CLINICAL STUDY PROTOCOL C21005 AMENDMENT 9

Orteronel (TAK-700)

A Phase 3, Randomized, Double-Blind, Multicenter Trial Comparing Orteronel (TAK-700) Plus Prednisone With Placebo Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer That Has Progressed During or Following Docetaxel-based Therapy

Protocol Number:	C21005
Indication:	Prostate cancer
Phase:	3
Sponsor:	Millennium Pharmaceuticals, Inc.
EudraCT Number:	2010-018662-23
Therapeutic Area:	Oncology

Protocol History

Original		21 July 2010
Amendment 1	*For use in Argentina only*	08 March 2011
Amendment 2	*Global*	13 May 2011
Amendment 3	*For use in Peru only*	13 May 2011
Amendment 4	*For use in Argentina only*	25 May 2011
Amendment 5	*Global*	22 June 2011
Amendment 6	*For use in Argentina only*	22 June 2011
Amendment 7	*For use in Peru only*	21 July 2011
Amendment 8	*For use in Japan only*	15 September 2011
Amendment 9	*Global*	26 March 2013

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Rationale for Amendment 9 (relative to global amendment 5)

The primary purpose of this amendment is to define the change in study procedures following a decision to unblind the study. At the time of unblinding, this study will have met its primary objective of determining the improvement of overall survival (OS) by orteronel plus prednisone. Therefore, the protocol has been modified to reflect changes in study procedures. After unblinding, patients who are still active on the study and who received placebo will be offered the opportunity to crossover to active treatment with orteronel. Those treatment-naïve patients will undergo procedures outlined in the Schedules of Events #1 (Patients Crossing From Placebo to Orteronel After Unblinding). Patients who received active study drug and who elect to continue receiving orteronel will undergo study procedures as outlined in the Schedules of Events #2 (Patients Continuing to Receive Orteronel After Unblinding). Portions of the study that are no longer relevant or no longer needed after unblinding (eg, short-term follow-up, collection of samples for measurement of circulating tumor cells [CTCs] and plasma orteonel concentrations, pharmacokinetic [PK] sampling, imaging studies, quality of life questionnaires, etc) have been removed from the Schedules of Events with the protocol text amended to reflect that this data is no longer collected.

Specific safety language has been updated to be consistent with current safety information and standard language used in the sponsor's protocols.

Instructions have been added to ensure that patients who received placebo met certain eligibility criteria to crossover to active treatment with orteronel.

Details on study conduct have been updated to clarify acceptable methods of contraception and provide a clear definition of abstinence from heterosexual intercourse. Guidance on contraception or abstention from heterosexual intercourse has been updated. In addition, allowable reasons for withdrawal of patients from the study have been updated.

Information on supply, labeling, and storage of study drug has been updated.

The method for recording, reporting, and monitoring of adverse events (AEs) and serious adverse events (SAEs) has been updated to be consistent with current procedures.

Purposes for Amendment 9

The purposes of this amendment are to:

Procedures

- Update the Study Flow Diagram to reflect the change in study procedures after unblinding
- Create 2 Schedules of Events at the time of unblinding: 1 for patients crossing over from placebo to orteronel and 1 for patients continuing to receive orteronel
- Remove the following study procedures for patients in the unblinded study, because sufficient data will have been collected before study unblinding, and limited inference can be made following crossover of all patients to active study drug:
  - PK sampling

  - Collection of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Module 30 (EORTC QLQ-C30) data
  - Computed tomography (CT) and magnetic resonance imaging (MRI) scans (however, scans may be performed by sites at the discretion of the investigator based on clinical need)
  - Collection of samples for the enumeration of CTCs
  - Collection of samples for germline DNA analysis
  - Evaluation of medical resource utilization (MRU)
  - Assessment of cost of treatment in each arm
- Clarify that prostate-specific antigen (PSA) results will not be withheld from the sponsor after unblinding
- Remove recording of complete medical histories after study unblinding, because this information will have already been collected from patients in the blinded study
- Remove recording of height after study unblinding, because this information will have already been collected from patients in the blinded study
- Clarify that informed consent will be collected from all patients at the time of study unblinding
- Update language on utility measurement, stating that this data will be continually collected until the patient discontinues study drug
- Add language indicating that the short-term follow-up portion of the study will no longer apply to patients at the time of unblinding

Eligibility

- Add inclusion criteria for patients crossing over from placebo to orteronel treatment
- Clarify that disease progression is not required for patients crossing over from placebo to orteronel treatment

Study Conduct

- Add language indicating that, per the recommendation of the independent data monitoring committee (IDMC), the study may be unblinded
- Clarify acceptable methods of contraception, and provide a clear definition of abstinence from heterosexual intercourse
- Clarify the allowable reasons for discontinuation of treatment with study drug
- Clarify the allowable reasons for withdrawal of patients from the study
- Remove instructions on emergency unblinding procedures as they no longer apply after study unblinding

Study Drug

- Update language on the supply of unblinded study drug
- Update language on the labeling of unblinded study drug
- Update language on the storage of unblinded study drug

- Clarify excluded concomitant medications nomenclature

Adverse Events

- Update procedures for recording and reporting AEs and SAEs to be consistent with the sponsor's current procedures
- Update details on the monitoring of AEs throughout the study to be consistent with the sponsor's current procedures
- Clarify that a listing of treatment-emergent adverse events (TEAEs) resulting in study drug discontinuation will be provided

Background Information

- Update status of ongoing clinical trials with orteronel to include Studies C21004, C21008, C21009, C21012, and C21013
- Add background information on enzalutamide and abiraterone acetate to the study rationale
- Update the risk language of orteronel, per the most recent IB data cutoff date, 29 September 2012
- Update pancreas-related SAEs, per the most recent IB data cutoff date, 29 September 2012
- Update the risk language for T-1358043 (a process impurity, drug product degradant, and minor metabolite of orteronel) based on nonclinical studies

Administrative

- Clarify details on study conduct in adherence to Good Clinical Practices (GCP) standards
- Update language on the procedures for product complaints and medication errors during the study
- Update procotol signatories
- Correct typographical errors, punctuation, grammar, and formatting

For specific examples of changes in text and where the changes are located, see Section 15.16.

PROTOCOL SUMMARY

Study Title: A Phase 3, Randomized, Double-Blind, Multicenter Trial Comparing Orteronel (TAK-700) Plus Prednisone With Placebo Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer That Has Progressed During or Following Docetaxel-based Therapy

Number of Patients: Approximately 1,083 patients will be randomized into this study from approximately 400 study centers worldwide.

Study Objectives:

Primary Objective:

- To determine if orteronel plus prednisone improves overall survival (OS)

Key Secondary Objectives:

- To determine if orteronel plus prednisone improves radiographic progression-free survival (rPFS)
- To determine if orteronel plus prednisone improves 50% prostate-specific antigen (PSA) response rate at 12 weeks
- To evaluate if orteronel plus prednisone improves pain response at 12 weeks

Exploratory Objectives:

- To assess tumor specimens for candidate biomarkers predictive of orteronel antitumor activity including, but not limited to, the *TMPRSS2:ERG* fusion gene
- To evaluate polymorphisms in the *CYP17* gene and other germline genes implicated in the safety or efficacy of orteronel
- To assess the functioning and symptom QOL subscales of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Module 30 (EORTC QLQ-C30)
- To evaluate medical resource utilization (MRU) and calculate utility values using a preference-based patient-reported outcome (PRO) instrument (European Quality of Life 5-Dimensional [EQ-5D]), while patients are on study treatment

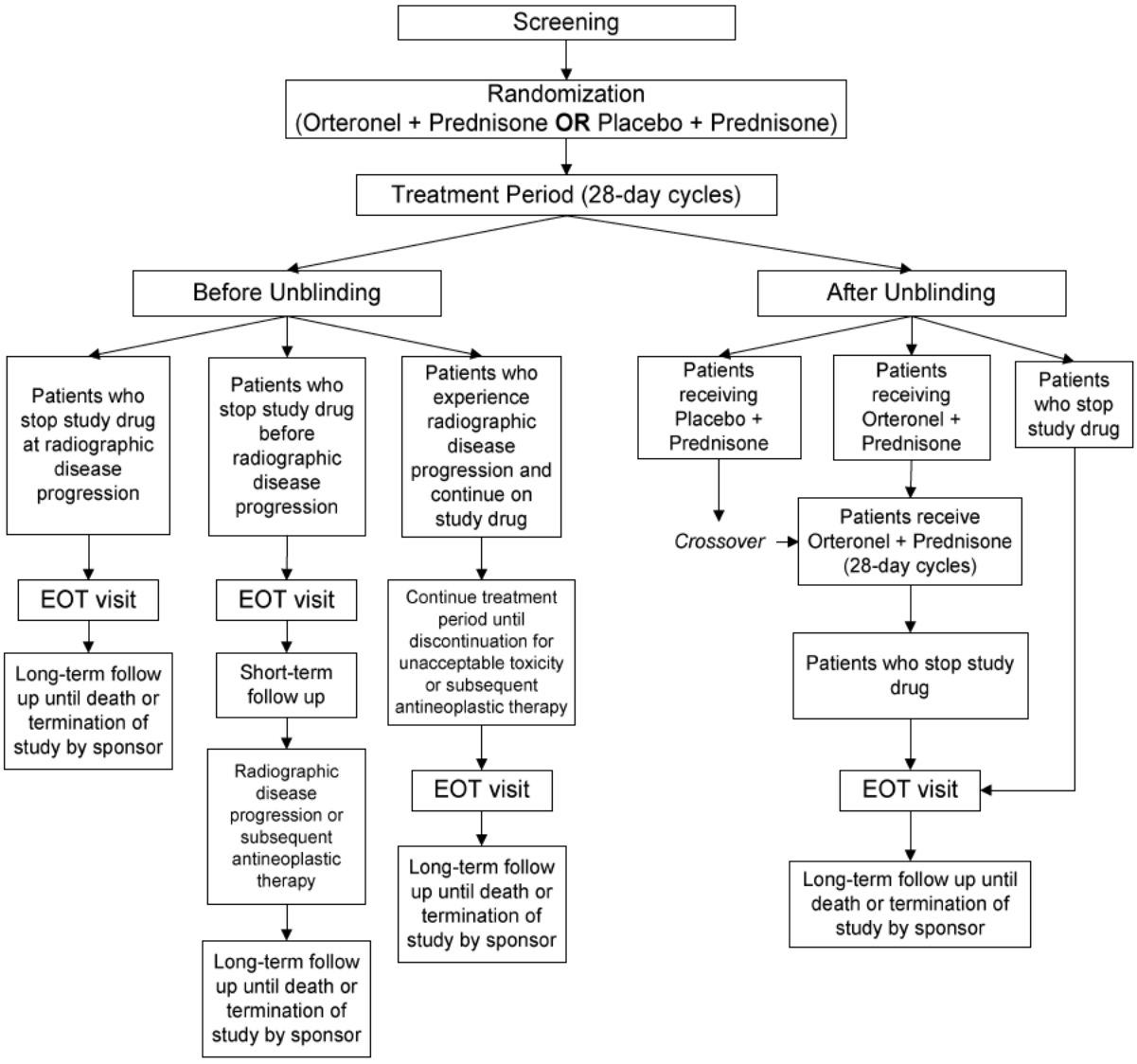
Overview of Study Design:

This is a randomized, double-blind, multicenter, phase 3 study evaluating orteronel plus prednisone, compared with placebo plus prednisone, in men with metastatic, castration-resistant prostate cancer (mCRPC). Gonadotropin-releasing hormone (GnRH) analogue therapy will be continued unless the patient is surgically castrate. Patients must have evidence of disease progression during or after receiving a total of ≥ 360 mg/m^2 docetaxel within a 6-month period. Patients who were clearly intolerant to docetaxel or have progressive disease before receiving ≥ 360 mg/m^2 are also eligible if they have received ≥ 225 mg/m^2 of docetaxel within a 6-month period and meet the other study entry criteria. Two formal interim analyses are planned for this study. Upon the recommendation of the independent data monitoring committee (IDMC) to unblind the study, patients receiving placebo will be allowed to crossover to orteronel treatment.

Patients will return for regularly scheduled study visits (treatment/short-term follow-up) for as long as they: 1) continue to take study drug, or 2) discontinue study drug but have not yet experienced disease progression. Patients will discontinue scheduled study visits if they experience disease progression and decide to discontinue study drug. Patients may remain on study drug after disease progression and return for scheduled visits until they receive subsequent antineoplastic therapy. The short-term follow-up portion of the study will no longer apply at the time of unblinding.

All patients will be followed for survival (long-term follow-up) after discontinuing the treatment/short-term follow-up portion of the study. Long-term follow-up will continue until death or discontinuation of the study by the sponsor.
Study Population: Men at least 18 years of age who have histologically confirmed or cytologically confirmed adenocarcinoma of the prostate that has progressed during or following 1 to 2 prior cytotoxic chemotherapies, at least 1 of which must have included docetaxel therapy. Patients can be symptomatic or asymptomatic. Patients must have progressive disease demonstrated by radiographic or PSA assessments, castrate levels of testosterone after surgical or medical castration, adequate renal and hepatic function and adequate bone marrow reserve based on laboratory assessments, adequate cardiac function, an ECOG performance status of ≤ 2, a stable medical condition, and a life expectancy of 6 months or longer. Patients cannot have documented evidence of CNS metastases, prostate cancer limited only to the prostate bed or immediate adjacent tissue, uncontrolled hypertension, a QTc interval > 460 msec, or uncontrolled nausea, vomiting, or diarrhea. Radioisotope therapy or external beam radiation therapy within 4 weeks of first dose of study drug will not be allowed. Prior ketoconazole, abiraterone, aminoglutethimide, or orteronel therapy will not be allowed. Any other therapies for prostate cancer, except for GnRH analogue therapy, such as progesterone, medroxyprogesterone, progestins (megesterol), or 5-alpha reductase inhibitors (eg, finasteride or dutasteride) must be discontinued 2 weeks before the first dose of study drug. Patients receiving placebo must meet additional criteria prior to crossing over to orteronel treatment.
Duration of Study: It is expected that the study will last approximately 36 to 38 months until reaching the final analysis of the OS endpoint. Patients will be followed for survival until 80% of patients have died or are lost to follow-up.

Study Flow Diagram



Schedules of Events

Refer to Section 15.7 for the Schedule of Events for patients who received blinded study drug.

Schedule of Events #1: Cycles for Patients Crossing From Placebo to Orteronel After Unblinding

Procedure	Baseline[b]	Treatment Period[a] 28-Day Cycles for Crossover Patients (± 3 Days for Cycles 1 through 7; ± 5 days for subsequent cycles)[c] C1	C2	C3	C4	C5	C6	C7	C10	C13	After C13[d]	Unsched[e]	EOT +10 days	Long-term Follow-up[a,f] ± 30 days
Informed Consent[g]	X													
Inclusion/Exclusion	X													
Physical Examination[h]	X		X	X	X	X	X	X	X	X	Q3C		X	
Vital Signs[i]	X	X	X	X	X	X	X	X	X	X	Q3C	X	X	
Weight	X	X	X	X	X	X	X	X	X	X	Q3C		X	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	Q3C		X	
MUGA Scan and/or ECHO[j]	X				X			X		X	Q6C		X	
Electrocardiogram (12-lead)	X		X					X		X	Q12C		X	
Sample collection														
Hematology[k]	X	X	X		X			X	X	X	Q3C		X	
Serum Chemistry[k]	X	X	X	X	X	X		X	X	X	Q3C		X	
Lipid Profile, HbA1c[k]	X							X		X	Q12C			
PSA[k]	X	X			X			X	X	X	Q3C		X	
Testosterone/DHEA-S[l]	X	X	X		X			X	X	X	Q3C		X	
ACTH, Cortisol, Corticosterone[l]	X	X	X		X			X	X	X	Q3C		X	
Archived Tumor Tissue[m]		Archived tumor tissue can be collected at anytime during the study.												
BPI-SF and Prior 24-hour Opioid-Use Recall[n,o]		X		X	X	X		X	X	X	Q3C	X	X	
EQ-5D Questionnaire[n]		X		X	X	X		X	X	X	Q3C	X	X	

Schedule of Events #1: Cycles for Patients Crossing From Placebo to Orteronel After Unblinding

Procedure	Baseline[b]	Treatment Period[a]											EOT +10 days	Long-term Follow-up[a,f] ± 30 days
		28-Day Cycles for Crossover Patients (± 3 Days for Cycles 1 through 7; ± 5 days for subsequent cycles)[c]												
		C1	C2	C3	C4	C5	C6	C7	C10	C13	After C13[d]	Unsched[e]		
Concomitant Medications		Continuous from first dose of study drug through EOT												
Concomitant Procedures		Continuous from first dose of study drug through EOT												
Adverse Event Reporting		Adverse events will be reported from the first dose of any study drug through 30 days after treatment with the last dose of any study drug or the start of subsequent antineoplastic therapy, whichever occurs first, and recorded in the eCRFs												
	Serious adverse events and serious pretreatment events will be collected from signing of the informed consent form through 30 days after the last dose of any study drug													
Administration of Study Drug[o]		Study drug will be given twice daily as a continuous dose												
Administration of Prednisone		Prednisone (or commercially available equivalent) will be given 5 mg twice daily as a continuous dose												
Co-administration of GnRH Analogue	Patients (unless surgically castrate) will receive GnRH analogue treatment throughout the study per standard of care													
New Antineoplastic Therapy Follow-up[p]														Q3mo
Survival Follow-up Contact[q]														Q3mo

Abbreviations: ACTH = adrenocorticotropic hormone; BPI-SF = Brief Pain Inventory-Short Form; DHEA-S = dehydroepiandrosterone sulfate; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; EOT = End of Treatment (visit); EQ-5D = European Quality of Life 5-Dimensional; GnRH = gonadotropin-releasing hormone; HbA1c = glycosylated hemoglobin; MUGA = multiple gated acquisition; PSA = prostate-specific antigen; Q3C = every 3 cycles; Q3mo = every 3 months; Unsched = unscheduled (visit).

a Definitions of treatment and follow-up periods:

- Active treatment is the portion of the study when patients are on study drug and participating in the study according to the treatment period. Following radiographic disease progression, patients will enter the long-term follow-up portion of the study, unless the patient remains on treatment. Patients may remain on study drug after disease progression and return for scheduled visits until they receive subsequent antineoplastic therapy.
- Long-term follow-up is the portion of the study when patients are off study drug and will no longer have scheduled visits or assessments, but are followed for alternative antineoplastic therapies and survival.

b Patients who are crossing over to orteronel treatment must meet the criteria outlined in Section 5.3. Patients may use values from their last cycle.

Schedule of Events #1: Cycles for Patients Crossing From Placebo to Orteronel After Unblinding

Procedure	Baseline[b]	Treatment Period[a] — 28-Day Cycles for Crossover Patients (± 3 Days for Cycles 1 through 7; ± 5 days for subsequent cycles)[c]											EOT +10 days	Long-term Follow-up[a,f] ± 30 days
		C1	C2	C3	C4	C5	C6	C7	C10	C13	After C13[d]	Unsched[e]		

c Patients continuing study drug following disease progression will remain in the treatment period and should continue to have these study assessments performed according to this schedule until treatment with study drug is discontinued. Testing for each cycle from Cycle 1 through Cycle 7 will be completed every 28 days on Day 1 of the cycle (± 3 days). After Cycle 7, Day 1 testing will be performed every 3 cycles (every 84 days ± 5 days).

d Frequency of assessment is based on Cycle 13 as the starting point, eg, Q3C assessments would occur at the beginning of Cycles 16, 19, etc.

e Recording of vital signs and completion of EQ-5D questionnaires are required at unscheduled visits. Other assessments should be done as clinically indicated

f Patients who discontinue study treatment prior to disease progression and receive subsequent antineoplastic therapy will *not* be followed centrally for disease progression but will be followed in the long-term follow-up portion of the study.

g Informed consent must be obtained before any study-specific procedures following unblinding are performed.

h A complete physical examination must be conducted at the screening and EOT visits. At all other visits, physical exams may be symptom/disease directed.

i Vital sign measurements include diastolic and systolic BP, heart rate, and temperature. Blood pressure will be taken after the patient has been in a seated position for 5 minutes. At screening, patients may have 2 BP measurements taken no more than 60 minutes apart to exclude uncontrolled hypertension. For eligible patients, only the BP measurement that confirms eligibility should be recorded on the eCRF.

j MUGA scans or ECHO; the same modality should be used for a patient throughout the study and the assessments should be performed at the same institution whenever possible.

k For Cycle 1, Day 1 only, all samples must be collected within 3 days prior to the first dose of study drug.

l DHEA-S, testosterone, ACTH, cortisol, and corticosterone samples will be collected prior to AM dosing.

m If available and consistent with local regulations, archived tumor tissue collected at the time of original diagnosis or subsequent procedures (unstained slides or a paraffin-embedded block) will be obtained and evaluated to assess *TMPRSS2:ERG* fusion gene product and other candidate biomarkers predictive of orteronel antitumor activity. Archived tumor tissue can be collected at anytime during the study.

n All questionnaires should be completed before any other study procedures are performed. The BPI-SF questionnaire should be completed first. Patients will be asked to report their use of opioids during the 24 hours before the study visit.

o The 24-hour opioid-use data collected during the treatment period and short-term follow-up will be recorded on both the opioid-use and the concomitant medication eCRFs.

p Patients will receive continuous oral study drug twice daily without a rest period.

q After EOT, information on newly prescribed antineoplastic therapies will be collected every 3 months (± 30 days from the last dose of study drug).

r Patients are to be contacted for survival every 3 months (± 30 days from the last dose of study drug).

Schedule of Events #2: Cycles for Patients Continuing to Receive Orteronel After Unblinding

Procedure	Treatment Period[a]											EOT +10 days	Long-term Follow-up[a, e] ± 30 days
	28-Day Cycle for Patients Continuing Orteronel Treatment (± 5 days for each cycle)[b]												
	C1	C2	C3	C4	C5	C6	C7	C10	C13	After C13[c]	Un-sched[d]		
Physical Examination[f]		X	X	X	X	X	X	X	X	Q3C		X	
Vital Signs[g]	X	X	X	X	X	X	X	X	X	Q3C	X	X	
Weight	X	X	X	X	X	X	X	X	X	Q3C		X	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	Q3C		X	
MUGA Scan and/or ECHO[h]				X			X		X	Q6C		X	
Electrocardiogram (12-lead)		X					X		X	Q12C		X	
Sample Collection													
Hematology	X	X		X			X	X	X	Q3C		X	
Serum Chemistry	X	X	X	X	X		X	X	X	Q3C		X	
Lipid Profile, HbA1c							X		X	Q12C			
PSA	X			X			X	X	X	Q3C		X	
Testosterone/ DHEA-S[i]	X	X		X			X	X	X	Q3C		X	
ACTH, Cortisol, Corticosterone[i]	X	X		X			X	X	X	Q3C		X	
Archived Tumor Tissue[j]	Archived tumor tissue can be collected at anytime during the study.												
BPI-SF and Prior 24-hour Opioid-Use Recall[k,l]	X		X	X	X		X	X	X	Q3C			
EQ-5D Questionnaire[k]	X		X	X	X		X	X	X	Q3C	X	X	
Concomitant Medications	Continuous from first dose of study drug through EOT												
Concomitant Procedures	Continuous from first dose of study drug through EOT												
Adverse Event Reporting	Adverse events will be reported from the first dose of any study drug through 30 days after treatment with the last dose of any study drug or the start of subsequent antineoplastic therapy, whichever occurs first, and recorded in the eCRFs												
	Serious adverse events and serious pretreatment events will be collected from signing of the informed consent form through 30 days after the last dose of any study drug												
Administration of Study Drug[m]	Study drug will be given twice daily as a continuous dose												
Administration of Prednisone	Prednisone (or commercially available equivalent) will be given 5 mg twice daily as a continuous dose												

Schedule of Events #2: Cycles for Patients Continuing to Receive Orteronel After Unblinding

Procedure	Treatment Period[a]											EOT +10 days	Long-term Follow-up[a, e] ± 30 days
	28-Day Cycle for Patients Continuing Orteronel Treatment (± 5 days for each cycle)[b]												
	C1	C2	C3	C4	C5	C6	C7	C10	C13	After C13[c]	Un-sched[d]		
Co-administration of GnRH Analogue	Patients (unless surgically castrate) will receive GnRH analogue treatment throughout the study per standard of care												
New Antineoplastic Therapy Follow-up[n]													Q3mo
Survival Follow-up Contact[o]													Q3mo

Abbreviations: ACTH = adrenocorticotropic hormone; BPI-SF = Brief Pain Inventory-Short Form; DHEA-S = dehydroepiandrosterone sulfate; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; EOT = End of Treatment (visit); EQ-5D = European Quality of Life 5-Dimensional; GnRH = gonadotropin-releasing hormone; HbA1c = glycosylated hemoglobin; MUGA = multiple gated acquisition; PSA = prostate-specific antigen; Q3C = every 3 cycles; Q3mo = every 3 months; Unsched = unscheduled (visit).

a Definitions of treatment and follow-up periods:

- Active treatment is the portion of the study when patients are on study drug and participating in the study according to the treatment period. Following radiographic disease progression, patients will enter the long-term follow-up portion of the study. Patients may remain on study drug after disease progression and return for scheduled visits until they receive subsequent antineoplastic therapy.
- Long-term follow-up is the portion of the study when patients are off study drug and will no longer have scheduled visits or assessments, but are followed for alternative antineoplastic therapies and survival.

b Patients continuing study drug following disease progression will remain in the treatment period and should continue to have these study assessments performed according to this schedule until treatment with study drug is discontinued. Informed consent must be obtained before any study-specific procedures following unblinding are performed.

c Frequency of assessments is based on Cycle 13 as the starting point, eg, Q3C assessments would occur at the beginning of Cycles 16, 19, etc.

d Recording of vital signs and completion of the EQ-5D questionnaire is required at unscheduled visits. Other assessments should be done as clinically indicated.

e Patients who discontinue study treatment prior to disease progression and receive subsequent antineoplastic therapy will *not* be followed centrally for disease progression but will be followed in the long-term follow-up portion of the study.

f A complete physical examination must be conducted at the EOT visit. At all other visits, physical exams may be symptom/disease directed.

g Vital sign measurements include diastolic and systolic BP, heart rate, and temperature. Blood pressure will be taken after the patient has been in a seated position for 5 minutes.

h MUGA scans or ECHO; the same modality should be used for a patient throughout the study and the assessments should be performed at the same institution whenever possible.

i DHEA-S, testosterone, ACTH, cortisol, and corticosterone samples will be collected prior to AM dosing.

j If available and consistent with local regulations, archived tumor tissue collected at the time of original diagnosis or subsequent procedures (unstained slides or a paraffin-embedded block) will be obtained and evaluated to assess *TMPRSS2:ERG* fusion gene product and other candidate biomarkers predictive of orteronel antitumor activity. Archived tumor tissue can be collected at anytime during the study.

Schedule of Events #2: Cycles for Patients Continuing to Receive Orteronel After Unblinding

	Treatment Period[a]												
	28-Day Cycle for Patients Continuing Orteronel Treatment (± 5 days for each cycle)[b]											EOT +10 days	Long-term Follow-up[a, e] ± 30 days
Procedure	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C10**	**C13**	**After C13[c]**	**Un-sched[d]**		

k All questionnaires should be completed before any other study procedures are performed. The BPI-SF questionnaire should be completed first. Patients will be asked to report their use of opioids during the 24 hours before the study visit.

l The 24-hour opioid-use data collected during the treatment period and short-term follow-up will be recorded on both the opioid-use and the concomitant medication eCRFs.

m Patients will receive continuous oral study drug twice daily without a rest period.

n After EOT, information on newly prescribed antineoplastic therapies will be collected every 3 months (± 30 days from the last dose of study drug).

o Patients are to be contacted for survival every 3 months (± 30 days from the last dose of study drug).

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LIST OF TABLES

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
ACTH	adrenocorticotropic hormone
ADL	activity of daily living
ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
AM	morning
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AR	androgen receptor
AST	aspartate aminotransferase
BID	twice daily
BP	blood pressure
BPI-SF	Brief Pain Inventory-Short Form
BSA	body surface area
CDF	Cumulative Distribution Function
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CR	complete response
CRPC	castration-resistant prostate cancer
CT	computed tomography
CTC	circulating tumor cell
CYP17	cytochrome P450 enzyme 17 gene
DHEA-S	dehydroepiandrosterone sulfate
DNA	deoxyribonucleic acid
DOC	deoxycorticosterone
DOR	duration of response
EAU	European Association of Urology
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Module 30
EOT	End of Treatment (visit)

Abbreviation	Term
EQ-5D	European Quality of Life 5-Dimensional
ERG	*v-ets* erythroblastosis virus E26 oncogene homolog (avian) gene
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GI	gastrointestinal
GnRH	gonadotropin-releasing hormone
HDL	high-density lipoprotein
HbA1c	glycosylated hemoglobin
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
HT	high-level term
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IR	immediate-release
IRB	institutional review board
ITT	intent-to-treat
IVRS	interactive voice response system
LDL	low-density lipoprotein
LVEF	left ventricular ejection fraction
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
mPC	metastatic prostate cancer
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MRI	magnetic resonance imaging
MRU	medical resource utilization
MUGA	multiple gated acquisition (scan)
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not estimable
OME	oral morphine equivalent
ORR	overall response rate
OS	overall survival
PC	prostate cancer
PCWG2	Prostate Cancer Working Group
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
PP	per-protocol
PR	partial response
PRO	patient-reported outcome

Abbreviation	Term
PSA	prostate-specific antigen
PSA50	50% PSA response
PT	preferred term
PTEN	phosphatase and tensin homolog
QALYs	quality adjusted life years
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	radiographic progression-free survival
SA	short axis
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SMA	Safety Management Attachment
SNP	single nucleotide polymorphism
SOC	system organ class
SRE	skeletal-related event
TAK-700	orteronel
TEAE	treatment-emergent adverse event
TMPRSS2	transmembrane protease, serine 2 gene
TPN	total parenteral nutrition
UK	United Kingdom
ULN	upper limit of the normal range
US	United States
WHO	World Health Organization
WNL	within normal limits

STUDY DEFINITIONS

Term	Definition
Active treatment	The portion of the study when patients are on study drug and participating in the study according to the treatment period in the Schedules of Events. Following radiographic disease progression, patients will enter the long-term follow-up portion of the study. Patients may remain on study drug after disease progression and return for scheduled visits until they receive subsequent antineoplastic therapy.
Short-term follow-up	The portion of the study that specifically includes patients who discontinue study drug, but have not yet experienced radiographic disease progression. After radiographic disease progression, patients will then enter the long-term follow-up portion of the study.
Long-term follow-up	The portion of the study when patients will no longer have scheduled visits or assessments, but are followed for alternative antineoplastic therapies and survival.
Baseline assessment	The assessment performed at the closest time before the start of study drug administration.
Study drug	The term study drug is used in this protocol to represent orteronel (TAK-700) tablets and matching placebo tablets. Orteronel is the International Proprietary Name for TAK-700 that is currently under final consideration.
Radiographic disease progression	Radiographic disease progression is defined as: • The appearance of 2 or more new lesions on radionuclide bone scan as defined by PCWG2. ○ Should 2 or more new bone lesions be evident at the first assessment on treatment, 2 or more additional new lesions must be evident on a confirmatory assessment at least 6 weeks later. • One or more new soft tissue/visceral organ lesions identified by CT/MRI. • Progression as defined by RECIST 1.1 criteria (see Section 15.1). NOTE: For the first assessment only, soft tissue disease progression requires confirmation 6 or more weeks later.
Radiographic progression-free survival (rPFS)	Time from patient randomization to radiographic disease progression or death from any cause, whichever occurs first.
Overall survival (OS)	Time from patient randomization to death from any cause.
Pain response	Pain response is defined as the occurrence of 1 of the following and confirmed by an additional assessment, at least 3 weeks but not more than 5 weeks later: • A ≥ 2 point reduction from baseline in BPI-SF worst pain score without an increase in analgesic use, or • A 25% reduction in analgesic use from baseline without an increase in worst pain score from baseline.
Pain progression	Pain progression is defined as the occurrence of 1 of the following and confirmed by an additional assessment, at least 3 weeks but not more than 5 weeks later: 1. The BPI-SF worst pain score is ≥ 4 with a ≥ 2 point increase over baseline in BPI-SF worst pain score with stable or increased analgesic use; 2. The BPI-SF worst pain score is ≥ 4 but not less than baseline with new or increased (relative to baseline) Step II or Step III analgesic use; 3. The BPI-SF worst pain score is ≤ 3 but not less than baseline with new or increased (relative to baseline) Step III analgesic use Confirmation at least 3 weeks later is not required if surgical treatment for pain,

Term	Definition
	palliative radiation for pain, or subsequent antineoplastic therapy has been received prior to a confirmatory assessment (refer to Section 15.2 for a list of Step II and III analgesics).
Stable analgesic use	Stable analgesic use is defined as less than a 25% change of the oral morphine equivalent (OME) dose from baseline
Increased analgesic use	Increased analgesic use is defined as an increase of 25% or more in OME from baseline.
Time to pain progression	Time from patient randomization to the date of the first detection of pain progression
Skeletal-related event (SRE)	Fracture or spinal cord compression or the need for radiation or surgery at the site of a prostate cancer metastatic lesion that is substantiated by radiographic or pathologic evidence
QOL response	An improvement of global QOL score in EORTC QLQ-C30 by at least 10 points from the baseline assessment, maintained on 2 consecutive visits at least 3 weeks apart.
50% PSA response	PSA decline of at least 50% occurring 4 or more weeks from the baseline assessment.
90% PSA response	PSA decline of at least 90% occurring 4 or more weeks from the baseline assessment.
Time to PSA progression	Time from randomization to 25% and 2 ng/mL or greater increase in PSA above the baseline assessment (if no PSA decline from the baseline assessment). If the PSA nadir occurs 4 or more weeks following randomization, progression is defined as a 25% increase in the nadir value and at least a 2 ng/mL rise.
Favorable change in CTC counts	Change in patient's CTC counts from ≥ 5 cells/7.5 mL whole blood at baseline to < 5 cells/7.5 mL whole blood.
Opioid use	Opioid use will be defined as the use of any opioid-containing analgesics, including codeine combinations (for the purpose of analyses, opioid use will be converted to OME [Section 15.2]).
Step III analgesic use	Step III analgesics include all potent opioids such as oral morphine, the fentanyl patch, doses of oxycodone above 5 mg, and parenteral or liquid high-strength formulations of weaker analgesics, including codeine. See Section 15.2 for a complete listing of Step I through III analgesics as defined by WHO.

Abbreviations: BPI-SF = Brief Pain Inventory-Short Form; CTC = circulating tumor cell(s); EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Module 30; OME = oral morphine equivalent; PC = prostate cancer; PCWG2 = Prostate Cancer Working Group; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors; QOL = quality of life; SRE = skeletal-related events; WHO = World Health Organization.

1. BACKGROUND AND STUDY RATIONALE

Orteronel (TAK-700; International Proprietary Name under consideration) is an orally bioavailable, reversible, nonsteroidal inhibitor of 17,20-lyase, a key enzyme in androgen synthesis. This study is designed to investigate whether the androgen synthesis inhibitor orteronel improves overall survival (OS) in men with progressive, metastatic, castration-resistant prostate cancer (mCRPC) that has progressed following at least 1 or 2 prior cytotoxic chemotherapies, 1 of which must have included docetaxel.

1.1 Scientific Background

Prostate cancer (PC), the most common malignancy in Western societies, is a common cause of male cancer-related death in the United Kingdom (UK), the United States (US), and Europe. Although less common in Asian countries, perhaps related to both environmental and other factors, the rates of prostate cancer are rapidly increasing.[1, 2] Over the past 2 decades, prostate-specific antigen (PSA) testing, where it is used frequently, has significantly decreased the number of men who present with metastatic PC (mPC) at diagnosis from 20% in the 1970s to 3.4% in the 1990s.[3] Despite the steady decline in the incidence of newly diagnosed mPC, following treatment(s) for localized disease, about one-third of patients will have recurrent disease within 10 to 15 years. Although androgen deprivation therapy (ADT) and other therapies can delay progression, mCRPC remains an incurable disease.[4]

Androgen deprivation achieved with medical intervention or surgical castration remains the mainstay of mPC treatment.[5, 6, 7, 8] First-line medical ADT consists of a gonadotropin-releasing hormone (GnRH) agonist or antagonist, which may be combined with an antiandrogen (combined androgen blockade [CAB]). Significant numbers of patients will have a clinical response to ADT; however, most will eventually develop progressive disease (PD; ie, mCRPC) despite castrate concentrations of testosterone.[9] Salvage therapy for patients with recurrent mCRPC includes second-line hormonal therapy,[10, 11, 12] systemic chemotherapy, systemic radiotherapy,[13, 14, 15, 16, 17, 18] or supportive care.

Treatment of Castration-Resistant Prostate Cancer

Currently, 3 classes of agents are widely used to treat PC that progresses despite ADT: antiandrogens (flutamide, nilutamide, or bicalutamide, unless previously administered), adrenal androgen suppressors (ketoconazole or, less commonly, aminoglutethimide), and estrogens. These therapies provide effective palliation, temporary tumor control, and

biochemical responses (decrease in PSA in approximately 40% to 87% of patients; 50% decline in PSA levels in 20% to 50% of patients).[19, 20, 21, 22, 23, 24] However, each of these drug classes produces only modest, short therapeutic responses in patients with mCRPC.[24, 25, 26, 27, 28] Clinical experience with newer drugs that more selectively target androgen production and/or are more potent androgen receptor (AR) antagonists confirms that CRPC commonly remains hormone dependent. For instance, treatment with abiraterone acetate, a reportedly irreversible steroidal inhibitor of both the 17,20-lyase and 17-hydroxylase activities of cytochrome P450 enzyme 17 (*CYP17*), the key enzyme in glucocorticoid, androgen, and estrogen biosynthesis, demonstrated efficacy in preliminary phase 2 trials in patients with PD. However, toxicities attributed to a syndrome of secondary mineralocorticoid excess have been noted with abiraterone and require administration of a mineralocorticoid receptor antagonist or glucocorticoid to suppress adrenocorticotropic hormone (ACTH).[29]

Metastatic CRPC that advances despite these therapies is often treated with docetaxel-based chemotherapy. Docetaxel is an antimicrotubule agent with significant clinical activity in a wide range of solid tumors. The US Food and Drug Administration (FDA) and other regulatory organizations in Europe and Japan have approved docetaxel in combination with prednisone for the treatment of mCRPC based on phase 3 data demonstrating a survival advantage (of 2.9 months) in comparison to the previous standard of care of mitoxantrone plus prednisone.[30] Nevertheless, median OS of mCRPC remains less than 2 years.[31, 32] There is no standard therapy for patients with ADT- and docetaxel-refractory disease.

Development of Orteronel

Androgen receptors (ARs) remain active in patients with CRPC, suggesting that further diminishing testosterone synthesis beyond that achieved by medical or surgical castration is an important therapeutic goal. Activity of ARs in the presence of low androgen concentrations may be due to AR gene amplification, increased coactivator expression, activation by growth factors, and selection of somatic AR mutations; the AR pathway is amplified in up to 20% of CRPC tumors.[33, 34, 35, 36] In addition, many androgen-responsive genes become upregulated in CRPC cells. Such tumors may respond to more effective ADT that suppresses circulating androgens and/or intracellular androgen activity.

Orteronel is a selective, nonsteroidal inhibitor of 17,20-lyase, a key enzyme in the production of the common precursor molecules for male and female sex steroid hormones, which are synthesized in both the gonads and the adrenal glands. The selectivity of

orteronel for 17,20-lyase over 17-hydroxylase enzymatic activity may afford it a safer toxicity profile than agents that inhibit both steps in the testosterone synthesis pathway and may therefore affect cortisol precursor synthesis. By disrupting the synthesis of testosterone but potentially not cortisol, orteronel could offer a more favorable therapeutic index in CRPC. Whether orteronel confers therapeutic benefits in patients with advanced cancer is the focus of phase 3 and supportive studies.

1.2 Nonclinical Experience With Orteronel

In vitro pharmacology studies indicate that orteronel is a potent inhibitor of human and monkey 17,20-lyase activity. The enzyme activities of both 17,20-lyase and 17-hydroxylase are associated with *CYP17*, with the specific enzyme activities likely depending on the phosphorylation state of the protein, and on available substrates and cofactors within the adrenal cortex. In vitro, orteronel suppressed androgen production in monkey adrenal cells, human adrenocortical tumor cells, and mouse and rat testicular cells. In vivo, orteronel potently suppressed serum testosterone and dehydroepiandrosterone (DHEA) production and, to a lesser extent, cortisol concentrations in intact and castrated male monkeys. Detailed information regarding the nonclinical pharmacology and toxicology of orteronel can be found in the Investigator's Brochure (IB).

At high exposures, orteronel has been associated with myocardial atrophy and necrosis in rats but has produced neither adverse cardiac or cardiovascular events nor histopathological changes in beagle dogs and cynomolgus monkeys. Data from 4-, 13-, and 26-week rat studies demonstrate an exposure threshold under which no adverse cardiac effects occur, even when daily dosing is extended to 26 weeks.

Orteronel induced histopathological hepatic changes, including centrilobular hepatocyte vacuolization, in rats at ≥ 10 mg/kg/day and in monkeys at 100 mg/kg/day. These hepatocellular changes were generally mild and lacked corroborative evidence of increased liver enzyme concentrations in plasma. Generally reversible, toxicologically significant findings were observed in the reproductive organs and the adrenal glands of animals treated with orteronel; these changes were considered secondary to hormonal shifts produced by the pharmacological action of orteronel.

1.3 Orteronel Clinical Experience

Seven phase 1 clinical trials have been completed with orteronel in healthy male subjects: 2 single-ascending oral dose studies using an immediate-release (IR) tablet formulation

(01-02-TL-700-001 and TAK-700/CPH-001), 1 single- and multiple-ascending oral dose study using a modified-release capsule formulation (TAK-700/EC-102), 1 relative bioavailability study of 2 IR tablet formulations (T1 and T2 formulations) (Study C21002), 1 crossover study on the effect of food on the absorption of orteronel (Study C21007), 1 study on the absorption, distribution, metabolism, and excretion of orteronel (Study C21008), and 1 crossover, bioequivalence study of 2 IR tablet formulations (T2 and T3 formulations [Study C21009]).

The key observations from the studies in healthy subjects and those in patients with advanced mCRPC are that:

- Orteronel has dose-proportional, single-dose and multiple-dose pharmacokinetics (PK). The PK of orteronel is linear. The steady-state PK profile of orteronel dosed twice daily (BID) allows for consistent inhibition of adrenal androgen and testosterone production throughout the day. Renal clearance accounts for at least one-third of the elimination of orteronel.
- Based on testosterone and dehydroepiandrosterone sulfate (DHEA-S) data in healthy subjects and in patients with mCRPC whose baseline serum concentrations of testosterone were in the castrate range (< 50 ng/dL), doses of orteronel at 300 mg BID or above appear to be highly effective for androgen inhibition. Orteronel 200 mg BID appears to be a less effective dose.
- Selectivity of orteronel inhibition of 17,20-lyase versus 17-hydroxylase activity is relative and appears to depend on orteronel dose. At orteronel doses < 300 mg BID, there is little evidence of 17-hydroxylase inhibition. Loss of selectivity, ie, partial inhibition of cortisol synthesis in response to ACTH stimulation and associated activation of the ACTH adrenal axis, is apparent in some men at 300 and 400 mg BID. At 600 mg twice daily, some inhibition of cortisol synthesis is clinically evident with below-normal serum cortisol concentrations and impaired cortisol responses to ACTH stimulation. Concomitant prednisone with orteronel doses at 400 mg or above appears to suppress ACTH and thus diminish endocrine adverse events related to 17-hydroxylase inhibition. Concomitant prednisone, through suppression of basal ACTH activity, is expected to support inhibition of adrenal androgen production.
- Orteronel appears to be generally well tolerated in both healthy subjects and in patients with mCRPC. According to preliminary data from the ongoing phase 1/2 study in patients with mCRPC (TAK-700_201):

- As of November 2010, the most frequently reported treatment-emergent adverse events (TEAEs) reported by 9 or more of the 26 patients in the phase 1 portion of the study were fatigue, nausea, constipation, anorexia, back pain, and headache. Grade 3 TEAEs experienced by 2 or more patients in phase 1 included fatigue (4 patients); diarrhea (3 patients); and hypertension, lymphopenia, pain in extremity, and vomiting (2 patients each). The most frequently reported TEAEs reported by 15 or more of the 96 patients (15%) in the phase 2 portion of the study were fatigue, nausea, constipation, diarrhea, anorexia, headache, hot flush, muscle spasms, dizziness, back pain, and hyperglycemia. Grade 3 TEAEs experienced by 2 or more patients in the phase 2 portion of the study included fatigue (9 patients), hypokalemia (5 patients), hyperglycemia (4 patients), diarrhea (3 patients), blood creatinine increased, hydronephrosis, hyponatremia, international normalized ratio (INR) increased, pneumonia, maculo-papular rash, and acute renal failure (2 patients each). Non-serious skin rash has been observed in patients at doses of 300 mg BID or higher. None of the skin rash cases required hospitalization. As of 19 July 2010, decreases in LVEF greater than 10% have been observed in 8 (5 Grade 1; 2 Grade 2; and 1 not graded) of 99 patients in Study TAK-700_201. See the IB for detailed safety information.

- The PSA response is the principal surrogate of efficacy in the ongoing TAK-700_201 study. The efficacy of orteronel based on PSA responses after 3 or more 28-day cycles of therapy was similar for dose regimens of 300 mg BID or higher. As of January 2011, 12 of 15 patients (80%) in the phase 1 portion of the study who received orteronel ≥ 300 mg for ≥ 3 cycles and had a 3-month (ie, 12-week) PSA determination had PSA decreases ≥ 50%, of whom 4 had reductions ≥ 90%. Interim data for patients in phase 2 are qualitatively similar, with 42 of 81 patients (52%) achieving a 50% PSA response by 12 weeks. The results confirm that orteronel dose regimens ≥ 300 mg BID are similarly effective regarding the PSA response rate.

Ongoing studies in patients with prostate cancer include:

- One phase 1/2 study in patients with chemotherapy-naïve mCRPC in the US (Study TAK-700_201)

- One phase 1 study in patients with CRPC (Study TAK 700/CPH-402) in Japan
- One phase 2 study in patients in the US with nonmetastatic CRPC (Study C21001)
- One phase 1/2 trial in patients with mCRPC in the US that combines orteronel with docetaxel and prednisone (Study C21003)
- One phase 1/2 trial in patients with CRPC in Japan and ex-Japan to characterize PK and pharmacodynamic response of orteronel plus prednisone (Study C21013)
- One phase 2 study to investigate the effects of orteronel plus prednisone on the QT/QTc interval in patients with mCRPC (Study C21012)
- One global, phase 3, randomized, placebo-controlled study that combines orteronel with prednisone in patients with mCRPC who have not received prior chemotherapy (Study C21004)

1.4 Study Rationale

Patients with mCRPC who have progressive disease following docetaxel-based therapy have limited chemotherapy options. Most often patients who are eligible for second-line chemotherapy receive mitoxantrone, an approved palliative treatment that improves Quality of Life (QOL), but not survival,[37, 38, 39] Cabazitaxel (Jevtana®), a second-generation taxane, given along with prednisone has been shown in a single randomized, open-label, phase 3 clinical trial to improve overall median survival compared with mitoxantrone plus prednisone in patients with progressive mCRPC following docetaxel-based therapy (15.1 months versus 12.7 months; HR 0.72).[40] In 2010, the US FDA approved cabazitaxel in combination with prednisone as second-line chemotherapy in patients with mCRPC. In January 2011, the Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion to recommend the granting of a marketing authorization for cabazitaxel in combination with prednisone or prednisolone as second-line chemotherapy in the European Union. However, taxane-based, second-line therapy is limited by the adverse event profile, which includes hematologic, cardiac, and peripheral neuropathy events. Additional phase 3 studies are planned to identify an optimal dose of cabazitaxel in men with mCRPC that would maintain the survival benefit while reducing the adverse event risk.[41, 42] Abiraterone acetate, an irreversible steroidal CYP enzyme 17 (CYP17) inhibitor of both the 17,20-lyase and 17-hydroxylase activities approved for patients with mCRPC who have received prior docetaxel, prolonged overall survival (OS) in patients with mCRPC who had previously

received docetaxel chemotherapy.[43, 44] Furthermore, abiraterone acetate showed improvement in progression-free survival and a trend in OS in chemotherapy-naïve mCRPC patients.[45] However, toxicities attributed to a syndrome of secondary mineralocorticoid excess have been noted with abiraterone and require administration of a mineralocorticoid receptor antagonist or glucocorticoid to suppress ACTH.[29] Enzalutamide, an androgen receptor inhibitor, was recently approved in the US for treatment of mCRPC in docetaxel-treated patients after showing improvement in OS compared with placebo in patients with mCRPC who had previously received docetaxel chemotherapy.[46, 47] The goal of this study is to determine if orteronel plus prednisone can improve the survival of patients with mCRPC progressing during or after docetaxel-based chemotherapy by inducing maximal androgen deprivation.

1.4.1 Dose Selection

The orteronel dose selected for the phase 3 studies in mCRPC is 400 mg BID with concomitant prednisone 5 mg BID. Orteronel 400 mg BID is a dose at which significant declines in serum PSA, testosterone, and adrenal androgen levels have been observed in the TAK-700_201 study. Although 400 mg BID is not the maximum tolerated dose for orteronel, non-dose-limiting but significant fatigue occurred in men treated at the 600-mg BID dose level, indicating that the higher dose is not expected to be well tolerated. The selection of the 400-mg twice-daily dose, the highest that is expected to be tolerated, gives the greatest potential for antitumor activity. Although significant declines in serum PSA, testosterone, and adrenal androgen levels have been observed in patients treated at both the 300-mg BID and 400-mg BID dose levels, it is not known whether decreases in the serum levels will be associated with similar reductions in testosterone and adrenal androgen levels in the bone and other sites of disease in patients. To maximize potential for antitumor activity, it is appropriate to select 400 mg BID, the higher of the 2 doses, for the phase 3 studies in mCRPC. Orteronel 400 mg BID will be administered in combination with prednisone 5 mg BID in the studies in mCRPC. Dosing in combination with prednisone will provide additional potential for efficacy and prevent the compensatory ACTH elevation that has been observed in some patients treated at 400 mg BID in the TAK-700_201 study.

1.4.2 Continuation of Study Drug Treatment Following Radiographic Disease Progression

Patients will be allowed to continue study drug following radiographic disease progression, so that very low androgen levels are maintained, potentially slowing the rate of subsequent tumor growth. Continuation of conventional ADT following disease progression is

recommended to prevent increased circulating androgen levels from interacting with the androgen receptor, which remains active in patients with progressive CRPC. Maintaining castrate levels of testosterone with continued ADT despite the development of CRPC is recommended in both the National Comprehensive Cancer Network (NCCN) and the European Association of Urology (EAU) guidelines for treatment of prostate cancer.[48, 49] This is based on the understanding that the androgen receptor remains active and reports that an increase in circulating androgens from castrate levels observed in patients receiving conventional ADT could accelerate tumor growth.[50, 51] It is therefore likely that increases in androgen levels following discontinuation of the androgen synthesis inhibitor orteronel could also promote tumor growth.

1.4.3 The Role of Prednisone

Role of Prednisone as Treatment for mCRPC

Prednisone administered as a single agent has antitumor activity as well as palliative effects on pain and quality of life (QOL) in patients with mCRPC. Corticosteroids (ie, prednisone, dexamethasone, or hydrocortisone) have been shown in both phase 2 and phase 3 studies in patients with mCRPC to have antitumor activity, positive disease palliation, improvement in pain and QOL, and minimal toxicity.[52] In phase 2 studies with single-agent corticosteroids, 50% prostate specific antigen (PSA) declines have been reported in 34% to 79% of patients, with time to progression of 2 to 9 months.[52, 53, 54, 55] In phase 3 studies with glucocorticoids as a control arm, 50% PSA responses have been documented in 16% to 22% of patients with time to progression of 2.3 to 3.8 months.[52, 56, 57] Response durations of greater than 1 year and prolonged symptomatic benefits have been reported.[52]

Role of Concomitant Prednisone for Orteronel Administration

As a treatment strategy, prednisone represents a minimally toxic therapy with several potential benefits for patients with mCRPC: activity against PC with a positive influence on QOL, prevention of development of drug resistance, and prevention of mineralocorticoid surge. In patients treated with other 17-hydroxylase inhibitors or in patients with congenital deficiency of 17-hydroxylase enzyme, inhibition of 17-hydroxylase results in transient falls in adrenal cortisol production with a compensatory rise in ACTH. Increased corticosterone, resulting from increased ACTH, may compensate for the fall in cortisol and prevent the emergence of adrenal insufficiency; however, increased ACTH may be associated with increased adrenal androgen precursors. The addition of low-dose glucocorticoids

(prednisone) blocks the physiological rise in ACTH and thus supports ongoing inhibition of adrenal androgen synthesis.

Similarly, elevated ACTH results in increased concentrations of the aldosterone precursors deoxycorticosterone (DOC) and 18-DOC that may cause hypertension or edema. This effect is also blocked by low-dose glucocorticoids. Elevations in ACTH levels have occurred in some patients at doses of 400 mg BID and have been more pronounced at 600 mg BID. This suggests that concomitant glucocorticoid administration with orteronel at doses ≥ 400 mg BID is likely necessary to support ongoing inhibition of adrenal androgens and to prevent or diminish certain potential adverse events related to the orteronel mechanism of action.

1.4.4 Concomitant Therapy Selection

Use of Concomitant Gonadotropin-Releasing Hormone Analogue

Orteronel inhibition of residual levels of circulating (adrenal) androgens is most effective if used in conjunction with surgical or medical castration because blockade of testosterone synthesis normally results in a feedback increase of luteinizing hormone, which in turn promotes testosterone synthesis. Consequently, all patients in this study will receive concomitant GnRH analogue therapy or will have previously undergone orchiectomy, which is considered to be the standard of care for patients with CRPC, and have a testosterone concentration of < 50 ng/dL.

1.4.5 Circulating Tumor Cells (CTCs)

Recent advances in the detection and analysis of CTCs has provided insights into the process of cancer cell metastasis, and provided a noninvasive means for assessing the prognosis and therapeutic response for patients with cancer. Circulating tumor cells are epithelial in origin and can be captured from whole blood using an antibody directed against the epithelial adhesion molecule EpCAM and magnetic bead separation technologies.[58] Investigations in breast, colorectal, and prostate cancer have shown that the number of CTCs in whole blood can serve as a prognostic marker.[58, 59] Patients with metastatic CRPC who have ≥ 5 CTCs per 7.5 mL of whole blood have a shorter OS and PFS than those patients who have < 5 CTCs.[60] In addition, recent data suggests that CTC enumeration may be a better predictor of patient OS than PSA decrement.[61] Molecular analysis of CTCs may also provide further insight into the underlying mechanisms of metastasis and drug resistance.

1.4.6 Rationale for Genotyping and Assessment of Biomarkers in Archived Tumor Tissue

Emerging data from studies of mCRPC are better defining the molecular mechanisms underlying the development of tumor sensitivity and resistance to hormone deprivation. Evidence indicates that upregulation of the AR gene can result in increased sensitivity to androgens. Hormone-driven expression of the *ERG* oncogene after fusion with *TMPRSS2* occurs in 30% to 70% of therapy-naïve PCs.[62] Hormone-dependent overexpression of *ERG* may persist in CRPC; tumors having *TMPRSS2:ERG* mutations may represent a subgroup of PCs that remain sensitive to *CYP17* blockade. Assessment of *ERG* rearrangements in therapy-naive CRPC tumors shows a significant association between *ERG* gene status and the magnitude of PSA decline ($p = 0.007$) in CRPC patients treated with abiraterone acetate.[63] Two potential mechanisms of resistance to *CYP17* blockade are AR mutations and loss of phosphatase and tensin homolog (PTEN), which could result in constitutive phosphorylation of the AR, leading to ligand-independent activation.[64, 65, 66]

Based on these observations, *TMPRSS2:ERG* translocation, AR, and PTEN mutation status in tumor cells will be assessed in tumor tissue as available from patients treated with orteronel. In addition, if warranted by PK, safety, and/or efficacy data, genomic DNA single nucleotide polymorphisms (SNPs) will be examined in the *CYP17* gene or in other genes thought to play a role in predicting the safety or efficacy of orteronel. The purpose of testing the archival tumor tissue specimens for DNA and blood samples for germline DNA is to identify biomarkers that will predict patient subpopulations that are more likely to respond to orteronel or have significant severe safety events. The biomarkers will be studied in germline DNA isolated from blood and DNA isolated from formalin-fixed, paraffin-embedded archival tumor blocks of tissue collected either at the time of initial diagnosis or during a subsequent procedure as part of the patient's standard of care. The genetic biomarkers being evaluated from tumor blocks or tumor samples are specific to a given tumor type and not germline DNA. In addition, CTCs remaining after completion of enumeration procedures will be assayed for the presence or absence of these genetic variations. These data may come from a combination of information from this study and from future confirmatory studies conducted with orteronel in patients with prostate cancer. As new data emerge over the course of this trial, additional biomarkers may be examined based on new scientific findings related to the 17,20-lyase pathway, the effects of testosterone lowering and PC biology, or to the type and number of safety events that are observed. The studies performed on the collected samples will add to our knowledge of

whether and, if so, which biomarkers might predict patient responses to orteronel. This can lead to better treatment options for patients with prostate cancer.

1.5 Risks and Benefits

GnRH therapy is considered the standard of care in this study and will be managed as background therapy for the patients participating in this study. The potential risks of orteronel and prednisone are outlined below.

1.5.1 Potential Benefits

Potential benefits of orteronel treatment are discussed in Section 1.1. A short summary of efficacy observed to date is provided in Section 1.3.

1.5.2 Identified Risks

Orteronel

To date, clinical data with orteronel have been collected in phase 1 studies in healthy subjects and in the phase 1 and 1/2, open-label studies in patients with different stages of prostate cancer. The identified risks associated with orteronel treatment include, but are not limited to nausea, vomiting, fatigue, hypertension, and non-serious skin rash. To mitigate the inherent risks in clinical studies of orteronel, patients are evaluated frequently while they are receiving treatment. See the IB and Safety Management Attachment (SMA) for detailed safety information.

1.5.3 Potential Risks

Orteronel

Due to its mechanism of action, orteronel treatment may elicit adverse events typically associated with androgen deprivation therapy (decreased bone mineral density, hyperglycemia, and prolonged QTc interval). Other potential risks include decreased left ventricular ejection fraction, hepatotoxicity, or adrenal insufficiency. See the IB and SMA for detailed safety information.

Androgen Deprivation Therapy

Patients in this study will be receiving ADT at study entry and will have castrate levels of testosterone. Certain risks have been associated with ADT: osteopenia and osteoporosis,[67, 68, 69] metabolic syndrome (hyperglycemia, central obesity),[70, 71] cardiovascular disease,[72,

[73, 74, 75] and other adverse events (hot flushes, decreased libido, negative impact on health-related QOL, impact on cognitive performance, fatigue, lack or loss of energy, loss of initiative, mood swings, and increased clinical depression and anxiety scores).[76, 77, 78, 79, 80, 81] With the exception of treatment-related fatigue, it is unknown if any of these risks will be altered by treatment with orteronel.

Androgens shorten the QT interval, which explains why the QT intervals in women and hypogonadal men tend to be longer than those in eugonadal men.[82] As expected, prolonged QT intervals have been observed in men with prostate cancer treated with either GnRH agonists or antagonists, although few men had markedly prolonged intervals (ie, > 500 msec).[83, 84, 85]

Prolongation of the QTc interval has been reported as an AE for some patients taking orteronel. No dose-related association or apparent effect with orteronel administration on ECG morphology was identified. Patients with QTc intervals > 460 msec are excluded from the clinical trial.

Other

Decreases in left ventricular ejection fraction (LVEF) have been observed in some (8 of 99) patients enrolled in Study TAK-700_201. These findings were in the setting of significant variation in LVEF measurements within the study. No correlated trends in patient symptoms, electrocardiograms, or cardiac enzymes have been defined. Additional functional data are being collected on patients on study drug to assess cardiac function.

As of 29 September 2012, 4 SAEs of pancreatitis and 20 SAEs of elevated pancreatic enzymes were reported for patients with prostate cancer receiving orteronel. All of these cases were considered related to study drug by the investigator. The role of orteronel in these cases remains unclear and a causal relationship between orteronel and pancreatitis has not been established. See the IB for detailed safety information.

Adrenal insufficiency has been reported for 1 patient in the 600-mg orteronel BID-plus-prednisone cohort in the phase 2 portion of Study TAK-700_201. Adrenal insufficiency may occur, especially in men with decreased adrenal reserve or in men who have acutely discontinued supplemental glucocorticoids.

T-1358043, a process impurity, drug product degradant, and minor metabolite of orteronel, tested positive for genotoxicity in laboratory tests and could potentially pose a risk to human

subjects. The potential clinical implications of these laboratory results are that any resulting genetic or chromosomal change could potentially lead to secondary malignancy and raise the risk of heritable defects to offspring.

2. STUDY OBJECTIVES

See the STUDY DEFINITIONS for specific term descriptions.

2.1 Primary Objective

The primary objective is to determine if orteronel plus prednisone improves OS.

2.2 Key Secondary Objectives

The key secondary objectives are:

- To determine if orteronel plus prednisone improves radiographic progression-free survival (rPFS)
- To determine if orteronel plus prednisone improves 50% PSA response at 12 weeks
- To evaluate if orteronel plus prednisone improves pain response at 12 weeks

2.3 Other Secondary Objectives

Other secondary objectives are:

- To assess the safety of orteronel plus prednisone
- To determine if orteronel plus prednisone improves 50% and 90% PSA response rates
- To determine if orteronel plus prednisone improves time to PSA progression
- To assess the relationship between changes in CTC counts and other clinical endpoints, such as OS and time to disease progression
- To determine tumor response rate and duration of tumor response in patients with tumor lesions that are measurable by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria

- To assess time to pain progression, best pain response, time to pain response, and duration of pain response
- To assess change in global health status as measured by the patient-reported outcome (PRO) instrument the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)
- To collect blood orteronel concentration data for use in a future integrated PK analysis

2.4 Exploratory Objectives

The exploratory objectives are:

- To assess archival tumor specimens for candidate biomarkers predictive of orteronel antitumor activity including, but not limited to, the *TMPRSS2:ERG* fusion gene
- To evaluate polymorphisms in the *CYP17* gene and other germline genes implicated in the safety or efficacy of orteronel
- To assess the functioning and symptom QOL subscales of the EORTC QLQ-C30
- To evaluate medical resource utilization (MRU) and calculate utility values using a preference-based PRO instrument (European Quality of Life 5-Dimensional [EQ-5D])

3. STUDY ENDPOINTS

See the STUDY DEFINITIONS for specific term descriptions.

3.1 Primary Endpoint

The primary endpoint is OS.

3.2 Key Secondary Endpoints

The key secondary endpoints are:

- rPFS

- 50% PSA response at 12 weeks
- Pain response rate at 12 weeks

3.3 Other Secondary Endpoints

The other secondary endpoints are:

- AEs, physical examinations, vital signs, weight, ECOG performance status, cardiac assessments, and clinical laboratory evaluations
- 50% PSA response at any time during the study, 90% PSA response at 12 weeks and at any time during the study, and best PSA response at any time during the study
- Time to PSA progression
- Changes in CTC counts
- Changes in target lesions in patients with measurable tumors by RECIST 1.1 criteria
- Time to pain progression, time to pain response, best pain response, and duration of pain response
- Health-related Quality-of-Life (HRQOL) response rate as measured by the 2-item global QOL index of the EORTC QLQ-C30
- Population pharmacokinetics of orteronel using sparse sampling time points

3.4 Exploratory Endpoints

The exploratory endpoints are:

- Presence or absence of the *TMPRSS2:ERG* fusion gene, and possibly other candidate biomarkers predictive of orteronel antitumor activity, in archival tumor specimens
- The presence or absence of polymorphisms in germline genes related to the safety or efficacy of orteronel, such as the presence or absence of the A2 allele of the *CYP17* gene
- Disease-specific QOL, as measured by a utility instrument (EQ-5D) score

- Mean change from the baseline QOL assessment as measured by the functioning and symptom QOL subscales of EORTC QLQ-C30

- MRU based on the number of medical care encounters as measured by the EQ-5D

4. STUDY DESIGN

Orteronel tablets and placebo tablets will be subsequently referred to as study drug.

4.1 Overview of Study Design

This phase 3 study will be conducted utilizing a randomized, double-blind, multicenter design to evaluate orteronel plus prednisone, compared with placebo plus prednisone, with continued ADT, in the treatment of men with mCRPC. Patients must have evidence of disease progression during or after receiving a total of ≥ 360 mg/m^2 docetaxel within a 6-month period. Patients who were clearly intolerant to docetaxel or have progressive disease before receiving ≥ 360 mg/m^2 are also eligible if they have received ≥ 225 mg/m^2 of docetaxel within a 6-month period and meet the other study entry criteria.

The patient population will consist of adult men who have histologically confirmed or cytologically confirmed adenocarcinoma of the prostate, received 1 or 2 lines of prior chemotherapy of which 1 must have included docetaxel, and documented progressive metastatic disease, despite castrate levels of testosterone (< 50 ng/dL). Patients may have, but are not required to have, opioid-requiring bone pain. Prior ketoconazole, abiraterone, aminoglutethimide, or orteronel therapy will not be allowed. Any other therapies for prostate cancer, except for GnRH analogue therapy, such as progesterone, medroxyprogesterone, progestins (megesterol), or 5-alpha reductase inhibitors (eg, finasteride or dutasteride) must be discontinued 2 weeks before the first dose of study drug.

Approximately 1,083 patients will be randomized to receive orteronel tablets plus prednisone or placebo tablets plus prednisone in a 2:1 ratio. Patients will receive study drug (orteronel 400 mg or matching placebo tablets) twice daily until radiographic disease progression is documented (see STUDY DEFINITIONS). Each 28-day treatment cycle is composed of continuous twice-daily study drug plus prednisone treatment. The study drug will be discontinued early if a patient experiences study drug-related toxicities judged by the

investigator to outweigh the benefits of the study drug. Patients may discontinue therapy at any time.

Upon the recommendation of the independent data monitoring committee (IDMC) to unblind the study, patients receiving placebo will be allowed to crossover to orteronel treatment. Patients who remain on orteronel treatment will continue with their scheduled cycle visits.

Patients will return for the regularly scheduled study visits during the treatment and short-term follow-up portions of the study for as long as they 1) continue to take study drug (treatment), or 2) discontinue study drug but have not yet experienced disease progression (short-term follow-up). Patients may remain on study drug after disease progression and return for scheduled visits until they receive subsequent antineoplastic therapy. Unscheduled visits may occur between treatment cycles as required. For example, symptomatic pain progression should result in an interim unscheduled visit, as would ongoing Grade 2 or worse AEs.

The short-term follow-up portion of the study will no longer apply to patients at the time of unblinding. All patients will be followed for collection of information on any subsequent antineoplastic therapies and for survival (long-term follow-up) after discontinuing the treatment/short-term follow-up portion of the study. Long-term follow-up will continue until death or discontinuation of the study by the sponsor.

Patients will attend an End of Treatment (EOT) visit 30 days after receiving their last dose of study drug and will continue to be followed for other follow-up assessments specified in the Schedules of Events. Patients discontinuing study drug prior to radiographic disease progression will continue to be assessed for radiographic disease progression during the short-term follow-up portion of the study.

Pain evaluation (using the Brief Pain Inventory-Short Form [BPI-SF]) will include quantified assessments of intensity, frequency and duration, degree of discomfort, location, and likely relationship to PC (versus prior therapy or comorbidities). The pain response endpoint will be assessed at each visit and based on the prior 24-hour pain assessments using the BPI-SF worst pain score, rated on a scale from 0 to 10. Time to pain progression will be based on pain assessments using the worst pain item on the BPI-SF rated on a scale from 0 to 10, collected as outlined in the Schedules of Events. Analgesic use will also be documented as concomitant medications, the recalled level of analgesic use during the 24 hours prior to pain assessment when progressing to Step II or Step III analgesics (refer to

STUDY DEFINITIONS and Section 15.2) will also be used to define pain progression. Patients who experience new onset cancer-related pain will have a confirmation assessment obtained at least 3 but not more than 5 weeks later. Patients who experience new or worsening pain between scheduled visits should be seen at an unscheduled visit, if necessary, particularly after Cycle 7, Day 1 or when the next scheduled visit is more than 4 weeks in the future. Similarly, between study visits, patients may report the new onset of significant, possibly cancer-related pain, and an unscheduled visit for BPI-SF evaluation and treatment if necessary will then be arranged.

Health-related QOL will also be evaluated through the patient self-reported instrument EORTC QLQ-C30 and an assessment of patient utilities with EQ-5D. In addition to assessing selected symptoms, these instruments elucidate the effects of disease on physical, social, psychological/emotional, and cognitive functioning. EQ-5D, but not EORTC QLQ-C30, will continue to be assessed after unblinding.

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.02.[86] Adverse events will be assessed, and laboratory values, vital signs, ECGs, and estimation of ejection fraction determined by MUGA scan or ECHO (the same modality should be used for a patient throughout the study) will be obtained to evaluate the safety and tolerability of orteronel.

Radiographic evaluations (computed tomography [CT] scan and/or magnetic resonance imaging [MRI] of the abdomen and pelvis, and bone scans) will be employed to assess the status of the patient's underlying disease at screening and as outlined in the Schedules of Events. Radiographic evaluations will not be collected routinely after study unblinding, but will be left to the discretion of the investigator based on clinical need.

Serial blood samples will be collected to quantify PSA and for scheduled safety and endocrine laboratory assessments. Archived tumor material and a CTC sample will be collected to assess the presence of the *TMPRSS2:ERG* fusion gene and other biomarkers predictive of orteronel antitumor activity, as appropriate. Evaluation of the utility of these potential biomarkers of orteronel-mediated antitumor activity may require analysis of the data from this study in combination with data from other clinical studies of orteronel. In addition, a blood sample for assessment of germline DNA polymorphisms will be collected from patients who consent to this optional procedure. Studies of germline polymorphisms in *CYP17* have been linked to PC risk and may play a role in outcome after therapy with

orteronel. Analysis of these exploratory biomarkers may refine the understanding of the most appropriate therapies for patients with prostate cancer.

Two interim analyses for OS are planned for this study. Full details of the interim analyses are provided in Section 8.1.9.

4.2 Number of Patients

Following screening, approximately 1,083 patients will be randomized into this study from approximately 400 study centers worldwide.

4.3 Duration of Study

It is expected that the study will last approximately 36 to 38 months until reaching the final analysis of the OS endpoint. Patients will be followed for survival until 80% of patients have died or are lost to follow-up.

5. STUDY POPULATION

Confirmation of eligibility must be obtained from the sponsor or designee following review and approval of a "Patient Eligibility Checklist" prior to randomization. See Section 7.4. After unblinding, patients who are crossing over from placebo to orteronel treatment must meet the criteria listed in Section 5.3 (criteria in Section 5.1 and Section 5.2 no longer apply).

5.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Male patients 18 years or older.
2. Voluntary written consent, given before performance of any study-related procedure not part of standard medical care, and with the understanding that consent may be withdrawn at any time without prejudice to future medical care.
3. Adenocarcinoma of the prostate histologically or cytologically confirmed.
4. Metastatic disease radiographically documented by CT/MRI or bone scan.

5. Progressive disease based on PSA and/or radiographic criteria, defined as 1 or more of the following:

    - Radiographic disease progression based on RECIST 1.1 (refer to Section 15.1) in patients with measurable soft tissue lesions. For patients with bone disease, progression will be assessed following recommendations by the Prostate Cancer Working Group (PCWG2; refer to Section 15.1); appearance of 2 or more new lesions on bone scan, confirmed, if necessary, by other imaging modalities (such as CT scan or MRI) if results of the bone scans are ambiguous.

    - PSA progression is defined as an increase in PSA, as determined by 2 separate measurements taken at least 1 week apart and confirmed by a third. If the third measurement is not greater than the second measurement, then a fourth measurement must be taken and must be greater than the second measurement for the subject to be eligible for randomization in the study. Furthermore, the confirmatory PSA measurement (ie, the third or, if applicable, fourth PSA measurement) must be ≥ 2 ng/mL. Notes: Determination of PSA progression can be based on results from a local laboratory. The PSA value obtained from the central laboratory during the screening process does not have to be used in the determination of PSA progression, but that value should be at least greater than the first PSA used for determination of PSA progression. If a patient has received prior antiandrogen therapy (eg, bicalutamide, MDV-3100), PSA progression must be evident and documented after discontinuation of antiandrogen therapy.

6. Prior surgical castration or concurrent use of an agent for medical castration (eg, GnRH analogue) with testosterone at screening < 50 ng/dL.

7. Screening PSA ≥ 2 ng/mL. (Screening PSA value must be obtained from the central laboratory.)

8. Must have received prior docetaxel therapy:

    - Must have received ≥ 360 mg/m^2 of docetaxel within a 6-month period. Patients who were clearly intolerant to docetaxel or develop progressive disease before receiving ≥ 360 mg/m^2 are also eligible if they have received at least 225 mg/m^2 of docetaxel within a 6-month period and meet the other study entry criteria.

- Have progressive disease during or following 1 or 2 regimens of cytotoxic chemotherapy, 1 of which must have included docetaxel. (A regimen is when docetaxel is administered either as a single agent or in combination with other therapies.)

9. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (see Section 15.3).

10. Screening clinical laboratory values as specified below:

    - Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) must be ≤ 3 × the upper limit of normal (ULN).

    - Total bilirubin ≤ 1.5 × ULN.

    - Estimated creatinine clearance using the Cockcroft-Gault formula must be > 40 mL/minute (see Section 15.4).

    - Absolute neutrophil count (ANC) ≥ 1500/μL and platelet count ≥ 100,000/μL.

11. Patients, even if surgically sterilized (ie, status postvasectomy), who:

    - Agree to practice effective barrier contraception during the entire study treatment period and for 4 months after the last dose of study drug, or

    - Agree to completely abstain from heterosexual intercourse.

12. Screening calculated ejection fraction of ≥ 50% by multiple gated acquisition (MUGA) scan, or by echocardiogram (ECHO). (The same modality should be used for a patient throughout the study.)

13. Stable medical condition, including the absence of acute exacerbations of chronic illnesses, serious infections, or major surgery within 28 days prior to randomization, and otherwise noted in other inclusion/exclusion criteria.

14. Life expectancy of 6 months or more based on general health and prostate cancer disease status as judged by the investigator.

5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Prior therapy with orteronel, ketoconazole, abiraterone, or aminoglutethimide.

2. Known hypersensitivity to compounds related to orteronel, orteronel excipients, prednisone, or GnRH analogue.

3. Any other therapies for prostate cancer, except for GnRH analogue therapy, such as progesterone, medroxyprogesterone, progestins (megesterol), or 5-alpha reductase inhibitors (eg, finasteride or dutasteride), must be discontinued 2 weeks before the first dose of study drug.

4. Exposure to radioisotope therapy within 4 weeks of receiving the first dose of study drug; exposure to external beam radiation within 4 weeks of receiving the first dose of study drug.

5. Documented central nervous system metastases.

6. Treatment with any investigational compound within 30 days prior to the first dose of study drug or ongoing active participation in another experimental trial related to the treatment of PC. (Patients who are in long-term follow-up following active treatment in other trials are eligible.)

7. Current spinal cord compression, current bilateral hydronephrosis, or current bladder neck outlet obstruction. Note: Patients with definitive local therapy for urinary tract obstruction, eg, with stents, may be eligible after a review by the study medical monitor.

8. Diagnosis of or treatment for another systemic malignancy within 2 years before the first dose of study drug, or previously diagnosed with another malignancy and any evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

9. History of myocardial infarction, unstable symptomatic ischemic heart disease, ongoing arrhythmias of Grade > 2 (NCI CTCAE, version 4.02),[86] or thromboembolic events (eg, deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events) or any other cardiac condition (eg, pericardial

effusion restrictive cardiomyopathy) within 6 months prior to first dose of study drug. Chronic stable atrial fibrillation on stable anticoagulant therapy is allowed.

10. New York Heart Association Class III or IV heart failure (see Section 15.5).

11. ECG abnormalities of:

    - Q-wave infarction, unless identified 6 or more months prior to screening
    - QTc interval > 460 msec

12. Uncontrolled hypertension despite appropriate medical therapy (blood pressure [BP] of greater than 160 mmHg systolic and 90 mmHg diastolic at 2 separate measurements no more than 60 minutes apart during the Screening visit). Note: Patients may be rescreened after adjustment of antihypertensive medications.

13. Known human immunodeficiency virus (HIV) infection, active chronic hepatitis B or C, life-threatening illness unrelated to cancer, or any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with participation in this study. Patients will be tested for hepatitis B or C or HIV infection during screening if they are considered by the investigator to be at higher risk for these infections and have not been previously tested, or if testing is required by the independent ethics committee or institutional review board.

14. Likely inability to comply with the protocol or cooperate fully with the investigator and site personnel.

15. Known gastrointestinal (GI) disease or GI procedure that could interfere with the GI absorption or tolerance of orteronel, including difficulty swallowing tablets.

16. Uncontrolled nausea, vomiting, or diarrhea despite appropriate medical therapy.

17. Those patients whose prostate cancer is confined to just the prostate bed or immediate adjacent tissue.

5.3 Criteria for Patients Crossing Over to Orteronel Treatment

Patients who are crossing over from placebo to orteronel treatment must meet all of the criteria listed below. Completion of a second eligibility checklist is not required.

1. Voluntary written consent, given before performance of any study-related procedure not part of standard medical care, and with the understanding that consent may be withdrawn at any time without prejudice to future medical care.

2. Stable medical condition at the time of crossover.

3. Screening clinical laboratory values as specified below (screening labs for patients who were taking placebo at the time of unblinding may use central laboratory values from their last cycle):

   - Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) must be ≤ 3 × the upper limit of normal (ULN).

   - Total bilirubin ≤ 1.5 × ULN.

   - Estimated creatinine clearance using the Cockcroft-Gault formula must be > 40 mL/minute (see Section 15.4).

4. Patients, even if surgically sterilized (ie, status postvasectomy), must:

   - Agree to practice effective barrier contraception during the entire study treatment period and for 4 months after the last dose of study drug, or

   - Agree to completely abstain from heterosexual intercourse.

5. No known hypersensitivity to compounds related to orteronel, orteronel excipients, prednisone, or GnRH analogue.

6. No likely inability to comply with the protocol or cooperate fully with the investigator and site personnel.

6. STUDY DRUG

6.1 Test Article

6.1.1 Orteronel and Placebo Supply

200 mg active orteronel tablets will be supplied by the sponsor and labeled in accordance with all applicable regulations. Placebo tablets will be identical in shape and size to the orteronel active tablets.

6.1.2 Gonadotropin-Releasing Hormone Analogue and Prednisone Supply

GnRH analogue therapy is supplied as a commercially available dosage formulation. Please refer to the GnRH prescribing information.

Prednisone (or equivalent) will be labeled as investigational material and will be provided to investigative sites by the sponsor. Packaging labels will fulfill all requirements specified by governing regulations.

6.2 Study Drug Administration

Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients may remain on study drug after disease progression until they pursue alternative antineoplastic therapy. Similarly, patients who discontinue study drug due to AEs may continue in the study and undergo the scheduled study assessments until disease progression or until they decide to pursue alternative antineoplastic therapy, whichever occurs first.

Study drug will be given orally twice daily (BID) throughout each treatment cycle of the study, except for dose modifications. Study drug should be taken BID at the same time each day, approximately 12 hours apart, and may be taken with or without food. Missed doses of study drug may be taken later, provided that the time of dosing is at least 6 hours before the next scheduled dose. Note: Patients who experience Grade 1 or 2 nausea or vomiting may be advised to take study drug with or following meals.

Patients will be given a diary to record study drug dosing. If a dose is missed entirely, the missed dose will be recorded as “not taken”.

Study drug compliance will be calculated for each patient by taking into account whether a patient takes all study drug as instructed. Patients will be instructed to bring study drug to each patient visit for reconciliation. The number of tablets taken will be calculated by

subtracting the number of tablets returned from the number of tablets dispensed. The dosing diary will provide supporting information if necessary.

Prednisone will be administered 5 mg BID, orally, throughout each treatment cycle. It will be taken at the same time as study drug.

6.3 Dose-Modification and Supportive Care Guidelines

The investigator should determine if an AE is related to study drug. Adverse events considered at least possibly related to study drug may require a dose reduction (Table 6-1), a temporary hold, or permanent discontinuation.

Depending on the AE, following partial or complete resolution of symptoms, the dose of study drug may be increased at 2-week intervals to the next higher dose level until the original dose level has been reached. Guidelines for modification of dose based on the severity of the AE are provided in this section.

6.3.1 Dose Levels for Study Drug

The study drug dose levels to be applied for all dose modifications are defined in Table 6-1.

Table 6-1 Dose Modifications for Study Drug

Dose Level	Dose (Tablets[a] and Timing of Administration)	Number of Tablets
0	400 mg BID (200 mg × 2 BID)	2 tablets BID
– 1	200 mg AM and 400 mg PM (200 mg × 1 in the morning; 200 mg × 2 in the evening) Note: A 100-mg tablet is not available.	1 tablet in the morning, 2 tablets in the evening.
– 2	200 mg BID (200 mg × 1 BID)	1 tablet BID
– 3	None (dosing hold or temporary discontinuation)	None

Abbreviations: AM = in the morning; BID = twice daily; PM = in the evening.

a Study drug is blinded. Tablets contain either placebo (0 mg) or orteronel (200 mg). The dose adjustments will be recorded in terms of possible orteronel dose in mg.

6.3.1.1 Dose Modifications

Dose modifications should be based on NCI CTCAE (version 4.02).[86] Dose reduction for Grade 1 AEs is not required. Dose reduction for Grade 2 events should be considered only when the AE is judged by the investigator to be clinically intolerable. For Grade ≥ 2 AEs, the dose modification should follow the Dose Reduction and Re-escalation guidelines (Sections 6.3.1.2 and 6.3.1.3, respectively). For events of fatigue, nausea, vomiting,

diarrhea, hypertension, rash, hyperglycemia, worsening renal function, and adrenal insufficiency, refer to the Specific Guidelines for Possible Study Drug-Related Toxicities (Section 15.6).

Note that in all cases, dosing with prednisone 5 mg BID should be continued at the time of dose modification of study drug, including Dose Level –3 (dosing hold).

6.3.1.2 Criteria for Study Drug Initial Dose Reduction

Dose modifications for Grade 3 or 4 events are described below.

- Asymptomatic Grade 3 or 4 laboratory findings may not require dose modification (ie, dose hold or reduction) especially if these are not considered to be clinically significant or related to study drug. The decision to modify the dose should be based on the investigator's clinical judgment. Dose modifications for Grade 3 or 4 hyperglycemia should follow the guidelines in Table 15-12 in Section 15.6.5.

- Grade 3 or 4 AEs that are considered at least possibly related to study drug require a dosing hold (Dose Level –3) for a minimum of 2 weeks. For a clinically intolerable Grade 2 AE that is considered at least possibly related to study drug, the dose should be decreased by 1 dose level for 2 weeks. The investigator should identify other potential causes of any AE or laboratory abnormality, and consult with the medical monitor for any questions regarding the need for dose modification.

Once the dose is reduced, reassessment is required at least every 2 weeks until the event is resolved or stabilized; however, the frequency of reassessment should be increased as clinically indicated. If the grade worsens at any time, the dose should be decreased in accordance with the guidelines for the worst grade.

6.3.1.3 Criteria for Study Drug Dose Re-escalation

6.3.1.3.1 Re-escalation for Grade 2 Intolerable Adverse Events

Re-escalation of study drug after resolution or improvement of a Grade 2 intolerable AE considered at least possibly related to study drug will follow the criteria below:

1. If the AE grade improves to Grade 0, 1, or Grade 2 tolerable AE, re-escalate the dose by 1 level.

2. If the AE remains at Grade 2 and is still intolerable after 2 weeks, decrease the dose by another level.

3. If the event worsens to Grade ≥ 3, hold study drug for 2 weeks followed by a reassessment. Follow the re-escalation guidelines for Grade 3 or 4 AEs as described in Section 6.3.1.3.2.

Note, the above refers to AEs considered at least possibly related to study drug. Reassess the AE after 2 weeks or sooner if the AE worsens. Continue to reassess at least every 2 weeks until the event is resolved or stabilized. Continue to adjust the study drug dose until the dose is optimally titrated. If the dose has been held (dose level –3) for 6 weeks, study drug should be discontinued permanently.

6.3.1.3.2 Re-escalation of Study Drug Following a Grade 3 or 4 Adverse Event

Re-escalation following a Grade 3 or 4 AE considered at least possibly related to study drug will follow the criteria below:

1. If the AE grade improves to Grade 0, 1, or Grade 2 tolerable AE, re-escalate the study drug dose by 1 level.

2. If the AE improves to Grade 2 but is still intolerable, hold dosing for another 2 weeks. Follow the re-escalation guidelines for Grade 2 intolerable AEs as defined in Section 6.3.1.3.1.

3. If the AE is Grade 3 or 4 after 2 weeks, hold dosing for another 2 weeks and reassess again after 2 weeks.

Note, the above refers to AEs considered at least possibly related to study drug. Reassess the AE after 2 weeks or sooner if the AE worsens. Continue to reassess at least every 2 weeks until the event is resolved or stabilized. Continue to adjust the study drug dose until the dose is optimally titrated. If the dose has been held (Dose Level –3) for 6 weeks, study drug should be discontinued permanently.

6.3.1.4 Criteria for Discontinuation of Study Drug

If the event, considered at least possibly related to study drug, persists at Grade ≥ 3 for more than 6 weeks, permanently discontinue treatment with study drug. The study drug dose may also be discontinued permanently if judged by the investigator to be clinically intolerable despite dose reduction, and the dose cannot be optimally titrated.

6.3.2 Specific Guidelines for Possible Study Drug-Related Toxicities

For events of fatigue, nausea, vomiting, diarrhea, hypertension, rash, hyperglycemia, worsening renal function, and adrenal insufficiency, refer to the Specific Guidelines for Possible Study Drug-Related Toxicities (Section 15.6).

6.4 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the treatment and short-term follow-up portion of the study:

- Any investigational agent other than study drug
- Other antineoplastic therapy, except for GnRH analogues
- Other hormonal therapies, including estrogens, progesterone, medroxyprogesterone, progestins (megesterol), or herbal products
- Ketoconazole
- Aminoglutethimide
- Cabazitaxel (Jevtana®)
- Enzalutamide (XTANDI®)
- Abiraterone (Zytiga®)
- Sipuleucel-T (Provenge®)
- 5-alpha reductase inhibitors (eg, finasteride or dutasteride)
- Chronic systemic corticosteroids other than prednisone or commercially available equivalent administered as described in this protocol

Patients must be instructed not to take any medications, including all over-the-counter products such as vitamins, minerals, and other dietary supplements, without first consulting with the investigator.

6.5 Permitted Concomitant Medications and Procedures

Medications (other than those specifically prohibited) may be administered to patients for maintenance of a condition existing at study randomization or a new condition that develops while on study, including, but not limited to, the following:

- Agents for the treatment of osteoporosis or control of bone metastases, including denosumab, oral or intravenous bisphosphonates, or calcitonins, as recommended according to local practice guidelines
- Warfarin
- Aspirin
- Antihypertensive medications
- Medications for the control of diabetes
- Anti-emetics
- Anti-diarrheals
- Lipid-lowering agents
- Antibiotics
- Pain medications, including, but not limited to, nonsteroidal anti-inflammatory drugs and opioids

6.6 Precautions and Restrictions

It is not known what effects orteronel has on human pregnancy or development of the embryo or fetus. Therefore, patients should avoid impregnating a female partner. Patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, or

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

6.7 Management of Overdose

An overdose is defined as deliberate or accidental administration of study medication at a dose above that which is assigned to that individual patient. In the event of drug overdose, the principal investigator should be notified immediately and the patient observed closely for adverse effects. The patient should be treated symptomatically as appropriate, and the incident of overdose and related AEs and/or treatment should be documented in the patient's medical record. Patients who may have overdosed and who have possible manifestations of adrenal insufficiency may be treated acutely with parenteral or oral steroids as tolerated.

6.8 Blinding and Unblinding

At the recommendation of the Independent Data Monitoring Committee (IDMC) upon review of the interim analysis (Section 9.1), the study may be unblinded based on evaluation of safety and efficacy parameters. After unblinding and crossover of patients is complete, the procedures performed during the blinded portion of the study will no longer apply.

To maintain the blind, all study site personnel will be blinded to the treatment assignments for the duration of the study.

Kit assignments will be obtained through the interactive voice response system (IVRS) according to the procedures outlined in the Study Manual. Information regarding the kit assignments will be kept securely at the sponsor's location or designee per its standard operating procedures.

Records of the patient number, the date study drug was dispensed, and the kit assignment will be maintained by the study site.

If the treatment assignment must be revealed for the safety of the patient or to treat an AE, the investigator will contact the medical monitor (contact information is in the Study Manual). A decision to break the blind must be reached by the medical monitor or designee, and the investigator. The investigator or designee may break the blind through the IVRS independent of the medical monitor only if it is considered to be an emergency by the investigator. The event requiring breaking the blind must be documented in the electronic

case report form (eCRF). In addition, the patient will be discontinued from further study drug administration in this study.

6.9 Description of Investigational Agents

Orteronel and matching placebo tablets are manufactured by Takeda Pharmaceutical Company, Ltd., Osaka, Japan. Orteronel tablets and placebo tablets will be supplied as pale red, film-coated tablets and will contain 200 mg or 0 mg of orteronel, respectively. Further details are provided in the orteronel IB.

6.10 Preparation, Reconstitution, and Dispensation

Orteronel is an antihormonal drug with anticancer activity. As with other potentially toxic compounds, caution should be exercised when handling study drug.

6.11 Packaging and Labeling

Orteronel and placebo tablets will be packaged in round, white, high-density polyethylene bottles with a child-resistant cap with induction seal. Each bottle of active orteronel or placebo study medication will be labeled with either a single-panel or multi-language booklet label containing pertinent study information, country-specific requirements, and a caution statement.

Prednisone (or commercially available equivalent) may be provided in bottles or blister packs and will be labeled per all requirements specified by governing regulations.

6.12 Storage, Handling, and Accountability

Orteronel and placebo study medication should be stored in the original dispensing bottles according to labeled conditions.

Prednisone (or equivalent) should be stored in its original packaging. Prednisone supplied in bottles should be stored under the conditions indicated on the product label. Prednisone supplied in blister packs should be stored as indicated on the label.[87]

Drug supply must be kept in an appropriate, limited-access, secure place until it is dispensed to the enrolled patients, returned to the sponsor, or forwarded to the sponsor's designee for destruction. Drug supplies will be counted and reconciled at the site before being returned to the sponsor. Drug supplies may be destroyed on site if requested by the sponsor.

The investigator must maintain 100% accountability for all study medication received and dispensed during his or her entire participation in the study. If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator must maintain a current inventory (drug accountability log) of all study medication delivered to the site, inventory at the site, and patients' use records. This log must accurately reflect the drug accountability of the study medication at all times. The following information will be recorded at a minimum: protocol number and title, name of the investigator, site identifier and number, description of the study medication, expiry and/or retest date, date and amount dispensed, and date and amount returned to the site by the patient, including the initials of the person dispensing and receiving the study medication. The log should include all required information as a separate entry for each patient to whom study medication is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform clinical study material accountability and reconciliation before clinical study materials are returned to the sponsor or its designee for destruction. The investigator will retain the original documentation regarding clinical study material accountability, return, and/or destruction, and copies will be sent to the sponsor.

The investigator will be notified of any expiry date or retest date extension of clinical study material during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired clinical study material for return to the sponsor or its designee for destruction.

7. STUDY CONDUCT

7.1 Study Personnel and Organizations

The contact information for the medical monitor, the central and any additional clinical laboratories, the IVRS provider and other vendors, and the contract research organization team can be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

7.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become

part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/independent ethics committee (IEC). It is not envisioned that prisoners or other populations that might be subject to coercion or exploitation will be enrolled into this study.

7.3 Treatment Group Assignments

Patient eligibility will be established before randomization into the study as patients will not be permitted to re-enroll. A centralized randomization and stratification using IVRS will be used. Patients will be randomized strictly sequentially at a center as they become eligible for randomization and will be stratified as detailed in Section 8.1.2. If a patient discontinues from the study, that randomization code will not be reused, and the patient will not be allowed to re-enter the study.

7.4 Study Procedures

Refer to the Schedules of Events for timing of assessments. The first dose of study drug must be administered within 7 days of randomization. Additional details are provided as necessary in the sections that follow.

During the screening process, a "Patient Eligibility Checklist" must be completed and submitted by the investigator for review and approval by the sponsor or designee prior to patient randomization. Completion of the eligibility checklist is necessary to verify that the patient has met all of the inclusion and exclusion criteria (Sections 5.1 and 5.2, respectively). Source documentation that demonstrates that the patient has documented PD at study entry (Section 5.1, Inclusion Criterion #5) must be provided along with the checklist. Unless specifically requested, additional source documentation does not need to be submitted with the checklist for the assessment of eligibility related to the other inclusion and exclusion criteria. Completion of a second Patient Eligibility Checklist is not required at the time of study unblinding.

7.4.1 Informed Consent

Each patient, or the patient's legal representative, must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard medical care. Informed consent will be collected from all patients at the time of study unblinding.

7.4.2 Patient Demographics

The date of birth, race, and ethnicity of the patient will be recorded during screening.

7.4.3 Medical History

During the Screening period, a complete medical history will be collected for each patient. The history will emphasize the background and progress of the patient's prostate cancer and include a description of all prior therapies for the disease. The Gleason score at diagnosis, if available, will be recorded. Complete medical histories will not be collected after the study is unblinded.

7.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the Schedules of Events.

7.4.5 Patient Height and Weight

Height and weight will be measured at the times specified in the Schedules of Events. Height will not be measured after the study is unblinded.

7.4.6 Vital Signs

Vital sign measurements include diastolic and systolic BP, heart rate, and temperature. Blood pressure will be taken after the patient has been in a seated position for 5 minutes. Vital signs will be performed at the times specified in the Schedules of Events.

7.4.7 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded from the first dose of study drug through the EOT visit. See Sections 6.4 and 6.5 for a list of medications and therapies that are prohibited and/or allowed during the study. Oral morphine equivalent (OME) score will be calculated from the narcotic medication information collected.

7.4.8 Adverse Events

Monitoring of AEs, both nonserious and serious, will be conducted throughout the study as specified in the Schedules of Events. Refer to Section 10 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and serious adverse events (SAEs).

If a patient develops a non-localized rash, additional descriptive information will be collected, such as the appearance, distribution, extent of skin involvement, and any associated symptoms (eg, pruritus). See Section 15.6.4.

7.4.9 Cardiac Assessments

Cardiac assessments will be performed as specified in the Schedules of Events and as clinically indicated. Assessments will include 12-lead ECGs and MUGA scans or ECHO; the same modality should be used for a patient throughout the study, and assessments should be performed at the same institution whenever possible.

7.4.10 ECOG Performance Status

ECOG performance status (see Section 15.3) will be assessed as specified in the Schedules of Events.

7.4.11 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed by a central laboratory. Local laboratories may be used as required for acute management of TEAEs. Handling and shipment of clinical laboratory samples are outlined in the Study Manual.

All clinical laboratory samples will be obtained as specified in the Schedules of Events:

Hematology

- Hemoglobin
- Hematocrit
- HbA1c
- White blood cell count with differential
- ANC (machine results acceptable)
- Platelet count

Serum Chemistry

- Blood urea nitrogen
- Creatinine
- Total bilirubin
- Uric acid
- Lactate dehydrogenase
- Phosphate
- Lipid profile (HDL, LDL, triglycerides)
- Albumin
- Alkaline phosphatase
- AST
- ALT
- Glucose
- Sodium
- Potassium
- Calcium
- Chloride
- Carbon dioxide
- Magnesium
- Cholesterol
- Amylase
- Lipase

Steroid Hormone Panel

- DHEA-S
- Testosterone
- Cortisol
- Corticosterone
- ACTH

7.4.12 Serology

Serum samples for HIV and hepatitis B and C testing, when testing is required, will be processed and analyzed at local laboratories.

7.4.13 Disease Assessment

Prestudy Documentation of Progressive Disease:

Patients must have documented PD either by radiographic or PSA criteria as defined in Inclusion Criterion #5 in Section 5.1.

Both radiographic PD and PSA PD must be assessed to evaluate eligibility; however, only 1 criterion (radiographic PD or PSA PD) must be met for Inclusion Criterion #5. For the radiographic PD assessment, 2 sets of scans using the same imaging modality (ie, CT/MRI or bone scan) and taken at separate time points are required to document radiographic disease progression during or following the patient's most recent antineoplastic therapy. Radiographic disease assessment is not formally required after study unblinding but is at the discretion of the PI with scans performed as per standard of care. Patients are not required to have disease progression to cross over from placebo to orteronel treatment.

PSA will be assessed at time points shown in the Schedules of Events. Results will be available to the investigators, but not to the sponsor. PSA results will not be withheld from the sponsor after study unblinding.

Scans (CT/MRI) of the chest, abdomen, and pelvis and radionuclide bone scans will be used to monitor and assess disease response and progression, as described in the Schedules of Events. The imaging modality for each patient must remain constant throughout the study. Additional scans should be performed at the investigator's discretion if progression is suspected or to confirm the existence of bone lesions. Radiographic disease progression will be defined as described in the STUDY DEFINITIONS.

Radiographic images will be maintained at the site, and test results and physician's findings will be filed in each patient's source documentation.

A central imaging center will review all films, images, and scans that are used in the documentation of progression. The review will be performed on a "real time" basis at the time of possible disease progression. Thus, investigators will be encouraged to await central imaging center review of images or scans that may indicate or confirm radiographic disease progression before recommending to the patient any treatment or management options, such as discontinuation from study drug treatment to pursue alternative antineoplastic therapy. A separate radiography manual and instructions for archiving and submitting images or films for review will be provided. The review of films, images, and scans by a central imaging center will not be performed after the study is unblinded, but scans may be performed by sites at the discretion of the investigator based on clinical need.

7.4.14 Tumor Specimen Measurements

Formalin-fixed, paraffin-embedded archived tumor specimens collected at the time of initial diagnosis or during any subsequent procedure (tumor blocks or tumor material sectioned onto slides) or CTCs collected specifically for tumor biomarker analysis or collected for enumeration and subsequently fixed for further evaluation will be collected as described in the Schedules of Events and assayed for the presence of candidate biomarkers predictive of orteronel antitumor activity, including the *TMPRSS2:ERG* fusion gene. All patients screened for the study will be asked to provide access to archival tumor specimens, if available, that have been stored from a previous procedure or biopsy. If archival tumor tissue is available, and consistent with local regulations, patients would be required to provide an archival tumor specimen for biomarker assessment as described.

Archived tumor specimens will be shipped to a central laboratory for processing. Tumor material sectioned onto 10 to 20 slides may also be submitted. Tumor block specimen material will be accessioned and any remaining material returned to sites on a quarterly basis. Archival tumor specimens sectioned onto slides will not be returned. Full instructions for processing and shipping of archived tumor specimens are provided in the Study Manual.

The archival tumor specimens will be only be identifiable by patient number and initials; sample labeling will be de-identified prior to statistical analysis. The archival tumor specimen will be stored securely at the sponsor's location or a designated central laboratory vendor until 10 years after orteronel receives approval from a governmental agency or until the orteronel program is stopped. The storage period for these samples may be adjusted by country in accordance with local regulatory and/or legal requirements for the storage of

research samples. Such changes will be reflected in the IRB/IEC country-specific informed consent form. After that time, the samples will be properly destroyed by the central laboratory or designee following approval by the sponsor. The investigator will keep records linking the patient identity with the samples for the time required by applicable law. Patients may also request at any time that their samples and material obtained from their samples be destroyed by contacting the investigator.

7.4.15 Circulating Tumor Cells

Blood samples for CTC counts will be collected as described in the Schedules of Events. The timing of CTC blood sample collection may be changed if the emerging data indicate that an alteration in the sampling scheme is needed to better characterize the effect of orteronel. The number of CTC blood samples may be reduced but not increased based on emerging data during the course of the study. Instructions for processing and shipping blood samples for CTC counts are provided in the Study Manual. At the central laboratory, the collected CTCs may be fixed for further evaluation as described in Section 7.4.14. At the Cycle 1, Day 1 visit only, 2 samples will be collected (1 sample for enumeration and 1 sample for biomarkers).

To maintain the integrity of this blinded study, results from the CTC analyses will not be returned to the investigative sites during the active study period. Samples for measurement of CTCs will not be collected after the study is unblinded.

7.4.16 Whole Blood Sample for Germline DNA

A venous whole blood sample (3 mL) for analysis of germline DNA will be collected at Cycle 1, Day 1 (before the study is unblinded) from patients who consent to this optional collection. This is an optional part of the study and will not be a mandatory requirement for the continued participation of a patient in the study. Patients who agree to participate in this optional part of the study must consent specifically for this procedure. The DNA sample will be assayed using a Good Laboratory Practices (GLP)-grade assay for the presence or absence of a single nucleotide polymorphism in the *CYP17* gene. CYP17 is the target of orteronel. If, over the course of this study, emerging scientific data indicate that other genes may be responsible for predicting response to orteronel or that may predict a safety event to orteronel, then those genetic variants may also be examined.

Individual blood samples for germline DNA analysis, including the result of the analyses, and corresponding identifying information will be identified only by a code in a computer

database. Identifying information, such as the patient initials or patient number, will not appear on the tube in which the blood is stored upon processing; instead only the code number will be visible. Once a sample is received, it will be logged into the electronic database. To de-identify the patient, an "I" will be entered in place of the patient number and "---" will be entered in place of the patient's initials.

The whole blood sample will be stored securely at the sponsor's location or its designated central laboratory vendor until 10 years after orteronel receives approval from a governmental agency or until the orteronel program is stopped. The storage period for these samples may be adjusted by country in accordance with local regulatory and/or legal requirements for the storage of research samples. Such changes will be reflected in the IRB/IEC country-specific informed consent form. After that time, the samples will be properly destroyed by the central laboratory or designee following approval by the sponsor. The investigator will keep records linking the patient identity with the samples for the time required by applicable law. Patients may also request by contacting the investigator at any time that their samples and material obtained from their samples be destroyed.

Directions for sample collection and handling can be found in the Study Manual.

Blood samples for germline DNA analysis will not be collected after the study is unblinded.

7.4.17 Pharmacokinetic Measurements

Blood specimens will be collected from each patient as described in the Schedules of Events. Only the PK samples obtained from orteronel-treated patients will be analyzed for the plasma concentrations of orteronel and its metabolite, M-I.

The actual date and time of each PK sample collection should be recorded accurately in the eCRF.

In addition, the following dosing information corresponding to each PK sample collection should be recorded in the eCRF:

- Time and dose of study drug taken by the patient on the day prior to PK sample collection and on the day of PK sampling (if the patient dosed himself on the morning of PK sampling).

The sampling schedule is outlined in the Schedules of Events. Instructions for collection and processing of the PK blood specimens are provided in the Study Manual.

To maintain the integrity of this blinded study, results from the PK analyses will not be returned to the investigative sites.

Blood samples for PK analyses will not be collected after the study is unblinded.

7.4.18 Pain Assessment

Pain assessments will be performed at study visits as described in the Schedules of Events. Patients who experience new or worsening pain between scheduled visits should be seen at an unscheduled visit, if necessary, particularly after Cycle 7, Day 1 or when the next scheduled visit is more than 4 weeks in the future. At the unscheduled visits, pain assessments should be completed and appropriate management instituted. In addition, patients who report new or worsening pain at either a regularly scheduled visit or are seen for pain at an unscheduled visit should have a follow-up visit 3 to 5 weeks later for confirmation of the pain progression and for appropriate pain management. During the first 6 cycles, this confirmation and pain management may be at the next scheduled visit (Day 1 of the next treatment cycle). After Cycle 7, Day 1, patients should be seen at an unscheduled visit within 3 to 5 weeks or at the next scheduled visit, whichever is earlier.

The Brief Pain Inventory-Short Form (BPI-SF) will be the principal pain assessment tool for this study. The BPI-SF contains 15 items designed to capture the pain severity ("worst," "least," "average," and "now" [current pain]), pain location, medication to relieve the pain, and the interference of pain with various daily activities including general activity, mood, walking activity, normal work, relations with other people, sleep, and enjoyment of life. The questionnaire employs a 24-hour recall period. The pain severity items are rated on a 0 to 10 scale, with 0 = no pain and 10 = pain as bad as you can imagine.

The PRO key secondary endpoint will be "pain response at 12 weeks" as measured by the worst pain item (Item 3) in the BPI-SF only.

The use of the single item, worst pain, is supported by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations for assessing pain in clinical trials and by the European Medicines Agency 2003 Guidance on Clinical Investigation of Medicinal Products for Nociceptive Pain issued by the Committee for Proprietary Medicinal Products.[88, 89, 90, 91] In addition, the newly released FDA Guidance uses the following example while discussing conceptual frameworks: "The conceptual framework of a PRO instrument may be straightforward if a single item is a reliable and valid measure of the concept of interest (eg, pain intensity). [92]"

Pain response is defined as the occurrence of 1 of the following and confirmed by an additional assessment, at least 3 weeks but not more than 5 weeks later:

- A ≥ 2 point reduction from baseline in BPI-SF worst pain score without an increase in analgesic use, or
- A 25% or more reduction in analgesic use from baseline without an increase in worst pain score from baseline.

The date of pain response is the date of the first measurement. Patients who have their first response detected at 12 weeks will be recorded as having "unconfirmed response" until the response is confirmed at least 3 weeks later.

Time to pain progression, time to pain response, best pain response, and duration of pain response are other secondary endpoints.

Pain progression is defined as the occurrence of 1 of the following and confirmed by an additional assessment, at least 3 weeks but not more than 5 weeks later:

1. The BPI-SF worst pain score is ≥ 4 with a ≥ 2 point increase over baseline in BPI-SF worst pain score with stable or increased analgesic use;
2. The BPI-SF worst pain score is ≥ 4 but not less than baseline with new or increased (relative to baseline) Step II or Step III analgesic use;
3. The BPI-SF worst pain score is ≤ 3 but not less than baseline with new or increased (relative to baseline) Step III analgesic use.

Analgesic use can be stable or increased according to the following definitions:

- Stable analgesic use is defined as less than a 25% change of the oral morphine equivalent (OME) dose from baseline.
- Increased analgesic use is defined as an increase of 25% or more in OME from baseline.

Confirmation at least 3 weeks later is not required if surgical treatment for pain, palliative radiation for pain, or subsequent antineoplastic therapy has been received prior to a confirmatory assessment (refer to Section 15.2 for a list of Step II and III analgesics).

At the time of each pain assessment including unscheduled visits (See Section 7.4.23), the patient will be queried regarding concomitant use of opioid analgesics, if any, as specified in the Schedules of Events. The patient-recalled amount of analgesic use during the 24 hours prior to pain assessment will be recorded on the opioid use and concomitant medication eCRFs.

A full BPI-SF instrument will be administered at each of the visits as specified in the Schedules of Events to collect the pain severity, location, and interference information with a 24-hour recall period. This must be completed prior to other assessments or study drug being administered. Note that the BPI-SF is not completed beyond Question 1 if the patient denies significant pain that may be related to his cancer.

Patients will complete the BPI-SF at each visit as specified in the Schedule of Events.

7.4.19 Quality of Life Assessment

The QOL instrument, EORTC QLQ-C30, will be administered as specified in the Schedules of Events.

The EORTC QLQ-C30 incorporates 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The time recall period for this instrument is 1 week (the week immediately preceding the assessment). It is a reliable and valid measure of health-related QOL in patients with cancer and takes about 11 minutes to administer. The instrument consists of a brief (30-item) questionnaire that has been validated and used in many countries.

The EORTC QLQ-C30 data will be collected as specified in the Schedules of Events, and it must be completed before other assessments are performed or study drug is administered.

EORTC QLQ-C30 data will not be collected after the study is unblinded.

7.4.20 Utility Measurement

Because oncology therapies may positively or negatively affect a subject's QOL, a common methodologic approach is used to quantify this effect by "quality-adjusting" survival in comparative treatment groups. The result, quality-adjusted life years (QALYs), is a measure of both the length and quality of life and is used as a measure of benefit in cost–utility

analysis. General PRO instruments, such as the EORTC QLQ-C30, are not designed to measure subject preferences (or utilities) in a way that is suitable for calculating QALYs. Therefore, a separate validated instrument, in this case the EuroQOL EQ-5D, will be used to quantify utilities to calculate QALYs for a cost–utility analysis.

The EQ-5D is a 5-item questionnaire and a "thermometer" visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) that will be administered as specified in the Schedules of Events. The utility measurement should be continually collected until the patient discontinues study drug.

7.4.21 Medical Resource Utilization Data Collection

During the treatment and short-term follow-up portions of the study (until the patient experiences radiographic disease progression), all medical care encounters will be collected from all patients regardless of the reason for the medical care encounter. Each time an AE or unscheduled physician visit occurs, MRU data will be captured. Examples of data to be collected are number of medical care encounters, such as inpatient/outpatient admissions, and major diagnostic and treatment procedures.

MRU data will not be captured after the study is unblinded.

7.4.22 Cost Assessment

The cost of treatment in each arm of the study will be assessed through the collection of MRU in each treatment arm of the study. Valuation of the costs will be undertaken separately.

The cost of treatment in each arm will not be assessed after the study is unblinded.

7.4.23 Unscheduled Visits

Unscheduled visits may occur between treatment cycles as required. Minimum assessments to be performed at unscheduled visits are described in the Schedules of Events. The EQ-5D questionnaire should be completed as the first assessment. Other assessments may be performed as clinically indicated at the discretion of the investigator.

7.4.24 Long-Term Survival Status

All patients will be followed for survival (long-term follow-up) after discontinuing the treatment /short-term follow-up portion of the study. Every 3 months (± 30 days from the

last dose of study drug), information on newly prescribed antineoplastic therapies will be collected as part of long-term follow-up as specified in the Schedules of Events. Long-term follow-up will continue until death or discontinuation of the study by the sponsor. Patients in short-term follow-up at the time of study unblinding will move to long-term follow-up.

7.5 Completion of Treatment

Patients will be considered to have completed study treatment if they receive study drug until radiographic disease progression (see STUDY DEFINITIONS section) or until discontinuation for unacceptable toxicity, withdrawal of consent, or death.

7.6 Completion of Study

Patients will be considered to have completed the study if they are followed until death or until the sponsor terminates the study.

7.7 Discontinuation of Treatment With Study Drug and Patient Replacement

Patients may receive study drug until:

- Withdrawal of consent
- Receipt of antineoplastic therapy other than study drug (or commercially available equivalent), including any experimental therapies
- Death

Study drug must be permanently discontinued for patients who initiate subsequent antineoplastic therapy. Patients who experience disease progression may remain on study drug until they receive subsequent antineoplastic therapy or other therapy. Patients who discontinue study drug will enter the long-term follow-up portion of the study per the Schedules of Events.

Treatment with study drug may also be discontinued for any of the following reasons:

- Adverse event
- Protocol violation
- Symptomatic deterioration

- Study terminated by the sponsor
- Withdrawal by subject
- Lost to follow-up
- Other

Within 30 days (+ 10 days) of the date of study drug discontinuation, all study procedures outlined for the EOT visit will be completed as specified in the Schedule of Events. The primary reason for study drug discontinuation will be recorded in the eCRF.

Patients who discontinue study drug will not be replaced.

7.8 Withdrawal of Patients From Study

A patient may be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Study terminated by the sponsor
- Withdrawal by subject
- Other

The consequence of the patient withdrawing consent is that no new information will be collected from the withdrawn patient or added to the existing data or any database. Collection will continue if the patient is withdrawn for another cause. In addition, survival information may be obtained from publicly-available records.

7.9 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

8. STATISTICAL AND QUANTITATIVE ANALYSES

A formal statistical analysis plan (SAP) will be developed and finalized before the formal interim analyses.

8.1 Statistical Methods

8.1.1 Determination of Sample Size

The primary objective of this study is to determine if orteronel plus prednisone improves OS compared with placebo plus prednisone in patients with mCRPC that has progressed during or following docetaxel-based chemotherapy. Assuming an exponential distribution for OS, a total number of 639 deaths is required with approximately 90% power to detect a hazard ratio of 1.32 (median survival of 15.8 months in the orteronel group versus 12 months in the placebo group) using a 2-sided log-rank test at a 5% overall significance level. A total of 1,083 patients will need to be randomized in a 2:1 ratio to receive either orteronel plus prednisone or placebo plus prednisone, assuming an average enrollment rate of 25 patients for the first 6 months, 65 patients per month thereafter, and a variable follow-up. Variable follow-up means that each patient who has not dropped out or died will be followed until the trial ends. Based on the enrollment assumption, the final analysis of OS is estimated to occur approximately 31 months from the enrollment of the first patient. This period includes a 21-month enrollment period and an additional 10-month follow-up period from the time of the enrollment of the last patient.

Two interim analyses for OS will be performed when approximately 320 deaths (one-half of the total expected deaths) and when 426 deaths (two-thirds of the total expected deaths) have occurred, with the opportunity to stop the trial for overwhelming evidence of efficacy or futility. These interim analyses (Section 8.1.9) will be tested at a significance level according to the O'Brien and Fleming type alpha spending functions.[93]

8.1.2 Randomization and Stratification

Eligible patients will be randomized to receive orteronel plus prednisone or placebo plus prednisone (with continued GnRH analogue therapy, as appropriate) in a ratio of 2:1, stratified by region (North America [US and Canada], Europe, rest of world) and BPI-SF worst pain score at screening (≤ 4 vs > 4).

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

- Safety population: The safety population is defined as all patients who receive at least 1 dose of any study drug. Patients will be analyzed according to the actual treatment they received. Patients who received any dose of orteronel will be included in the orteronel plus prednisone arm, and patients who did not receive any dose of orteronel will be included in the placebo plus prednisone arm, regardless of their randomized treatment.

- Intent-to-treat (ITT) population: The ITT population is defined as all patients who are randomized. Patients in this population will be analyzed according to the treatment they were randomized to receive, regardless of any errors of dosing.

- Per-protocol (PP) population: the PP population consists of all ITT patients who do not violate the terms of the protocol in a way that would affect the study outcome significantly, as determined by the medical monitor, who is blinded to study drug assignment. All decisions to exclude patients from the PP population will be made prior to the unblinding of the study.

- RECIST-evaluable population: The RECIST-evaluable population is defined as the subset of patients who have measurable disease by RECIST 1.1 at the baseline assessment.

8.1.4 Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and safety data will be included in data listings and tabulations. The relevance of missing sample data will be assessed. Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures. Details on any sensitivity analyses and data handling details regarding issues such as missing data will be discussed in the SAP.

8.1.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics, including age, race, weight, height, and other parameters, as appropriate, will be summarized by treatment groups using descriptive statistics only.

8.1.6 Efficacy Analyses

8.1.6.1 General Methodology

Summary tabulations will be presented by treatment group and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data. The Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable) will also be provided, along with their 2-sided 95% confidence intervals (CIs) for time-to-event data.

The SAP will be developed and finalized by the sponsor or its designee prior to unblinding of treatment assignment and the first interim analysis. The SAP will outline all data handling conventions and specify all statistical methods to be used for safety and efficacy data analysis.

Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the final clinical study report.

8.1.6.2 Analysis of Primary Efficacy Endpoint

The analysis of the primary endpoint, OS, will be based on the ITT population. The OS will be calculated from date of patient randomization to the date of patient death due to any cause. Patients without documentation of death at time of the analysis will be censored as of the date the patient was last known to be alive, or the data cut-off date, whichever is earlier. Two formal interim analyses for OS will be performed when approximately 320 deaths (one-half of the total expected deaths) and when 426 deaths (two-thirds of the total expected deaths) have occurred. A detailed description of the interim analysis can be found in Section 8.1.9.

A 2-sided, stratified log-rank test will be used to compare the treatment groups with respect to OS (see Section 8.1.2 for stratification factors). The test significance level at the interim analysis and final analysis is decided by the O'Brien-Fleming type of alpha spending function. In addition, an unadjusted stratified Cox model will be used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors. The Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

The proportional hazards assumptions will be examined, and sensitivity analysis using PP population will be conducted.

8.1.6.3 Analyses of Key Secondary Endpoints

In addition to the primary comparison of OS, there are 3 key secondary endpoints: 50% PSA response (PSA50) at 12 weeks, rPFS, and pain response at 12 weeks. The key secondary endpoints will be tested only once at 0.05 level when OS is significant. A fixed sequential testing procedure will be used to test the key secondary endpoints. PSA50 will be tested first. Then the Hochberg method will be used to test rPFS and pain response at 12 weeks in parallel. The details will be fully described in the SAP.

Fifty Percent Prostate-Specific Antigen Response at 12 Weeks

The number and percentage of patients who have a 50% PSA response at 12 weeks will be summarized by treatment groups. The PSA response rates between the 2 treatment groups will be tested using the Cochran-Mantel-Haenszel (CMH) chi-square test at a 5% significance level, stratified by the randomization factors. The CMH chi-square p-value and the relative risk, along with its 95% 2-sided CI, will also be provided. In addition, the absolute treatment difference in PSA response rates will be provided, along with the 95% 2-sided CI.

Radiographic Progression-Free Survival

Radiographic progression-free survival is defined as time from randomization to radiographic disease progression or death due to any cause, whichever occurs earlier. Radiographic disease progression-free survival will be analyzed in the same fashion as the primary endpoint. The stratified log-rank test will be used to compare the treatment effect and an unadjusted stratified Cox model will be used to estimate the hazard ratio and its 95% CIs for the treatment effect. The Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

Pain Response at 12 Weeks

The number and percentage of patients who have a pain response at 12 weeks will be summarized by treatment groups. The pain response rates between the 2 treatment groups will be analyzed in the same fashion as the PSA response rates. The CMH chi-square test will be used to compare the 2 treatment groups, stratified by randomization factors. In addition, the absolute treatment difference in pain response rates will be provided, along with the 95% 2-sided CI.

8.1.6.4 Analyses of Other Secondary Endpoints

Prostate-Specific Antigen Responses and Time to Prostate-Specific Antigen Progression

The number and percentage of patients who have a 90% PSA response at 12 weeks, those who have a 90% PSA response at any time during the study, and those who have a 50% PSA response at any time during the study will be summarized by treatment groups. The PSA response rates between the 2 treatment groups will be tested using the CMH chi-square test at a 5% significance level, stratified by the randomization factors. The CMH chi-square p-value and the relative risk, along with its 95% 2-sided CI, will also be provided. In addition, the absolute treatment difference in PSA response rates will be provided, along with the 95% 2-sided CI.

Duration of PSA response will be summarized descriptively. Kaplan-Meier survival curves will be presented for each treatment groups, and no formal statistical comparison will be performed for this endpoint.

Time to PSA progression will be analyzed in the same fashion as rPFS. The stratified log-rank test and an unadjusted stratified Cox model will be used to compare the 2 treatment groups, and Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

Quantitation of Circulating Tumor Cells

The number and percentage of patients who have a favorable CTC enumeration count (defined as < 5 counts/7.5 mLs of blood) at baseline and each scheduled assessment time point will be summarized descriptively by treatment groups.

The number and percentage of patients whose CTC enumeration meet the following criteria will be summarized descriptively at each scheduled assessment time point by treatment groups: convert from unfavorable (defined as ≥ 5 counts/7.5 mLs of blood) at baseline to favorable; convert from favorable at baseline to unfavorable; favorable at baseline and status unchanged; unfavorable at baseline and status unchanged.

The favorable CTC enumeration response rate is defined as the percentage of patients who convert from unfavorable at baseline to favorable. The response rates at Day 1 of Cycle 3 (8 weeks), Cycle 4 (12 weeks), Cycle 5 (16 weeks), Cycle 7 (24 weeks), Cycle 10 (36 weeks), and EOT between the 2 treatment groups will be analyzed in the same fashion

as the PSA response rates, stratified by the randomization factors. The CMH chi-square test will be used to compare the 2 treatment groups, stratified by the randomization factors. In addition, the absolute treatment difference in CTC response rates will be provided, along with the 95% 2-sided CI.

The relationship between changes in CTC counts and other clinical endpoints, such as OS and PFS, will be investigated in an exploratory fashion. The details of this analysis will be specified in the SAP.

RECIST-based Responses

The overall response rate (ORR) and duration of response (DOR; defined using RECIST 1.1 and PCWG2 criteria) will be calculated in the RECIST-evaluable population (Section 8.1.3). The ORR will be tabulated descriptively with 95% CIs. The DOR will be analyzed using standard survival analysis techniques based on Kaplan-Meier estimates. In addition, the comparison of ORR between the 2 treatment groups will be tested using the CMH chi-square test at a 5% significance level stratified by the randomization factors.

8.1.7 Safety Analysis

Safety will be evaluated by the incidence of TEAEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, ECOG performance status, ECG, cardiac ejection fraction test results (MUGA or ECHO), and clinical laboratory results using the safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

All TEAEs will be tabulated. A TEAE is defined as any AE that occurs after administration of the first dose of study drug and up to 30 days after the last dose of study drug, any event that is considered drug related regardless of the start date of the event, or any event that is present at baseline but worsens in severity after baseline or is subsequently considered drug related by the investigator. Adverse events will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class (SOC), high-level term (HT), and preferred terms (PTs) and will include the following categories:

- TEAEs
- Study drug–related TEAEs
- Grade 3 or higher TEAEs

- Grade 3 or higher drug-related TEAEs
- TEAEs resulting in study drug discontinuation
- SAEs, including study drug–related SAEs

The most commonly reported TEAEs (ie, those events reported by ≥ 10% of all patients) will be tabulated by HT and PT. A listing of treatment-emergent AEs resulting in study drug discontinuation will be provided.

Descriptive statistics for both the actual values and change from baseline values of the clinical laboratory parameters (hematology and chemistry) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters. Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE grade from baseline to the worst postbaseline value.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and weight over time will be tabulated by scheduled time point.

Eastern Cooperative Oncology Group performance status and change from baseline will be summarized.

All concomitant medications collected from first dose of study drug through the study period will be classified to PTs according to the World Health Organization Drug Dictionary.

Investigators' assessments of ECG monitoring (normal, abnormal and clinically significant, or abnormal and not clinically significant), including unscheduled or retested measurements, will be documented on the appropriate eCRF.

Additional safety analyses may be performed to most clearly establish rates of toxicities and further define the safety profile of orteronel. The baseline for crossover patients is after unblinding and just prior to the first dose of orteronel administration.

8.1.8 Analyses of Patient-Reported Outcomes

The PRO endpoint of pain response at 12 weeks is considered 1 of the 3 key secondary endpoints of this study (see Section 8.1.6.3). The analyses of other PRO endpoints are described below.

Quality of Life Assessment: HRQOL Response Rate

The global health status/QOL secondary endpoint will be measured as the HRQOL response rate at 12 weeks using the 2-item global health status index of the EORTC QLQ-C30 instrument. HRQOL response is defined as a 17-point increase from the baseline assessment on the QOL index, after the score has been linearly transformed to a 0 to 100 scale (see EORTC scoring manual and SAP for details). A confirmatory measurement obtained at least 3 weeks later will be required. The HRQOL response rates between the 2 treatment groups will be tested using the CMH chi-square test at a 5% significance level, stratified by the randomization factors. The CMH chi-square p-value and the relative risk, along with the 95% 2-sided CI will also be provided. In addition, the absolute treatment difference in HRQOL response rates will be provided along with the 95% 2-sided CI.

Additional Cumulative Distribution Function (CDF) analysis will also be used to compare QOL response differences between the two arms with respect to differences from baseline to 12 weeks and 24 weeks using the 2-item global health status index of the EORTC QLQ-C30 instrument. CDF does not require a pre-specified threshold for response. Kolmogorov-Smirnov test will be employed for the comparison of two arms.

Best Pain Response

The number and percent of patients who have a pain response will be summarized by treatment groups. The pain response rates between the 2 treatment groups will be analyzed in the same fashion as the PSA response rates. The CMH chi-square test will be used to compare the 2 treatment groups, stratified by the randomization factors. In addition, the absolute treatment difference in pain response rates will be provided, along with the 95% 2-sided CI.

Time to Pain Progression

Time to pain progression will be analyzed in the same fashion as the key PRO endpoint. The stratified log-rank test and an unadjusted stratified Cox model will be used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factors. The Kaplan-Meier survival curves and Kaplan-Meier medians (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

Time to Pain Response and Duration of Pain Response

Time to pain response and duration of pain response will be summarized descriptively. The Kaplan-Meier survival curves will be presented for each treatment group, and no formal statistical comparison will be performed for these endpoints.

EORTC QLQ-C30

Descriptive summaries of the observed data will be provided for EORTC QLQ-C30 at each scheduled assessment time point. Analysis of covariance (ANCOVA) models will be used to compare the treatment groups with respect to outcomes, controlling for the baseline score and stratification factors. Two-sided 95% CI will be calculated for the differences between the 2 treatment groups. Longitudinal models will also be examined for the treatment comparisons.

Health Economics Analysis Using MRU and Utility

The primary health economic outcome is cost–utility, defined as the difference in the total costs of the orteronel group versus the control group, divided by the difference in the QALYs accrued by patients in both study groups of the study.

Costs will be assigned to the medical care encounters and concomitant medications at the conclusion of the trial. These costs will be assigned by matching medical resource data collected on the MRU, Concomitant Medications, Adverse Event, Concomitant Procedures, and Serious Adverse Event Summary eCRFs to databases containing standardized costs for these resources.

Utilities will be calculated using the appropriate scoring algorithms for the EQ-5D. Average utilities for both treatment arms will be multiplied by the average survival in each group to determine QALYs.

The secondary health economic outcomes include: 1) cost–effectiveness analysis, defined similarly to cost–utility analysis with the exception that the denominator of the ratio is life-years gained (not quality-adjusted); 2) total costs by treatment; and 3) frequency of MRU by treatment.

The economic data will be analyzed using an intent-to-treat approach. Secondary analyses using patient populations defined by various measures of protocol compliance will also be

performed. Data for categorical variables will be presented as rates (N, number, percentage).

Data for continuous variables will be summarized using measures of central tendency and dispersion. Variables will be compared between the orteronel and the placebo groups using appropriate methods: CI, rather than p-values, will be emphasized.

8.1.9 Interim Analyses

Two formal interim analyses of OS are planned when approximately one-half (320) and two-thirds (426) of the total expected deaths (639) have occurred during the study. The interim analyses will be conducted at a significance level according to O'Brien and Fleming type alpha spending functions. Based on the projected number of deaths, the trial will be stopped for overwhelming efficacy at the first interim analysis if the observed p-value is ≤ 0.0031 and the trial would be stopped for futility if the observed p-value is ≥ 0.8343. At the second interim analysis, the trial will be stopped for overwhelming efficacy if the observed p-value is ≤ 0.0111 and the trial would be stopped for futility if the observed p-value is ≥ 0.4275. The trial may be stopped for clear evidence of efficacy or futility. If the study does not stop early at the interim analyses, a final p value of ≤ 0.0461 is required to be statistically significant at the final analysis of OS.

8.1.10 Other Exploratory Analyses

Tumor Biomarkers

The analysis of tumor specimens for candidate biomarkers of orteronel response including, but not limited to, *TMPRSS:ERG* fusion gene will be primarily descriptive in nature unless the data warrant further analysis.

Germline Polymorphisms

The analysis of germline polymorphisms will be primarily descriptive in nature unless the data warrant further analysis.

8.2 Population Pharmacokinetic Modeling

Plasma concentration-time data and the associated information of demographics, clinical laboratory test results, and concomitant medications obtained from this study will be combined with those from selected clinical studies for an integrated PK meta-analysis. Planning for and results of the PK meta-analysis will be described in a separate document.

9. STUDY COMMITTEES

9.1 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) will review safety and efficacy data at the interim analyses. The IDMC will provide a recommendation regarding study continuation based on the safety and efficacy parameters. In the event that the study is terminated early based on an IDMC recommendation, the sponsor will notify the appropriate regulatory authorities. In addition, the IDMC will periodically review safety data at regularly scheduled meetings prespecified in the IDMC charter. Intensive safety monitoring will be performed in the early portion of the study. The first formal safety review will occur after approximately 100 subjects have been randomized and received at least 1 cycle of study treatment. Subsequently, periodic safety reviews will also occur as prespecified in the IDMC charter.

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Event Definition

Adverse event means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

10.1.2 Serious Adverse Event Definition

Serious adverse event (SAE) means any untoward medical occurrence that at any dose:

- Results in death.

- Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).

- Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph below on planned hospitalizations).

- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).

- Is a congenital anomaly/birth defect.

- Is a medically important event. This refers to an AE that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE (version 4.02).[86] Clarification should be made between a SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a Leukocyte value of 1000 to 2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.1.3 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation. A serious pretreatment AE meets the criterion of a pretreatment event (as above) and satisfies any 1 of the 6 criteria specified for an SAE as shown in Section 10.1.2 (results in death, is life-threatening, requires hospitalization or prolongation of present hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is a medically important event).

10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.4 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 10.1) must be reported (see Section 10.4 for the period of observation) by the investigator to the Millennium Department of Pharmacovigilance's designee, PPD, (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Millennium. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information – North America & South America
PPD Pharmacovigilance
Fax: 1-888-488-9697
24-hour helpline: 1-800-201-8725

SAE Reporting Contact Information – Rest of World
PPD Pharmacovigilance
Fax: +44-122-337-4102
24-hour helpline: +44-122-337-4240

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE (version 4.02).[86] The criteria are provided in the Study Manual and also are available online at ctep.cancer.gov/reporting/ctc.html.

Relationship to study drug administration will be determined by the investigator responding yes or no to this question: Is there a reasonable possibility that the AE is associated with the study drug?

10.3 Reporting of Suspected Unexpected Serious Adverse Reactions

The sponsor will expedite the reporting of suspected unexpected serious adverse reactions to concerned regulatory authorities, independent ethics committees, and investigators in accordance with all relevant laws and regulations governing the reporting of adverse drug reactions from clinical trials.

For purposes of regulatory reporting, expectedness will be based on the orteronel IB.

10.4 Monitoring of Adverse Events and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the first dose of study drug through 30 days after treatment with the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first, and recorded in the eCRFs. That is, if a patient

begins a new antineoplastic therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started.

- Serious pretreatment events will be reported to the Millennium Department of Pharmacovigilance or designee from the time of the signing of the ICF up to first dose of study drug, but will not be recorded in the eCRF.

- Related and unrelated serious adverse events will be reported to the Millennium Department of Pharmacovigilance or PPD from the first dose of study drug through the last treatment visit (30 days after administration of the last dose of study drug) and recorded in the eCRFs. After this period, only related SAEs must be reported to the Millennium Department of Pharmacovigilance or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

10.5 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11. ADMINISTRATIVE REQUIREMENTS

11.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and the IB.

11.2 Data Quality Assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Study data will be entered into an eCRF by site personnel using a secure, validated,

web-based electronic data capture (EDC) application. The sponsor will have access to all data upon entry in the EDC application.

Study monitors will discuss instances of missing or uninterpretable data with the investigator for resolution. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

11.3 Electronic Case Report Form Completion

The sponsor or designee will provide the study sites with secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for whom they are responsible.

eCRFs will be completed for each study patient. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF.

The investigator, or designated representative, should complete the eCRF as soon as possible after information is collected.

The investigator must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for which he or she is responsible. The audit trail entry will show the user's identification information and the date and time of the correction.

The sponsor, or a designee, will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk or other electronic media will be placed in the investigator's study file.

11.4 Study Monitoring

Monitoring and auditing procedures developed or approved by the sponsor will be followed to comply with GCP guidelines.

All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner that ensures that patient confidentiality is maintained.

11.5 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or the sponsor, as allowed by local regulations.

11.6 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH GCP and all applicable regulatory requirements.

11.7 Patient Confidentiality

To maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by initials where permitted and/or by the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

11.8 Investigator Compliance

The investigator will conduct the trial in compliance with the protocol provided by the sponsor and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol are not to be made without agreement of both the investigator and the sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard or hazards to patients. The sponsor, or a designee, will submit all protocol modifications to the appropriate regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard or hazards to patients, the investigator will contact the sponsor, or a designee, if

circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

11.9 On-site Audits

Regulatory authorities, the IRB/IEC, and/or the sponsor may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

11.10 Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at the trial site is the responsibility of the investigator. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to the sponsor, or a designee (or disposal of the drug, if approved by the sponsor) will be maintained by the clinical site. The sponsor or its designee will review drug accountability at the site on an ongoing basis.

All material containing study drug will be treated and disposed of in accordance with governing regulations.

11.11 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

For Product Complaints,
call MedComm Solutions at
[redacted]
(US and International)

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to PPD (refer to Section 10.2)

11.12 Closure of the Study

Within 90 days of the end of the study, the sponsor will notify the competent authorities and the IRBs/IECs in all member states where the study is being carried out that the study has ended.

Within 1 year of the end of the study, a summary of the clinical trial results will be submitted to the competent authorities and IRBs/IECs in all member states involved in the study.

Study participation by individual sites or the entire study may be prematurely terminated if, in the opinion of the investigator or the sponsor, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or the sponsor by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete, and/or unevaluable data
- Determination of efficacy based on interim analyses
- Plans to modify, suspend, or discontinue the development of the study drug

Should the study be closed prematurely, the site will no longer be able to access the EDC application, will not have a right to use the EDC application, and will cease using the password or access materials once their participation in the study has concluded. In the event that any access devices for the EDC application have been provided, these will be returned to the sponsor once the site's participation in the study has concluded.

Within 15 days of premature closure, the sponsor must notify the competent authorities and IRBs/IECs of any member state where the study is being conducted, providing the reasons for study closure.

11.13 Record Retention

The investigator will maintain all study records according to the ICH GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and the sponsor notified.

12. USE OF INFORMATION

All information regarding orteronel supplied by the sponsor to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the sponsor. It is understood that there is an obligation to provide the sponsor with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of orteronel and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

Upon completion of the clinical study and evaluation of results by the sponsor, the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. A publications plan will be developed by the sponsor employees and study investigators. Subsequently, individual investigators may publish results from the study in compliance with their agreements with the sponsor.

A prepublication manuscript or abstract is to be provided to the sponsor a minimum of 30 days before the intended submission date of the manuscript or abstract to a publisher. Within 30 days after receipt by the sponsor of the notification, the sponsor shall inform the study centers whether it has objections to the publication for reasons including, but not limited to, those defined below:

- If patentable patient matter is disclosed, the publication shall be delayed for a period not to exceed 90 days from the sponsor's receipt of the proposed publication to allow time for the filing of patent applications covering patentable patient matter.

- If confidential information is contained in any proposed publication or public disclosure, such confidential information will be removed at the sponsor's request.

13. INVESTIGATOR AGREEMENT

I have read Protocol C21005 Amendment 9: A Phase 3, Randomized, Double-Blind, Multicenter Trial Comparing Orteronel (TAK-700) Plus Prednisone With Placebo Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer That Has Progressed During or Following Docetaxel-based Therapy

I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for GCP and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____
Principal investigator printed name

_____ _____
Principal investigator signature Date

_____

_____

_____
Investigational site or name of institution and location (printed)

14. REFERENCES

1. Cheng C, Akaza H, Chen KK, Moore MA, Naito S, Song JM, et al. Prostate cancer control--aims of the UICC Asia Regional Office Consortium. Asian Pacific Journal of Cancer Prevention: Apjcp 2006;7(3):350-68.
2. Park S, Bae J, Nam BH, Yoo KY. Aetiology of cancer in Asia. Asian Pacific Journal of Cancer Prevention: Apjcp 2008;9(3):371-80.
3. Chu KC, Tarone RE, Freeman HP. Trends in prostate cancer mortality among black men and white men in the United States. Cancer 2003;97(6):1507-16.
4. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. Jama 1999;281(17):1591-7.
5. Moul JW. Rising PSA after local therapy failure: immediate vs deferred treatment. Oncology (Williston Park) 1999;13(7):985-90, 993; discussion 993-5, 999.
6. Moul JW. Treatment of PSA only recurrence of prostate cancer after prior local therapy. Curr Pharm Des 2006;12(7):785-98.
7. Moul JW, Banez LL, Freedland SJ. Rising PSA in nonmetastatic prostate cancer. Oncology (Williston Park) 2007;21(12):1436-45; discussion 1449, 1452, 1454.
8. Moul JW, Ward JF. Management of the patient with a rising PSA alone. Hematol Oncol Clin North Am 2006;20(4):897-908.
9. Diaz M, Patterson SG. Management of androgen-independent prostate cancer. Cancer Control 2004;11(6):364-73.
10. Sartor O. Prostate specific antigen (PSA) may be a poor marker for progression of prostate cancer after treatment with a combination of chemo-hormonal therapies. J La State Med Soc 2008;160(2):99-100.
11. Harris KA, Small EJ. Secondary hormonal manipulation of prostate cancer. Curr Urol Rep 2001;2(3):224-30.
12. Harris KA, Weinberg V, Bok RA, Kakefuda M, Small EJ. Low dose ketoconazole with replacement doses of hydrocortisone in patients with progressive androgen independent prostate cancer. Journal of Urology 2002;168(2):542-5.
13. Zhou EH, Ellis RJ, Cherullo E, Colussi V, Xu F, Chen WD, et al. Radiotherapy and survival in prostate cancer patients: a population-based study. Int J Radiat Oncol Biol Phys 2009;73(1):15-23.

14. Rosenthal SA, Bae K, Pienta KJ, Sobczak ML, Asbell SO, Rajan R, et al. Phase III multi-institutional trial of adjuvant chemotherapy with paclitaxel, estramustine, and oral etoposide combined with long-term androgen suppression therapy and radiotherapy versus long-term androgen suppression plus radiotherapy alone for high-risk prostate cancer: preliminary toxicity analysis of RTOG 99-02. Int J Radiat Oncol Biol Phys 2009;73(3):672-8.

15. Speight JL, Roach M, 3rd. Advances in the treatment of localized prostate cancer: the role of anatomic and functional imaging in men managed with radiotherapy. J Clin Oncol 2007;25(8):987-95.

16. Sherr DL. Advanced prostate cancer and postoperative radiotherapy. Jama 2007;297(9):950; author reply 951.

17. Kalkner KM, Wahlgren T, Ryberg M, Cohn-Cedermark G, Castellanos E, Zimmerman R, et al. Clinical outcome in patients with prostate cancer treated with external beam radiotherapy and high dose-rate iridium 192 brachytherapy boost: a 6-year follow-up. Acta Oncol 2007;46(7):909-17.

18. Pisansky TM. External-beam radiotherapy for localized prostate cancer. N Engl J Med 2006;355(15):1583-91.

19. Scher HI, Kelly WK. Flutamide withdrawal syndrome: its impact on clinical trials in hormone-refractory prostate cancer. J Clin Oncol 1993;11(8):1566-72.

20. Dupont A, Labrie F, Cusan L, Gomez JL, Tremblay M, Lacourciere Y, et al. Combination therapy with flutamide and castration (orchiectomy or LH-RH agonist) in untreated patients with advanced prostate cancer. Recent Results in Cancer Research 1992;124:43-54.

21. Miyake H, Hara I, Eto H. Clinical outcome of maximum androgen blockade using flutamide as second-line hormonal therapy for hormone-refractory prostate cancer. BJU Int 2005;96(6):791-5.

22. Narimoto K, Mizokami A, Izumi K, Mihara S, Sawada K, Sugata T, et al. Adrenal androgen levels as predictors of outcome in castration-resistant prostate cancer patients treated with combined androgen blockade using flutamide as a second-line anti-androgen. Int J Urol 2010;17(4):337-45.

23. Okegawa T, Nutahara K, Higashihara E. Alternative antiandrogen therapy in patients with castration-resistant prostate cancer: a single-center experience. Int J Urol 2010;17(11):950-5.

24. Oh WK. Secondary hormonal therapies in the treatment of prostate cancer. Urology 2002;60(3 Suppl 1):87-92; discussion 93.

25. Crawford ED. Hormonal therapy in prostate cancer: historical approaches. Rev Urol 2004;6 Suppl 7:S3-S11.

26. Small EJ, Carducci MA, Burke JM, Rodriguez R, Fong L, van Ummersen L, et al. A phase I trial of intravenous CG7870, a replication-selective, prostate-specific antigen-targeted oncolytic adenovirus, for the treatment of hormone-refractory, metastatic prostate cancer. Mol Ther 2006;14(1):107-17.

27. Fong L, Small EJ. Immunotherapy for prostate cancer. Current Urology Reports 2006;7(3):239-46.

28. Scholz M, Jennrich R, Strum S, Brosman S, Johnson H, Lam R. Long-term outcome for men with androgen independent prostate cancer treated with ketoconazole and hydrocortisone. J Urol 2005;173(6):1947-52.

29. Attard G, Reid AH, A'Hern R, Parker C, Oommen NB, Folkerd E, et al. Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer. Journal of Clinical Oncology 2009;27(23):3742-8.

30. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. New England Journal of Medicine 2004;351(15):1502-12.

31. Hahn NM, Zon RT, Yu M, Ademuyiwa FO, Jones T, Dugan W, et al. A phase II study of pemetrexed as second-line chemotherapy for the treatment of metastatic castrate-resistant prostate cancer (CRPC); Hoosier Oncology Group GU03-67. Ann Oncol 2009.

32. Sartor A, Petrylak D, Witjes J, Berry W, Chatta G, Vaughn D, et al. Satraplatin in patients with advanced hormonerefractory prostate cancer (HRPC): Overall survival (OS) results from the phase III satraplatin and prednisone against refractory cancer (SPARC) trial. J Clin Oncol (ASCO Meeting Abstracts) 2008;26:250s.

33. Sharifi N, Farrar WL. Androgen receptor as a therapeutic target for androgen independent prostate cancer. Am J Ther 2006;13(2):166-70.

34. Holzbeierlein J, Lal P, LaTulippe E, Smith A, Satagopan J, Zhang L, et al. Gene expression analysis of human prostate carcinoma during hormonal therapy identifies androgen-responsive genes and mechanisms of therapy resistance. Am J Pathol 2004;164(1):217-27.

35. LaTulippe E, Satagopan J, Smith A, Scher H, Scardino P, Reuter V, et al. Comprehensive gene expression analysis of prostate cancer reveals distinct transcriptional programs associated with metastatic disease. Cancer Res 2002;62(15):4499-506.

36. Mousses S, Bubendorf L, Wagner U, Hostetter G, Kononen J, Cornelison R, et al. Clinical validation of candidate genes associated with prostate cancer progression in the CWR22 model system using tissue microarrays. Cancer Res 2002;62(5):1256-60.

37. Mohler J, Bahnson RR, Boston B, Busby JE, D'Amico A, Eastham JA, et al. NCCN clinical practice guidelines in oncology: prostate cancer. J Natl Compr Canc Netw 2010;8(2):162-200.

38. Horwich A, Parker C, Bangma C, Kataja V. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21 Suppl 5:v129-33.

39. Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al. EAU Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Treatment of Clinically Localised Disease. Eur Urol 2011;59(1):61-71.

40. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376(9747):1147-54.

41. Shigeta K, Miura Y, Naito Y, Takano T. Cabazitaxel for castration-resistant prostate cancer. Lancet 2011;377(9760):121; author reply 122-3.

42. Froehner M, Wirth MP. Cabazitaxel for castration-resistant prostate cancer. Lancet 2011;377(9760):121-2; author reply 122-3.

43. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364(21):1995-2005.

44. Pal SK, Sartor O. Phase III data for abiraterone in an evolving landscape for castration-resistant prostate cancer. Maturitas 2011;68(2):103-5.

45. Sonpavde G. Abiraterone acetate for metastatic prostate cancer. Lancet Oncol 2012;13(10):958-9.

46. Scher HI, Beer TM, Higano CS, Anand A, Taplin ME, Efstathiou E, et al. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. Lancet 2010;375(9724):1437-46.

47. Scher H, Fizazi K, Saad F, Taplin M-E, Sternberg C, Miller K, et al. Effect of MDV3100, an androgen receptor signaling inhibitor (ARSI), on overall survival in patients with prostate cancer postdocetaxel: Results from the phase III AFFIRM study. . J Clin Oncol (ASCO Meeting Abstracts) 2012;30(5 (February 10 Suppl)):abstr LBA1.

48. Scherr D, Swindle PW, Scardino PT. National Comprehensive Cancer Network guidelines for the management of prostate cancer. Urology 2003;61(2 Suppl 1):14-24.

49. Heidenreich A, Aus G, Abbou C, Bolla M, Joniau S, Matveev V, et al. Guidelines on Prostate Cancer. In. European Association of Urology; 2008.

50. Manni A, Bartholomew M, Caplan R, Boucher A, Santen R, Lipton A, et al. Androgen priming and chemotherapy in advanced prostate cancer: evaluation of determinants of clinical outcome. Journal of Clinical Oncology 1988;6(9):1456-66.

51. Taylor CD, Elson P, Trump DL. Importance of continued testicular suppression in hormone-refractory prostate cancer. Journal of Clinical Oncology 1993;11(11):2167-72.

52. Fakih M, Johnson CS, Trump DL. Glucocorticoids and treatment of prostate cancer: a preclinical and clinical review. Urology 2002;60(4):553-61.

53. Sartor O, Weinberger M, Moore A, Li A, Figg WD. Effect of prednisone on prostate-specific antigen in patients with hormone-refractory prostate cancer. Urology 1998;52(2):252-6.

54. Storlie JA, Buckner JC, Wiseman GA, Burch PA, Hartmann LC, Richardson RL. Prostate specific antigen levels and clinical response to low dose dexamethasone for hormone-refractory metastatic prostate carcinoma. Cancer 1995;76(1):96-100.

55. Nishimura K, Nonomura N, Yasunaga Y, Takaha N, Inoue H, Sugao H, et al. Low doses of oral dexamethasone for hormone-refractory prostate carcinoma. Cancer 2000;89(12):2570-6.

56. Kantoff PW, Halabi S, Conaway M, Picus J, Kirshner J, Hars V, et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the cancer and leukemia group B 9182 study. J Clin Oncol 1999;17(8):2506-13.

57. Fossa SD, Slee PH, Brausi M, Horenblas S, Hall RR, Hetherington JW, et al. Flutamide versus prednisone in patients with prostate cancer symptomatically progressing after androgen-ablative therapy: a phase III study of the European organization for research and treatment of cancer genitourinary group. Journal of Clinical Oncology 2001;19(1):62-71.

58. Miller MC, Doyle GV, Terstappen LW. Significance of Circulating Tumor Cells Detected by the CellSearch System in Patients with Metastatic Breast Colorectal and Prostate Cancer. J Oncol 2010;2010:617421.

59. Dotan E, Cohen SJ, Alpaugh KR, Meropol NJ. Circulating tumor cells: evolving evidence and future challenges. Oncologist 2009;14(11):1070-82.

60. de Bono JS, Scher HI, Montgomery RB, Parker C, Miller MC, Tissing H, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. Clinical Cancer Research 2008;14(19):6302-9.

61. Scher HI, Jia X, de Bono JS, Fleisher M, Pienta KJ, Raghavan D, et al. Circulating tumour cells as prognostic markers in progressive, castration-resistant prostate cancer: a reanalysis of IMMC38 trial data. Lancet Oncology 2009;10(3):233-9.

62. Tomlins SA, Rhodes DR, Perner S, Dhanasekaran SM, Mehra R, Sun XW, et al. Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. Science 2005;310(5748):644-8.

63. Attard G, Reid AH, Olmos D, de Bono JS. Antitumor activity with CYP17 blockade indicates that castration-resistant prostate cancer frequently remains hormone driven. Cancer Research 2009;69(12):4937-40.

64. Bubendorf L, Kononen J, Koivisto P, Schraml P, Moch H, Gasser TC, et al. Survey of gene amplifications during prostate cancer progression by high-throughout fluorescence in situ hybridization on tissue microarrays. Cancer Research 1999;59(4):803-6.

65. Attard G, Sarker D, Reid A, Molife R, Parker C, de Bono JS. Improving the outcome of patients with castration-resistant prostate cancer through rational drug development. British Journal of Cancer 2006;95(7):767-74.

66. Wang Y, Kreisberg JI, Ghosh PM. Cross-talk between the androgen receptor and the phosphatidylinositol 3-kinase/Akt pathway in prostate cancer. Current Cancer Drug Targets 2007;7(6):591-604.

67. Oefelein MG, Ricchiuti V, Conrad W, Resnick MI. Skeletal fractures negatively correlate with overall survival in men with prostate cancer. Journal of Urology 2002;168(3):1005-7.

68. Lopez AM, Pena MA, Hernandez R, Val F, Martin B, Riancho JA. Fracture risk in patients with prostate cancer on androgen deprivation therapy. Osteoporosis International 2005;16(6):707-11.

69. Diamond T, Campbell J, Bryant C, Lynch W. The effect of combined androgen blockade on bone turnover and bone mineral densities in men treated for prostate carcinoma: longitudinal evaluation and response to intermittent cyclic etidronate therapy. Cancer 1998;83(8):1561-6.

70. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. Journal of Clinical Oncology 2006;24(27):4448-56.

71. Braga-Basaria M, Dobs AS, Muller DC, Carducci MA, John M, Egan J, et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. Journal of Clinical Oncology 2006;24(24):3979-83.

72. Saigal CS, Gore JL, Krupski TL, Hanley J, Schonlau M, Litwin MS, et al. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. Cancer 2007;110(7):1493-500.

73. Tsai HK, D'Amico AV, Sadetsky N, Chen MH, Carroll PR. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. Journal of the National Cancer Institute 2007;99(20):1516-24.

74. D'Amico AV, Denham JW, Crook J, Chen MH, Goldhaber SZ, Lamb DS, et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. Journal of Clinical Oncology 2007;25(17):2420-5.

75. Efstathiou JA, Bae K, Shipley WU, Hanks GE, Pilepich MV, Sandler HM, et al. Cardiovascular mortality after androgen deprivation therapy for locally advanced prostate cancer: RTOG 85-31. Journal of Clinical Oncology 2009;27(1):92-9.

76. Van Andel G, Visser AP, Hulshof MC, Horenblas S, Kurth KH. Health-related quality of life and psychosocial factors in patients with prostate cancer scheduled for radical prostatectomy or external radiation therapy. BJU International 2003;92(3):217-22.

77. Regine WF, Schmitt FA, Scott CB, Dearth C, Patchell RA, Nichols RC, Jr., et al. Feasibility of neurocognitive outcome evaluations in patients with brain metastases in a multi-institutional cooperative group setting: results of Radiation Therapy Oncology Group trial BR-0018. International Journal of Radiation Oncology, Biology, Physics 2004;58(5):1346-52.

78. Salminen EK, Portin RI, Koskinen A, Helenius H, Nurmi M. Associations between serum testosterone fall and cognitive function in prostate cancer patients. Clinical Cancer Research 2004;10(22):7575-82.

79. Stone P, Hardy J, Huddart R, A'Hern R, Richards M. Fatigue in patients with prostate cancer receiving hormone therapy. European Journal of Cancer 2000;36(9):1134-41.

80. Llorente MD, Burke M, Gregory GR, Bosworth HB, Grambow SC, Horner RD, et al. Prostate cancer: a significant risk factor for late-life suicide. American Journal of Geriatric Psychiatry 2005;13(3):195-201.

81. Almeida OP, Waterreus A, Spry N, Flicker L, Martins RN. One year follow-up study of the association between chemical castration, sex hormones, beta-amyloid, memory and depression in men. Psychoneuroendocrinology 2004;29(8):1071-81.

82. Charbit B, Christin-Maitre S, Demolis JL, Soustre E, Young J, Funck-Brentano C. Effects of testosterone on ventricular repolarization in hypogonadic men. Am J Cardiol 2009;103(6):887-90.

83. Garnick M, Pratt C, Campion M, Shipley J, Bernardy J. Increase in the electrocardiographic QTC interval in men with prostate cancer undergoing androgen deprivation therapy: Results of three randomized controlled clinical studies. European Urology 2004;3(2 (suppl)):57; abstr 217.

84. Garnick MB, Pratt CM, Campion M, Shipley J. The effect of hormonal therapy for prostate cancer on the electrocardiographic QT interval: phase 3 results following treatment with leuprolide and goserelin, alone or with bicalutamide, and the GnRH antagonist abarelix. Journal of Clinical Oncology 2010 ASCO Annual Meeting Proceedings 2004;22(14S (July 15 suppl)):abstr 4578.

85. Smith MR, Klotz L, Persson BE, Olesen TK, Wilde AAM. Cardiovascular Safety of Degarelix: Results From a 12-Month, Comparative, Randomized, Open Label, Parallel Group Phase III Trial in Patients With Prostate Cancer. Journal of Urology 2010;184(6):2313-2319.

86. U.S. Department of Health and Human Services, National Institutes of Health National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.02. 28 May 2009.

87. Prednisone Tablets USP [package insert]. Corona, CA: Watson Pharma, Inc.; 2008.

88. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113(1-2):9-19.

89. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. Journal of Pain 2008;9(2):105-21.

90. Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain 2003;106(3):337-45.

91. The European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products (CPMP). CPMP/EWP/612/00. Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain. 21 November 2002.

92. US Department of Health and Human Services, Food and Drug Administration. Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009.

93. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35(3):549-56.

94. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. Journal of Clinical Oncology 2008;26(7):1148-59.

95. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

96. World Health Organization. Cancer Pain Relief. 1996.

97. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Adult Cancer Pain, v.1.2010; 2010.

98. Foley KM. The treatment of cancer pain. New England Journal of Medicine 1985;313(2):84-95.

99. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology 1982;5(6):649-55.

100. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

101. The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9 ed. Boston, MA: Little, Brown & Co; 1994.

102. Arlt W, Allolio B. Adrenal insufficiency. Lancet 2003;361(9372):1881-93.

103. Salvatori R. Adrenal insufficiency. JAMA 2005;294(19):2481-8.

104. Fauci A, Kasper D, Longo D, Braunwald E, Hauser S, Jameson J, et al. Harrison's Principles of Internal Medicine, 17th Edition. Columbus, OH: McGraw-Hill; 2008.

15. APPENDICES

15.1 Radiographic Disease Assessment According to Prostate Cancer Clinical Trials Working Group (PCWG2) and Modified Response Criteria in Solid Tumors (RECIST Version 1.1)

Radiographic Disease Assessment will be performed using the PCWG2 guidelines. The PCWG2 recommended that for soft tissue lesions that RECIST 1.1 assessment be applied and that results be compiled separately from the overall disease assessment, which includes both bone scan and RECIST 1.1 results.

Under RECIST 1.1, radionuclide bone scan lesions are considered not measurable, and hence nontarget. Under RECIST, bone scan progression occurs when the changes are "unequivocal." Under PCWG2, however, radionuclide bone scan results are treated semi-quantitatively and occurrence of new lesions may define progression as outlined further below. For this protocol, soft tissue and bone scan disease are evaluated separately, and the results of each are then considered in an overall radiographic disease assessment.

15.1.1 Recording Baseline Assessments

All sites of disease, target and nontarget lesions must be assessed at baseline. Objective disease status is to be recorded at each evaluation using the response categories and definitions provided in this section.

15.1.1.1 Soft Tissue Lesion Assessment

Selection of Target and Nontarget Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for reproducible repeated measurements. Measurements must be provided for target measurable lesions.

Selection of a Lymph Node as a Target Lesion

Only lymph nodes with the longest diameter of ≥ 2 cm,[*(94)] and a minimum short axis diameter of ≥ 1.5 cm by CT scan will be considered as target lesions at baseline. All other

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* PCWG2 guidelines.

lesions may be considered as nontarget, and are to be identified but not specifically measured at baseline, with the exception of bone scan metastases, which are identified and enumerated.

15.1.1.2 Soft Tissue Assessments Following Baseline

Confirmation of response is not required, except as follows:

If either 1) a new soft tissue lesions or 2) a 20% increase in the sum of diameters of target lesions (see below) are identified at the first follow-up assessment after start of study drug, then the new lesions or increase in sum of diameters must be confirmed as still present at the second follow-up assessment 6 or more weeks later.

Beginning at the second follow-up assessment and thereafter, no subsequent confirmation is required for 1) newly occurring soft tissue lesions; or 2) a new increase in lesion sum of diameters meeting disease progression criteria, or 3) unequivocal progression of non-target soft tissue lesions.

For the assessment of lymph nodes, only report changes in lymph nodes that were 2 cm in the longest diameter at baseline.*(94)

15.1.2 Response Definitions for RECIST-Evaluable Soft Tissue Lesions

15.1.2.1 Definition of Complete Response

Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.

15.1.2.2 Definition of Partial Response

At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of longest diameters of non-lymph node lesions and of the *short diameter(s) or short axis (SA) of lymph nodes*.

15.1.2.3 Definition of Stable Disease

Neither sufficient shrinkage to qualify for partial response (PR) nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

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* PCWG2 guidelines.

15.1.2.4 Definition of Soft Tissue Progression

At least a 20% increase in the sum of longest diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

NOTE: The appearance of 1 or more new lesions is also considered progression, except for lymph node and bone lesions as follows.

15.1.2.4.1 Assessment of Soft Tissue Time Point Response

The following table summarizes the RECIST 1.1 response status calculation at each time point for patients who have measurable soft tissue disease at baseline. Note that this assessment does not include bone scan assessment and is not the overall assessment of radiographic disease status.

Table 15-1 Time Point Response: Patients with Target (± Nontarget) Disease

Target Lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.[95]

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable.

15.1.3 Radionuclide Bone Scan Assessment

15.1.3.1 Baseline Assessment

Bone scan lesions should be enumerated at baseline. Questionable lesions, eg, sites of previous fracture, may require confirmation by CT or MRI.

15.1.3.2 Postbaseline Assessments and Definition of Progression of Bone Metastatic Disease Based on Radionuclide Bone Scan

Bone scan lesions should be assessed and enumerated at each follow-up assessment.

Progression on bone scan is defined as 2 or more new lesions on radionuclide bone scans**.** Should 2 or more new bone lesions be evident at the first assessment on treatment (Cycle 3, Day 1), 2 or more *additional* new lesions must be evident on a confirmatory assessment at least 6 weeks later (and no sooner than 12 weeks after the start of dosing, per protocol scheduled at Cycle 5, Day 1). This confirmation is not required when 2 or more *new* lesions (compared to baseline or to the Cycle 3, Day 1 assessment) first appear after the first follow-up assessment, ie, at Cycle 5, Day 1 or thereafter.

Should new bone lesions be documented at Cycle 3, Day 1 but *not* confirmed at Cycle 5, Day 1, then Cycle 3, Day 1 becomes the new baseline and 2 or more new lesions at subsequent assessments relative to Cycle 3 Day 1 defines bone scan progression.

Stable disease (SD) on bone scan stable disease is defined as the absence of progression. Bone scan lesions are considered non-evaluable under RECIST, and thus there can be no partial response. Complete response is very rare. Thus, almost all bone scans will be rated as NE (no lesions present), SD, or PD.

15.1.4 Overall Response Assessment

The following table summarizes the overall response status calculation at each time point for patients who have either RECIST 1.1 evaluable soft tissue lesions and/or radionuclide bone scan lesions. Note that CR can only occur if there are RECIST 1.1-evaluable lesions and no bone lesions based on radionuclide bone scan. PR can occur if patients have CR or PR based on soft tissue evaluation *and* bone scan lesions that are stable.

Table 15-2 Overall Assessment Time Point Response

PCWG2 Target/Nontarget soft tissue /RECIST 1.1	Bone Scan (PCWG2)	Overall
CR	No metastases	CR
CR, PR	SD	PR
SD	SD	SD
PD	SD	PD
SD	PD	PD

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

15.2 World Health Organization Steps of Analgesics and OME Conversions

15.2.1 World Health Organization Steps of Analgesics

Table 15-3 Pain Medication List Categorized by World Health Organization (WHO) Steps I, II, and III

WHO Step I
ACETAMINOPHEN & ASPIRIN
ACETAMINOPHEN & ASPIRIN & CAFFEINE
ACETAMINOPHEN & BUTALBITAL
ACETAMINOPHEN & BUTALBITAL & CAFFEINE
ACETAMINOPHEN & CAFFEINE
ACETAMINOPHEN CAP 500 MG
ACETAMINOPHEN CHEW TAB 80, 160 MG
ACETAMINOPHEN ELIXIR 80, 120 or 160 MG/5ML
ACETAMINOPHEN SOLN 100 MG/ML, 120 MG/2.5ML, 130 MG/5 ML, 160 MG/5ML
ACETAMINOPHEN SUPPOS 120 MG, 325 MG, 650 MG
ACETAMINOPHEN SUSP 80, 160 MG/5ML
ACETAMINOPHEN TAB 160, 325, 500, 650 MG
ACETAMINOPHEN TAB CR 650 MG
ACETAMINOPHEN W/ CALCIUM CARBONATE TAB 500-250 MG
ACETAMINOPHEN-BUTALBITAL CAP 650-50 MG
ACETAMINOPHEN-BUTALBITAL TAB 325-50 MG
ACETAMINOPHEN-BUTALBITAL TAB 650-50 MG
ACETAMINOPHEN-CAFFEINE-BUTALBITAL CAP 325-40-50 MG; 325-40-50 MG; 500-4-50 MG
ALUMINUM GLYCOLATE & ASPIRIN & MAGNESIUM CARBONATE
ALUMINUM HYDROXIDE & ASPIRIN & MAGNESIUM HYDROXIDE
ASPIRIN & BUTALBITAL & CAFFEINE
ASPIRIN & BUTALBITAL & CAFFEINE & PHENACETIN

Table 15-3 Pain Medication List Categorized by World Health Organization (WHO) Steps I, II, and III

ASPIRIN & CAFFEINE

ASPIRIN & CAFFEINE & PHENACETIN

ASPIRIN & PHENOBARBITAL

ASPIRIN BUFFERED (MG CARBONATE-AL GLYCINATE) TAB 325 MG

ASPIRIN BUFFERED (MG CARBONATE-AL GLYCINATE) TAB 500 MG

ASPIRIN BUFFERED TAB 325 MG; 500 MG

ASPIRIN CHEW TAB 75 MG

ASPIRIN EC TAB 81; 165; 325; 500;650;975 MG

ASPIRIN TAB 325; 500; 650 MG

ASPIRIN TAB CR 800 MG

ASPIRIN-ACETAMINOPHEN TAB 325-325 MG

ASPIRIN-ACETAMINOPHEN-CAFFEINE POWDER 260-130-16 MG

ASPIRIN-ACETAMINOPHEN-CAFFEINE TAB 230-125-30 MG;240-125-32 MG

ASPIRIN-ACETAMINOPHEN-CAFFEINE TAB 250-250-65 MG

ASPIRIN-AL HYDRO-MG HYDRO-CA CARB TAB 325-50-50-87 MG; 325-75-75-71 MG; 500-80-80-71 MG

ASPIRIN-AL HYDROXIDE-MG HYDROXIDE TAB 325-150-150 MG

ASPIRIN-AL HYDROXIDE-MG HYDROXIDE TAB 325-75-75 MG

ASPIRIN-APAP-CAFFEINE-CALCIUM GLUCONATE TAB 230-160-33-60 MG

ASPIRIN-BUTALBITAL TAB 650-50 MG

ASPIRIN-CAFFEINE TAB 400-30 MG; 500-30 MG

ASPIRIN-CAFFEINE-BUTALBITAL CAP 200-40-50 MG; 325-40-50 MG; 200-4-50 MG; 325-40-50 MG

ASPIRIN-CAL CARB-MAG CARB-MAG OXIDE TAB 325-158-34-63 MG

ASPIRIN & PHENYLTOLOXAMINE CITRATE & SALSALATE

ASPIRIN EFFER TAB 325, 500 MG

ASPIRIN GUM 210 MG

ASPIRIN SUPPOS 125; 325; 650 MG

APC TAB 260-130-15 MG

BENOXAPROFEN

CHOLINE & MAGNESIUM SALICYLATES LIQ 500 MG/5ML

CHOLINE & MAGNESIUM SALICYLATES TAB 500, 750, 1000 MG

CHOLINE MAGNESIUM TRISALICYLATE

CHOLINE SALICYLATE

CINNAMEDRINE

DICLOFENAC POTASSIUM TAB 50 MG

DICLOFENAC SODIUM EC TAB 25, 50, 75 MG

DIFLUNISAL TAB 250, 500 MG

DIHYDROXYALUMINUM AMINOACETATE

ETHOHEPTAZINE CITRATE

Table 15-3 Pain Medication List Categorized by World Health Organization (WHO) Steps I, II, and III

ETODOLAC CAP 200, 300, 400 MG
FENOPROFEN CALCIUM CAP 200, 300, 600 MG
FLURBIPROFEN TAB 50, 100 MG
IBUPROFEN CHEW TAB 100 MG
IBUPROFEN POWDER
IBUPROFEN SUSP 100 MG/5ML
IBUPROFEN SUSP 40 MG/ML
IBUPROFEN TAB 100,200,300,400,600,800 MG
INDOMETHACIN CAP 25,50, 75 MG
INDOMETHACIN SODIUM IV FOR SOLN 1 MG
INDOMETHACIN SUPPOS 50 MG
INDOMETHACIN SUSP 25 MG/5ML
KETOPROFEN CAP 12.5, 25, 50, 75 MG
KETOPROFEN CAP CR 100, 150,200 MG
KETOROLAC TROMETHAMINE IM INJ 15, 30 MG/ML
KETOROLAC TROMETHAMINE TAB 10 MG
MAGNESIUM SALICYLATE TAB 500, 545, 600 MG
MAGNESIUM TRISILICATE
MECLOFENAMATE SODIUM CAP 50, 100 MG
MEFENAMIC ACID CAP 250 MG
MEPROBAMATE
METHOTRIMEPRAZINE HYDROCHLORIDE
NABUMETONE TAB 500, 750 MG
NAPROXEN SODIUM TAB 220, 275,550 MG
NAPROXEN SUSP 125 MG/5ML
NAPROXEN TAB 250, 375,500 MG
OXYPHENBUTAZONE
OXAPROZIN TAB 600 MG
PAMABROM
PHENYLBUTAZONE
PHENYLTOLOXAMINE
PHENYLTOLOXAMINE CITRATE
PIROXICAM CAP 10, 20 MG
PYRILAMINE
PYRILAMINE MALEATE
SALICYLAMIDE
SALSALATE TAB 500, 750 MG
SODIUM SALICYLATE TAB 325, 650 MG

Table 15-3 Pain Medication List Categorized by World Health Organization (WHO) Steps I, II, and III

SODIUM THIOSALICYLATE
SODIUM THIOSALICYLATE INJ 50 MG/ML
SULINDAC TAB 150, 200 MG
SUPROFEN
TOLMETIN SODIUM TAB 200, 400, 600 MG
ZOMEPIRAC SODIUM
WHO Step II
ACETAMINOPHEN & BUTALBITAL & CAFFEINE & CODEINE PHOSPHATE
ACETAMINOPHEN & HYDROCODONE BITARTRATE
ACETAMINOPHEN & OXYCODONE HYDROCHLORIDE
ACETAMINOPHEN & PROPOXYPHENE HYDROCHLORIDE
ACETAMINOPHEN & PROPOXYPHENE NAPSYLATE
ACETAMINOPHEN W/ CODEINE CAP 300-30 MG
ACETAMINOPHEN W/ CODEINE ELIXIR 120-12 MG/5ML
ACETAMINOPHEN W/ CODEINE TAB 300-15 MG; 300-30 MG; 300-60 MG; 300-7.5 MG; 650-30 MG
ACETAMINOPHEN W/ HYDROCODONE CAP 500-5 MG
ACETAMINOPHEN W/ HYDROCODONE ELIXIR 167-2.5 MG/5ML; 120-2.5 MG/5ML
ACETAMINOPHEN W/ HYDROCODONE TAB 500-2.5 MG;500-5 MG; 500-7.5 MG; 650-10 MG; 650-7.5 MG; 750-7.5 MG
ACETAMINOPHEN-CAFF-BUTALBITAL W/ COD CAP 325-40-50-30 MG
ACETAMINOPHEN-CAFFEINE-DIHYDROCODEINE CAP 356.4-30-16 MG
AL. HYDROXIDE & ASPIRIN & CODEINE PHOSPHATE & MG. HYDROXIDE
ASPIRIN & BUTALBITAL & CAFFEINE & CODEINE
ASPIRIN & BUTA & CAFF & CODEINE PHOSPHATE & PHENACETIN
ASPIRIN & CAFFEINE & CODEINE PHOSPHATE & PHENACETIN
ASPIRIN & CAFFEINE & HYDROCODONE BITARTRATE
ASPIRIN & CAFFEINE & PHENACETIN & PROPOXYPHENE HYDROCHLORIDE
ASPIRIN & CAFFEINE & PROPOXYPHENE HYDROCHLORIDE
ASPIRIN & CODEINE PHOSPHATE
ASPIRIN & PROPOXYPHENE HYDROCHLORIDE
ASPIRIN & PROPOXYPHENE NAPSYLATE
ASPIRIN W/ CODEINE TAB 325-15 MG; 325-30 MG; 325-60 MG
ASPIRIN W/ HYDROCODONE TAB 500-5 MG
ASPIRIN-CAFF-BUTALBITAL W/ CODEINE CAP 325-40-50-30 MG
ATROPINE SULFATE & MEPERIDINE HYDROCHLORIDE
ATROPINE SULFATE & MORPHINE SULFATE
BUPRENORPHINE HCL INJ 0.324 MG/ML
BUPRENORPHINE HYDROCHLORIDE
BUTORPHANOL TARTRATE INJ 1 MG/ML; 2 MG/ML

Table 15-3 Pain Medication List Categorized by World Health Organization (WHO) Steps I, II, and III

BUTORPHANOL TARTRATE NASAL SOLN 10 MG/ML
DEZOCINE INJ 10, 15 MG/ML
DIHYDROCODEINE COMPOUND CAP
MEPERIDINE W/ APAP TAB 50-300 MG
MEPERIDINE W/ ATROPINE INJ 50-0.4 MG/ML; 75-0.4 MG/ML
NALBUPHINE HCL INJ 10, 20 MG/ML
NALOXONE
NALTREXONE HCL TAB 50 MG
OXYCODONE W/ ACETAMINOPHEN SOLN 5-500 MG/5ML
OXYCODONE W/ ACETAMINOPHEN 5-325; 5-500 MG
OXYCODONE W/ ASPIRIN TAB FULL/half STRENGTH
OXYCODONE TEREPHTHALATE
PENTAZOCINE LACTATE INJ 30 MG/ML
PENTAZOCINE W/ APAP TAB 25-650 MG;12.5-325 MG
PROMAZINE HCL
PROMETHAZINE HCL (CAP & INJ)
PROPOXYPHENE COMPOUND CAP 65 MG
PROPOXYPHENE HCL W/ APAP TAB 65-650 MG;100-650 MG; 50-325 MG
WHO Step III
ALFENTANIL INJ 500 MCG/ML
CODEINE PHOSPHATE INJ 30, 60 MG/ML
CODEINE PHOSPHATE SOLN 15 MG/5ML
CODEINE PHOSPHATE SOLUBLE TAB 30, 60 MG
CODEINE SULFATE
CODEINE SULFATE TAB 30, 60 MG
FENTANYL CITRATE INJ 0.05 MG/ML
FENTANYL CITRATE POWDER
FENTANYL TD SYS 25, 50, 75, 100 MCG/HR
HYDROCODONE BITARTRATE
HYDROMORPHONE HCL INJ 1,2,3,4, 10 MG/ML
HYDROMORPHONE HCL LIQD 1 MG/ML
HYDROMORPHONE HCL POWDER
HYDROMORPHONE HCL SUPPOS 3 MG
HYDROMORPHONE HCL TAB 2,3,4,8 MG
LEVOMETHADYL ACETATE HCL SOLN 10 MG/ML
LEVORPHANOL TARTRATE INJ 2 MG/ML
LEVORPHANOL TARTRATE TAB 2 MG
MEPERIDINE HCL INJ 25, 50, 75, 100 MG/ML

Table 15-3 Pain Medication List Categorized by World Health Organization (WHO) Steps I, II, and III

MEPERIDINE HCL SYRUP 50 MG/5ML
MEPERIDINE HCL TAB 50, 100 MG
METHADONE HCL CONC 10 MG/ML
METHADONE HCL SOLN 5, 10 MG/5ML
METHADONE HCL TAB 5, 10, 40 MG
METHADONE HYDROCHLORIDE
MORPHINE SULFATE CAP 15, 30 MG
MORPHINE SULFATE IN DEXTROSE INJ 0.2 MG/ML
MORPHINE SULFATE IN DEXTROSE INJ 1 MG/ML
MORPHINE SULFATE INJ 1,2,3,4,5,8, 10,15,25,50 MG/ML
MORPHINE SULFATE INJ PF 0.5, 1 MG/ML
MORPHINE SULFATE ORAL SOLN 10, 20 MG/5ML; 20 MG/ML
MORPHINE SULFATE SUPPOS 5, 10, 20, 30 MG
MORPHINE SULFATE TAB 10, 15, 30 MG
MORPHINE SULFATE TAB CR 15, 20,60,100,200 MG
OXYCODONE HCL CONC 20 MG/ML
OXYCODONE HCL SOLN 5 MG/5ML
OXYCODONE HCL TAB 5 MG
OXYCODONE HYDROCHLORIDE
OXYMORPHONE HCL INJ 1 MG/ML
OXYMORPHONE HCL SUPPOS 5 MG
OXYMORPHONE HYDROCHLORIDE
PROPOXYPHENE HCL CAP 65 MG
PROPOXYPHENE NAPSYLATE SUSP 50 MG/5ML
PROPOXYPHENE NAPSYLATE TAB 100 MG
SUFENTANIL CITRATE INJ 50 MCG/ML
TRAMADOL HCL TAB 50 MG

Source: World Health Organization. Cancer Pain Relief. Geneva: World Health Organization, 1986.[96]

15.2.2 Oral Morphine Equivalent (OME) Conversions

Table 15-4 Oral and Parenteral Opioid Equivalences and Relative Potency of Drugs as Compared with Morphine

Opioid Agonists[a]	Oral Dose (mg)	Parenteral Dose (mg)	Factor (IV to PO)
Morphine[b]	***30***[b]	10	3
Codeine	200	130	1.5
Fentanyl[c]		0.1 (100 μg)	
Hydrocodone	30 to 200		
Hydromorphone	7.5	1.5	5
Levorphanol	4	2	2
Oxycodone	15 to 20		
Oxymorphone	10	1	10
Tramadol[d]	50 to 100		

Source: Adapted from the National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology, Adult Cancer Pain, V.1.2010.[97]

a Opioid drugs NOT recommended include meperidine, methadone, propoxyphene, partial agonists (buprenorphine), and mixed agonist-antagonists (pentazocine, nalbuphine, butorphanol, dezocine).

b Oral morphine equivalent (OME) score is based on an oral morphine dose of 30 mg; the conversion factor listed is for chronic dosing. Avoid using morphine in renal failure.

c Available in transdermal system for extended dosing. See the calculation below for dose conversion from other opioids to transdermal fentanyl.

d Weak opioid receptor agonist with some antidepressant activity; for mild to moderate pain. Recommended dose of 100 mg 4 times daily (maximum daily dose of 400 mg) to avoid central nervous system toxicity. At maximum dose, tramadol is less potent than other opioid analgesics.

Oral Morphine Equivalence Conversion Calculation

To calculate the oral morphine equivalent (OME) score of an opioid in Table 15-4:

X = dose of an opioid equivalent to an oral morphine dose of 30 mg

Y = dose of that opioid consumed by the patient in the last 24 hours

OME of that opioid consumed in the last 24 hours = Y / X × 30

Example: A patient consumed 100 mg of oral codeine in the last 24 hours. The OME calculation is:

X = 200 mg

Y = 100 mg

OME of oral codeine = 100 / 200 × 30 = 15 mg

Table 15-5 Recommended Dose Conversion From Other Opioids to Transdermal Fentanyl

Transdermal Fentanyl (μg/d)	*Morphine*		Oxycodone		Hydromorphone		Codeine	
	Oral[a] (mg/d)	IV/SubQ[b] (mg/d)	Oral (mg/d)	IV/Sub Q (mg/d)	Oral (mg/d)	IV/Sub Q (mg/d)	Oral (mg/d)	IV/Sub Q (mg/d)
25	***60***	20	30	15	7.5	1.5	200	130
50	120	40	60	30	15	3.0	400	260
75	180	60	90	45	22.5	4.5	600	390
100	240	80	120	60	30.0	6.0	800	520

Source: Adapted from the National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology, Adult Cancer Pain, V.1.2010.[97]

Due to patient variability the recommended doses are estimates; clinical judgment should be used to titrate to the desired response.

a Oral morphine equivalent (OME) score is based on an oral morphine dose of 60 mg (as adapted from Foley KM. The treatment of cancer pain. NEJM 1985; 313:84-95[98]).

b Parenteral dosing such as intravenous or subcutaneous.

15.3 Eastern Cooperative Oncology Group Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.[99]

15.4 Cockcroft-Gault Formula

$$\text{Creatinine Clearance} = \frac{(140 - \text{age [yr]}) \times \text{Weight (kg)}}{\text{Serum creatinine (mg/dL)} \times 72}$$

OR

$$\frac{(140 - \text{age [yr]}) \times \text{Weight (kg)}}{\text{Serum creatinine (}\mu\text{mol/L)} \times 0.81}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.[100]

15.5 New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.[101]

15.6 Specific Guidelines for Possible Study Drug-Related Toxicities

15.6.1 Fatigue

Fatigue is defined as a disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities.

In the open-label, phase1/2 study (TAK-700_201), patients have experienced fatigue. Most events were Grade 1 or 2 in severity. Grade 3 fatigue was experienced by some patients, including those who received concomitant prednisone. Other factors, such as acute androgen deprivation, may also be contributing to symptoms. Prior to dose modification, the investigator should confirm that the patient is receiving prednisone 5 mg BID. Table 15-6 summarizes the NCI CTCAE criteria (version 4.02)[86] for fatigue and the appropriate actions to be followed.

Table 15-6 NCI CTCAE Criteria and Appropriate Actions for Fatigue

NCI CTCAE Grade	Event Definition	Action Required
1	Fatigue relieved by rest	No action required
2	Fatigue not relieved by rest; limits instrumental ADL	Dose modification is optional. If Grade 2 fatigue is intolerable, dose reduction and re-escalation should follow Dose Reduction and Dose Re-escalation guidelines (Section 6.3).
3	Fatigue not relieved by rest, limiting self-care ADL	Dose reduction follows Dose Reduction and Dose Re-escalation guidelines (Section 6.3).

Source: NCI CTCAE version 4.02.[86]
Abbreviation: ADL = activity of daily living.

Dose modification for Grade 2 fatigue is optional but may be helpful by slowing the induction to full androgen deprivation. Grade 3 fatigue should be treated according to the general outlines in Section 6.3, including initial hold of dosing and re-introduction of study drug with subsequent titration at 2-week intervals to the patient's tolerated dose level.

15.6.2 Gastrointestinal Adverse Events

In previous and ongoing clinical studies, episodic and not necessarily dose-related GI toxicities have occurred.

Nausea and Vomiting

Nausea is defined as a disorder characterized by a queasy sensation and/or the urge to vomit. Table 15-7 summarizes the NCI CTCAE criteria (version 4.02)[86] for nausea and the appropriate actions to be followed.

Table 15-7 NCI CTCAE Criteria and Appropriate Actions for Nausea

NCI CTCAE Grade	Event Definition	Action Required
1	Loss of appetite without alteration in eating habits	No action required
2	Oral intake decreased without significant weight loss, dehydration or malnutrition	Concomitant anti-emetics may initially be administered without dose reduction. If Grade 2 nausea persists and is intolerable, dose reduction and re-escalation should follow Grade 2 Dose Reduction and Dose Re-escalation guidelines (Section 6.3).
3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	Supportive care regimen should follow local standard of care. Follow Dose Reduction and Dose Re-escalation guidelines (Section 6.3).

Source: NCI CTCAE version 4.02.[86]
Abbreviation: TPN = total parenteral nutrition.

Vomiting is defined as a disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth. Table 15-8 summarizes the NCI CTCAE criteria (version 4.02)[86] for vomiting and the appropriate actions to be followed.

Table 15-8 NCI CTCAE Criteria and Appropriate Actions for Vomiting

NCI CTCAE Grade	Event Definition	Action Required
1	Vomiting 1 to 2 episodes (separated by 5 minutes) in a 24 hour period	No action required
2	Vomiting 3 to 5 episodes (separated by 5 minutes) in a 24 hour period	Concomitant anti-emetics may initially be administered without dose reduction. If Grade 2 vomiting persists and is intolerable, dose reduction should follow Grade 2 Dose Reduction and Dose Re-escalation guidelines (Section 6.3).
3	Vomiting ≥ 6 episodes (separated by 5 minutes) in a 24 hour period; tube feeding, TPN, or hospitalization indicated	Dose reduction follows Grade 3 Dose Reduction and Dose Re-escalation guidelines (Section 6.3).
4	Life-threatening consequences; urgent intervention indicated	Dose reduction follows Grade 4 Dose Reduction and Dose Re-escalation guidelines (Section 6.3).

Source: NCI CTCAE version 4.02.[86]

Note: It is possible that nausea and vomiting could be secondary to acute adrenal insufficiency, eg, caused by sudden cessation of prednisone dosing. If nausea and vomiting occur in the setting of severe fatigue, prostration, or hypotension, blood should be obtained to check the electrolytes. Institutional standard of care should follow in the presence of electrolytes imbalance. Even if the vomiting occurs shortly following the study drug dose, no re-dosing of study drug will be done.

Diarrhea

Diarrhea is defined as a disorder characterized by frequent and watery bowel movements. Table 15-9 summarizes the NCI CTCAE criteria (version 4.02)[86] for diarrhea and the appropriate actions to be followed.

Table 15-9 NCI CTCAE Criteria and Appropriate Actions for Diarrhea

NCI CTCAE Grade	Event Definition	Action Required
1	Diarrhea increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	No action needed
2	Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output	Concomitant anti-diarrheal agents may initially be administered without dose reduction. If Grade 2 diarrhea persists, dose reduction should follow Grade 2 Dose Reduction and Dose Re-escalation

Table 15-9 NCI CTCAE Criteria and Appropriate Actions for Diarrhea

NCI CTCAE Grade	Event Definition	Action Required
	compared to baseline	guidelines (Section 6.3). Supportive care regimen should follow local standard of care
3	Increase of ≥ 7 stools per day over baseline; incontinence ~ hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Dose reduction follows Grade 3 Dose Reduction and Dose Re-escalation guidelines (Section 6.3).
4	Life-threatening consequences; urgent intervention indicated	Dose reduction follows Grade 4 Dose Reduction and Dose Re-escalation guidelines (Section 6.3).

Source: NCI CTCAE version 4.02.[86]
Abbreviation: ADL = activity of daily living.

15.6.3 Hypertension

If new onset or worsening of established hypertension occurs and the potassium level is < 3.5 mg/dL, in the absence of other causes such as new diuretic therapy, it suggests a study drug-related mineralocorticoid syndrome and should be followed by review of the patient's compliance with the prednisone regime. A plasma renin activity that is undetectable or low also suggests such a syndrome rather than a secondary cause. While addressing either underlying factors or compliance with current antihypertensives or prednisone dosing, dose modification should be initiated according to the general guidelines outlined in Section 6.3.

If other causes are identified as the reason for new or worsening hypertension, the investigator should follow the institution's local standard of care treatment, and the dose of study drug can be adjusted upwards in accordance with the general guidelines, Section 6.3. Table 15-10 summarizes the NCI CTCAE criteria (version 4.02)[86] for hypertension and the appropriate actions to be followed.

Table 15-10 NCI CTCAE Criteria and Appropriate Actions for Hypertension

CTCAE Grade	Event Definition	Action Required
1	Pre-hypertension (systolic BP 120 to 139 mmHg or diastolic BP 80 to 89 mmHg)	No dose modification needed; increase the frequency of BP monitoring as necessary
2	Stage 1 hypertension (systolic BP 140 to 159 mmHg or diastolic BP 90 to 99 mmHg); medical intervention indicated; recurrent or persistent (≥ 24 hrs); symptomatic increase by > 20 mmHg (diastolic) or to > 140/90 mmHg if previously WNL; monotherapy indicated.	Concomitant anti-hypertensive agents may initially be administered without dose reduction. If Grade 2 hypertension persists, dose reduction should follow Grade 2 Dose Reduction and Dose Re-escalation guidelines (Section 6.3). Supportive care regimen should follow local standard of care
3	Stage 2 hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg); medical intervention indicated; more than 1 drug or more intensive therapy than previously used indicated	Dose reduction follows Grade 3 Dose Reduction and Dose Re-escalation guidelines (Section 6.3). Supportive care regimen should follow local standard of care
4	Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Dose reduction follows Grade 4 Dose Reduction and Dose Re-escalation guidelines (Section 6.3). Supportive care regimen should follow local standard of care

Source: NCI CTCAE version 4.02.[86]
Abbreviation: BP = blood pressure.

15.6.4 Rash (Acneiform or Maculopapular, Localized or Generalized)

Acneiform rash is defined as a disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest, and back. Maculo-papular rash is defined as a disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbiliform rash, it is one of the most common cutaneous AEs.

Other types of dermatitis may occur during the study treatment; some of them may require dose modification and supportive care. Please follow the Dose Reduction and Dose Re-escalation guidelines (Section 6.3), as well as standard of care for the treatment of dermatitis. For patients experiencing Grade 3 or 4 Stevens-Johnson Syndrome, discontinue study drug immediately.

For patients who develop a non-localized rash, additional descriptive information will be collected, such as the appearance, distribution, extent of skin involvement, and any associated symptoms (eg, pruritus). See Section 7.4.8. Digital photographs and/or skin biopsies may be requested by the sponsor.

Table 15-11 summarizes the NCI CTCAE criteria (version 4.02)[86] for rash and the appropriate actions to be followed.

Table 15-11 NCI CTCAE Criteria and Appropriate Actions for Rash (Acneiform or Maculo-papular, Localized or Generalized)

NCI CTCAE Grade	AE	Event Definition	Action Required
1	Acneiform Rash	Papules and/or pustules covering < 10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	No dose reduction is necessary. Topical steroids and/or antibiotics as necessary; do not increase prednisone dose to treat skin rash. Reassess after 2 weeks.
	Maculo-papular Rash	Macules/papules covering < 10% BSA with or without symptoms (eg, pruritus, burning, tightness)	No dose reduction is necessary. Topical steroids and/or antibiotics as necessary; do not increase prednisone dose to treat skin rash. Reassess after 2 weeks.
2	Acneiform Rash	Papules and/or pustules covering 10% to 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Follow General Dose Modification Guidelines for Grade 2 toxicity. Topical steroids and/or antibiotics as necessary; do not increase prednisone dose to treat skin rash. Other types of systemic treatment such as antihistamine may be required. Repeat incidence of Grade 2 skin rash may require prophylactic antihistamine treatment.
	Maculo-papular Rash	Macules/papules covering 10% to 30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL	Follow Grade 2 Dose Reduction and Dose Re-escalation guidelines Topical steroids and/or antibiotics as necessary; do not increase prednisone dose to treat skin rash. Other types of systemic treatment such as antihistamine may be required. Repeat incidence of Grade 2 skin rash may require prophylactic antihistamine treatment.
3	Acneiform Rash	Papules and/or pustules covering > 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local super-infection with oral antibiotics indicated	Follow Grade 3 Dose Reduction and Dose Re-escalation guidelines (Section 6.3). Systemic treatment may be considered, including the use of short-term oral steroid (eg, prednisone up to 20 mg), tapering over 7 to 10 days. Monitor signs of GI AEs when prednisone dose

Table 15-11 NCI CTCAE Criteria and Appropriate Actions for Rash (Acneiform or Maculo-papular, Localized or Generalized)

NCI CTCAE Grade	AE	Event Definition	Action Required
			is increased. Before adding another oral steroid, consider other options including a combination of topical and oral treatment.
	Maculo-papular Rash	Macules/papules covering > 30% BSA with or without associated symptoms; limiting self care ADL	Follow Grade 3 Dose Reduction and Dose Re-escalation guidelines (Section 6.3). Systemic treatment may be considered, including the use of short-term oral steroid (eg, prednisone up to 20 mg), tapering over 7 to 10 days. Monitor signs of GI toxicity when prednisone dose is increased. Before adding another oral steroid, consider other options including a combination of topical and oral treatment.
4	Acneiform Rash	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive super-infection with IV antibiotics indicated life-threatening consequences	Follow Grade 4 Dose Reduction and Dose Re-escalation guidelines (Section 6.3). Systemic treatment may be considered, including the use of short-term oral steroid (eg, prednisone up to 20 mg), tapering over 7 to 10 days. Monitor signs of GI AEs when prednisone dose is increased. Do not resume treatment until the rash is resolved, no further intervention is indicated, or the rash is controlled with adequate treatment. Frequent monitoring and assessments are necessary when resuming treatment.
	Maculopapular Rash	Not applicable	Not applicable

Source: NCI CTCAE version 4.02.[86]

Abbreviations: ADL = activity of daily living; AE = adverse event; BSA = body surface area; GI = gastrointestinal; IV = intravenous.

15.6.5 Hyperglycemia

Hyperglycemia is a disorder characterized by laboratory test results that indicate an elevation in the concentration of blood sugar. It is usually an indication of diabetes mellitus or glucose intolerance. Androgen deprivation has been associated with new onset of diabetes. Prednisone, at the doses used in this protocol, may also worsen underlying glucose tolerance or pre-existing diabetes. However, because the progression of prostate cancer is of immediate importance to the patient, study investigators are encouraged to not modify the prednisone or orteronel therapeutic dose regimen unless other adjustments to the antidiabetic regimen are unsuccessful or for Grade 3 or 4 hyperglycemia (see Table 15-12).

If the patient has a medical history of diabetes mellitus (type I or type II), the patient's diabetes should be followed frequently per local standard of care. A physician experienced in the management of diabetes should be involved in the patient's care. Patients should be counseled for the importance of diet and antidiabetic treatment compliance throughout the study; any change in symptoms or home glucose monitoring results should be reviewed at each scheduled visit and the patient encouraged to follow up as required with the physician managing the patient's diabetes. The physician managing the patient's diabetes should be informed that the patient is on or has recently started on prednisone therapy. Changes in diabetic medication should be supervised by or be based on consultation with the physician managing the patient's diabetes.

At baseline, if the HbA1c is > 7%, the patient should be referred for further assessment to ensure adequate or improved diabetes control while on study. During the study treatment, if there is an increase in HgbA1c of 1.5 % above baseline or to > 8.0%, the patient should be referred to the physician managing the patient's diabetes for additional management support. The management of hyperglycemia or diabetes should be addressed before considering study drug or prednisone dose reduction or hold.

Worsening of diabetic control is often associated with acute or chronic infection, other acute illness, new medication (diuretics or beta blockers), or electrolyte abnormalities (hypokalemia). Assessment for these underlying precipitating factors should always be considered in addition to adjusting the diabetes treatment regimen.

The following guidelines apply to either new onset or previously diagnosed diabetes.

Table 15-12 CTCAE Criteria and Appropriate Actions for Hyperglycemia

Grade	Event Definition	Action Required
1	Fasting glucose value > 130 up to 160 mg/dL; Fasting glucose value > 6.0 up to 8.9 mmol/L	Review compliance with diabetic medications, check HbA1c. Refer the patient to a physician experienced with management of the diabetes if HbA1c is > 7.0%. No dose modification is required.
2	Fasting glucose value > 160-250 mg/dL; Fasting glucose value > 8.9-13.9 mmol/L	Check HbA1c. If > 7.0%, make sure that the patient is currently under care of a physician experienced with management of the diabetes and refer the patient to that physician for evaluation. Seek precipitating cause(s). Reassess after 2 weeks. No dose modification is required.
3	> 250-500 mg/dL; > 13.9-27.8 mmol/L; hospitalization indicated	Review and assure treatment of precipitating causes, including new infections or hypokalemia. Reduce prednisone to 5 mg once daily for 2 weeks, then reassess. Resume prednisone 5 mg BID after improvement in blood glucose to Grade ≤ 2. If blood glucose does not improve, hold both study drug and prednisone for 2 weeks then reassess. Monitor patient for signs and symptoms of adrenal insufficiency. Both study drug and prednisone 5 mg BID may be resumed if blood glucose improves to Grade ≤ 2.
4	> 500 mg/dL; > 27.8 mmol/L; life-threatening consequences	Treat precipitating cause (infection or other acute illness) concurrently with acute diabetic management. Hold both study drug and prednisone for 2 weeks then reassess. Consider corticosteroid dosing for coverage of physiologic stress if indicated. Monitor patient for signs and symptoms of adrenal insufficiency if no corticosteroid administered. Resume study drug and prednisone 5 mg once daily if blood glucose improves to Grade 3. Both study drug and prednisone 5 mg BID may be resumed if blood glucose improves to Grade ≤ 2.

Source: CTCAE version 4.02.[86]
Abbreviations: BID = twice daily; HbA1c = glycosylated hemoglobin.

15.6.6 Renal Disorders

Acute renal injury is defined as a disorder characterized by the acute loss of renal function and is traditionally classified as prerenal (low blood flow into kidney), renal (kidney damage), and postrenal causes (ureteral or bladder outflow obstruction). The toxicity grade of acute renal injury will be assessed based on the serum creatinine level. Other clinical signs and symptoms, including proteinuria and hematuria, as detected by qualitative or quantitative laboratory test results, may be monitored in addition to creatinine value.

In studies of patients with advanced prostate cancer, the incidence of worsening renal function is relatively common and largely associated with worsening or exacerbation of urinary outflow obstruction. In addition, new use of diuretics or other precipitants of volume depletion commonly results in prerenal azotemia.

Table 15-13 summarizes the CTCAE Criteria (version 4.02[86]) for acute renal disorder and the appropriate actions to be followed.

Table 15-13 CTCAE Criteria and Appropriate Actions for Acute Renal Disorder

CTCAE Grade	Event Definition	Action Required
1	Creatinine level increase of > 0.3 mg/dL; creatinine 1.5-2 × above baseline	Evaluate patient for urinary tract infection, volume depletion or sub(acute) obstruction. If creatinine remains ≤ 2 × above baseline, no dose adjustment is required.
2	Creatinine > 2-3 × above baseline	Evaluate patient for urinary tract infection, volume depletion or sub(acute) obstruction. Hold study drug for 2 weeks. Resume at dose level reduced by 1 once creatinine is ≤ 2 × baseline. If the event recurs, reduce dose by 1 additional level and reassess. Final dose should be no higher than 1 level below starting dose.
3	Creatinine > 3 × baseline or > 4.0 mg/dL; hospitalization indicated	Hold study drug until the patient is discharged from the hospital and creatinine level has recovered to < 2 × baseline and resume at one reduced level, then follow Grade 2 guidelines.
4	Life-threatening consequences; dialysis indicated	Discontinue orteronel permanently.

Source: CTCAE version 4.02.[86]

15.6.7 Suspected or Possible Adrenal Insufficiency

If patients experience adrenal insufficiency, the adrenal insufficiency will have the more nonspecific manifestations of glucocorticoid insufficiency, rather than the more specific electrolyte abnormalities of mineralocorticoid insufficiency. Discontinuing prednisone and continuing orteronel while on study may lead to the symptoms of chronic or acute adrenal (glucocorticoid) insufficiency. Patients experiencing severe physiological stress (eg, surgery, severe infection) should be carefully monitored for adrenal insufficiency. Concomitant medications may complicate the picture of adrenal insufficiency, in particular in patients who are on beta-blockers or diuretics. Concomitant illness such as infection might similarly trigger or worsen symptoms of otherwise mild adrenal insufficiency.

Grading of adrenal insufficiency, the clinical manifestations associated with the specific grade, and suggested management options are provided in Table 15-14. In all cases, 'actions' should include a thorough review for other possible causes or contributors to the presenting symptoms (eg, infection, anemia, or newly introduced concomitant medications).

Table 15-14 Criteria and Appropriate Actions for Adrenal Insufficiency

Severity	Symptoms/Signs	Action Required/Study Drug Modifications
Possible mild insufficiency	• Chronic Grade 1 or Grade 2 fatigue, anorexia • < 5% weight loss • BP normal, possible mild orthostatic hypotension • Weight loss	• Review medications, check electrolytes, cortisol, and ACTH concentrations • Continue study drug as per protocol
Possible or probable moderate adrenal insufficiency, acute or chronic	• Grade 2 or 3 fatigue, anorexia, intermittent nausea and vomiting, orthostatic lightheadedness, or weakness • Weight loss • Definite orthostatic hypotension or below baseline supine BP • Possible hyponatremia	• Review medications, check electrolytes, cortisol, and ACTH concentrations • Review medications, including compliance with concomitant steroids and new diuretic use • Dose reduction follows Grade 3 Dose Reduction and Dose Re-escalation guidelines
Possible or probable severe chronic or acute adrenal insufficiency	• Grade 3/4 fatigue, definite anorexia, nausea and vomiting, • Severe orthostatic symptoms • Prostration • Nausea and/or vomiting • Hypotension at rest and unable to stand due to orthostatic hypotension, possible hyponatremia	• Manage in an acute care facility. • Administer IV hydrocortisone[a] and electrolyte/volume replacement • Review medications, check electrolytes, cortisol, and ACTH concentrations • Dose reduction follows Grade 3 Dose Reduction and Dose Re-escalation guidelines if a reversible precipitating cause can be identified and reversed • Discontinue study drug permanently if a

Table 15-14 Criteria and Appropriate Actions for Adrenal Insufficiency

Severity	Symptoms/Signs	Action Required/Study Drug Modifications
		reversible precipitating cause cannot be identified and reversed

Sources: Arlt W, Allolio B. Adrenal insufficiency. Lancet 2003;361(9372):1881-93.[102] Salvatori R. Adrenal insufficiency. JAMA 2005;294(19):2481-8.[103] Fauci A, Kasper D, Longo D, Braunwald E, Hauser S, Jameson J, et al. Harrison's Principles of Internal Medicine, 17th Edition. Columbus, OH: McGraw-Hill; 2008.[104]

Abbreviations: ACTH = adrenocorticotropic hormone; BP = blood pressure; IV = intravenous.

a Note: Prior to any glucocorticoid administration for suspected adrenal insufficiency, an unscheduled endocrine laboratory sample should be obtained, if possible, for subsequent determination of ACTH, cortisol and corticosterone concentrations. The sample, which will be sent to the study central laboratory for analysis and the results used to further understand the clinical event, will not be used for immediate clinical management of the patient.

15.7 Schedule of Events for Patients Receiving Blinded Study Drug

Procedure	Screen[b] (Day –28 to Day –1)	Treatment Period[a] 28-Day Cycle (± 3 Days for Cycles 1 through 7; ± 5 days for subsequent cycles)[c] C1	C2	C3	C4	C5	C6	C7	C10	C13	After Cycle 13[d]	Unsched[e]	EOT[f] +10 days	Short-term Follow-up[a, g] ± 10 days	Long-term Follow-up[a, g] ± 10 days
Informed Consent[h]	X														
Inclusion/Exclusion	X														
Demographics	X														
Complete Medical History	X														
Physical Examination[i]	X		X	X	X	X	X	X	X	X	Q3C		X		
Vital Signs[j]	X	X	X	X	X	X	X	X	X	X	Q3C	X	X		
Weight	X	X	X	X	X	X	X	X	X	X	Q3C		X		
Height	X														
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	Q3C		X		
MUGA Scan and/or ECHO[k]	X				X			X		X	Q6C		X		
Electrocardiogram (12-lead)	X		X					X		X	Q12C		X		
Sample collection															
Hematology[l]	X	X	X		X			X	X	X	Q3C		X		
Serum Chemistry[l]	X	X	X	X	X	X		X	X	X	Q3C		X		
Lipid Profile, HbA1c[l]	X							X		X	Q12C				
PSA[l]	X	X			X			X	X	X	Q3C		X	Q3mo	
Testosterone/DHEA-S[m]	X	X	X		X			X	X	X	Q3C		X		
ACTH, Cortisol, Corticosterone[m]	X	X	X		X			X	X	X	Q3C		X		
PK sampling[n]		X	X		X										
CTC Enumeration[l, o]	X	X		X	X	X		X	X				X		

Procedure	Screen[b] (Day –28 to Day –1)	Treatment Period[a] 28-Day Cycle (± 3 Days for Cycles 1 through 7; ± 5 days for subsequent cycles)[c] C1	C2	C3	C4	C5	C6	C7	C10	C13	After Cycle 13[d]	Unsched[e]	EOT[f] +10 days	Short-term Follow-up[a, g] ± 10 days	Long-term Follow-up[a, g] ± 10 days
CTC Biomarker[o, p]		X													
Whole Blood Sample for Germline DNA[q]		X													
CT/MRI[r]	X			X		X		X	X	X	Q3C			Q3mo	
Bone Scan[s]	X			X		X		X	X	X	Q3C			Q3mo	
Archived Tumor Tissue[t]		Archived tumor tissue can be collected at anytime during the study.													
BPI-SF and Prior 24-hour Opioid-Use Recall[u, v]	X	X	X	X	X	X	X	X	X	X	Q3C	X	X	Q3mo	
EORTC QLQ-C30 Questionnaire[u]		X		X	X	X		X	X	X	Q3C		X	Q3mo	
EQ-5D Questionnaire[u]		X		X	X	X		X	X	X	Q3C	X	X	Q3mo	
Medical Resource Utilization		Continuous from first dose of study drug through short-term follow-up													
Concomitant Medications		Continuous from first dose of study drug through EOT[v]												Pain medications[aa]	
Concomitant Procedures		Continuous from first dose of study drug through EOT													
Adverse Event Reporting		Adverse events will be reported from the first dose of any study drug through 30 days after treatment with the last dose of any study drug or the start of subsequent antineoplastic therapy, whichever occurs first, and recorded in the eCRFs													
	Serious adverse events and serious pretreatment events will be collected from signing of the informed consent form through 30 days after the last dose of any study drug														
Administration of Study Drug[w]		Study drug (orteronel or placebo) will be given twice daily as a continuous dose													
Administration of Prednisone		Prednisone (or commercially available equivalent) will be given 5 mg twice daily as a continuous dose													

Procedure	Screen[b] (Day –28 to Day –1)	Treatment Period[a] 28-Day Cycle (± 3 Days for Cycles 1 through 7; ± 5 days for subsequent cycles)[c] C1	C2	C3	C4	C5	C6	C7	C10	C13	After Cycle 13[d]	Unsched[e]	EOT[f] +10 days	Short-term Follow-up[a, g] ± 10 days	Long-term Follow-up[a, g] ± 10 days
Co-administration of GnRH Analogue[x]	Patients (unless surgically castrate) will receive GnRH analogue treatment throughout the study per standard of care														
New Antineoplastic Therapy Follow-up[y]															Q3mo
Survival Follow-up Contact[z]															Q3mo

Abbreviations: ACTH = adrenocorticotropic hormone; BPI-SF = Brief Pain Inventory-Short Form; CT = computed tomography; CTC = circulating tumor cell(s); DHEA-S = dehydroepiandrosterone sulfate; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Module 30; EOT = End of Treatment (visit); EQ-5D = European Quality of Life 5-Dimensional; GnRH = gonadotropin-releasing hormone; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition; PK = pharmacokinetic(s); PSA = prostate-specific antigen; Q3C = every 3 cycles; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1, Unsched = unscheduled (visit).

a Definitions of treatment and follow-up periods:

- Active treatment is the portion of the study when patients are on study drug and participating in the study according to the treatment period. Following radiographic disease progression, patients will enter the long-term follow-up portion of the study. Patients may remain on study drug after disease progression and return for scheduled visits until they receive subsequent antineoplastic therapy.
- Short-term follow-up is the portion of the study that specifically includes patients who discontinue study drug, but have not yet experienced radiographic disease progression. After radiographic disease progression, patients will then enter the long-term follow-up portion of the study.
- Long-term follow-up is the portion of the study when patients will no longer have scheduled visits or assessments, but are followed for alternative antineoplastic therapies and survival.

b Screening assessments must begin within 28 days prior to Cycle 1, Day 1. All screening laboratory tests, including PSA, must be performed at the central laboratory.

c Patients continuing study drug following disease progression should continue to have these study assessments performed according to this schedule until treatment with study drug is discontinued. Testing for each cycle from Cycle 1 through Cycle 7 will be completed every 28 days on Day 1 of the cycle (± 3 days). After Cycle 7, Day 1 testing will be performed every 3 cycles (every 84 days ± 5 days).

d Frequency of assessment is based on Cycle 13 as the starting point, eg, Q3C assessments would occur at the beginning of Cycles 16, 19, etc.

e Recording of vital signs and completion of the BPI-SF and EQ-5D questionnaires are required at unscheduled visits. Other assessments should be done as clinically indicated

Procedure	Screen[b] (Day –28 to Day –1)	Treatment Period[a] 28-Day Cycle (± 3 Days for Cycles 1 through 7; ± 5 days for subsequent cycles)[c] C1	C2	C3	C4	C5	C6	C7	C10	C13	After Cycle 13[d]	Unsched[e]	EOT[f] +10 days	Short-term Follow-up[a, g] ± 10 days	Long-term Follow-up[a, g] ± 10 days

f The EOT visit will be conducted 30 days (+ 10 days) after the last dose of study drug. If subsequent antineoplastic therapy is required prior to 30 days after the last dose, the EOT visit should be conducted prior to the initiation of the subsequent antineoplastic therapy.

g Patients who discontinue study treatment prior to radiographic disease progression may remain in the study and will be followed in the short-term follow-up period for as long as they continue to meet other eligibility criteria. Patients who discontinue study treatment prior to disease progression and receive subsequent antineoplastic therapy will *not* be followed for disease progression but will be followed in the long-term follow-up portion of the study.

h Informed consent must be obtained before any study-specific procedures are performed.

i A complete physical examination must be conducted at the screening and EOT visits. At all other visits, physical exams may be symptom/disease directed.

j Vital sign measurements include diastolic and systolic BP, heart rate, and temperature. Blood pressure will be taken after the patient has been in a seated position for 5 minutes. At screening, patients may have 2 BP measurements taken no more than 60 minutes apart to exclude uncontrolled hypertension. For eligible patients, only the BP measurement that confirms eligibility should be recorded on the eCRF.

k MUGA scans or ECHO; the same modality should be used for a patient throughout the study and the assessments should be performed at the same institution whenever possible.

l For Cycle 1, Day 1 only, all samples must be collected within 3 days prior to the first dose of study drug.

m DHEA-S, testosterone, ACTH, cortisol, and corticosterone samples will be collected prior to AM dosing.

n PK samples will be obtained at the following times:

Cycle 1, Day 1: 1 sample obtained 1 to 2 hours postdose.

Cycle 2: 2 samples are to be obtained during the clinic visit with the second sample obtained at least 2 hours after the first.

Cycle 4: 1 sample obtained during the clinic visit.

o CTC enumeration and biomarker samples (8.5 mL) must be collected and shipped to the vendor's laboratory at ambient temperature on the same day.

p CTC biomarker samples will be obtained from approximately 300 patients enrolled in selected countries.

q Germline genetic testing is optional for patients.

r Radiographic evaluation will be performed at screening; at Cycles 3, 5, and 7; and then every 3 cycles until disease progression; additional scans should be performed at the physician's discretion if progression is suspected. Testing will include CT with intravenous contrast or MRI of the chest, abdomen, and pelvis. The imaging modality should remain consistent throughout the study. Patients who experience radiographic disease progression and continue to receive study drug are not required to undergo radiographic assessments; however, subsequent radiographic assessments may be performed as clinically indicated.

s Bone scanning will be performed at screening; at Cycles 3, 5, and 7; and every 3 cycles thereafter. Requirements for additional scans to confirm progression are defined in the STUDY DEFINITIONS. Patients who experience radiographic disease progression and continue on study drug will have radiographic assessments performed as clinically indicated.

Procedure	Screen[b] (Day –28 to Day –1)	Treatment Period[a] 28-Day Cycle (± 3 Days for Cycles 1 through 7; ± 5 days for subsequent cycles)[c] C1	C2	C3	C4	C5	C6	C7	C10	C13	After Cycle 13[d]	Unsched[e]	EOT[f] +10 days	Short-term Follow-up[a, g] ± 10 days	Long-term Follow-up[a, g] ± 10 days

t If available and consistent with local regulations, archived tumor tissue collected at the time of original diagnosis or subsequent procedures (unstained slides or a paraffin-embedded block) will be obtained and evaluated to assess *TMPRSS2:ERG* fusion gene product and other candidate biomarkers predictive of orteronel antitumor activity. Archived tumor tissue can be collected at anytime during the study.

u All questionnaires should be completed before any other study procedures are performed. The BPI-SF questionnaire should be completed first. Patients will be asked to report their use of opioids during the 24 hours before the study visit.

v The 24-hour opioid-use data collected during the treatment period and short-term follow-up will be recorded on both the opioid-use and the concomitant medication eCRFs.

w Patients will receive continuous oral study drug twice daily without a rest period. The first dose of study drug must be administered within 7 days of randomization.

x Patients who have undergone orchiectomy and have testosterone concentration of < 50 ng/dL may enter the study without concomitant GnRH analogue treatment.

y After EOT, information on newly prescribed antineoplastic therapies will be collected every 3 months.

z Patients are to be contacted for survival every 3 months.

aa All pain medications including non-steroidal anti-inflammatory drugs and opioids are to be collected from the first dose of study drug through short-term follow-up.

15.8 Rationale and Purposes for Amendment 1

Rationale for Amendment 1 (Argentina-specific amendment relative to the original protocol)

The primary purpose of this amendment is to clarify the inclusion and exclusion criteria and patient assessments based on recommendations made by the Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT). The recommendations for the inclusion and exclusion criteria from ANMAT included restricting the confirmation of prostate cancer by histologic, not cytologic, methods and increasing the minimum calculated creatinine clearance for patients who might have renal insufficiency. The screening procedures were revised to include cranial computed tomography (CT) or magnetic resonance imaging (MRI) procedures to ensure that patients with metastases to the central nervous system (CNS) are excluded, and serologic testing of patients who have not been tested previously for infections with human immunodeficiency virus (HIV) or hepatitis B or C.

Purposes for Amendment 1

The purposes of this amendment are to:

- Clarify that prostate cancer will be confirmed histologically
- Increase the minimum calculated creatinine clearance from 40 mL/min to 60 mL/min
- Add cranial CT or MRI procedures at screening to exclude patients with CNS metastases
- Add serologic testing for HIV and hepatitis B and C to the screening procedures for those patients who are at high risk and have not been previously tested or if testing is required by the institutional review board or ethics committee
- Add criteria for prostate-specific antigen (PSA) and disease progression as reasons for discontinuing study treatment
- Remove definition of disease progression that does not apply to the study population
- Clarify the data collection timing in the Schedules of Events
- Update the contact information for reporting serious adverse events (SAEs)
- Correct typographical errors, punctuation, grammar, and formatting

15.9 Rationale and Purposes for Amendment 2

Rationale for Amendment 2 (global amendment relative the original protocol)

The primary purpose of this amendment is to refine the eligibility criteria. This amendment also clarifies specific study procedures, updates the safety information for orteronel, adds the collection of data on rashes, clarifies the disease assessment guidelines, and adds another interim analysis.

The eligibility criteria have been refined to eliminate the washout period of prior antiandrogen therapy since any recent prior therapy with these agents would have already failed. The minimum exposure to prior docetaxel has been reduced to ≥ 360 mg/m^2 received within a 6-month period for patients who tolerated docetaxel and ≥ 225 mg/m^2 received within a 6-month period for those patients experiencing prostate cancer progression while receiving docetaxel or were intolerant of docetaxel. The reduction in the minimum cumulative docetaxel dose will accommodate regional or local guidelines or practices for docetaxel administration and will allow enrollment of otherwise eligible patients in this global study.

Prior therapy with other therapies for prostate cancer, other than gonadotropin-releasing hormone GnRH analogues, such as progesterone, medroxyprogesterone, progestins (megesterol), or 5-alpha reductase inhibitors (eg, finasteride or dutasteride) must be discontinued 2 weeks before first dose of study drug. Patients with disease localized to the prostate or adjacent tissue are excluded, ie patients must have regional or distant metastases.

Some study samples have been clarified, refined, or expanded. The serologic testing for patients who are at risk for human immunodeficiency virus (HIV), hepatitis B, or hepatitis C and have not been previously tested may be done at screening. The number and timing of the pharmacokinetic (PK) samples have been expanded so that data are collected at sufficient sparse time points to permit population PK modeling.

The rationale, collection, and labeling of samples for the germline and tumor DNA analyses have been refined to ensure that investigators and patients understand which assessments are optional and that the samples will be labeled and handled according to regional and local regulations with removal of patient identifiers from these samples.

The disease assessments for this study are based on the guidelines from the Prostate Cancer Working Group (PCWG2) that incorporate evaluation of soft tissue lesions according to the Response Criteria in Solid Tumors (RECIST), version 1.1. The assessment guidelines provided in the protocol have been revised for clarity. Other clarifications in procedures are summarized below.

An additional interim analysis to occur at approximately 50% of the total events will permit an earlier assessment of the treatment effect. The alpha spending function used to control the overall type I error remained unchanged.

Purposes for Amendment 2 (global amendment relative the original protocol)

The purposes of this amendment are to:

Eligibility

- Clarify the definition of PSA progression as an inclusion criterion
- Clarify that screening PSA values for determination of eligibility must be obtained from the central laboratory
- Revise the minimum prior exposure docetaxel received within a 6-month period for patients with progressive disease and clarify that patients must have received 1 or 2 lines or regimens of prior therapy
- Clarify that the serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) must be ≤ 3 × the upper limit of normal (ULN) for eligible patients
- Clarify that multiple gated acquisition (MUGA) scans or echocardiogram (ECHO) can be used to assess cardiac function, but the same modality should be used for the patient throughout the study
- Require that eligible patients have a life expectancy of 6 months or longer
- Eliminate a washout period for discontinued prior antiandrogen therapy for patients enrolling in the study
- Exclude prior therapy, other than GnRH analogue, such as progesterone, medroxyprogesterone, progestins (megesterol), or 5-alpha reductase inhibitors (eg, finasteride or dutasteride) within 2 weeks of first dose of study drug
- Extend the exclusionary period of external beam radiation from 2 weeks to 4 weeks before first dose of study drug
- Refine the cardiac disease exclusion criteria
- Clarify that the QTc interval must be > 460 msec
- Clarify that patients in the active participation period in another clinical trial are excluded; however, patients in the long-term follow-up period are eligible
- Permit the enrollment of patients who have had definitive local therapy for urinary tract obstruction, eg with stents, after a review with the medical monitor
- Add that serologic testing for HIV and hepatitis B and C may be performed at local laboratories at the time of screening for patients who are at high risk and have not been previously tested or if testing is required by the institutional review board (IRB) or independent ethics committee (IEC)
- Exclude patients who have uncontrolled nausea, vomiting, or diarrhea
- Exclude patients whose cancer is limited to only the prostate bed or immediate adjacent tissue
- Affirm that patient eligibility must be confirmed with the sponsor

Endpoints

- Add population pharmacokinetics as an endpoint

Dose Modifications

- Clarify that dose modifications apply to blinded study drug (ie, orteronel or placebo)
- Clarify that patients with asymptomatic Grade 3 or 4 laboratory findings not related to study drug may not require dose modification (ie, dose hold or reduction)
- Clarify the language for dose re-escalation

Drugs and Concomitant Medications

- Refine the list of prohibited concomitant medications
- Expand the list of permitted agents for the treatment of osteoporosis or control of bone metastases to include denosumab, oral or intravenous bisphosphonates, and calcitonins
- Refine the description of study drug
- Clarify the storage conditions for prednisone
- Add information on the number of tablets contained in bottles of study drug

Procedures

- Clarify that patients must receive their first dose of study drug within 7 days of randomization
- Clarify that documentation demonstrating that a patient has progressive disease must be submitted to the sponsor along with a Patient Eligibility Worksheet
- Clarify that information on medications being taken at the time of screening is not collected
- Add collection of additional information on development of any non-localized rash
- Modify the number and timing of planned pharmacokinetic sample collection to permit population PK modeling for orteronel from sparse sampling time points
- Clarify the collection of dosing information for the PK analysis
- Add serum amylase and lipase to the tests to be performed as part of routine serum chemistry analyses
- Permit collection of information on alternative antineoplastic therapies from patients during long-term follow-up
- Add the collection of patient information on new antineoplastic therapy during long-term follow-up
- Clarify the acceptable windows for assessments and laboratory tests
- Clarify that informed consent must be obtained from patients before any study procedures are performed
- Clarify information that will be collected during short-term follow-up

- Clarify that the Brief-Pain Inventory – Short Form (BPI-SF) questionnaires will be completed before other procedures are performed
- Update the Schedule of Events
- Identify the laboratory results that will not be returned to the investigative sites
- State that serologic testing for HIV and hepatitis B and C will be done at a local laboratory
- Clarify the procedures for documentation of progressive disease
- Clarify the procedures for tumor specimen measurements
- Clarify the procedures for germline DNA analyses
- Clarify the procedures for collection and managing patient anonymity on labels of tumor tissue and CTC samples used for genotyping

Analysis

- Add an early interim analysis to occur after approximately 50% of planned events
- Condense the information on the Independent Data Monitoring Committee (IDMC) procedures (Detailed information is in the IDMC charter.)

Definitions

- Clarify the definition of active treatment
- Clarify the definition of pain progression
- Clarify the definition of pain response
- Clarify that evaluation of pain is to be performed at unscheduled visits
- Refine the medical care information to be collected during treatment and short-term follow-up

Adverse Events

- Update the contact information for reporting of serious adverse events (SAEs)
- Clarify the collection period for serious adverse events (SAEs)

Section 15 Appendices

- Clarify the radiographic disease assessments according to the Prostate Cancer Working Group (PCWG2) and modified Response Criteria in Solid Tumors (RECIST)
- Update information on fatigue
- Add a request that an unscheduled endocrine laboratory sample be collected prior to any glucocorticoid administration from patients who might be experiencing adrenal insufficiency

Background Information

- Update information on available therapies for metastatic castration resistant prostate cancer
- Update safety information from ongoing clinical trials with orteronel
- Update the PSA data from Study TAK-700_201
- Provide the rational for enumeration of CTCs
- Clarify the rationale for genotyping and assessment of biomarkers in tumor tissue
- Update information on the potential risks of orteronel

Administrative

- Refine the number of planned investigative sites
- Provide additional details on the use of information
- Correct typographical errors, punctuation, grammar, and formatting

15.10 Rationale and Purposes for Amendment 3

Rationale for Amendment 3 (Peru-specific amendment relative to the original protocol)

The primary purpose of this amendment is to revise the eligibility criteria based on recommendations made by the Instituto Nacional de Salud (INS). The guidelines from the National Comprehensive Cancer Network state that cabazitaxel is considered a first line treatment for patients with metastatic castration-resistant prostate cancer who have failed treatment with docetaxel plus prednisone. Additionally, according to the International Council on Harmonization guidelines, possible benefits, risks, costs, and efficacy of every new intervention must be evaluated through their comparison with best existing proven intervention, as well as with its exceptions. As a result, the inclusion criteria were revised to include those patients who have had prior treatment with cabazitaxel when available. The dose and timeframe for prior docetaxel therapy is also specified.

Purposes for Amendment 3

The purposes of this amendment are to:

- Revise the minimum prior exposure of docetaxel received within a 6-month period for patients with progressive disease
- Revise the eligibility criteria to include progressive disease during or following 1 or 2 regimens of cytotoxic chemotherapy
- Revise the eligibility criteria to include patients who have had prior treatment with cabazitaxel
- Correct typographical errors, punctuation, grammar, and formatting

15.11 Rationale and Purposes for Amendment 4

Rationale for Amendment 4 (Argentina-specific amendment relative to amendment 1 and incorporating amendment 2)

The primary purpose of this amendment is to refine the eligibility criteria. This amendment also clarifies specific study procedures, updates the safety information for orteronel, adds the collection of data on rashes, clarifies the disease assessment guidelines, and adds another interim analysis.

The eligibility criteria have been refined to eliminate the washout period of prior antiandrogen therapy since any recent prior therapy with these agents would have already failed. The minimum exposure to prior docetaxel has been reduced to $\geq$ 360 mg/m^2 received within a 6-month period for patients who tolerated docetaxel and $\geq$ 225 mg/m^2 received within a 6-month period for those patients experiencing prostate cancer progression while receiving docetaxel or were intolerant of docetaxel. The reduction in the minimum cumulative docetaxel dose will accommodate regional or local guidelines or practices for docetaxel administration and will allow enrollment of otherwise eligible patients in this global study.

Prior therapy with other therapies for prostate cancer, other than gonadotropin-releasing hormone GnRH analogues, such as progesterone, medroxyprogesterone, progestins (megesterol), or 5-alpha reductase inhibitors (eg, finasteride or dutasteride) must be discontinued 2 weeks before first dose of study drug. Patients with disease localized to the prostate or adjacent tissue are excluded, ie patients must have regional or distant metastases.

Some study samples have been clarified, refined, or expanded. The number and timing of the pharmacokinetic (PK) samples have been expanded so that data are collected at sufficient sparse time points to permit population PK modeling.

The rationale, collection, and labeling of samples for the germline and tumor DNA analyses have been refined to ensure that investigators and patients understand which assessments are optional and that the samples will be labeled and handled according to regional and local regulations with removal of patient identifiers from these samples.

The disease assessments for this study are based on the guidelines from the Prostate Cancer Working Group (PCWG2) that incorporate evaluation of soft tissue lesions according to the Response Criteria in Solid Tumors (RECIST), version 1.1. The assessment guidelines provided in the protocol have been revised for clarity. Other clarifications in procedures are summarized below.

An additional interim analysis to occur at approximately 50% of the total events will permit an earlier assessment of the treatment effect. The alpha spending function used to control the overall type I error remained unchanged.

Purposes for Amendment 4 (Argentina-specific amendment relative to amendment 1 and incorporating amendment 2)

The purposes of this amendment are to:

Eligibility

- Clarify the definition of PSA progression as an inclusion criterion
- Clarify that screening PSA values for determination of eligibility must be obtained from the central laboratory
- Revise the minimum prior exposure docetaxel received within a 6-month period for patients with progressive disease and clarify that patients must have received 1 or 2 lines or regimens of prior therapy
- Clarify that the serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) must be ≤ 3 × the upper limit of normal (ULN) for eligible patients
- Clarify that multiple gated acquisition (MUGA) scans or echocardiogram (ECHO) can be used to assess cardiac function, but the same modality should be used for the patient throughout the study
- Require that eligible patients have a life expectancy of 6 months or longer
- Eliminate a washout period for discontinued prior antiandrogen therapy for patients enrolling in the study
- Exclude prior therapy, other than GnRH analogue, such as progesterone, medroxyprogesterone, progestins (megesterol), or 5-alpha reductase inhibitors (eg, finasteride or dutasteride) within 2 weeks of first dose of study drug
- Extend the exclusionary period of external beam radiation from 2 weeks to 4 weeks before first dose of study drug
- Refine the cardiac disease exclusion criteria
- Clarify that the QTc interval must be > 460 msec
- Clarify that patients in the active participation period in another clinical trial are excluded; however, patients in the long-term follow-up period are eligible
- Permit the enrollment of patients who have had definitive local therapy for urinary tract obstruction, eg with stents, after a review with the medical monitor
- Exclude patients who have uncontrolled nausea, vomiting, or diarrhea
- Exclude patients whose cancer is limited to only the prostate bed or immediate adjacent tissue
- Affirm that patient eligibility must be confirmed with the sponsor

Endpoints

- Add population pharmacokinetics as an endpoint

Dose Modifications

- Clarify that dose modifications apply to blinded study drug (ie, orteronel or placebo)

- Clarify that patients with asymptomatic Grade 3 or 4 laboratory findings not related to study drug may not require dose modification (ie, dose hold or reduction)
- Clarify the language for dose re-escalation

Drugs and Concomitant Medications

- Refine the list of prohibited concomitant medications
- Expand the list of permitted agents for the treatment of osteoporosis or control of bone metastases to include denosumab, oral or intravenous bisphosphonates, and calcitonins
- Refine the description of study drug
- Clarify the storage conditions for prednisone
- Add information on the number of tablets contained in bottles of study drug

Procedures

- Clarify that patients must receive their first dose of study drug within 7 days of randomization
- Clarify that documentation demonstrating that a patient has progressive disease must be submitted to the sponsor along with a Patient Eligibility Worksheet
- Clarify that information on medications being taken at the time of screening is not collected
- Add collection of additional information on development of any non-localized rash
- Modify the number and timing of planned pharmacokinetic sample collection to permit population PK modeling for orteronel from sparse sampling time points
- Clarify the collection of dosing information for the PK analysis
- Add serum amylase and lipase to the tests to be performed as part of routine serum chemistry analyses
- Permit collection of information on alternative antineoplastic therapies from patients during long-term follow-up
- Add the collection of patient information on new antineoplastic therapy during long-term follow-up
- Clarify the acceptable windows for assessments and laboratory tests
- Clarify that informed consent must be obtained from patients before any study procedures are performed
- Clarify information that will be collected during short-term follow-up
- Clarify that the Brief-Pain Inventory – Short Form (BPI-SF) questionnaires will be completed before other procedures are performed
- Update the Schedule of Events
- Identify the laboratory results that will not be returned to the investigative sites
- State that serologic testing for HIV and hepatitis B and C will be done at a local laboratory

- Clarify the procedures for documentation of progressive disease
- Clarify the procedures for tumor specimen measurements
- Clarify the procedures for germline DNA analyses
- Clarify the procedures for collection and managing patient anonymity on labels of tumor tissue and CTC samples used for genotyping

Analysis

- Add an early interim analysis to occur after approximately 50% of planned events
- Condense the information on the Independent Data Monitoring Committee (IDMC) procedures (Detailed information is in the IDMC charter.)

Definitions

- Clarify the definition of active treatment
- Clarify the definition of pain progression
- Clarify the definition of pain response
- Clarify that evaluation of pain is to be performed at unscheduled visits
- Refine the medical care information to be collected during treatment and short-term follow-up

Adverse Events

- Clarify the collection period for SAEs

Section 15 Appendices

- Clarify the radiographic disease assessments according to the Prostate Cancer Working Group (PCWG2) and modified Response Criteria in Solid Tumors (RECIST)
- Update information on fatigue
- Add a request that an unscheduled endocrine laboratory sample be collected prior to any glucocorticoid administration from patients who might be experiencing adrenal insufficiency

Background Information

- Update information on available therapies for metastatic castration resistant prostate cancer
- Update safety information from ongoing clinical trials with orteronel
- Update the PSA data from Study TAK-700_201
- Provide the rational for enumeration of CTCs
- Clarify the rationale for genotyping and assessment of biomarkers in tumor tissue
- Update information on the potential risks of orteronel

Administrative

- Refine the number of planned investigative sites
- Provide additional details on the use of information
- To correct typographical errors, punctuation, grammar, and formatting

15.12 Rationale and Purposes for Amendment 5

Rationale for Amendment 5 (relative to global amendment 2)

The primary purpose of this amendment is to increase the period of contraception to be followed by patients after the last dose of study drug from 30 days to 4 months. The extension of the contraception period is a precaution based on in vitro results of genotoxicity testing of a degradant in the TAK-700 tablet. Although the degradant was negative for mutagenic structural alerts in the in silico assessments, the degradant tested positive for mutagenicity in 1 of 5 bacterial strains tested in the Ames assay, and it induced structural and numerical chromosomal aberrations in an in vitro chromosomal aberration assay. The potential clinical implications of these in vitro assay results are that any resulting genetic or chromosomal change could potentially lead to secondary tumors and may pose a risk to an unborn child.

Given the potential benefit of TAK-700 to patients with progressive castrate resistant prostate cancer (CRPC) for whom alternative treatments and life expectancy are limited, the anticipated risk of the degradant is considered to be low. To minimize potential risks to an unborn child, the requirement for the use of barrier contraception or abstention from heterosexual intercourse has been extended to 4 months after the last dose of study drug. The risk language for the study drug was updated to include the reference to potential clinical implications of the possible genotoxic degradant in the drug product.

Purposes for Amendment 5

The purposes of this amendment are to:

- Align the period of exclusion of prior radiotherapy in the Protocol Summary with Exclusion Criterion 4
- Remove reference to the 1-hour time window for dehydroepiandrosterone sulfate (DHEA-S), testosterone, adrenocorticotropic hormone (ACTH), cortisol, and corticosterone sample collection
- Clarify the definition of radiographic disease progression based on radionuclide bone scans
- Update risk language for the study drug to include potential clinical implications of a degradant in the tablet
- Extend the duration of contraception or abstention from heterosexual intercourse to 4 months after the last dose of study drug
- Clarify that dose modifications are required for Grade 3 or 4 adverse events (AEs) or intolerable Grade 2 AEs that are considered at least possibly related to study drug

- Correct typographical errors, punctuation, grammar, and formatting

15.13 Rationale and Purposes for Amendment 6

Rationale for Amendment 6 (Argentina-specific amendment relative to Amendment 4)

The primary purpose of this amendment is to increase the period of contraception to be followed by patients after the last dose of study drug from 30 days to 4 months. The extension of the contraception period is a precaution based on in vitro results of genotoxicity testing of a degradant in the TAK-700 tablet. Although the degradant was negative for mutagenic structural alerts in the in silico assessments, the degradant tested positive for mutagenicity in 1 of 5 bacterial strains tested in the Ames assay, and it induced structural and numerical chromosomal aberrations in an in vitro chromosomal aberration assay. The potential clinical implications of these in vitro assay results are that any resulting genetic or chromosomal change could potentially lead to secondary tumors and may pose a risk to an unborn child.

Given the potential benefit of TAK-700 to patients with progressive castrate resistant prostate cancer (CRPC) for whom alternative treatments and life expectancy are limited, the anticipated risk of the degradant is considered to be low. To minimize potential risks to an unborn child, the requirement for the use of barrier contraception or abstention from heterosexual intercourse has been extended to 4 months after the last dose of study drug. The risk language for the study drug was updated to include the reference to potential clinical implications of the possible genotoxic degradant in the drug product.

Purposes for Amendment 6

The purposes of this amendment are to:

- Align the period of exclusion of prior radiotherapy in the Protocol Summary with Exclusion Criterion 4
- Remove reference to the 1-hour time window for dehydroepiandrosterone sulfate (DHEA-S), testosterone, adrenocorticotropic hormone (ACTH), cortisol, and corticosterone sample collection
- Clarify the definition of radiographic disease progression based on radionuclide bone scans
- Update risk language for the study drug to include potential clinical implications of a degradant in the tablet
- Extend the duration of contraception or abstention from heterosexual intercourse to 4 months after the last dose of study drug
- Clarify that dose modifications are required for Grade 3 or 4 adverse events (AEs) or intolerable Grade 2 AEs that are considered at least possibly related to study drug
- Correct typographical errors, punctuation, grammar, and formatting

15.14 Rationale and Purposes for Amendment 7

Rationale for Amendment 7

(Peru-specific protocol amendment 7 is written relative to the Peru-specific protocol amendment 3 and incorporates changes in global protocol amendments 2 and 5)

The primary purpose of this amendment is to increase the period of contraception and refine the eligibility criteria. This amendment also clarifies specific study procedures, updates the safety information for orteronel, adds the collection of data on rashes, clarifies the disease assessment guidelines, and adds another interim analysis.

The primary purpose of this amendment is to increase the period of contraception to be followed by patients after the last dose of study drug from 30 days to 4 months. The extension of the contraception period is a precaution based on in vitro results of genotoxicity testing of a degradant in the TAK-700 tablet. Although the degradant was negative for mutagenic structural alerts in the in silico assessments, the degradant tested positive for mutagenicity in 1 of 5 bacterial strains tested in the Ames assay, and it induced structural and numerical chromosomal aberrations in an in vitro chromosomal aberration assay. The potential clinical implications of these in vitro assay results are that any resulting genetic or chromosomal change could potentially lead to secondary tumors and may pose a risk to an unborn child.

Given the potential benefit of TAK-700 to patients with progressive castrate resistant prostate cancer (CRPC) for whom alternative treatments and life expectancy are limited, the anticipated risk of the degradant is considered to be low. To minimize potential risks to an unborn child, the requirement for the use of barrier contraception or abstention from heterosexual intercourse has been extended to 4 months after the last dose of study drug. The risk language for the study drug was updated to include the reference to potential clinical implications of the possible genotoxic degradant in the drug product.

The eligibility criteria have been refined to eliminate the washout period of prior antiandrogen therapy since any recent prior therapy with these agents would have already failed.

Prior therapy with other therapies for prostate cancer, other than gonadotropin-releasing hormone GnRH analogues, such as progesterone, medroxyprogesterone, progestins (megesterol), or 5-alpha reductase inhibitors (eg, finasteride or dutasteride) must be discontinued 2 weeks before first dose of study drug. Patients with disease localized to the prostate or adjacent tissue are excluded, ie patients must have regional or distant metastases.

Some study samples have been clarified, refined, or expanded. The serologic testing for patients who are at risk for human immunodeficiency virus (HIV), hepatitis B, or hepatitis C and have not been previously tested may be done at screening. The number and timing of the pharmacokinetic (PK) samples have been expanded so that data are collected at sufficient sparse time points to permit population PK modeling.

The rationale, collection, and labeling of samples for the germline and tumor DNA analyses have been refined to ensure that investigators and patients understand which assessments are optional and that the samples will be labeled and handled according to regional and local regulations with removal of patient identifiers from these samples.

The disease assessments for this study are based on the guidelines from the Prostate Cancer Working Group (PCWG2) that incorporate evaluation of soft tissue lesions according to the Response Criteria in Solid Tumors (RECIST), version 1.1. The assessment guidelines provided in the protocol have been revised for clarity. Other clarifications in procedures are summarized below.

An additional interim analysis to occur at approximately 50% of the total events will permit an earlier assessment of the treatment effect. The alpha spending function used to control the overall type I error remained unchanged.

Purposes for Amendment 7

(Peru-specific protocol amendment 7 is written relative to the Peru-specific protocol amendment 3 and incorporates changes in global protocol amendments 2 and 5)

The purposes of this amendment are to:

Eligibility

- Clarify the definition of PSA progression as an inclusion criterion
- Clarify that screening PSA values for determination of eligibility must be obtained from the central laboratory
- Clarify that the serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) must be ≤ 3 × the upper limit of normal (ULN) for eligible patients
- Extend the duration of contraception or abstention from heterosexual intercourse to 4 months after the last dose of study drug
- Clarify that multiple gated acquisition (MUGA) scans or echocardiogram (ECHO) can be used to assess cardiac function, but the same modality should be used for the patient throughout the study
- Require that eligible patients have a life expectancy of 6 months or longer
- Eliminate a washout period for discontinued prior antiandrogen therapy for patients enrolling in the study
- Exclude prior therapy, other than GnRH analogue, such as progesterone, medroxyprogesterone, progestins (megesterol), or 5-alpha reductase inhibitors (eg, finasteride or dutasteride) within 2 weeks of first dose of study drug
- Extend the exclusionary period of external beam radiation from 2 weeks to 4 weeks before first dose of study drug
- Refine the cardiac disease exclusion criteria
- Clarify that the QTc interval must be < 460 msec
- Clarify that patients in the active participation period in another clinical trial are excluded; however, patients in the long-term follow-up period are eligible
- Permit the enrollment of patients who have had definitive local therapy for urinary tract obstruction, eg with stents, after a review with the medical monitor

- Add that serologic testing for HIV and hepatitis B and C may be performed at local laboratories at the time of screening for patients who are at high risk and have not been previously tested or if testing is required by the institutional review board (IRB) or independent ethics committee (IEC)
- Exclude patients who have uncontrolled nausea, vomiting, or diarrhea
- Exclude patients whose cancer is limited to only the prostate bed or immediate adjacent tissue
- Affirm that patient eligibility must be confirmed with the sponsor

Endpoints

- Add population pharmacokinetics as an endpoint

Dose Modifications

- Clarify that dose modifications apply to blinded study drug (ie, orteronel or placebo)
- Clarify that patients with asymptomatic Grade 3 or 4 laboratory findings not related to study drug may not require dose modification (ie, dose hold or reduction) and that dose modifications are required for Grade 3 or 4 adverse events (AEs) or intolerable Grade 2 AEs that are considered at least possibly related to study drug
- Clarify the language for dose re-escalation

Drugs and Concomitant Medications

- Refine the list of prohibited concomitant medications
- Expand the list of permitted agents for the treatment of osteoporosis or control of bone metastases to include denosumab, oral or intravenous bisphosphonates, and calcitonins
- Refine the description of study drug
- Clarify the storage conditions for prednisone
- Add information on the number of tablets contained in bottles of study drug

Procedures

- Clarify that patients must receive their first dose of study drug within 7 days of randomization
- Clarify that documentation demonstrating that a patient has progressive disease must be submitted to the sponsor along with a Patient Eligibility Worksheet
- Clarify that information on medications being taken at the time of screening is not collected
- Add collection of additional information on development of any non-localized rash
- Modify the number and timing of planned pharmacokinetic sample collection to permit population PK modeling for orteronel from sparse sampling time points
- Clarify the collection of dosing information for the PK analysis

- Add serum amylase and lipase to the tests to be performed as part of routine serum chemistry analyses
- Permit collection of information on alternative antineoplastic therapies from patients during long-term follow-up
- Add the collection of patient information on new antineoplastic therapy during long-term follow-up
- Clarify the acceptable windows for assessments and laboratory tests
- Clarify that informed consent must be obtained from patients before any study procedures are performed
- Clarify information that will be collected during short-term follow-up
- Remove reference to the 1-hour time window for dehydroepiandrosterone sulfate (DHEA-S), testosterone, adrenocorticotropic hormone (ACTH), cortisol, and corticosterone sample collection
- Clarify that the Brief-Pain Inventory – Short Form (BPI-SF) questionnaires will be completed before other procedures are performed
- Update the Schedule of Events
- Identify the laboratory results that will not be returned to the investigative sites
- State that serologic testing for HIV and hepatitis B and C will be done at a local laboratory
- Clarify the procedures for documentation of progressive disease
- Clarify the procedures for tumor specimen measurements
- Clarify the procedures for germline DNA analyses
- Clarify the procedures for collection and managing patient anonymity on labels of tumor tissue and CTC samples used for genotyping

Analysis

- Add an early interim analysis to occur after approximately 50% of planned events
- Condense the information on the Independent Data Monitoring Committee (IDMC) procedures (Detailed information is in the IDMC charter.)

Definitions

- Clarify the definition of active treatment
- Clarify the definition of radiographic disease progression based on radionuclide bone scans
- Clarify the definition of pain progression
- Clarify the definition of pain response
- Clarify that evaluation of pain is to be performed at unscheduled visits
- Refine the medical care information to be collected during treatment and short-term follow-up

Adverse Events

- Update the contact information for reporting of serious adverse events (SAEs)
- Clarify the collection period for serious adverse events (SAEs)

Section 15 Appendices

- Clarify the radiographic disease assessments according to the Prostate Cancer Working Group (PCWG2) and modified Response Criteria in Solid Tumors (RECIST)
- Update information on fatigue
- Add a request that an unscheduled endocrine laboratory sample be collected prior to any glucocorticoid administration from patients who might be experiencing adrenal insufficiency

Background Information

- Update information on available therapies for metastatic castration resistant prostate cancer
- Update safety information from ongoing clinical trials with orteronel
- Update the PSA data from Study TAK-700_201
- Provide the rational for enumeration of CTCs
- Clarify the rationale for genotyping and assessment of biomarkers in tumor tissue
- Update information on the potential risks of orteronel
- Update risk language for the study drug to include potential clinical implications of a degradant in the tablet

Administrative

- Align the period of exclusion of prior radiotherapy in the Protocol Summary with Exclusion Criterion 4
- Refine the number of planned investigative sites
- Provide additional details on the use of information
- Correct typographical errors, punctuation, grammar, and formatting

15.15 Rationale and Purposes for Amendment 8

Rationale for Amendment 8 (Japan-specific amendment relative to global amendment 5)

The primary purpose of this amendment is to modify the dose for orteronel in Japanese patients and to adjust the dose modification schema for study drug administration accordingly. Refer to Section 1.4.1 for further information.

Purposes for Amendment 8

The purposes of this amendment are to:

- Modify the dose for orteronel in Japanese patients from 400 mg BID to 300 mg BID
- Adjust the study drug supply specifications to accommodate the dose modification
- Adjust the dose modification schema for study drug administration to accommodate the dose reduction
- Correct typographical errors, punctuation, grammar, and formatting

15.16 Amendment 9 Detailed Summary of Changes

THE PRIMARY SECTION(S) OF THE PROTOCOL AFFECTED BY THE CHANGES IN AMENDMENT 9 ARE INDICATED. THE CORRESPONDING TEXT HAS BEEN REVISED THROUGHOUT THE PROTOCOL.

Purpose: Update the Study Flow Diagram to reflect the change in study procedures after unblinding

The primary change occurs in the Study Flow Diagram:

Formerly read:	The former Study Flow Diagram that summarized study activities for patients in the blinded study has been removed.
Now reads:	The new Study Flow Diagram that adds a summary of study activities for patients after study unblinding has been added. Descriptions of the short-term follow-up portion of the study and discontinuation for unacceptable toxicity or subsequent antineoplastic therapy were removed from the unblinded portion of the study as these no longer apply.

Purpose: Create 2 Schedules of Events at the time of unblinding: 1 for patients crossing over from placebo to orteronel and 1 for patients continuing to receive orteronel

The primary change occurs in the Schedules of Events:

Formerly read:	The former Schedule of Events (Section 15.7) that described study activities for all patients in the blinded study has been removed.
Now reads:	Two Schedules of Events were created to go into effect at the time of unblinding: 1 for patients crossing over from placebo to orteronel (Schedule of Events #1) and 1 for patients continuing to receive orteronel (Schedule of Events #2). The former Schedule of Events was moved to Section 15.7 for reference.

Section 15.7 also contains this change.

Purpose: Remove PK sampling for patients in the unblinded study, because sufficient data will have been collected before study unblinding, and limited inference can be made following crossover of all patients to active study drug

The primary change occurs in Section 7.4.17, Pharmacokinetic Measurements:

Added text:	**Blood samples for PK analyses will not be collected after the study is unblinded.**

Purpose: Remove collection of EORTC QLQ-C30 data for patients in the unblinded study, because sufficient data will have been collected before study unblinding, and limited inference can be made following crossover of all patients to active study drug

The primary change occurs in Section 7.4.19, Quality of Life Assessment:

Formerly read:	The EORTC QLQ-C30 will be ~~administered~~ as specified in the Schedules of Events, and it must be completed before other assessments are performed or study drug is administered.
Now reads:	The EORTC QLQ-C30 **data** will be **collected** as specified in the Schedules of Events, and it must be completed before other assessments are performed or study drug is administered. **EORTC QLQ-C30 data will not be collected after the study is unblinded.**

Section 4.1 also contains this change.

Purpose: Remove CT and MRI scans for patients in the unblinded study, because sufficient data will have been collected before study unblinding, and limited inference can be made following crossover of all patients to active study drug (however, scans may be performed by sites at the discretion of the investigator based on clinical need)

The primary change occurs in Section 7.4.13, Disease Assessment:

Added text:	**The review of films, images, and scans by a central imaging center will not be performed after the study is unblinded, but scans may be performed by sites at the discretion of the investigator based on clinical need.**

Section 4.1 also contains this change.

Purpose: Remove collection of samples for the enumeration of CTCs for patients in the unblinded study, because sufficient data will have been collected before study unblinding, and limited inference can be made following crossover of all patients to active study drug

The primary change occurs in Section 7.4.15, Circulating Tumor Cells:

Added text:	**Samples for measurement of CTCs will not be collected after the study is unblinded.**

Purpose: Remove collection of samples for germline DNA analysis for patients in the unblinded study, because sufficient data will have been collected before study unblinding, and limited inference can be made following crossover of all patients to active study drug

The primary change occurs in Section 7.4.16, Whole Blood Sample for Germline DNA:

Added text: **Blood samples for germline DNA analysis will not be collected after the study is unblinded.**

Purpose: Remove evaluation of MRU from patients in the unblinded study, because sufficient data will have been collected before study unblinding, and limited inference can be made following crossover of all patients to active study drug

The primary change occurs in Section 7.4.21, Medical Resource Utilization Data Collection:

Added text: **MRU data will not be captured after the study is unblinded.**

Purpose: Remove assessment of cost of treatment in each arm for patients in the unblinded study, because sufficient data will have been collected before study unblinding, and limited inference can be made following crossover of all patients to active study drug.

The primary change occurs in Section 7.4.22, Cost Assessment:

Added text: **The cost of treatment in each arm will not be assessed after the study is unblinded.**

Purpose: Clarify that PSA results will not be withheld from the sponsor after unblinding

The primary change occurs in Section 7.4.13, Disease Assessment:

Added text: **PSA results will not be withheld from the sponsor after study unblinding.**

Purpose: Remove recording of complete medical histories after study unblinding, because this information will have already been collected from patients in the blinded study

The primary change occurs in Section 7.4.3, Medical History:

Added text: **Complete medical histories will not be collected after the study is unblinded.**

Purpose: Remove recording of height after study unblinding, because this information will have already been collected from patients in the blinded study

The primary change occurs in Section 7.4.5, Patient Height and Weight:

Added text:	**Height will not be measured after the study is unblinded.**

Purpose: Clarify that informed consent will be collected from all patients at the time of study unblinding

The primary change occurs in Section 7.4.1, Informed Consent:

Added text:	**Informed consent will be collected from all patients at the time of study unblinding.**

Purpose: Update language on utility measurement, stating that this data will be continually collected until the patient discontinues study drug

The primary change occurs in Section 7.4.20, Utility Measurement:

Formerly read:	The utility measurement should ~~also~~ be continually collected until the ~~development of confirmed PD~~.
Now reads:	The utility measurement should be continually collected until the **patient discontinues study drug**.

Purpose: Add language indicating that the short-term follow-up portion of the study will no longer apply to patients at the time of unblinding

The primary change occurs in Section 7.4.24, Long-Term Survival Status:

Added text:	**Patients in short-term follow-up at the time of study unblinding will move to long-term follow-up.**

Sections that also contain this change are:

- PROTOCOL SUMMARY
- Section 4.1
- Section 7.7

Purpose: Add inclusion criteria for patients crossing over from placebo to orteronel treatment

The primary change occurs in Section 5.3, Criteria for Patients Crossing Over to Orteronel Treatment:

Added text:

Patients who are crossing over from placebo to orteronel treatment must meet all of the criteria listed below. Completion of a second eligibility checklist is not required.

1. **Voluntary written consent, given before performance of any study-related procedure not part of standard medical care, and with the understanding that consent may be withdrawn at any time without prejudice to future medical care.**
2. **Stable medical condition at the time of crossover.**
3. **Screening clinical laboratory values as specified below (screening labs for patients who were taking placebo at the time of unblinding may use central laboratory values from their last cycle):**
   - **Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) must be ≤ 3 × the upper limit of normal (ULN).**
   - **Total bilirubin ≤ 1.5 × ULN.**
   - **Estimated creatinine clearance using the Cockcroft-Gault formula must be > 40 mL/minute (see Section 15.4).**
4. **Patients, even if surgically sterilized (ie, status postvasectomy), must:**
   - **Agree to practice effective barrier contraception during the entire study treatment period and for 4 months after the last dose of study drug, or**
   - **Agree to completely abstain from heterosexual intercourse.**
5. **No known hypersensitivity to compounds related to orteronel, orteronel excipients, prednisone, or GnRH analogue.**
6. **No likely inability to comply with the protocol or cooperate fully with the investigator and site personnel.**

Sections that also contain this change are:

- PROTOCOL SUMMARY
- Section 5

Purpose: Clarify that disease progression is not required for patients crossing over from placebo to orteronel treatment

The primary change occurs in Section 7.4.13, Disease Assessment:

Added text: **Radiographic disease assessment is not formally required after study unblinding but is at the discretion of the PI with scans performed as per standard of care. Patients are not required to have disease progression to cross over from placebo to orteronel treatment.**

Purpose: Add language indicating that, per the recommendation of the IDMC, the study may be unblinded

The primary change occurs in Section 6.8, Blinding and Unblinding:

Added text: **At the recommendation of the Independent Data Monitoring Committee (IDMC) upon review of the interim analysis (Section 9.1), the study may be unblinded based on evaluation of safety and efficacy parameters. After unblinding and crossover of patients is complete, the procedures performed during the blinded portion of the study will no longer apply.**

Sections that also contain this change are:

- PROTOCOL SUMMARY
- Section 4.1

Purpose: Clarify acceptable methods of contraception, and provide a clear definition of abstinence from heterosexual intercourse

The primary change occurs in Section 6.6, Precautions and Restrictions:

Formerly read: Male patients, even if surgically sterilized (~~eg~~, status postvasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and ~~for~~ 4 months after the last dose of study drug, or
- ~~Completely abstain from heterosexual intercourse.~~

Now reads: Male patients, even if surgically sterilized (**ie**, status postvasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and **through** 4 months after the last dose of study drug, or
- **Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable**

methods of contraception.)

Purpose: Clarify the allowable reasons for discontinuation of treatment with study drug

The primary change occurs in Section 7.7, Discontinuation of Treatment With Study Drug and Patient Replacement:

Formerly read:

Treatment with study drug may also be discontinued for any of the following reasons:

- ~~Unacceptable study drug related AE~~
- Protocol violation
- Symptomatic deterioration
- Study terminated by the sponsor
- Withdrawal ~~of informed consent~~ by ~~the patient~~
- Lost to follow-up
- Other

Within 30 days (+ 10 days) of the date of study drug discontinuation, all study procedures outlined for the EOT visit will be completed. The primary reason for study drug discontinuation will be recorded in the eCRF.

Now reads:

Treatment with study drug may also be discontinued for any of the following reasons:

- **Adverse event**
- Protocol violation
- Symptomatic deterioration
- Study terminated by the sponsor
- Withdrawal **by subject**
- Lost to follow-up
- Other

Within 30 days (+ 10 days) of the date of study drug discontinuation, all study procedures outlined for the EOT visit will be completed **as specified in the Schedule of Events**. The primary reason for study drug discontinuation will be recorded in the eCRF.

Purpose: Clarify the allowable reasons for withdrawal of patients from the study

The primary change occurs in Section 7.8, Withdrawal of Patients From Study:

Formerly read:

A patient may be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Study terminated by the sponsor
- Withdrawal ~~of informed consent~~ by ~~the patient~~
- Other

Now reads:

A patient may be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Study terminated by the sponsor
- Withdrawal by **subject**
- Other

Purpose: Remove instructions on emergency unblinding procedures as they no longer apply after study unblinding

The primary change occurs in Section 6.8, Blinding and Unblinding:

Deleted text:

Kit assignments will be obtained through the interactive voice response system (IVRS) according to the procedures outlined in the Study Manual. Information regarding the kit assignments will be kept securely at the sponsor's location or designee per its standard operating procedures. ~~Emergency unblinding, if necessary, will be conducted via the IVRS.~~

Purpose: Update language on the supply of unblinded study drug

The primary change occurs in Section 6.1.1, Orteronel and Placebo Supply:

Formerly read:

~~Orteronel~~ active ~~tablets will be supplied as film-coated tablets, each containing 200 mg of~~ orteronel. Placebo tablets will be identical in shape and size to the orteronel active tablets. ~~Each bottle of orteronel active tablets and placebo will contain 64 tablets. Both the active and placebo tablets of orteronel will be supplied by the sponsor.~~

Now reads:

200 mg active orteronel **tablets will be supplied by the sponsor and labeled in accordance with all applicable regulations.** Placebo tablets will be identical in shape and size to the orteronel active tablets.

Purpose: Update language on the labeling of unblinded study drug

The primary change occurs in Section 6.11, Packaging and Labeling:

Formerly read:	Orteronel and placebo tablets will be packaged in ~~120 cc,~~ round, white, high-density polyethylene bottles with a ~~38 mm,~~ child-resistant cap with induction seal. Each bottle of active orteronel or placebo study medication will be labeled with either a single-panel or multi-language booklet label containing pertinent study information, country-specific requirements, and a caution statement. Prednisone (or commercially available equivalent) may be provided in bottles or blister packs and will be labeled ~~as investigational material. The packaging labels will fulfill~~ all requirements specified by governing regulations.
Now reads:	Orteronel and placebo tablets will be packaged in round, white, high-density polyethylene bottles with a child-resistant cap with induction seal. Each bottle of active orteronel or placebo study medication will be labeled with either a single-panel or multi-language booklet label containing pertinent study information, country-specific requirements, and a caution statement. Prednisone (or commercially available equivalent) may be provided in bottles or blister packs and will be labeled **per** all requirements specified by governing regulations.

Purpose: Update language on the storage of unblinded study drug

The primary change occurs in Section 6.12, Storage, Handling, and Accountability:

Formerly read:	Orteronel and placebo study medication should be stored in the original dispensing bottles ~~at 20°C to 25°C (68°F 77°F) with temperature excursions permitted from 15°C to 30°C (59°F 86°F)~~.
Now reads:	Orteronel and placebo study medication should be stored in the original dispensing bottles **according to labeled conditions**.

Purpose: Clarify excluded concomitant medications nomenclature

The primary change occurs in Section 6.4, Excluded Concomitant Medications and Procedures:

Formerly read:	The following medications and procedures are prohibited during the treatment and short-term follow-up portion~~s~~ of the study: … • Cabazitaxel

- ~~MDV 3100~~
- Abiraterone

Now reads:

The following medications and procedures are prohibited during the treatment and short-term follow-up portion of the study:

…

- Cabazitaxel **(Jevtana®)**
- **Enzalutamide (XTANDI®)**
- Abiraterone **(Zytiga®)**

Purpose: Update procedures for recording and reporting AEs and SAEs to be consistent with the sponsor's current procedures

The primary change occurs in Section 10.2, Procedures for Recording and Reporting Adverse Events and Serious Adverse Events:

Formerly read:

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE ~~and must be recorded on the appropriate pages of the eCRF~~. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

~~All~~ SAEs and serious pretreatment events (as defined in Section 10.1) must be reported (see Section 10.4 for the period of observation) by the investigator to the Millennium Department of Pharmacovigilance's designee, PPD, (contact information provided below)by faxing the SAE Form within ~~1 working day~~ after becoming aware of the event. ~~All SAEs and serious pretreatment events (which include all deaths) must be reported whether or not considered causally related to the study drug or study procedures.~~ The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Millennium~~'s designee~~. ~~The~~ SAE report information ~~and~~ the data provided on the eCRF ~~must match.~~

Now reads:

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF **(see Section 10.4 for the period of observation)**. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1

comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 10.1) must be reported (see Section 10.4 for the period of observation) by the investigator to the Millennium Department of Pharmacovigilance's designee, PPD, (contact information provided below)**. This should be done** by faxing the SAE Form within **24 hours** after becoming aware of the event. The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Millennium. SAE report information **must be consistent with** the data provided on the eCRF**.**

Purpose: Update details on the monitoring of AEs throughout the study to be consistent with the sponsor's current procedures

The primary change occurs in Section 10.4, Monitoring of Adverse Events and Period of Observation:

Formerly read:

AEs, both nonserious and serious ~~(which include all deaths)~~, will be monitored throughout the study as follows~~. Adverse events~~:

- will be reported from the first dose of study drug through 30 days after treatment with the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first, and recorded in the eCRFs. That is, if a patient begins a new antineoplastic therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started.
- Serious pretreatment events will be reported to the Millennium Department of Pharmacovigilance~~'s~~ designee~~, PPD,~~ from the time of the signing of the ~~informed consent form (~~ICF~~)~~ up to ~~the~~ first dose of study drug, but not be recorded in the eCRFs~~; nonserious pretreatment events will not be reported~~.
- ~~S~~erious adverse events will be reported to PPD from the first dose of study drug through the last treatment visit (30 days after administration of the last dose of study drug) and recorded in the eCRFs. ~~All~~ SAEs ~~(which include all deaths)~~ must ~~also~~ be reported to ~~PPD (see Section 10.2). All~~ SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

~~Any SAE that occurs at any time after completion of the study and the designated follow-up period that the investigator considers to be related to study drug must be reported to PPD.~~

Now reads:

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- **AEs** will be reported from the first dose of study drug through 30 days after treatment with the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first, and recorded in the eCRFs. That is, if a patient begins a new antineoplastic therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started.
- Serious pretreatment events will be reported to the Millennium Department of Pharmacovigilance **or** designee from the time of the signing of the ICF up to first dose of study drug, but **will** not be recorded in the eCRF.
- **Related and unrelated s**erious adverse events will be reported to **the Millennium Department of Pharmacovigilance or** PPD from the first dose of study drug through the last treatment visit (30 days after administration of the last dose of study drug) and recorded in the eCRFs. **After this period, only related** SAEs must be reported to **the Millennium Department of Pharmacovigilance or designee.** SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Purpose: Clarify that a listing of TEAEs resulting in study drug discontinuation will be provided

The primary change occurs in Section 8.1.7, Safety Analysis:

Added text:

A listing of treatment-emergent AEs resulting in study drug discontinuation will be provided.

Purpose: Update status of ongoing clinical trials with orteronel to include Studies C21004, C21008, C21009, C21012, and C21013

The primary change occurs in Section 1.3, Orteronel Clinical Experience:

Formerly read:

~~Five~~ phase 1 clinical trials have been completed with orteronel in healthy male subjects: 2 single-ascending oral dose studies using an immediate-release (IR) tablet formulation (01-02-TL-700-001 and TAK-700/CPH-001), 1 single- and multiple-ascending oral dose study using a modified-release capsule formulation (TAK-700/EC-102), 1 relative bioavailability study of 2 IR tablet formulations (T1 and T2 formulations) (Study C21002), ~~and 1 crossover study on the effect of food on the absorption of orteronel (Study C21007), In addition, a phase 1/2, open-label, multiple-dose clinical trial of twice-daily dosing of TAK-700 (IR tablet) in patients with chemotherapy-naïve, androgen-independent mCRPC (TAK-700_201) is ongoing in the US,~~

~~and a phase 1 study in patients with CRPC (TAK-700/CPH-402) is ongoing in Japan. A phase 2, open-label study evaluating the safety and efficacy of orteronel in patients with nonmetastatic CRPC and a rising PSA (C21001) is ongoing in the US, as is a phase 1/2 open-label study of orteronel in combination with docetaxel and prednisone in patients with mCRPC (C21003).~~

Now reads:

Seven phase 1 clinical trials have been completed with orteronel in healthy male subjects: 2 single-ascending oral dose studies using an immediate-release (IR) tablet formulation (01-02-TL-700-001 and TAK-700/CPH-001), 1 single- and multiple-ascending oral dose study using a modified-release capsule formulation (TAK-700/EC-102), 1 relative bioavailability study of 2 IR tablet formulations (T1 and T2 formulations) (Study C21002), **1 crossover study on the effect of food on the absorption of orteronel (Study C21007), 1 study on the absorption, distribution, metabolism, and excretion of orteronel (Study C21008), and 1 crossover, bioequivalence study of 2 IR tablet formulations (T2 and T3 formulations [Study C21009]).**

…

Ongoing studies in patients with prostate cancer include:

- **One phase 1/2 study in patients with chemotherapy-naïve mCRPC in the US (Study TAK-700_201)**
- **One phase 1 study in patients with CRPC (Study TAK 700/CPH-402) in Japan**
- **One phase 2 study in patients in the US with nonmetastatic CRPC (Study C21001)**
- **One phase 1/2 trial in patients with mCRPC in the US that combines orteronel with docetaxel and prednisone (Study C21003)**
- **One phase 1/2 trial in patients with CRPC in Japan and ex-Japan to characterize PK and pharmacodynamic response of orteronel plus prednisone (Study C21013)**
- **One phase 2 study to investigate the effects of orteronel plus prednisone on the QT/ QTc interval in patients with mCRPC (Study C21012)**
- **One global, phase 3, randomized, placebo-controlled study that combines orteronel with prednisone in patients with mCRPC who have not received prior chemotherapy (Study C21004)**

Purpose: Add background information on enzalutamide and abiraterone acetate to the study rationale

The primary change occurs in Section 1.4, Study Rationale:

Added text: **Abiraterone acetate, an irreversible steroidal CYP enzyme 17 (CYP17) inhibitor of both the 17,20-lyase and 17-hydroxylase activities approved for patients with mCRPC who have received prior docetaxel, prolonged overall survival (OS) in patients with mCRPC who had previously received docetaxel chemotherapy.[43, 44] Furthermore, abiraterone acetate showed improvement in progression-free survival and a trend in OS in chemotherapy-naïve mCRPC patients.[45] However, toxicities attributed to a syndrome of secondary mineralocorticoid excess have been noted with abiraterone and require administration of a mineralocorticoid receptor antagonist or glucocorticoid to suppress ACTH.[29] Enzalutamide, an androgen receptor inhibitor, was recently approved in the US for treatment of mCRPC in docetaxel-treated patients after showing improvement in OS compared with placebo in patients with mCRPC who had previously received docetaxel chemotherapy.[46, 47]**

Purpose: Update the risk language of orteronel, per the most recent IB data cutoff date, 29 September 2012

The primary change occurs in Section 1.5.3, Potential Risks:

Formerly read: Due to its mechanism of action, orteronel treatment may elicit ~~expression of~~ adverse events typically associated with androgen deprivation therapy (decreased bone mineral density, hyperglycemia, and prolonged QTc interval). Other potential risks include decreased left ventricular ejection fraction, ~~increased serum amylase and/or lipase~~, or adrenal insufficiency. See the IB for detailed safety information.

Now reads: Due to its mechanism of action, orteronel treatment may elicit adverse events typically associated with androgen deprivation therapy (decreased bone mineral density, hyperglycemia, and prolonged QTc interval). Other potential risks include decreased left ventricular ejection fraction, **hepatotoxicity**, or adrenal insufficiency. See the IB **and SMA** for detailed safety information.

Purpose: Update pancreas-related SAEs, per the most recent IB data cutoff date, 29 September 2012

The primary change occurs in Section 1.5.3, Potential Risks:

Formerly read:	As of ~~9 May 2011~~, ~~3~~ SAEs of pancreatitis and ~~2~~ SAEs of elevated pancreatic enzymes were reported for patients with prostate cancer receiving orteronel. ~~Four~~ of these cases were considered related to study drug by the investigator. The role of orteronel in these cases remains unclear and a causal relationship between orteronel and pancreatitis has not been established.
Now reads:	As of **29 September 2012**, **4** SAEs of pancreatitis and **20** SAEs of elevated pancreatic enzymes were reported for patients with prostate cancer receiving orteronel. **All** of these cases were considered related to study drug by the investigator. The role of orteronel in these cases remains unclear and a causal relationship between orteronel and pancreatitis has not been established. **See the IB for detailed safety information.**

Purpose: Update the risk language for T-1358043 (a process impurity, drug product degradant, and minor metabolite of orteronel) based on nonclinical studies

The primary change occurs in Section 1.5.3, Potential Risks:

Formerly read:	~~A degradant in the TAK-700 tablet~~ tested positive for genotoxicity in ~~in vitro~~ tests and could potentially pose a risk to human subjects. The potential clinical implications of these ~~in vitro~~ results are that any resulting genetic or chromosomal change could potentially lead to secondary malignancy and ~~may pose a risk to an unborn child~~.
Now reads:	**T-1358043, a process impurity, drug product degradant, and minor metabolite of orteronel,** tested positive for genotoxicity in **laboratory** tests and could potentially pose a risk to human subjects. The potential clinical implications of these **laboratory** results are that any resulting genetic or chromosomal change could potentially lead to secondary malignancy and **raise the risk of heritable defects to offspring**.

Purpose: Clarify details on study conduct in adherence to Good Clinical Practices (GCP) standards

The primary change occurs in Section 11.5, Ethical Considerations:

Formerly read:	The study will be conducted in accordance with ~~ethical principles founded in the Declaration of Helsinki~~. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients (including diary cards), safety updates,

annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or the sponsor, as allowed by local regulations.

Now reads: The study will be conducted in accordance with **applicable regulatory requirement(s) and will adhere to GCP standards**. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or the sponsor, as allowed by local regulations.

Purpose: Update language on the procedures for product complaints and medication errors during the study

The primary change occurs in Section 11.11, Product Complaints:

Deleted text: ~~A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error situation should immediately contact MedComm Solutions (see below) and report the event.~~

For Product Complaints ~~or Medication Errors~~,

call MedComm Solutions at

[redacted]

(US and International)

Product complaints ~~and medication errors~~ in and of themselves are not AEs. If a product complaint ~~or medication error~~ results in an SAE, an SAE form should be completed and sent to PPD (refer to Section 10.2).

Purpose: Update protocol signatories

The primary change occurs on the Cover Page:

Formerly read: [redacted] MD

Senior ~~Vice President,~~

Clinical ~~Chair,~~ Clinical ~~Review Board~~

(or designee)

	[redacted] MD ~~Interim Global~~ Clinical ~~Head~~ ~~Clinical~~ Researach ~~& Distinguished Medical Fellow, Clinical Development~~ (or designee)
Now reads:	[redacted] MD Senior **Medical Director,** **Global** Clinical **Lead** **Oncology** Clinical **Research** (or designee) [redacted] MD **Medical Director** **Oncology** Clinical Research (or designee)

Purpose: Correct typographical errors, punctuation, grammar, and formatting

These changes are not listed individually.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	26-Mar-2013 17:35
[redacted]	Medical Monitor Approval	26-Mar-2013 20:16