Statistical Analysis Plan

A Multicenter, Open-label, Single-arm, Phase 2 Study of Abiraterone Acetate Plus Prednisone in Subjects with Advanced Prostate Cancer Without Radiographic Evidence of Metastatic Disease

IMAAGEN

Protocol 212082PCR2005; Phase 2
Amendment 2

JNJ-212082 (abiraterone acetate)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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AMENDMENT HISTORY

N/A

ABBREVIATIONS

AA	abiraterone acetate
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CI	confidence interval
CRF	case report form
CRPC	castration resistant prostate cancer
CSR	Clinical Study Report
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDA	Food and Drug Administration
GGT	Gamma-glutamyltransferase
GnRH	gonadotropin-releasing hormone
ICH	International Conference on Harmonization
IMAAGEN	**IM**pact of **A**biraterone **A**cetate on Prostate Specific Anti**GEN**
IVRS	interactive voice response system
LDH	lactate dehydrogenase
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
PI	principal investigator
PK	pharmacokinetic(s)
PP	per protocol (population)
PSA	prostate-specific antigen
PSADT	prostate-specific antigen doubling time
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
TTRP	Time to radiographic evidence of disease progression
TTPP	Time to PSA progression
ULN	upper limit of normal
WBC	white blood cell

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses.

1.1. Trial Objectives

Primary Objective

To demonstrate that abiraterone acetate plus prednisone effectively decreases PSA in subjects with non-metastatic CRPC who have a rising PSA despite castrate levels of testosterone.

Secondary Objectives

- ☐ To describe the time to radiographic progression of disease in subjects treated with abiraterone acetate in addition to the current standard of care.
- ☐ To describe the safety profile of abiraterone acetate when taken with prednisone 5 mg daily.

1.2. Trial Design

This is a Phase 2, prospective, multicenter, open-label, single-arm study of abiraterone acetate plus prednisone in subjects with non-metastatic CRPC with a rising PSA despite castrate levels of testosterone.

The study consists of a 4-week Screening Phase; a Core Study Treatment Phase (comprised of six 28-day cycles); a Pre-metastatic Disease Follow-up Phase; and an Optional Post-metastatic Disease Follow-up Phase.

After completion of written informed consent, eligible subjects will receive abiraterone acetate 1,000 mg once daily, prednisone 5 mg once daily, and continue their regularly prescribed GnRH monotherapy. Study agents (abiraterone acetate and prednisone) will be dispensed on day 1 of each cycle. Note that if prednisone and/or GnRH monotherapy are discontinued, a subject may continue to receive abiraterone acetate and continue on study as scheduled. If a subject needs to discontinue either of these therapies, the appropriate medical management of the subject needs to be discussed with the Medical Monitor. If abiraterone acetate is discontinued, prednisone should also be discontinued; and the subject should be discontinued from the study.

During the Core Study Treatment Phase, in Cycles 1, 2, and 3 subjects will be required to return to the study site twice per cycle (Days 1 and 15). In Cycles 4 through 6, subjects will be required to return to the study site on Day 1 of each cycle. Additional visits may occur as clinically indicated. The End of Core Study Visit is to occur as follows:

- ☐ On Day 1 of Cycle 7;
- ☐ At the time of discontinuation of abiraterone acetate if discontinuation occurs prior to completion of the Core Study Treatment Phase;
- ☐ If possible, at the time of withdrawal from the study, if withdrawal occurs prior to completion of the Core Study Treatment Phase; or

- ☐ In the event of radiographic evidence of disease progression prior to completion of the Core Study Treatment Phase

When the last enrolled subject completes the Core Study Treatment Phase, a database lock will be performed and all analyses, as described in this analysis plan using all efficacy and safety data accumulated to date, will be performed.

Between the time that the last enrolled subject completes the Core Study Treatment Phase and the time that the last subject completes the study, safety analyses, new therapies for prostate cancer, and time to disease progression will be updated on an annual basis, and at the end of the study.

The protocol language for the primary endpoint has been revised slightly to remove potential ambiguity in the definition of PSA response as maximal decrease in PSA up to a certain time-point.

1.3. Statistical Hypotheses for Trial Objectives

The primary efficacy endpoint is the proportion of subjects achieving a ≥ 50% reduction in PSA by the End of Core Study Visit.

The null hypothesis to be tested is Ho: p =0.35, and the alternative hypothesis is Ha: p = 0.50, where p is the proportion of subjects who achieve a ≥ 50% reduction in PSA by the End of Core Study Visit.

1.4. Sample Size Justification

The sample size estimate for this study is based upon testing the primary endpoint of the proportion of subjects achieving a ≥ 50% reduction in PSA by the End of Core Study Visit. Assuming a null hypothesis proportion equals 0.35 vs. the alternative of 0.50; a 1-sided, alpha equal to 0.025; and 90% power, a sample size of 111 subjects would have been required. Accounting for an approximate dropout rate of 10%, 125 subjects were planned for enrollment.

1.5. Randomization and Blinding

Not applicable due to the open-label design.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

Subjects' time on study will be determined in Study Days. Study Day 1 will be defined as the first day of dosing. Positive study days will count forward from Study Day 1. Study Day -1 will be the day before Study Day 1, and all subsequent negative study days will be measured backward from Study Day -1. There will be no Study Day 0. A cycle is defined as a 28-day period in this protocol. A value obtained on Study Day 1 before administration of study treatment will be considered the baseline value. If a value is not available on Study Day 1, the last available value collected prior to the first dose of study drug will be used as the baseline value.

Study visits as captured on each case report form (CRF) will be used for analyses. Visit windows will not be created.

2.2. Pooling Algorithm for Analysis Centers

This is a multi-center study with approximate 40 investigating US sites participating. The "center" effect will not be evaluated for this study.

2.3. Analysis Sets

2.3.1. Efficacy Analysis Set(s)

There are three efficacy analysis sets for the Core Study Treatment Phase:

- ☐ Efficacy evaluable set: All subjects who receive at least one non zero dose of primary study drug (AA); and completed at least one cycle of treatment; and have at least one post baseline PSA measurement. This set will be used for the primary efficacy analysis and all secondary efficacy analyses except time-to-event analyses.
- ☐ All enrolled set: includes all subjects who received at least one dose of study agents. This set will be used for the sensitivity analysis on the primary efficacy endpoint and time-to-event analyses.
- ☐ Per-protocol set: includes all subjects who met all inclusion and exclusion criteria, did not have a major protocol violation during the Core Study Treatment Phase, received abiraterone acetate, completed at least 6 cycles of treatment, and had at least one post-baseline PSA. See Section 4.4 for more details. This set will be used for the sensitivity analysis on the primary efficacy endpoint.

2.3.2. Safety Analysis Set

Safety evaluable set is defined as all subjects exposed to study agents (Abiraterone acetate or Prednisone). This set will be used for all safety analyses.

2.4. Definition of Subgroups

No subgroup analyses will be performed.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

No interim analysis was planned.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized for the All Enrolled set as described below.

Baseline Demographics

Continuous Variables (n, mean, SD, median, minimum, and maximum):

- ☐ Age (years)

Categorical Variables (n, %):

- ☐ Age group (<65, 65 to 69, 70 to 74, ≥ 75)
- ☐ Sex (Male)
- ☐ Ethnicity (Hispanic or Latino; Not Hispanic or Latino)
- ☐ Race (White, Black, Asian, American Indian or Alaskan Native; Native Hawaiian or Other Pacific Islander; Other)

Baseline Vital Signs

Continuous Variables (n, mean, SD, median, minimum, and maximum):

- ☐ Weight (kg)
- ☐ Height (cm)
- ☐ Body mass index (BMI, kg/m^2)
- ☐ Body Temperature (^oC)
- ☐ Systolic/ Diastolic Blood Pressure (mmHg)
- ☐ Heart Rate (beats/min)
- ☐ Respiratory Rate (breaths/min).

Baseline Disease Status

Continuous Variables (n, mean, SD, median, minimum, and maximum):

- ☐ Time from initial diagnosis to first dose (years)
- ☐ Time from first castration (surgical or GnRH) to first dose (years)
- ☐ PSA (prostate specific antigen) at screening (ng/mL)
- ☐ PSADT at screening (Prostate Specific Antigen Doubling Time, months, not available if PSA≥10)
- ☐ Calculated Gleason score
- ☐ Left Ventricular Ejection Fraction (%EF)
- ☐ Baseline Serum PSA(ng/mL)
- ☐ Alanine Aminotransferase (U/L)
- ☐ Albumin (g/L)
- ☐ Alkaline Phosphatase (U/L)
- ☐ Aspartate Aminotransferase (U/L)
- ☐ Bilirubin (umol/L)
- ☐ Lactate Dehydrogenase (U/L)
- ☐ Potassium (umol/L)
- ☐ Baseline testosterone (ng/mL).

Categorical Variables (n, %):

- ☐ Tumor stage at initial diagnosis (T1-T3, cannot be assessed)
- ☐ Calculated Gleason score (< 7, 7 [3+4, 4+3], ≥ 8)
- ☐ Previous prostate treatment (Currently receiving GnRH monotherapy and at least 6 months prior to screening, Undergone orchiectomy without receiving any previous GnRH monotherapy, Undergone orchiectomy and previously received GnRH monotherapy)
- ☐ ECOG performance status (0, 1, 2) ☐

Atrial Fibrillation (Yes, No)

- ☐ Myocardial Infarction (Yes, No)
- ☐ Hypertension (Yes, No)
- ☐ Diabetes (Yes, No)
- ☐ Does the subject smoke now, or did the subject ever smoke? (Yes, No).

4.2. Disposition Information

Study discontinuation will be summarized according to reasons for discontinuation as documented in the eCRF (Adverse Event, Disease Progression, Death, Physician Decision, Protocol Violation, Withdrawal of Consent, and Other) overall and by treatment phase.

Protocol amendment 3, which requires that a subject should terminate study upon AA discontinuation, will be implemented shortly. To date only one subject has undergone 1 visit after discontinuation of AA and will be discontinued as soon as IRB approval has been obtained at the site. Therefore, this subject will be considered as having discontinued from study at the 30-day safety follow-up visit for this and all subsequent analyses,

4.3. Extent of Exposure

Extent of exposure will be summarized separately for abiraterone acetate and prednisone at each cycle and at end of core study treatment phase (cumulative). Summaries will be reported using descriptive statistics for discrete variables and will be performed using the safety population. The summaries will consist of the number and percentage of subjects who completed the specified range of daily dose level, starting at <75%, and then ≥75% compliance in increments of 5% to a maximum of >100%. The calculation of the percentages will be the ratio of the total cumulative dose (mg) given divided by the total planned dose (mg) for abiraterone acetate and prednisone, respectively. In addition, the number of subjects completing each cycle will also be presented (regardless of the percent of dose compliance). Since dose reduction is permitted in the study; the number and percentage of subjects with dose reduction will be recorded and summarized according to no dose reduction, 1 or 2 dose reductions (2 dose reductions are the maximum allowed for abiraterone acetate per protocol) at end of study. A subject experiencing dose reduction of abiraterone acetate during the study will be counted according to the highest number of reductions experienced.

Total number of doses and duration of exposure will be descriptively and categorically summarized (descriptive: N, mean, standard deviation, median, range; and categorical: 1, 2, 3, *etc.*).

4.4. Protocol Deviations

Protocol deviations will be captured in the EDC (electronic data capture system) and reviewed by a medical monitor.
Protocol deviations will be listed by subject number, and categorized according to the deviation reasons. If a significant number of deviations occur, a summary table will be produced showing the number of subjects for each deviation reason.

Major protocol violations (or deviations) are those deviations that may have potential impact to the efficacy and/or safety of abiraterone acetate. Subjects with any major protocol violations will be excluded from the per-protocol set.

After reviewing all protocol deviations, none were considered to impact safety or efficacy. Therefore, no subject will be excluded from the per-protocol set due to major protocol violations.

4.5. Prior and Concomitant Medications

For summarization purposes, medications will be coded to a generic term based on the World Health Organization (WHO) dictionary. Medications administered prior to the expected first dose of study treatment will be considered prior medications. Concomitant therapies will be those that are taken on or after Study Day 1 through 30 days after the last dose of study drugs. Medications started prior to Study Day 1 and continued into the study treatment period will be included in the summary of concomitant therapies. Incidence of prior medication and concomitant therapies by generic term will be summarized.

Summaries of subjects' prior prostate cancer hormonal therapy, prior prostate cancer radiotherapy, and prior prostate cancer related surgery will be presented.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Level of Significance

The significance level for the primary endpoint will be 0.025 (one-sided). A 2-sided 95% confidence interval (CI) interval will also be computed for all efficacy endpoints.

5.1.2. Data Handling Rules

Imputation rules for missing or partial event dates

The following imputation rule will be used for missing date in the assessment of an event:

- ☐ If all parts of the date are missing, the date will not be imputed.
- ☐ If only the start day of an event is missing, it will be replaced by the start day of study treatment if the event occurs in the same month and year. Otherwise, it will be replaced by the first of the month.
- ☐ If both the start day and month of an event are missing, the start day and month will be replaced by the start day and month of study treatment if the event and the start of the treatment occur in the same year; otherwise, it will be replaced by 1st of January.
- ☐ If the stop day is missing, the stop day of the event will be replaced by the stop day of study treatment. Otherwise, the last day of the month will be used to replace the missing stop day.

5.2. Primary Efficacy Endpoint(s)

5.2.1. Definition

The primary endpoint of this study is the proportion of subjects achieving a ≥ 50% reduction in PSA from baseline by the End of Core Study Visit.

5.2.2. Analysis Methods

The primary endpoint will be analyzed using a normal approximation to the binomial distribution comparing the observed proportion to a reference of 0.35 with a 1-sided significance level of 0.025; and the 2-sided 95% confidence interval (CI) interval will also be computed for the estimated proportion. The primary analysis will be performed using the Efficacy Evaluable set, and two additional sensitivity analyses will be performed on the All Enrolled set and Per-protocol set.

5.3. Major Secondary Endpoints

5.3.1. Definition

Major secondary endpoints are:

- ☐ Time to radiographic evidence of disease progression (TTRP)
- ☐ Time to PSA progression (TTPP).

Progression of soft tissue lesions measured by CT or MRI is as defined in the modified RECIST criteria. A subject is considered to have progressed by bone scan if:

1) The appearance of ≥ 2 new lesions, and, for the first assessment only (< 12 weeks), a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions
2) If ≥2 new lesions are seen on scans on or after 12 weeks, the confirmation is still required after 6 weeks; however, 2 addition lesions are NOT required to confirm progression
3) The date of progression is the date of the first scan that shows the changes.

Time to radiographic evidence of disease progression (TTRP) is defined as the time interval from the date of enrollment (Study Day 1) to the date of progression.

Imaging studies were assessed by site radiologist and used by investigators to make treatment decisions. The imaging scans were also forwarded to an independent third party, a central imaging reader, for verification. The main analysis of TTRP will be performed using the evaluations from the investigators. It will also be conducted using the central reader assessments as a sensitivity analysis.

A subject is considered to have a PSA progression if the PSA level had a 25% or greater increase and an absolute increase of 2 ng/mL or more from the nadir is documented, which is confirmed by a second value obtained in 3 or more weeks (Scher et al, 2008). For subjects who do not experience any decrease, nadir will be defined as the baseline value.

Time to PSA progression (TTPP) is defined as the time interval from the date of enrollment (Study Day 1) to the date of first evidence of PSA progression.

Time to disease progression or PSA progression will be tracked while subjects are on abiraterone acetate. Once a subjects is off abiraterone acetate, his or her time to radiographic disease progression or PSA progression will be censored at the last assessment (bone scan or PSA) while on abiraterone acetate.

5.3.2. Analysis Methods

Time-to-event endpoints will be analyzed using Kaplan-Meier product limit methods to estimate the survival distributions such as quartiles and the median time-to-event and the corresponding 95% confident intervals, using the All Enrolled Set.

Subjects without radiographic evidence of radiographic disease progression or PSA progression will be censored based on the following censoring rules:

1. If the subject does not have baseline assessment or any on-study assessments, the subject will be censored on the date of enrollment (Study Day 1);
2. If the subject does not show progression, the subject will be censored on the date of the last scheduled assessment;
3. Subjects will also be censored on the date of the last assessment that shows no progression if:
   a) the subject receives another therapy known or intended for treatment of CRPC during the study;
   b) the subject misses ≥2 planned assessments or has ≥2 consecutive unreadable scans.

5.4. Other Efficacy Variable(s)

5.4.1. Definition

Other secondary endpoints include:

- ☐ The proportion of subjects achieving a ≥ 50% reduction in PSA by Cycle 4
- ☐ The proportion of subjects achieving a ≥ 50% reduction in PSA by the End of Core Study Visit by local therapy status (with or without). Local therapy refers to how the primary tumor was treated before the study entry (surgery, radiation, or both). Since all enrolled subjects had local therapy prior to study entry, this analysis will not be performed.
- ☐ The proportion of Subjects achieving a ≥30%, ≥50% , or ≥ 90% Reduction in PSA by the End of Core Study Visit
- ☐ PSA levels and change from baseline
- ☐ Testosterone levels after 3 cycles and 6 cycles of treatment, and change from baseline.

5.4.2. Analysis Methods

Other secondary endpoints will be summarized descriptively using the Efficacy Evaluable set. PSA levels and change from baseline will be summarized descriptively by

cycle and day. Testosterone levels after 3 cycles of treatment and 6 cycles of treatment, and change from baseline will also be summarized.

6. SAFETY

The safety variables to be analyzed include vital sign measurements, AEs, routine laboratory values, and deaths. Unless otherwise noted, safety variables will be tabulated by descriptive statistics (n, mean, median, SD, minimum, and maximum; or n and percent) using the Safety Population.

6.1. Adverse Events

Adverse events are coded to System Organ Class (SOC) and preferred terms (PT) using the MedDRA® coding system. The severity of AEs will be graded on a scale of 1 to 5 according to the adult NCI Common Terminology Criteria for Adverse Events where higher grades indicate events of higher severity. Treatment-emergent adverse events will be summarized by grade according to the worst grade experienced.

Treatment-emergent AEs will be defined as all reported events with a start date on or after Study Day 1 or that increase in severity on or after Study Day 1. All AEs are collected through 30 days post last dose of study treatment.

All AEs will have their relationship to study drug assessed by the investigator as not related, doubtful, possible, probable, very likely. Adverse events will be categorized and summarized according to their highest relationship to study drug. Adverse events reported as unlikely, possibly related, or related will be classified as treatment-related AEs.

Summary	Sorted By	All Study Events	Treatment-Related Events
AE	SOC, PT	□	□
Most common (≥ 5%[1]) AEs	SOC, PT	□	
AEs by toxicity grade	SOC, PT	□	
Grade ≥3, AEs by toxicity grade	SOC, PT	□	□
Grade ≥3, AEs (≥5%[1]) by toxicity grade	SOC, PT	□	□
SAEs by toxicity grade	SOC, PT	□	
SAEs (≥5%[1]) by toxicity grade	SOC, PT	□	
AEs of special interest by toxicity grade	PT	□	
SAEs of special interest by toxicity grade	PT	□	

AEs, SAEs, and AEs of special interest, event rate per 100-subject years of treatment duration	SOC (no SOC for AEs of special interest), PT	□	
AEs leading to discontinuation of study medication	SOC, PT	□	
AEs leading to death	SOC, PT	□	□
AEs leading to dose modification or interruption of abiraterone acetate or prednisone	SOC, PT	□	
AEs of special interest leading to discontinuation of study medication	PT	□	

[1]The 5% may be adjusted if warranted to better represent the safety data

To adjust for unequal lengths of study treatment duration among subjects, an additional summary of SAEs and AE of special interest based on event rate per 100-subject years of treatment duration will also be provided. The event rate per 100-subject years of treatment duration is calculated as the total number of a given event divided by the total treatment duration per 100-subject years. Adverse events of special interest will be identified based on the SMQ (Standardized MedDRA Queries) terms (Appendix 1) and will be summarized.

Listings will be provided for subjects who experienced any Grade 3 or higher AEs, TEAEs of Special Interest, and others as described below.

6.2. Premature Discontinuations due to Adverse Events

A summary of reasons for discontinuation will be provided summarizing the number and percentage of subjects for each reason indicated. A listing of premature discontinuations due to AEs including the subject number, site, start date and study day of AE, severity, relationship to study regimen, action taken, and outcome of AE will be provided. Additional summary table summarizing preferred term may be provided if warranted.

6.3. Serious Adverse Events (SAE)

A listing of SAEs including the subject number, site, start date and study day of SAE, severity, relationship to study drug, action taken, and outcome of SAE will be provided. Additional summary table by preferred term may be provided if warranted.

6.4. Deaths

A listing of deaths including the subject number, site, date and study day of death, and cause of death will be provided.

6.5. Mineralocorticoid Excess

The proportion of subjects with mineralocorticoid excess (those with hypokalemia, hypertension, and/or volume overload [edema, refractory edema, or pulmonary edema]) will be summarized by each component and overall and the 95% CI interval will be computed. As a subset of adverse events of special interest, mineralocorticoid excess will also be identified based on the SMQ (Standardized MedDRA Queries) terms (Appendix 1) and will be summarized.

Subjects who increased the Prednisone dose (>5 mg/day) for managing mineralocorticoid excess will also be summarized or listed.

A listing of mineralocorticoid excess including the subject number, site, start date and study day of mineralocorticoid excess, severity, relationship to study regimen, action taken, outcome, and Prednisone dose at the time of the event will be provided.

6.6. Clinical Laboratory Tests

Routine laboratory results will be classified according to the NCI CTC version 4.03. Baseline grade and the worst grade per subject during post baseline will be tabulated. Mean change will be summarized at scheduled visits and, for selected variables. Shift table analyses are to be performed summarizing the number of subjects using baseline grade and worst grade post baseline. A listing of baseline laboratory values will be presented.

6.7. Additional Laboratory Tests

The additional laboratory tests include PSA and testosterone. These variables will be summarized similar to the routine laboratory results.

6.8. VITAL SIGNS AND PHYSICAL EXAMINATION FINDINGS

Vital signs include upright blood pressure, heart rate, respiratory rate, and body temperature. Vital signs, weight, and examination for volume overload will be performed at each visit. After the start of study agents, clinically relevant abnormalities in these evaluations are to be reported as an adverse event.

Vital signs and change from baseline in vital signs will be summarized by descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) at each scheduled visit.

- ☐ Abnormalities in low blood pressure (BP) will be summarized by number and percent of subjects with values and changes as defined below: For systolic BP, <90 mmHg and >30 mmHg decrease from baseline.

- ☐ For diastolic BP, <50 mmHg and >20 mmHg decrease from baseline.

REFERENCES

APPENDICES

APPENDIX 1: ADVERSE EVENT OF INTEREST (AEOI) SEARCH CRITERIA -ABIRATERONE ACETATE

The search criteria of adverse event (s) of interest (AEOI) are based on two areas of analysis, the adverse event term (SMQ) and the laboratory assessment as applicable.

If a SMQ does not exist a compilation of terms that reflect the event will be proposed for extraction and analysis of the data. Standardized MedDRA Queries (SMQ) version 14.0 (2011) will be used.

The adverse events of interest include hypokalemia, edema or fluid retention, liver function test abnormalities, hypertension and cardiac disorders. Each of these events is defined below:

1. **Hypokalemia**

A hypokalemia adverse will be defined as any treatment-emergent adverse event of low potassium, decreased potassium, potassium abnormal, potassium, or hypokalemia. Additional clinical events may be added to this definition based on product labels of similar drugs or drug classes. The MedDRA (most current version) preferred terms that correspond to the clinical adverse events of low potassium, decreased potassium, potassium abnormal, or hypokalemia will be used for the purposes of analysis. The preferred terms in V14.0 are:

BLOOD POTASSIUM ABNORMAL
BLOOD POTASSIUM DECREASED
HYPOKALAEMIA
HYPOKALAEMIC SYNDROME

Laboratory Assessment of Hypokalemia

Laboratory assessment of hypokalemia will be defined as any serum potassium laboratory assessment with an NCI CTCAE Version 4.0 grade shift increase from baseline.

2. **Hypertension (SMQ)**

Hypertension is defined according to category

1. HYPERTENSION (SMQ) narrow search.

Additional clinical events may be added to this definition based on product labels of similar drugs or drug classes. The Standardized MedDRA Queries that correspond to these events will be used for the purposes of analysis.

3. Edema or Fluid Retention

Edema or fluid retention is defined according to category:

1. HAEMODYNAMIC OEDEMA, EFFUSIONS AND FLUID OVERLOAD (SMQ) (Narrow search)

Additional clinical events may be added to this definition based on product labels of similar drugs or drug classes. The Standardized MedDRA Queries that correspond to these events will be used for the purposes of analysis.

4. Liver function test abnormalities (Hepatic Dysfunction or Hepatic function abnormal)

The following Standardized MedDRA Queries (SMQ) will be used to define events considered as liver function test abnormalities. This section includes the two SMQs recommended by MedDRA Maintenance and Support Service Organization (MSSO) to have a complete search of all biliary tract and liver-related investigations terms [*Liver related investigations, signs and symptoms- SMQ and Biliary system related investigation, signs and symptoms- SMQ*]. Additionally, potential drug related hepatic disorders are searched by selecting the following within the *Drug related hepatic disorders - comprehensive search - SMQ: Cholestasis and jaundice of hepatic origin -SMQ, Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions-SMQ), and Hepatitis, non-infectious- SMQ.*

Specifically, the 5 distinct SMQs are:

1. Liver related investigations, signs and symptoms- SMQ - Broad
2. Biliary system related investigation, signs and symptoms- SMQ - narrow
3. Cholestasis and jaundice of hepatic origin (SMQ) - Broad
4. Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ) - Broad
5. Hepatitis, non-infectious (SMQ) - Broad

Additional clinical events may be added to this definition based on product labels of similar drugs or drug classes. The Standardized MedDRA Queries that corresponds to these events will be used for the purposes of analysis.

Laboratory Assessment of Liver Functions Test Abnormalities

Laboratory assessment of liver function test abnormalities will be defined as any serum ALT/SGPT, AST/SGOT, bilirubin, and alkaline phosphatase laboratory assessment with an NCI CTCAE Version 4.0 grade shift increase from baseline.

5. Cardiac Disorders

The following Standardized MedDRA Queries (SMQ) version 14.0 will be used to define events considered as Cardiac Disorders. Ischaemic Heart Disease (SMQ), Myocardial Infarction (SMQ), Supraventricular tachyarrhythmias (SMQ), Ventricular tachyarrhythmias (SMQ), Cardiac failure (SMQ), and Possible arrhythmia related investigations, signs and symptoms (SMQ).

1. Ischaemic Heart Disease (SMQ) - This includes OTHER ISCHAEMIC HEART DISEASE (SMQ), Myocardial Infarction (SMQ) (Broad Search)
2. ARRHYTHMIA RELATED INVESTIGATIONS, SIGNS AND SYMPTOMS (SMQ) (Broad Search)
3. SUPRAVENTRICULAR TACHYARRHYTHMIAS (SMQ) (Broad Search)
4. VENTRICULAR TACHYARRHYTHMIAS (SMQ) (Broad Search)
5. CARDIAC FAILURE (SMQ) Narrow (Broad Search)

6. Osteoporosis

The following Standardized MedDRA Queries (SMQ) version 14.0 will be used to define events considered as Osteoporosis.

1. Osteoporosis / Osteopenia (SMQ) -(Broad Search)

7. Osteoporosis Related Fractures

The following preferred terms will be used to identify osteoporosis related fractures.

Ankle fracture
Avulsion fracture
Comminuted fracture
Complicated fracture
Compression fracture
Cervical vertebral fracture
Facial bones fracture Fibula fracture
Foot fracture
Fracture displacement
Fracture coccyx
Fractured skull depressed
Femoral neck fracture
Hand fracture
Humerus fracture
Impacted fracture
Jaw fracture
Lower limb fracture
Open fracture
Patella fracture

Scapula fracture
Skull fracture

Skull fracture base

Sternal fracture Stress
facture Tibia fracture
Tooth fracture Torus
fracture Traumatic
fracture Upper limb
fracture Ulna fracture

APPENDIX II:

MODIFIED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS

The following information was extracted from Section 3, Section 4, and Appendix I of the new response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1) authored by Eisenhauer et al (2009). Refer to the European Journal of Cancer article (2009;45(2):228-247) for the complete publication, references cited herein, and additional Appendices.

Evaluation of Progression
In this study, subjects will have no evidence of metastatic disease at baseline. Scans (CT or MRI, and bone) performed up to 28 days prior to Cycle 1 Day 1 may be used for screening assessments. If disease progression is observed on a scan during the Core Study Treatment Phase or the Follow-up phase, a confirmatory scan is required 6 or more weeks later. Study treatment should continue in the interim.

Measurability of tumor lesions
Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a *minimum* size of:

- ☐ 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- ☐ 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- ☐ 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 2 cm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Measurement of lesions
All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

New lesions denote progression
The appearance of new malignant lesions denotes disease progression. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal. A lesion identified on any post-baseline scan in any anatomical location is considered a new lesion and will indicate disease progression. If a new lesion is equivocal, for example, because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.