplied by 100 for each treatment month and averaged over the number of treatment months.

### **4.3 Missing Data and Imputation**

Summary of the observed data missing will be reported for serum testosterone and PSA, for the safety population in Table 1.7.1.

### **4.4 Baseline Measures**

Descriptive statistics of serum testosterone and PSA levels at baseline will be summarized by preceding treatment group in Table 2.1.1.

### **4.5 Efficacy Results and Tabulations**

#### **4.5.1 Results of Efficacy analysis**

Descriptive statistics and inferential statistics on screening and Days 180 and 360 will be presented in Table 2.1.1 for serum testosterone levels and in Table 2.1.2 for PSA levels for safety population.

Individual subjects' serum testosterone and PSA levels will be listed in Listing 7.

#### **4.5.2 Results of other efficacy analyses**

The results of analyses of proportion of subjects with complete suppression of testosterone among those who achieved testosterone response will be presented in Table 2.2.1. The results of analyses of proportion of subjects with PSA-50 response among those who achieved PSA response will be presented in Table 2.2.2. The results of analyses of subjects' disease progression status will be presented in Table 2.2.3.

## **5 SAFETY EVALUATION**

### **5.1 Extent of Drug Exposure**

Treatment exposure to study medication will be tabulated by period, using the categories of 1-2 months, 3-4 months, 5-6 months, 7-8 months, 9-10 months, and 11-12 months, in Table 3.1.1 for the safety population.

Individual subjects' drug dose will be listed for the safety population (Listing 4).

## **5.2 Early Termination**

Early termination will be categorically summarized in Table 1.5.1 for the safety population. Subjects' study termination details will be listed (Listing 3).

## **5.3 Adverse Events**

An overall summary of AEs reported in this study will be provided in Table 4.1.1. Incidences of subjects reporting pre-treatment AEs will be reported in Table 4.1.2 for the pre-treatment period. Incidences of subjects reporting treatment-emergent AEs will be reported in Table 4.1.3. Those treatment-emergent AEs by preferred terminology that are reported by more than 5% of subjects in the safety population will be tabulated in Table 4.1.4.

The severity of the treatment-emergent AEs will be summarized in Table 4.2.1. The relationship to study drug of the treatment-emergent AEs will be summarized in Table 4.3.1. The severity and relationship to study drug of the treatment-emergent AEs will be summarized in Table 4.4.1. Treatment-emergent AEs associated with early terminations will be summarized by preferred terminology in Table 4.5.1. Serious AEs will be summarized by preferred terminology in Table 4.5.2.

Narratives will be presented for all deaths, non-fatal serious adverse events and subjects withdrawn due to adverse events.

Details of all TEAEs will be listed in for each subject of the safety population in Listing 8. Details of AEs associated with early terminations will be listed for each subject in Listing 9. SAEs including deaths will be listed for each event in Listing 10.

## **5.4 Vital Signs**

Descriptive and inferential statistics of vital signs will be presented at baseline and post-baseline time points by preceding treatment group in Tables 5.1.1 to 5.1.4, respectively, for pulse, systolic BP, diastolic BP and respiratory rate.

## **5.5 Physical Examination**

Abnormality findings of physical examination at each post-baseline visit will be tabulated by body system and by treatment in Table 6.1.1 for the safety population.

## **5.6 Clinical Laboratory Evaluation**

Descriptive and inferential statistics of clinical laboratory tests will be presented at baseline and post-baseline visits by preceding treatment group in Tables 7.1.1 to 7.1.3, respectively, for hematology, chemistry, and urinalysis (specific gravity and pH) for the safety population. Qualitative findings in terms of abnormal low, normal, and abnormal high at both screening and final study visits will be tabulated by treatment in Tables 7.2.1 to 7.2.3 for hematology, chemistry, and urinalysis, respectively.

Any clinically significant abnormalities observed during the study will be listed for hematology (Listing 13), chemistry (Listing 14), and urinalysis (Listing 15).

### **5.7 Prior and Concomitant Medication**

Number and percent of subjects who take pre-baseline medications will be reported in Table 8.1.1. Number and percent of subjects who take post-randomization concomitant medications will be reported by preceding treatment in Table 8.2.1.

### **5.8 ECOG Performance Status**

Number and percent of subjects with the ECOG performance status of 'fully active (0)' or 'restricted activity (1)' or other status score will be reported by preceding treatment in Table 9.1.1 for post-baseline visits.

## **6 REFERENCE**

Study Protocol No. CHL-AA-202 (v 1.1, dated June 2, 2017).



## 7 List of Statistical Table Shells

Statistical table shells are provided after the text portion. Table shells are presented only for those tables with a unique format. Tables with duplicate formats are indicated under 'Comments' in the TOC of the planned tables listed below.

Table Title	Comments
Table 1.1.1 Enrollment Summary: All Subjects Enrolled	
Table 1.1.2 Treatment Summary: Safety Population	
Table 1.2.1 Demography	
Table 1.3.1 Disease Baseline Characteristics	
Table 1.4.1 Subject Disposition	
Table 1.5.1 Protocol Deviations	
Table 1.5.2 Treatment Compliance	
Table 1.6.1 Summary of Missing Data in Testosterone and PSA	
Table 2.1.1 Summary and Analysis of Serum Testosterone Levels	
Table 2.1.2 Summary and Analysis of PSA Levels	Similar to Table 2.1.1
Table 2.2.1 Proportion of Subjects with Testosterone Complete Suppression	
Table 2.2.2 Proportion of Subjects with PSA-50 Response	Similar to Table 2.2.1
Table 2.2.3 Proportion of Subjects with Disease Progression	Similar to Table 2.2.1
Table 3.1.1 Treatment Exposure to Study Medication	
Table 4.1.1 Overall Summary of Adverse Events: All Subjects Enrolled in the Extension Study	
Table 4.1.2 Incidence of Subjects Reporting Pre-Treatment AEs by Preferred Terminology	
Table 4.1.3 Incidence of Subjects Reporting Treatment-Emergent AEs by Preferred Terminology	
Table 4.1.4 Treatment-Emergent AEs with >5% Subjects Reporting by Preferred Terminology	Similar to Table 4.1.3
Table 4.2.1 TEAEs by Severity	
Table 4.2.2 TEAEs by Toxicity Grade	
Table 4.3.1 TEAEs by Relationship to Study Drug	
Table 4.4.1 TEAEs by Severity and Relationship to Study Drug	
Table 4.4.2 TEAEs by Toxicity and Relationship to Study Drug	
Table 4.5.1 Incidence of TEAEs Associated with Treatment Discontinuation by Preferred Terminology	Similar to Table 4.1.3
Table 5.1.1 Summary and Analysis of Vital Signs: Pulse (bpm)	
Table 5.1.2 Summary and Analysis of Vital Signs: Systolic BP (mmHg)	Similar to Table 5.1.1
Table 5.1.3 Summary and Analysis of Vital Signs: Diastolic BP (mmHg)	Similar to Table 5.1.1
Table 5.1.4 Summary and Analysis of Vital Signs: Respiratory Rate (bpm)	Similar to Table 5.1.1
Table 6.1.1 Summary of Physical Examination Abnormalities	
Table 7.1.1 Summary and Analysis of Laboratory Tests: Hematology	
Table 7.1.2 Summary and Analysis of Laboratory Tests: Chemistry	Similar to Table 7.1.1



Table Title	Comments
Table 7.1.3 Summary and Analysis of Laboratory Tests: Urinalysis	Similar to Table 7.1.1
Table 7.2.1 Qualitative Change in Laboratory Tests: Hematology	
Table 7.2.2 Qualitative Change in Laboratory Tests: Chemistry	Similar to Table 7.2.1
Table 7.2.3 Qualitative Change in Laboratory Tests: Urinalysis	Similar to Table 7.2.1
Table 8.1.1 Summary of Pre-Baseline Medications	
Table 8.1.2 Summary of Post-Baseline Concomitant Medications	Similar to Table 8.1.1
Table 9.1.1 Proportion of Subjects with ECOG Status	

## 8 List of Key Listing Shells

Listing shells are provided after the statistical table shells. Listing shells are presented only for those listings with a unique format. Listings with duplicate formats are indicated under 'Comments' in the TOC of the planned listings listed below.

Listing Title	Comments
Listing 1 Subject Demography and Population	
Listing 2 Disease Diagnosis and Baseline Severity	
Listing 3 Early Termination Details	
Listing 4 Exposure Details	
Listing 5 Efficacy Data of Serum Testosterone Levels and PSA Levels	
Listing 6 Treatment-Emergent Adverse Events Reported in This Study	
Listing 7 Adverse Events Associated with Study Discontinuation	Similar to Listing 6
Listing 8 Serious Adverse Events (Including Deaths)	Similar to Listing 6
Listing 9 Abnormal Findings of Physical Examination	
Listing 10 Clinically Significant Laboratory Abnormalities: Hematology	
Listing 11 Clinically Significant Laboratory Abnormalities: Chemistry	Similar to Listing 10
Listing 12 Clinically Significant Laboratory Abnormalities: Urinalysis	Similar to Listing 10