A Phase 2 Study Determining Safety and Tolerability of Enzalutamide (Formerly MDV3100) in Combination With Abiraterone Acetate in Bone Metastatic Castration-resistant Prostate Cancer Patients

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STATISTICAL ANALYSIS PLAN

Final Version 2.0, dated 04-JAN-2016

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I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse Event
ALT	Alanine Aminotransferase
APGD	Astellas Pharma Global Development
AR	Androgen Receptor
ASCM	Analysis Set Classification Meeting
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutical Classification
BES	Biomarker Evaluable Set
BID	Twice a Day
BMI	Body Mass Index
CAT (CT scan)	Computed Axial Tomography
CFR	Code of Federal Regulations
CI	Confidence Interval
CM	Concomitant Medication
CR	Complete Response
CRPC	Castration-Resistant Prostate Cancer
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
CXR	Chest x-ray
CV	Coefficient of Variation
DHT	Dihydrotestosterone
DRM	Data Review Meeting
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EOT	End of Treatment
ESV	End of Study Visit
ET	End of Treatment
GM	Geometric Mean
GnRH	Gonadotropin Releasing Hormone
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
IND	Investigational New Drug (Application)
INR	International Normalized Ratio
ISN	International Study Number
LDH	Lactate Dehydrogenase
LOQ	Limit of Quantitation
LLOQ	Lower Limit of Quantitation
LVEF	Left Ventricle Ejection Fraction
K-M	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory
mg	Milligram
mmHg	Millimeters of Mercury

Abbreviations	Description of abbreviations
MRI	Magnetic Resonance Imaging
MUGA	Multi-Gated Acquisition
NCI	National Cancer Institute
NYHA	New York Heart Association
PCWG2	Prostate Cancer Clinical Trials Working Group 2
PD	Progressive Disease
PES	Plasma Evaluable Set
PFS	Progression Free Survival
PK	Pharmacokinetics
PKAS	Pharmacokinetic Analysis Set
PR	PR Interval
PR	Partial Response
PSA	Prostate-Specific Antigen
PT	Prothrombin Time
PT	Preferred Term
PTT	Partial Thromboplastin Time
QD	Once Daily
QRS	QRS Interval
QTcB	QTC Bazett Calculator
QTcF	QTC Fridericia Calculator
RECIST	Response Evaluation Criteria In Solid Tumors
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SD	Stable Disease
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
WHO-DRL	World Health Organization-Drug Reference List

List of Key Terms

Terms	Definition of terms
Adverse Event	An adverse event with an onset date on or after starting administration of the study drug or any ongoing AE on the date of first dose that has worsened in severity after administration of the study drug. All adverse events collected that begin within 30 days of taking the last dose of study drug will also be counted as TEAE.
Baseline	A period that begins at the Screening visit where all initial subject assessments and findings will be obtained prior to study drug administration on Day 1.
Discontinuation	A discontinuation is a subject who is enrolled in the study and for whom study drug is terminated for any reason.
Enroll	To register or enter into the study following the signing of informed consent.
Investigational Period	Period of time between Day 1 to Safety F/U.
Screening failure	Screened subject, but did not fulfill protocol inclusion and/or exclusion criteria and failed to receive open label study treatment, or decided not to participate anymore (withdrew consent) prior to completing pre- investigational period.
Screening period	Period of time between Day -28 and Day -1.
Study Drug	Agents given as part of a clinical trial. In this study, enzalutamide, abiraterone acetate and prednisone are the study drugs.
Subject	An individual who participates in this clinical trial, and will be a recipient of the study drug.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

The SAP is finalized and signed before the database soft lock at the latest. Any deviations from the SAP will be justified in the Clinical Study Report (CSR).

Prior to Database Lock, a Final Review of Data and Tables, Listings, and Figures (TLFs) Meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed.

This SAP is created to accommodate the production of a Clinical Study Report based on the final efficacy evaluation of the data from the study. Only data from visits which took place on or before the cutoff date will be included in this report. Subjects still in the study at the data cutoff date will be censored based on the data cutoff date if appropriate.

2 FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart

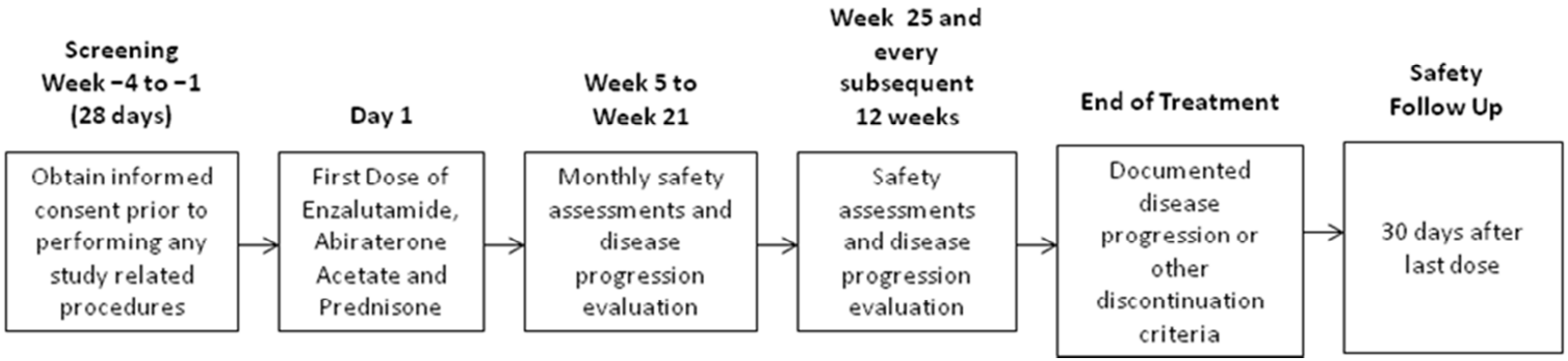

Table 1 Schedule of Assessments

Study Day	**Screening Visit**	**1**	**4**	**29**	**57**	**85**	**113**	**141**	**169**	**ET**	**Safety F/U**
Week	**−4 to −1 (28 days)**	**1**	**1**	**5**	**9**	**13**	**17**	**21**	**25 and every subsequent 12 weeks**	**End of Treatment**	**30 Days after last dose[e]**
Window (days)				**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**
Informed Consent	X										
Medical History	X										
Inclusion/Exclusion Criteria	X	X									
Vital Signs[a]	X	X		X	X	X	X	X	X	X	X
Physical Examination, Weight, Height [J]	X	X[d]		X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]
12-Lead ECG	X	X[d]		X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]	X[r]
PT/PTT [b]	X	X[d]		X	X	X	X	X	X	X	X
Clinical Labs [b] Including liver function test [c]	X	X[d]		X	X	X	X	X	X	X	X
PK of Abiraterone [l]			X	X							
PK of enzalutamide [m]				X							
PSA	X	X[d]		X	X	X	X	X	X	X	X
Urine N-telopeptide	X				X					X[g]	
Blood testosterone and DHT levels [q]	X				X					X[g]	
CT/MRI and Bone Scan	X[i]					X			X	X	
CXR or Chest CT	X[k]					X[k]				X[k]	
MUGA or ECHO [f]	X										
ECOG Performance Status	X	X		X	X	X	X	X	X	X	X
Bone Marrow Aspirate and Biopsy		X[h]			X					X[g]	
Archival Tumor Tissue [o]	X										
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Previous & Concomitant Medications	X	X		X	X	X	X	X	X	X	X
Study Drug Dispensing		X		X	X	X	X	X	X		
Study Drug Treatment		X		X	X	X	X	X	X		
Blood Sample for Genotyping[p]		X									

a. Vital signs will be obtained prior to study drug administration and 1-2 hours after study drug administration.

b. Clinical labs (hematology and chemistry) and, PT/PTT, will be obtained prior to study drug administration. Day 1 chemistry and hematology do not need to be completed if the screening assessments were completed within 3 days prior to Day 1.

c. Subjects will have liver function tests (including alkaline phosphatase, AST, ALT, direct and total bilirubin, and LDH) every 2 weeks for the first 12 weeks of treatment.

Footnotes continued on next page

d. If Day 1 visit occurs within 72 hours after screening, these assessments do not need to be repeated.
e. Safety follow-up visit will occur after 30 days following the last dose of study drug.
f. A MUGA scan or echocardiogram showing LVEF ≥ 45% is required for subjects with a history of anthracycline or anthracenedione (mitoxantrone) treatment, or if the subjects has Congestive heart failure New York Heart Association (NYHA) class 3 or 4, or subjects with history of congestive heart failure NYHA class 3 or 4 in the past.
g. Blood sample for testosterone and DHT and urine sample for N-telopeptide will be collected if not obtained at Week 9 (Day 57) or if subject terminates study drug or study prior to Week 9 (Day 57).
h. Bone marrow aspirate and biopsy should be taken between screening and prior to first dose of study drug.
i. Subjects must be assessed with CT/MRI and bone scan within 6 weeks prior to study drug administration (Day 1).
j. Height will be recorded at the screening visit only.
k. At screening a chest X-ray will be performed. A chest CT is required if the screening chest X-ray demonstrates metastatic chest disease. In this case, additional chest CT's should be performed as follow up at Week 13 (Day 85) and end of treatment (ET) visit.
l. Optional PK blood sample for determination of plasma concentrations of abiraterone will be obtained predose on Day 4 and Day 29.
m. Optional PK blood sampling for determination of plasma concentrations of enzalutamide and its metabolites MDPC0001 and MDPC0002 will be obtained predose on week 5 (Day 29).
n. Only weight to be measured.
o. Archival tumor tissue will be obtained any time prior to Day 1.
p. Sample for optional genotyping sub-study will be collected prior to Day 1 dosing.
q. Blood sample testosterone and DHT should be collected within 2 hours of bone marrow biopsy and aspirate.
r. ECG must be performed prior to dosing.

3 STUDY OBJECTIVES AND DESIGN

3.1 Study Objectives

3.1.1 Primary Objective

To explore the safety, and tolerability of enzalutamide in combination with abiraterone acetate plus prednisone.

3.1.2 Secondary Objectives

- To explore the effect of enzalutamide in combination with abiraterone acetate plus prednisone on androgen receptor signaling and androgen levels.
- To explore the antitumor activity of enzalutamide in combination with abiraterone
- acetate plus prednisone as assessed by serum prostate-specific antigen (PSA), imaging of soft tissue and bone metastases, and markers of bone metabolism.

3.1.3 Exploratory Objective

To measure pre-dose concentrations of abiraterone on Day 4 and Day 29 (optional).

3.2 Study Design

This is an open label study to determine the safety and tolerability of enzalutamide in combination with abiraterone acetate plus prednisone in castration-resistant prostate cancer (CRPC) subjects with bone metastases by clinical evaluations at protocol specified intervals.

The study will also determine the modulation of androgen receptor (AR) signaling in bone marrow biopsy and androgen levels as measured by testosterone concentration in bone marrow aspirate and blood by Liquid Chromatography Mass spectrometry, expression of AR and its subcellular localization by immunohistochemistry (IHC), presence of known and assessable splice variants and CYP17 expression in epithelial and host compartment of the cancer by IHC. Tumor tissue will be collected to determine AR signaling and candidate pathways that may be part of a signaling network implicated in therapy resistance.

Approximately 60 subjects will receive enzalutamide 160 mg daily, abiraterone acetate 1000 mg daily, and prednisone 5 mg twice daily to be taken orally. Subjects will be unable to continue in the study if one of the above study drugs is discontinued.

Throughout the study, safety and tolerability will be assessed by the recording of adverse events, monitoring of vital signs and physical examinations, safety laboratory evaluations, and 12-lead electrocardiograms (ECGs). Subjects will have a safety follow-up visit 30 days after their last dose of study drug.

The occurrence of an adverse event or toxicity, where continued administration of study drug is deemed to be not in the subject's best interest by the investigator and/or the sponsor, will result in the removal of the subject from therapy.

For the study duration, all subjects will maintain androgen deprivation with an GnRH agonist or antagonist or orchiectomy.

Study drug will be administered until disease progression. Disease progression is defined as a composite endpoint, consisting of either clinical deterioration, radiographic progression or PSA progression according to the prostate cancer clinical trials working group 2 (PCWG2) criteria. Subjects with PSA progression alone will not be withdrawn from the study.

The following assessments of prostate cancer status will be collected during the course of the trial: soft tissue disease on computed tomography (CT) scan or on magnetic resonance imaging (MRI), bone disease on radionuclide bone scans, and PSA.

Study films (abdominopelvic CT/MRI [lung when applicable] and bone scan) should be read on site.

Optional pharmacokinetics (PK) blood samples for determination of plasma concentrations of abiraterone will be collected pre-dose on Day 4 and Day 29. In addition optional PK blood sampling for determination of plasma concentrations of enzalutamide and its metabolites MDPC0001 and MDPC0002 will be collected on Day 29.

Archival tumor tissue samples will be collected to allow for tumor profiling. Samples will be obtained and stored until qualified assays become available.

3.3 Randomization

This is an open-label study, subjects who meet all inclusion criteria and no exclusion criteria are assigned to begin study treatment. Registration must occur following informed consent process and prior to initiation of investigational therapy. A unique subjects/treatment number is assigned to each subjects enrolled in the study. Discontinued subjects are not replaced.

4 SAMPLE SIZE

A total of 60 subjects will provide sufficient data to assess the safety of the drug combination. The sample size and power calculation are based on the change of testosterone concentration or gene expressions (i.e., AR and CYP17) before and after therapy, which can be characterized based on effect size (i.e., mean difference of testosterone concentration or gene expression divided by standard deviation). Considering subjects with baseline and Week 9 laboratory results derived from bone marrow samples, a sample of 30 subjects provides 82% power to detect a change of testosterone concentration or gene expression with an effect size of at least 0.55, using a two sided paired t-test at a 0.05 significance level. A total of 60 subjects will be accrued to obtain at least 30 evaluable patients based on the prediction that the yield of evaluable bone marrow samples with prostate cancer cells is approximately 50%.

5 ANALYSIS SETS

Detailed criteria for analysis sets will be laid out in Classification Specifications and the allocation of subjects to analysis sets will be determined prior to database hard-lock. In accordance with ICH recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

Four populations will be used for the analyses; the Safety Analysis Population (SAF), the Biomarker Evaluable Set (BES), Plasma Evaluable Set (PES), and the Pharmacokinetic Analysis Set (PKAS). However the number of subjects with evaluable biomarker parameter results may differ, resulting in several Biomarker and Plasma Evaluable Sets. If case-by-case review is required to allocate subjects to analysis sets then this will be determined at the Analysis Set Classification Meeting (ASCM) prior to database hard lock.

5.1 Safety Analysis Set (SAF)

The Safety Analysis Set will consist of all subjects who received at least one dose of any drug of the study combination treatment (i.e., enzalutamide, abiraterone acetate, and prednisone).

The SAF will be used to report all safety and efficacy analyses.

5.2 Biomarker Evaluable Set (BES)

The Biomarker Evaluable Set (BES) will consist of all subjects with baseline and Week 9 laboratory results derived from bone marrow samples. The number of subjects with evaluable results may differ for each parameter:

- Biomarker <*parameter*> Evaluable Set: Subjects from the SAF population with bone marrow results at baseline and at Week 9 assessments for the following parameters: Testosterone (BTES), Cortisol (BCES), Androstenedione (BAOS), Progesterone (BOES), and Pregnenolone (BEES).

5.3 Plasma Evaluable Set (PES)

The Plasma Evaluable Set (PES) will consist of all subjects with baseline and Week 9 assessment of testosterone and DHT results derived from plasma samples. The number of subjects with evaluable results may differ for each parameter:

- Plasma <*parameter*> Evaluable Set: Subjects from the SAF population with blood testosterone results at baseline and at Week 9 assessments for the following parameters: Testosterone (PTES), Cortisol (PCES), Androstenedione (PAOS), Progesterone (POES), and Pregnenolone (PEES).

5.4 Pharmacokinetics Analysis Set (PKAS)

The Pharmacokinetic Analysis Set will include the subjects from the SAF population for whom at least one PK pre-dose concentration is available. Additional subjects may be excluded from the PKAS at the discretion of the pharmacokineticist.

The PKAS will be used for all tabular and graphical summaries of the PK data.

5.5 Protocol Deviations

All protocol deviations and whether they lead to the exclusion of the subject from the SAF, any of the Biomarker Evaluable Sets and/or PKAS will be listed. Additional other protocol deviations that are identified during the ASCM will also be presented.

The following protocol deviations will be defined:

- Subjects who entered the study even though they did not satisfy the entry criteria
- Subjects who developed withdrawal criteria during the study but were not withdrawn
- Subject who received the wrong treatment or incorrect dose
- Subjects who received an excluded concomitant medication
- Other:
  - The actual PK sampling time deviates from the planned sampling day or time
  - (e.g., post-dose instead of pre-dose)
  - Visit outside protocol visit windows
  - Further protocol deviation may be determined by the team during the ASCM

Subjects with protocol deviations will not be excluded from the analyses of the safety data (except in the case of subjects with all post-baseline safety data missing). The PK specialist will be consulted whether there are any protocol deviations which lead to exclusion of subjects or plasma concentrations at single time-points from the PK analysis.

6 ANALYSIS VARIABLES

6.1 Efficacy Variables

All efficacy analyses will be carried out on secondary variables.

6.1.1 Overview

The efficacy of the treatment combination will be assessed by:

- Androgens
  - Testosterone concentration in bone marrow aspirate and blood
- Androgen pre-cursors and other associated metabolites. For example:
  - Cortisol
  - Androstenedione
  - Pregnenolone
  - Progresterone
- Androgen receptor signaling
  - Expression and localization of AR
  - CYP17 expression
  - Splice variant
- Pathways linked with non-classical AR signaling & Bone development
- Anti-tumor activity
  - PSA levels
  - Objective response according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1
  - Bone scan results
  - Progression Free Survival (PFS)
- Markers of bone metabolism
  - Bone specific alkaline phosphatase

- Urine N-telopeptides

6.1.2 Androgen and Androgen Pre-cursors

Bone marrow aspirate and blood measuring androgen and androgen pre-cursors will be collected at the Screening visit and Week 9, and at the end of treatment if the sample was not obtained at Week 9, or subject terminates study drug or study prior to Week 9 bone marrow assessment.

Baseline value will be defined as the screening value prior to first dose of study drug. Change from baseline and percent change from baseline will be calculated as (Week 9 – Baseline) and ((Week 9 – Baseline)/Baseline)*100, respectively.

6.1.3 Expression and Localization of AR

The study will also determine the modulation of AR signaling in and its subcellular localization in bone marrow biopsy by IHC as described per the schedule of assessment [Table 1].

It will be collected at the Screening visit and Week 9, and at the end of treatment if the sample was not obtained at Week 9, or subject terminates study drug or study prior to Week 9 bone marrow assessment.

For purposes of this report the variables related to expression and localization of Androgen Receptors will only be listed in the report and no further analyses will be performed.

6.1.4 Splice Variants and CYP17 Expression

The study will determine the presence of known and assessable splice variants and CYP17 expression in epithelial and host compartment of the cancer by IHC as described per the schedule of assessment [Table 1].

It will be collected at the Screening visit and Week 9, and at the end of treatment if the sample was not obtained at Week 9, or subject terminates study drug or study prior to Week 9 bone marrow assessment.

For purposes of this report the variables related to Splice Variants and CYP17 expression will only be listed in the report and no further analyses will be performed.

6.1.5 PSA Levels

Samples for PSA will be collected and analyzed at the local laboratory. Prostate-specific antigen testing will be performed as per the schedule of assessment [Table 1]. The PSA test performed at the Screening visit does not need to be repeated on Day 1 if the Day 1 visit occurs within 72 hours of screening.

Baseline value will be defined as the latest value prior to first dose of study drug. For the PSA levels the following variables will be derived and summarized:

- PSA response is the change from baseline and percent change from baseline that will be calculated as (Post-baseline – Baseline) and ((Post-baseline – Baseline)/Baseline)*100, respectively.

- The best PSA response is the largest decline in PSA, expressed as the percentage change from baseline, that occurs at any point after treatment start. For subjects with no decrease, the best PSA response is the smallest increase in PSA.

The following time intervals will be used for the best PSA response:

  - over the first 12 weeks on treatment
  - up to and including the end of treatment (EOT) visit but excluding the end of study visit (ESV)
  - up to and including the end of study visit (ESV)

- Proportion of subjects with a decline from baseline in PSA blood concentrations of ≥30%, ≥50% and ≥90% observed at every visit as well as the proportion of subjects with the largest decline in PSA from baseline (Nadir), ≥30%, 50% and ≥90%.

6.1.6 RECIST and Bone Scan Results

The overall objective response assessment is based on RECIST version 1.1 for soft tissue lesion on CT/MRI and the PCWG2 guidelines for bone lesions on bone scans. The baseline is the last assessment prior to the first drug intake.

All assessments will be done by the investigator, no independent central review.

TimePointResponsefortargetlesionsandnon-targetlesions.

Response assessments for target and non-target lesions are reported in the eCRF by the investigator at each of the time-points mentioned in the schedule of assessments [Table 1 above], to one of the following categories:

- CR = complete response
- PR = partial response (Target only)
- SD = stable disease (Target only)
- PD = progressive disease
- Non CR/non PD= not complete response rate and not progressive disease (Non-Target only)
- NE = not evaluable
- NA= not applicable

TimePointResponseforbonelesions.

Response assessments for bone lesions are reported in the eCRF by the investigator at each of the time-points mentioned in the schedule of assessments to one of the following categories:

- CR = complete response
- PD = progressive disease
- PDu = unconfirmed progressive disease
- Non CR/non PD= not complete response rate and not progressive disease
- NE = not evaluable
- NA = not applicable

OverallTimePointResponse

In the CRF the Overall Time Point Response assessment reported by the investigator incorporates both the RECIST overall time point response assessment for soft tissue lesions by CT/MRI [see Table 2 and Table 3 below] and the response assessment on bone lesion according to PCWG2.

The following categories have been used:

- CR = complete response
- PR = partial response
- SD = stable disease
- PD = progressive disease
- Non CR/non PD= not complete response rate and not progressive disease
- NE= not evaluated

All the above parameters will be summarized by visit.

RESISTOverallTimePointResponse

At each time point, the RECIST overall time point response in patients with measurable soft tissue lesions at study entry can be derived according to RECIST for all possible combinations [Table 2] of tumor response assessments in target and non-target lesions in soft tissues with or without appearance of new unequivocal lesions.

Table 2 RECIST Overall Responses for All Possible Combinations of Tumor Responses in Target and Non-target Lesions With or Without The Appearance of New Lesions

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

*Any unequivocal new lesions

Based on the methodology described in [Table 2] above, the best overall response per RECIST 1.1, during the entire investigational period will be derived and summarized.

6.1.7 Progression Free Survival

Progression free survival (PFS) will be measured as time from the date of first dose of any drug of the study combination treatment until the first evidence of documented progression (a composite endpoint consisting of radiographic progression or PSA progression by PCWG2 or clinical deterioration) or death in absence of progression (whichever comes first) or the date

last known to be progression free. In other words, PFS is the time interval (in days) between the earliest date among the date of first evidence of PD (radiographic progression or PSA progression by PCWG2 or clinical deterioration) or the date of death in absence of progression or the date last known to be progression free and the date of first dose of any drug of the study combination plus1.

Definition radiographic progression

Radiographic progression is defined as either a progression in soft tissue on CT/MRI according to RECIST 1.1, and/or a progression in bone lesions on the bone scan (when a minimum of two new lesions are observed). In the CRF, at each time-point, radiographic disease progression has been assessed by the investigator as progression based on both RECIST (for soft tissue) and bone lesions. In the absence of bone lesion unequivocal progression based on bone scan, the radiographic progression assessment will correspond to the RECIST overall response assessment if available; if not available radiographic progression is considered absent. In the presence of a bone lesion unequivocal progression or a new bone lesion on bone scan, which leads to treatment discontinuation, radiographic progression is considered present, whatever the RECIST overall tumor response assessment is.

Definition clinical progression (deterioration)

Clinical progression will be defined based on the observation of clinical signs and symptoms due to disease progression, assessed by the investigator and reported in the eCRF, as AEs at any time during the course of the study. Adverse event with “disease progression” as the reported term, corresponding to disease progression as the cause of death will also be considered as clinical progression.

Definition PSA progression

Prostate-specific antigen progression by PCWG2 is defined as a PSA increase ≥ 25% and ≥ 2 ng/ml above the post-baseline nadir, and which is confirmed by the first subsequent value of 3 or more weeks later. The date of the PSA progression is the date the first evidence of PSA progression is documented.

6.1.8 Markers of Bone Metabolism, Bone specific Alkaline Phosphatase and Urine N-telopeptide

Bone alkaline phosphatase will be measured from the same serum tube of the chemistry parameters as per the schedule of assessment [Table 1]. The lab test performed at the Screening visit does not need to be repeated on Day 1 if the Day 1 visit occurs within 72 hours of screening.

A 30 mL random urine sample will be collected for measurement of urine N-telopeptide at the Screening visit and Week 9, and at the end of treatment if the sample was not obtained at Week 9, or subject terminates study drug or study prior to Week 9 bone marrow assessment.

Baseline value will be defined as the screening value prior to first dose of study drug. Change from baseline and percent change from baseline will be calculated as (Week 9 – Baseline) and ((Week 9 – Baseline)/Baseline)*100, respectively.

6.2 Safety Variables

All safety analyses will be carried on primary variables.

6.2.1 Overview

The safety of the treatment combination will be assessed by:

- Nature, frequency and severity of adverse events
- Safety laboratory tests: chemistry and hematology
- Vital signs (blood pressure, pulse rate and temperature)
- 12 Lead electrocardiogram (ECG) parameters
- Physical examination results.

6.2.2 Adverse Events (AEs)

Adverse events (AEs) will be assessed regularly as per schedule of assessments [Table 1]. Adverse event collection will begin at the time the informed consent form is signed and continue through to the last assessments.

For purposes of safety assessment in this study, recorded AEs will be classified as either treatment emergent adverse events (TEAEs) or pre-treatment adverse events.

Adverse events which started or worsened during the pre-investigational period (i.e., during the period from obtaining informed consent to the start and prior to administration of study drug) will be considered as pre-treatment AEs.

An adverse event whose onset date is on the first day of drug intake and ‘onset after first dose of study drug’ is marked as ‘yes’ by the investigator in the eCRF or whose onset date is after the first dose of any study drug of the study combination treatment will be considered as TEAE. If a subject experiences an event both during the pre-investigational period and during the investigational period, the event will be considered as TEAE only if it has worsened in severity (i.e., it is reported with a new start date). Severity of AEs is reported by the investigator using the NCI (National Cancer Institute) CTCAE (Common Terminology Criteria for Adverse Events) Version 4.03. For AEs with incomplete or missing start date and/or time, a worst-case scenario will be used to determine treatment emergence of this adverse event (see algorithm in Section 7.9.2).

The duration of each adverse event will be calculated as the difference between the onset date and the end date, and presented in days. Section 7.9.2 contains an elaboration on how to deal with missing dates.

The following counting rules for AEs are used:

- A subject having experienced the same event (i.e., same preferred term) more than once will be counted only once in the number of subjects experiencing AEs.

- When the table counts AEs only by severity, then only the most severe severity will be counted for each event.
- When the table counts AEs only by relationship (by study drug), then only the most related AE will be counted for each event.

Adverse events whose relationship to study drug is assessed as "possible" or "probable" by the investigator, or whose relationship to study drug is missing on the eCRF will be defined as "treatment related AE".

AEs with a start data after the data cutoff date will be excluded

6.2.3 Clinical Laboratory

Routine laboratory assessments for hematology, chemistry and PT/PTT will be collected and analyzed at the local laboratory and will be obtained as per schedule of assessment. The laboratory assessments performed at the Screening visit do not need to be repeated on Day 1 if the Day 1 visit occurs within 3 days of screening. Laboratory assessments must be obtained prior to study drug administration. Laboratory test specifications can be found in Section 10.1 Appendix 1.

If the results of clinical laboratory tests are outside the normal range and considered clinically significant, the investigator may decide to repeat tests on new samples.

Liver function tests (including alkaline phosphatase, AST, ALT, direct and total bilirubin, and LDH) will be assessed every 2 weeks for the first 12 weeks of treatment. See Section 10.2 Appendix 2 for liver function test and abnormalities.

Severity of each clinical laboratory parameter will be calculated using the NCI CTCAE Version 4.03 (see Section 10.3 Appendix 3).

Baseline lab value will be defined as the latest value prior to first dose of study drug. Change from baseline will be calculated as (Post-baseline – Baseline) respectively.

6.2.4 Vital Signs

Vital signs including blood pressure, pulse rate, and temperature will be assessed at Screening, at every clinic visit while on study drug, and at the safety follow-up visit.

Per schedule of assessment vital signs will be obtained prior to and 1 to 2 hours after study drug administration. Subjects should withhold dosing of study medication on clinic visit days. Study drug will be administered in clinic.

Vital signs should be assessed after 3 minutes rest, preferably supine position or in semirecumbent, if supine is not tolerated.

6.2.5 12-lead ECG

A standard 12-lead ECG will be performed on all subjects at Screening, Day1, and at every clinic visit while on study drug, and at the safety follow-up visit. The ECG test performed at the Screening visit does not need to be repeated on Day 1 if the Day 1 visit occurs within 72 hours of screening. All ECGs will be performed prior to study drug administration. The

subject should have rested in supine position (or semirecumbent, if supine is not tolerated) for 5-10 minutes.

Electrocardiogram parameters including heart rate, PR interval, RR interval, QRS interval, QT interval (QTcF and QTcB) as well as an overall conclusion will be collected on the eCRF. The overall conclusion will be recorded as normal, abnormal not clinically significant, or abnormal clinically significant. If the overall conclusion is abnormal, the abnormality recorded by the investigator on the CRF (provided in the eCRF) will be reported.

6.2.6 Physical Examination

Standard, full physical examinations will be performed to assess weight, general appearance, head, eyes, ears, nose, throat, neck, cardiovascular, chest and lungs, abdomen, musculoskeletal, neurologic status, mental status, lymphatic, and genitourinary system. Any clinically significant abnormalities will be collected as medical history (for baseline assessment) or adverse events (for post dose assessments). Weight will be recorded at each visit. Height will be recorded at the screening visit only. The physical examination performed at the screening visit does not need to be repeated on Day 1 if the Day 1 visit occurs within 72 hours of Screening visit.

6.2.7 Other Safety Variables

Other safety variables, such as ECOG, will be listed only.

6.3 Exploratory Pharmacokinetic Variables

Pre-dose concentrations of abiraterone on Day 4 and Day 29 (optional) as well as pre-dose concentration of enzalutamide on Day 29 will be collected.

6.4 Other Variables

Time of discontinuation

For subjects that did not complete the study, the time of discontinuation is calculated as: (withdrawal date – date of first intake of study drug) + 1

7 STATISTICAL METHODOLOGY

7.1 General Considerations

All statistical analyses and summary information are to be generated according to this analysis plan. Any deviation from this plan will be documented in the clinical study report.

All data processing, summarization, and analyses will be performed using SAS® Version 9.1 or higher on Unix. Specifications for table, figures, and data listing formats can be found in the TLF (Tables, Listings and Figures) specifications for this study.

All subject data collected in the eCRF for patient exposed to study drug will be listed. In data listings, baseline values will be flagged.

For continuous variables, descriptive statistics will include the number of subjects (N), mean, standard deviation (SD), median (MED), minimum (MIN), and maximum (MAX). In

addition to the above for plasma concentration data, the coefficient of variation (CV), geometric mean (GM) will also be calculated.

For categorical variables, frequencies and percentages will be presented. Percentages by categories will be based on the number of subjects with no missing data, i.e., will add up to 100%.

All statistical testing (e.g., t-test) will be 2-sided at the nominal alpha 5% level. Kaplan-Meier (KM) method will be used to summarize time-to-event analysis.

Data summaries and analyses will be presented for enzalutamide and by visit, where multiple visit assessments are available for a given parameter. Visits will be presented as Baseline, Weeks 5, 9, 13,…, 25, 25+12 week repeats, …, End of Treatment, and 30 Days After Last Dose.

Prior to database lock, a Final Review of Data and TLFs meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required consequences for the statistical analysis will be discussed.

7.2 Study Population

7.2.1 Disposition of Subjects

The following subject data will be summarized:

- Number and percentage of subjects in SAF, BES, PES, and PKAS for all enrolled subjects. For each biomarker parameter (testosterone, cortisol, androstenedione, progresterone, pregenelone, AR, Splice Variants, and CYP17) the corresponding BES will consist of the number of subjects who had both baseline and Week 9 bone marrow samples of the biomarker. Also for blood testosterone, cortisol, androstenedione, progresterone and pregenelone the corresponding PES will consist of the number of subjects who had both baseline and Week 9 blood samples of the biomarker.
- Number and percentage of subjects who completed the study or prematurely discontinued from the investigational period by reasons for discontinuation, will be tabulated for each analysis set
- Number and percentage of subjects who prematurely discontinued treatment during the investigational period by reasons for discontinuation, will be tabulated for each analysis set

7.2.2 Protocol Deviations

A summary table of the number (and percentage) of SAF subjects with protocol deviations will be presented. All protocol deviations will be listed as well as subjects or data that are excluded from the PKAS along with the reason for their exclusion will also be listed.

Subjects with protocol deviations will not be excluded from the analyses of the safety data (except in the case of subjects with all post-baseline safety data missing); such subjects may be excluded from the analysis of the PK data at the discretion of the responsible pharmacokineticist.

7.2.3 Demographics and Other Baseline Characteristics

Demographic information collected at Screening and other baseline characteristics will be summarized and presented using descriptive statistics (for continuous variables), frequencies and percentages (for categorical variables).

Age (years), Sex, weight (kg), height (cm) at Screening, and body mass index (BMI) where BMI (kg/m^2) = weight (kg) / [height (m) * height (m)] will be presented using descriptive statistics. Frequency (%) tabulations for race and ethnicity as described by the subject will be presented. In addition, frequency (%) tabulation will also be presented for age categories:

<55, 55 to <65, 65 to <75, & ≥75 years.

Summaries will be based on SAF, BES, PES and PKAS. The summaries for BES, PES and PKAS will not be created if the number of subjects in SAF and BES/PES/PKAS are identical. All data will be provided in subject data listings.

7.2.4 Previous and Concomitant Medications

Previous medications or therapies are those with a start date between four weeks prior to Sreening and Day 1. Concomitant medications are those medications or therapies taken after the first dose of study drug during the investigational period.

Previous, concomitant medications and non-medication therapies will be coded with World Health Organization Drug Reference List (WHO-DRL) and summarized by anatomical therapeutical classification (ATC, 4^{th} level, chemical subgroup) and coded term for the SAF. Subjects taking the same medication multiple times will be counted once per medication and treatment period.

A summary table and listing of all previous and concomitant medications used will be presented. The listing will include the days/time of start and stop of administration and time since study drug administration will be presented.

Medications with a start date after the data cutoff date will be excluded. A summary of non-medication therapies will also be provided.

7.2.5 Medical History

Medical history will include any significant conditions or diseases other than prostate cancer that occurred prior to informed consent.

A complete disease history of the target disease will be recorded at Screening. This includes documenting the subject's initial diagnosis of prostate cancer, Gleason score at time of diagnosis dates and other disease specific information as designated in the eCRF, as well as prior therapy for treatment of prostate cancer (prior radiotherapy, prior procedures and prior/current drug therapy).

Medical history will be coded in Medical Dictionary for Regulatory Activities (MedDRA) and will be provided in a summary tables as well as a listing.

7.3 Study Drugs

Compliance with the dosing regimen in terms of study drug exposure of enzalutamide (160mg/QD/oral), abiraterone acetate (1000mg/QD/oral), and prednisone (5mg/BID/oral) will be presented descriptively for the number of days on the study drug, the cumulative number of doses received during the study period, the average dose per day and the average dose per day in percentage of the planned study drug exposure of enzalutamide (defined as treatment compliance in the summary table) (160mg/QD/oral), abiraterone acetate (1000mg/QD/oral), and prednisone (5mg/BID/oral).

Number (%) of subjects with a dose reductions and interruptions in abiraterone acetate and in enzalutamide will also be presented.

Summaries of study drug exposure, dose reduction and dose interruptions will be presented for SAF. Study drug dosing data will also be provided in subject data listings.

Exposure to the data cutoff date only.

7.4 Analysis of Efficacy

- Bone marrow androgens, summaries and analyses will be presented for the corresponding biomarker parameter evaluable set.

  For each biomarker (e.g., testosterone, cortisol, androgestenedione, pregenelone and progesterone), descriptive statistics including number of subjects, mean, standard deviation, median, minimum, and maximum will be provided for baseline, Week 9, change from baseline, percent change from baseline. The effect size (i.e., the mean difference divided by the SD) will also be displayed. Summaries of change and percent change from baseline to EOT will be presented for BES subjects who also had an EOT assessment of the corresponding biomarker parameter sample.

  Baseline and post-baseline biomarker results will also be presented graphically using waterfall plots (per subject, the largest reduction or smallest increase in case of no reduction).

  Biomarker results collected at baseline and at Week 9 will be compared using the paired

  t-test to evaluate the effect of enzalutamide*. The following generic SAS code for paired t-test can be used:

  ```
  proc ttest data=pairedsample;
        paired baseline * week_9;
   ods output ttests=ttest;
  run
  ```

  * If warranted the wilcoxon-signed rank test can be used instead.

  For each biomarker, summaries of baseline, post-baseline, change from baseline, and percent change from baseline will be also presented by PSA response category, where

PSA response is defined as at least 50% reduction (improvement) in PSA from baseline to Week 9 in SAF. The correlation between each biomarker and PSA level at baseline and at Week 9 will be estimated using Spearman's method. The following generic

SAS code for Spearman's correlation coefficient can be used:

```
proc corr data=corr outp=spearmancorr1 spearman;
        var variable1 variable2;
        ods output spearmancorr=spearmancorr2;
run;
```

- Blood androgens, summaries and analyses will be presented for the corresponding plasma parameter evaluable set.

  Analyses and summaries of blood testosterone, cortisol, androgestenedione, pregenelone and progesterone will be conducted and presented similar to the bone marrow testosterone, cortisol, androgestenedione, pregenelone and progesterone as stated above.

Following secondary endpoints will be presented for SAF:

- Baseline, post-baseline, change from baseline, and percent change from baseline values of PSA measurements will be summarized descriptively.

  The largest decline from baseline in PSA blood concentrations

  - over the first 12 weeks on treatment
  - up to and including EOT but excluding ESV
  - up to and including ESV

  will be summarized descriptively.

  The number (%) of subjects with a ≥30%, ≥50% and ≥90% decline from baseline as well as undetectable values in PSA blood concentration will be tabulated per visit over time. Also the number (%) of subjects with the largest decline in PSA from baseline (Nadir), ≥30%, ≥50% and ≥90%, will be provided.

- Baseline, post-baseline, change from baseline, and percent change from baseline values in bone specific alkaline phosphatise (ug/L) and in urine N-telopeptides (nmolBCE/mmol) will be summarized descriptively.
- Number (%) of subjects with tumor identification results (i.e., target, non-target, new, bone) and lesion location (e.g., bone, breast, colorectal, kidney, etc) will be summarized.
- Subjects without radiologic PD or clinical PD or PSA progression or death will be censored at the last known date to be alive and progression free. Subjects still PSA progression free as of the data cutoff date will be right censored. Kaplan-Meier method will be used to draw the survival curve. Also the median, 25%, and 75% percentile of survival time will be tabulated, including the corresponding 95% confidence interval (CI) using a robust non-parametric method due to Brookmeyer and Crowley. The number of events and subjects at risk over time (at visit dates) will also be tabulated.

- Time to study drug discontinuation will be calculated as the number of days from start of study drug to date of last dose of study drug using the safety populations. Subjects still on study drug as of the data cutoff date will be right censored. Kaplan-Meier method will be used to draw the survival curve. Also the median, 25%, and 75% percentile of survival time will be tabulated, including the corresponding 95% confidence interval (CI) using a robust non-parametric method due to Brookmeyer and Crowley. The number of events and subjects at risk over time (at visit dates) will also be tabulated.
- Number (%) of subjects for the time point response variables (soft tissue and bone) will be tabulated per visit over time. Also the number (%) of subjects with the the best overall response per RECIST 1.1, during the entire investigational period will be derived and summarized. In addition to that, number (%) subjects with objective response (CR or PR) will be summarized.

7.5 Analysis of Safety

All safety and tolerability data will be summarized using descriptive statistics and will be listed and summarized in tabular and/or graphical form. No formal statistical testing will be performed on these data.

7.5.1 Adverse Events

All summaries of adverse events (AEs), unless otherwise stated, will include TEAEs only. All AEs will be coded into system organ class (SOC) and preferred term (PT) using

MedDRA. Severity of AEs will be coded using NCI (National Cancer Institute) CTCAE (Common Terminology Criteria for Adverse Events) Version 4.03. The following TEAEs summaries will be provided by SOC and PT:

- Number of reported TEAEs (= actual events)
- Number (%) of subjects reporting at least one TEAEs
- Number (%) of subjects reporting at least one TEAEs by maximum severity of NCI CTCAE grade
- Number (%) of subjects reporting at least one TEAEs of NCI CTCAE grade 3, 4, or 5
- Number (%) of subjects with at least one enzalutamide related TEAE by maximum severity of NCI CTCAE grade
- Number (%) of subjects with at least one abiraterone related TEAE by maximum severity of NCI CTCAE grade
- Number (%) of subjects with at least one prednisone related TEAE by maximum severity of NCI CTCAE grade
- Number of reported serious TEAEs (= actual events)
- Number (%) of subjects with at least one enzalutamide related serious TEAEs
- Number (%) of subjects with at least one abiraterone related serious TEAEs
- Number (%) of subjects with at least one prednisone related serious TEAEs
- Incidence of TEAE leading to permanent discontinuation
- Incidence of enzalutamide related TEAE leading to permanent discontinuation of enzalutamide

- Incidence of abiraterone related TEAE leading to permanent discontinuation of abiraterone
- Incidence of prednisone related TEAE leading to permanent discontinuation of prednisone
- Incidence of deaths

All AEs recorded on the CRF will be presented in data listing.

A listing of subjects with NCI CTCAE grade 3, 4 or 5 TEAEs will be provided separately. Adverse events with a start date after the data cutoff date will be excluded.

7.5.2 Clinical Laboratory Evaluation

All clinical laboratory values will be summarized using international system of units (SI). Quantitative clinical laboratory variables, i.e., hematology, biochemistry, coagulation and liver function tests will be summarized descriptively by visit. Additionally, a within-subject change from baseline will be summarized for each post-baseline visit.

Each quantitative laboratory result will be classified as low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges. Values equal to the limits of the normal range are still considered normal. The incidence (and percentage) of subjects with these classifications will be displayed by laboratory parameter and visit as a shift table from baseline to each particular post-baseline visit.

In addition, a summary table of each quantitative laboratory variable classified by CTCAE severity will be produced. The incidence (and percentage) of subjects with these classifications will be displayed by laboratory parameter and time-point.

A listing of all laboratory measurements, including the derived outcomes, will be made; all quantitative laboratory values outside of the normal range will be flagged as high or low on the listing and the CTCAE grade will be specified. Baseline records will be flagged.

A separate listing of all values which fall outside of the respective normal range will also be produced for each laboratory test along with the CTCAE grade. A listing of subjects with CTCAE grade 4 laboratory values will be provided separately.

Clinically significant values in liver function test and their shift from baseline will be summarized.

Laboratory assessments with a collection date after the data cutoff date will be excluded.

7.5.3 Vital Signs

Vital signs which include systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse rate (bpm) and body temperature (◦C) will be summarized descriptively by visit. Additionally, a within-subject change from baseline will be summarized by visit.

For all parts figures will be made of the mean change from baseline over time, by visit. Each vital signs result will be classified as low (L), normal (N), or high (H) at each visit according to the vital signs reference ranges mentioned in [Table 3]. Shift tables indicating shifts between baseline and post-baseline measurements will be displayed by visit.

Table 3 Vital Signs Reference Ranges

	Low	Normal	High
Pulse (bpm)	<40	40-100	>100
DBP (mm Hg)		≤ 100	>100
SBP (mm Hg)		≤ 160	>160

Source: Adapted from "The seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure" 2004, [Table 3]

A listing of all vital signs outcomes, including any derived measurements, will be presented. A listing of subjects with SBP >160 mmHg or DBP >100 mmHg and also a listing of subjects with pulse rate <40 bpm (bradycardia) or pulse rate >100 bpm (tachycardia) will be provided separately.

Vital Signs assessments with a collection date after the data cutoff date will be excluded.

7.5.4 12- Lead ECG

A standard 12-lead ECG will be performed on all subjects prior to dosing at each visit. The ECG parameters including hear rate (bpm), PR interval (ms), RR interval (ms), QRS interval (ms), QT interval (ms), QTcF interval (ms), QTcB interval (ms) will be collected on the eCRF. Baseline, post-baseline, and their changes from baseline in ECG values will be presented using descriptive statistics.

Also overall ECG interpretation (i.e. normal, abnormal-not clinically significant, and abnormal-clinically significant) as reported by the investigator will be tabulated by visit. Shift tables indicating shifts between baseline and post-dose measurements will be displayed by visit.

A listing of all ECG outcomes will be presented. A separate listing of subjects with CTCAE grade 3 or 4 based on prolonged QTc (i.e., QTc>0.5 second; life threatening signs or symptoms (e.g., arrthythmia, chronic hear failure, hypotension, shock, syncope); torsade de pointes) will also be provided.

ECG assessments with a collection date after the data cutoff date will be excluded.

7.5.5 Physical Examination

Body mass index over time will be calculated using the weight at the given visit and the height at screening. Physical examination findings will only be listed within the medical history or adverse event listings as appropriate.

7.6 Analysis of Pharmacokinetics and/or Pharmacodynamics

7.6.1 PK Concentrations

Individual and mean pre-dose plasma concentration of abiraterone, and enzalutamide and its metabolities MDPC0001 and MDPC0002 will be summarized by scheduled visit using mean (arithmetic and geometric), standard deviation, minimum, maximum, median, and coefficient of variation. Values below the lower limit of quantitation (LLOQ) will be set to 0 for calculation of descriptive statistics.

Descriptive statistics will not be calculated if all values are LLOQ. In cases where more than half of the individual data are LLOQ, SD and CV will not be calculated. If one or more values are LLOQ, the geometric mean will not be calculated.

7.7 Other Analyses

Not applicable.

7.8 Interim Analysis (and Early Discontinuation of the Clinical Study)

The interim analysis as defined in Section 7.8 of the protocol will not be subject of this SAP. A separate "Charter for Interim Safety Review" has been written for this purpose. This internal document was finalized and signed on January 10th, 2013.

7.9 Handling of Missing Data, Outliers, Visit Windows, and Other Information

7.9.1 Missing Data

As a general rule, missing data will not be imputed. Exceptions include the imputation of (partly) missing onset and end dates of AE and the computation of "Time since study drug" for AEs.

7.9.2 Missing Adverse Event Dates

If a subject experiences an event both during the pre-investigational period and during the investigational period, the event will be considered as TEAE only if it has worsened in severity (i.e., it is reported with a new start date). For AEs with incomplete or missing start date, a worst-case scenario will be used to determine treatment emergence of this adverse event:

- If the investigator has ticked the box that AE onset was after the first dose of study drug then the AE will be considered TEAE.
- If the AE onset date is the same day as the study drug start date or if the onset date is incomplete and the investigator has not ticked the box that the onset was before the first dose of study drug AND:
  - if the AE start date is non-missing and equal or greater the date of treatment dose then the AE will be considered TEAE;
  - if the AE day is missing, then if the AE month is equal or greater the month in which treatment was administered then the AE will be considered TEAE;
  - if the AE month is missing and the AE year is equal or greater the year in which treatment was administered then the AE will be considered TEAE;
  - if the AE year is missing then the AE will be considered TEAE;
  - for TEAEs with partial dates the AE will be allocated to the treatment period using the available partial information, without imputations.
- Other cases of incomplete onset date of an AE will be addressed prior to or during the data review meeting (DRM) in order to determine whether the AE must be considered treatment emergent or not.

Listings will always show the original date information without imputation, but derived parameters (TEAE indicator and duration of AEs) would be flagged.

7.9.3 Baseline Assessments

Baseline will be defined as the latest (non-missing) assessment taken prior to study drug administration on Day 1. If all pre-dose measurements are missing then baseline will be considered as missing, and no changes from baseline and no percentage reduction from baseline will be computed.

7.9.4 Visit Windows

The following analysis visit windows will be used for safety and efficacy analyses for the week visits in terms of study days:

Week (Planned Study Day)	Visit Window
1 (Day 4)	4
5 (Day 29)	16 to 43
9 (Day 57)	44 to 71
13…25 (Day x[a])	Day x[a]-13 to Day x[a]+14
25+12 Weeks * i Repeats, Where i= 1, 2, 3,…	169+12*i±3, Where i=1, 2, 3
End of Treatment	End of Treatment±3
Safety F/U	Safety F/U

a. See Table 1 Schedule of Assessments for the corresponding planned study days.

7.9.5 Outliers

All values will be included in the analyses.

7.9.6 Values Below LOQ in PK Data

For the purpose of summary statistics, graphs and statistical analyses of PK data, values below the LOQ will be set to 0. For laboratory safety data, values recorded as "<X" or ">Y" will be imputed by "X" and "Y" respectively for descriptive statistics, graphs and inferential statistics. This will be documented in a footnote to all summary tables and all output where such a replacement was performed.

8 DOCUMENT REVISION HISTORY

Version	Date	Changes	Comment/rationale for change
1.00	02-OCT-2014	NA	Document finalized
2.00	14-DEC-2015	Deleted reference to specific 01JUL2014 cutoff date	Cutoff date was delayed until complete bone marrow was in-house, more efficient to use a general data cut reference.
2.00	14-DEC-2015	Added document revision history section, needed to change relevant TOC and body of document section numbers	Needed to track revisions to SAP
2.00	14-DEC-2015	Added new study statistician and medical monitor for signoff	Sign off to reflect current study team members.

9 REFERENCES

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; 45:228-247.

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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. J Clin Oncol 2008;26:1148-5

The seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure. 2004; [Table 3]

10 APPENDICES

10.1 Appendix 1: Laboratory Tests

Test	Visit	Collecting Tube	Parameters to be Analyzed
Hematology	All visits, except Day 4	EDTA tube	Hemoglobin Hematocrit Erythrocytes (RBC) Leukocytes (WBC) Differential WBC Platelets
PT/PTT	All visits, except Day 4	Citrate tube	PT/PTT
Chemistry	All visits, except Day 4	Serum tube	Sodium Potassium Calcium Chloride Magnesium Phosphorus Glucose Creatinine Alkaline phosphatase LDH AST ALT Direct bilirubin Total bilirubin Total protein Albumin CO_2 BUN Bone alkaline phosphatase
PSA	Screening, Week 5 and every subsequent 4 weeks and end of treatment.	Serum tube	PSA
Urine N-telopeptide	Screening, Week 9 and at the end of treatment if the sample was not obtained at Week 9	30 mL random urine sample	Urine N-telopeptide
Testosterone and DHT	Screening, Week 9 and at the end of treatment if the sample was not obtained at Week 9	Serum tube	Testosterone and DHT
Blood sample for genotype analysis	Day 1	K3EDTA tube	Genotype analysis
Blood sample for PK analysis	Day 4 and Week 5	K2EDTA tube	PK analysis

10.2 Appendix 2: Liver Function Test

If laboratory testing for a subject enrolled in study and receiving study drug reveals an increase of serum aminotransferases (AT) to > 3X ULN, or bilirubin > 2X ULN, at least all four of the usual serum hepatic measures (ALT, AST, ALP, and TBL) should be repeated. Testing should be repeated within 48-72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central lab regarding moderate and marked liver abnormality to inform the investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

DefinitionofLiverAbnormalities

Confirmed abnormalities will be characterized as moderate and marked where ULN:

	ALT or AST		**Total Bilirubin**
Moderate	> 3 x ULN	or	> 2 x ULN
Marked	> 3 x ULN	and	> 2 x ULN

In addition, the subject should be considered to have marked hepatic abnormalities for any of the following:

- ALT or AST > 8X ULN
- ALT or AST > 5X ULN for more than 2 weeks
- ALT or AST > 3X ULN and INR > 1.5
- ALT or AST > 3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or marked abnormalities and require additional monitoring and follow-up.

10.3 Appendix 3: Common Terminology Criteria for Adverse Events (CTCAE)

CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition	Errata
Blood and lymphatic system disorders	Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.	
Blood and lymphatic system disorders	Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death	A disorder characterized by the inability of the bone marrow to produce hematopoietic elements.	
Blood and lymphatic system disorders	Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors.	
Blood and lymphatic system disorders	Febrile neutropenia	-	-	ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an ANC <1000/mm^3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more thanonehour	

Table continued on next page

CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition	Errata
Blood and lymphatic system disorders	Hemolysis	Laboratory evidence of hemolysis only(e.g., direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin)	Evidence of hemolysis and >=2 gm decrease in hemoglobin	Transfusion or medical intervention indicated (e.g., steroids)	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by laboratory test results that indicate widespread erythrocyte cell membrane destruction.	
Blood and lymphatic system disorders	Hemolytic uremic syndrome	Evidence of RBC destruction (schistocytosis) without clinical consequences	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death	A disorder characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia.	
Blood and lymphatic system disorders	Leukocytosis	-	-	>100,000/mm^3	Clinical manifestations of leucostasis; urgent intervention indicated	Death	A disorder characterized by laboratory test results that indicate an increased number of white blood cells in the blood.	
Blood and lymphatic system disorders	Thrombotic thrombocytopenic purpura	Evidence of RBC destruction (schistocytosis) without clinical consequences	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death	A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities and neurological abnormalities such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition.	
Cardiac disorders	Acute coronary syndrome	-	Symptomatic, progressive angina; cardiac enzymes normal; hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically unstable	Death	A disorder characterized by signs and symptoms related to acute ischemia of the myocardium secondary to coronary artery disease. The clinical presentation covers a spectrum of heart diseases from unstable angina to myocardialinfarction.	

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CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition	Errata
Cardiac disorders	Myocardial infarction	-	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes	Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction	Life-threatening consequences; hemodynamically unstable	Death	A disorder characterized by gross necrosis of the myocardium; this is due to an interruption of blood supply to the area.	
Investigations	Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage	-	-	An abnormal laboratory test result in which the partial thromboplastin time is found to be greater than the control value. As a possible indicator of coagulopathy, a prolonged partial thromboplastin time (PTT) may occur in a variety of diseases and disorders, both primary and related to treatment.	
Investigations	Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-	A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.	
Investigations	Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-	A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.	
Investigations	Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-	A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.	

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CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition	Errata
Investigations	Blood antidiuretic hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-	A finding based on laboratory test results that indicate abnormal levels of antidiuretic hormone in the blood specimen.	
Investigations	Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-	A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.	
Investigations	Blood corticotrophin decreased	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-	A finding based on laboratory test results that indicate an decrease in levels of corticotrophin in a blood specimen.	
Investigations	Blood gonadotrophin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A finding based on laboratory test results that indicate abnormal levels of gonadotrophin hormone in a blood specimen.	
Investigations	Blood prolactin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	-	-	-	A finding based on laboratory test results that indicate abnormal levels of prolactin hormone in a blood specimen.	
Investigations	Carbon monoxide diffusing capacity decreased	3 - 5 units below LLN; for follow-up, a decrease of 3 - 5 units (ml/min/mm Hg) below the baseline value	6 - 8 units below LLN; for follow-up, an asymptomatic decrease of >5 - 8 units (ml/min/mm Hg) below the baseline value	Asymptomatic decrease of >8 units drop; >5 units drop along with the presence of pulmonary symptoms (e.g., >Grade 2 hypoxia or >Grade 2 or higher dyspnea)	-	-	A finding based on lung function test results that indicate a decrease in the lung capacity to absorb carbon monoxide.	

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CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition	Errata
Investigations	Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-	A laboratory test result which indicates increased levels of cardiac troponin I in a biological specimen.	
Investigations	Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-	A laboratory test result which indicates increased levels of cardiac troponin T in a biological specimen.	
Investigations	CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 -0.2 x 10^9 /L	<200 - 50/mm^3; <0.2 x 0.05 - 10^9 /L	<50/mm^3; <0.05 x 10^9 /L	-	A finding based on laboratory test results that indicate an decrease in levels of CD4 lymphocytes in a blood specimen.	
Investigations	Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	-	A finding based on laboratory test results that indicate higher than normal levels of cholesterol in a blood specimen.	
Investigations	CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	-	A finding based on laboratory test results that indicate an increase in levels of creatine phosphokinase in a blood specimen.	
Investigations	Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-	A finding based on laboratory test results that indicate increased levels of creatinine in a biological specimen.	
Investigations	Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN or 50 - <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	-	A finding based on laboratory test results that indicate an decrease in levels of fibrinogen in a bloodspecimen.	

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CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition	Errata
Investigations	GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-	A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gamma-glutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water.	
Investigations	Growth hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	-	-	-	A finding based on laboratory test results that indicate abnormal levels of growth hormone in a biological specimen.	
Investigations	Haptoglobin decreased	<LLN	-	-	-	-	A finding based on laboratory test results that indicate an decrease in levels of haptoglobin in a blood specimen.	
Investigations	Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-	-	A finding based on laboratory test results that indicate increased levels of hemoglobin in a biological specimen.	
Investigations	INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation	-	-	A finding based on laboratory test results that indicate an increase in the ratio of the patient's prothrombin time to a control sample in the blood.	
Investigations	Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-	A finding based on laboratory test results that indicate an increase in the level of lipase in a biological specimen.	

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CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition	Errata
Investigations	Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 -0.5 x 10^9/L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9/L	<200/mm^3; <0.2 x 10^9/L	-	A finding based on laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen.	
Investigations	Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3	-	-	A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow.	
Investigations	Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9/L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9/L	<1000 - 500/mm^3; <1.0 - 0.5 x 10^9/L	<500/mm^3; <0.5 x 10^9/L	-	A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.	
Investigations	Pancreatic enzymes decreased	<LLN and asymptomatic	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency	-	-	A finding based on laboratory test results that indicate an decrease in levels of pancreatic enzymes in a biological specimen.	
Investigations	Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9/L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9/L	<50,000 - 25,000/mm^3; <50.0 - 25.0 x 10^9/L	<25,000/mm^3; <25.0 x 10^9/L	-	A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.	
Investigations	Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-	A finding based on laboratory test results that indicate an increase in the levels of amylase in a serum specimen.	
Investigations	White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9/L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9/L	<2000 - 1000/mm^3; <2.0 - 1.0 x 10^9/L	<1000/mm^3; <1.0 x 10^9/L	-	A finding based on laboratory test results that indicate an decrease in number of white blood cells in abloodspecimen.	

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CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition	Errata
Metabolism and nutrition disorders	Acidosis	pH <normal, but >=7.3	-	pH <7.3	Life-threatening consequences	Death	A disorder characterized by abnormally high acidity (high hydrogen-ion concentration) of the blood and other body tissues.	
Metabolism and nutrition disorders	Alkalosis	pH >normal, but <=7.5	-	pH >7.5	Life-threatening consequences	Death	A disorder characterized by abnormally high alkalinity (low hydrogen-ion concentration) of the blood and other body tissues.	
Metabolism and nutrition disorders	Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL;>3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death	A disorder characterized by laboratory test results that indicate an elevation in the concentration of calcium (corrected for albumin) in blood.	
Metabolism and nutrition disorders	Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences	Death	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.	
Metabolism and nutrition disorders	Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death	A disorder characterized by laboratory test results that indicate an elevation in the concentration of potassium in the blood; associated with kidney failure or sometimes with the use of diuretic drugs.	
Metabolism and nutrition disorders	Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences	Death	A disorder characterized by laboratory test results that indicate an elevation in the concentration of magnesiumintheblood.	

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CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition	Errata
Metabolism and nutrition disorders	Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death	A disorder characterized by laboratory test results that indicate an elevation in the concentration of sodium in the blood.	
Metabolism and nutrition disorders	Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death	A disorder characterized by laboratory test results that indicate an elevation in the concentration of triglyceride concentration in the blood.	
Metabolism and nutrition disorders	Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences	>10 mg/dL; >0.59 mmol/L; life-threatening consequences	Death	A disorder characterized by laboratory test results that indicate an elevation in the concentration of uric acid.	
Metabolism and nutrition disorders	Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood.	
Metabolism and nutrition disorders	Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN -2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death	A disorder characterized by laboratory test results that indicate a low concentration of calcium (corrected for albumin) in the blood.	
Metabolism and nutrition disorders	Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 -2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures	Death	A disorder characterized by laboratory test results that indicate a low concentration of glucose in the blood.	
Metabolism and nutrition disorders	Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death	A disorder characterized by laboratory test results that indicate a low concentration ofpotassiumintheblood	

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CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition	Errata
Metabolism and nutrition disorders	Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 -0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 -0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences	Death	A disorder characterized by laboratory test results that indicate a low concentration of magnesium in the blood.	
Metabolism and nutrition disorders	Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences	Death	A disorder characterized by laboratory test results that indicate a low concentration of sodium in the blood.	
Metabolism and nutrition disorders	Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 0.6 mmol/L -	<2.0 - 1.0 mg/dL; <0.6 -0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; life-threatening consequences	Death	A disorder characterized by laboratory test results that indicate a low concentration of phosphates in the blood.	
Metabolism and nutrition disorders	Iron overload	-	Moderate symptoms; intervention not indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by accumulation of iron in the tissues.	
Renal and urinary disorders	Acute kidney injury	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated	Death	A disorder characterized by the acute loss of renal function and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction).	
Renal and urinary disorders	Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m^2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m^2	eGFR or CrCl 29 - 15 ml/min/1.73 m^2	eGFR or CrCl <15 ml/min/1.73 m^2; dialysis or renal transplant indicated	Death	A disorder characterized by gradual and usually permanent loss of kidney function resulting in renal failure.	

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CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition	Errata
Renal and urinary disorders	Proteinuria	1+ proteinuria; urinary protein <1.0 g/24 hrs	Adults: 2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Pediatric: urine P/C (Protein/Creatinine) ratio0.5-1.9	Adults: urinary protein >=3.5 g/24 hrs; Pediatric: urine P/C >1.9	-	-	A disorder characterized by laboratory test results that indicate the presence of excessive protein in the urine. It is predominantly albumin,butalsoglobulin.	

10.4 Appendix 4: Review and Approval Signatures

This SAP was prepared and reviewed with respect to completeness, consistency with the protocol, and scientific content:

Prepared by:	e-signature at end of document	Date:
	[redacted] M.Sc.	Date (DD Mmm YYYY)
Approved by:	e-signature at end of document	Date:
	[redacted] M.P.H. Astellas Pharma Development	Date (DD Mmm YYYY)
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	[redacted] B.Sc. Astellas Pharma Development	Date (DD Mmm YYYY)
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