Janssen Research & Development *

Addendum to the Statistical Analysis Plan

A Phase 3 Randomized, Placebo-controlled Double-blind Study of JNJ-56021927 in Combination with Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone in Subjects with Metastatic Castration-resistant Prostate Cancer (mCRPC)

Protocol 56021927PCR3001; Phase 3

JNJ-56021927

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BACKGROUND AND RATIONALE

At the first and second interim analysis of the study (for overall survival), the IDMC has recommended that the study continue without modification, continue to collect data on all the secondary endpoints and remain blinded until the final analysis of OS. This addendum provides clarification on the data sources in this study that will be used in the primary analysis (and the relevant sensitivity analyses) for the secondary endpoint of CCI [redacted]

[redacted]

CCI [redacted]

Overall type 1 error will be controlled between Group 1 and Group 2.

SECONDARY ENDPOINT OF TIME TO PAIN PROGRESSION

The main feature of this addendum to the SAP for the final analysis is to include the CRF CCI [redacted] in addition to that described in the original SAP which included patient reported BPI3 worst pain score and the use of chronic opioid, whichever occurs first. CCI [redacted]

An additional sensitivity analysis of this endpoint is included in this addendum that incorporates selected deaths as pain progression events. Specifically, a death event meeting at least one of the CCI [redacted]

FINAL ANALYSIS OF SECONDARY ENDPOINTS IN GROUP 1

CCI [redacted]

BIOMARKER SUBGROUP ANALYSIS

Additional biomarker analyses are also pre-specified in this addendum based on the most recent tumor analysis findings from the two unblinded apalutamide phase 3 trials, SPARTAN and TITAN, using CCI [redacted].

The association between a biomarker signature and primary and secondary endpoints will be evaluated from archival tumor samples collected from a subset of patients enrolled in this study who consented for optional biomarker collections. CCI [redacted] The frequency of subjects in each biomarker subtype in the overall biomarker population and in each treatment arm will be tabulated with 95% confidence intervals. The association of treatment arm with rPFS, time to PSA progression, PSA response rate, objective response rate, and overall survival will be evaluated in groups defined by the biomarker subtypes. In addition, association of the biomarker subtype with rPFS, time to PSA progression, PSA response rate, objective response rate, and overall survival will be evaluated in each treatment arm. Association with time to event endpoints will be evaluated using CCI [redacted]

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AMENDMENT HISTORY

SAP Version	Issue Date
Original	3 May 2018
Amendment 1	31 Oct 2018

Amendment 1 (31 October 2018)

The rationale for and description of the changes are listed below, when revisions are provided verbatim, bold font denotes new text, and strikethrough denotes deleted text.

Applicable Section(s)	Description of Change(s)
Section 5.3.1 Secondary endpoints definition	Rationale: The secondary endpoints (time to pain progression and time to chronic opioid use) are assessed from time of randomization to pain progression (as defined in Section 5.3.1) and to time to chronic opioid use (as defined in Section 5.3.1). The original text regarding censoring in the last paragraph of Section 5.3.1 has been amended to clarify that censoring for subsequent therapy was intended as an additional sensitivity analysis for these endpoints. Original text: Additionally, for time to chronic opioid use and time to pain progression endpoints, the initiation of anti-cancer subsequent therapy will be used to censor the event after the therapy. Replaced with: Additionally, **sensitivity analyses will be performed** for time to chronic opioid use and time to pain progression endpoints, the initiation of anti-cancer subsequent therapy will be used to censor the event after the therapy.

ABBREVIATIONS

AA	abiraterone acetate
AAP	abiraterone acetate plus prednisone or prednisolone
ADT	androgen deprivation therapy
AE	adverse event
ALB	albumin
ALK-P	alkaline phosphatase
ALT/SGPT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AR	androgen receptor
AST/SGOT	aspartate aminotransferase
BICR	Blinded Independent Central Review
BID	twice daily
BPI-SF	Brief Pain Inventory-Short Form
CI	confidence interval
CRF	case report form
CRO	Contract Research Organization
CRPC	castration-resistant prostate cancer
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DHEA-S	dihydroepiandrosterone sulphate
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EU	European Union
FACT-P	Functional Assessment of Cancer Therapy – Prostate
FDA	Food and Drug Administration
GnRH	gonadotropin releasing hormone
HDL	high density lipoprotein
HR	hazard ratio
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
ITT	Intent-to-Treat
LE	Investigator or local site evaluation (imaging)
IWRS	Interactive Web Response System
LOCF	last observation carried forward
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LHRH	luteinizing hormone-releasing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MRU	medical resource utilization
NCI	National Cancer Institute
OS	overall survival
PCWG2	Prostate Cancer Working Group
PD	Phgroupacodynamic
PI	principal investigator
PK	phgroupacokinetic(s)
PRO	patient-reported outcome
PS	performance status
PSA	prostate specific antigen
PT	preferred term
QD	once daily

RECIST	Response Evaluation Criteria in Solid Tumors
ROW	Rest of World
rPFS	radiographic progression-free survival
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
SSRE	symptomatic skeletal-related event
TLGs	tables, listings, and graphs
ULN	upper limit of normal
US	United States
WHO	World Health Organization

1. INTRODUCTION

This document describes the planned statistical analyses for Protocol 56021927PCR3001: A Phase 3 Randomized, Placebo-controlled Double-blind Study of JNJ-56021927 in Combination with Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone in Subjects with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer (mCRPC). This statistical analysis plan (SAP) is intended to supplement the study protocol. Any deviations from this analysis plan will be described in the clinical study report.

1.1. Trial Objectives

1.1.1. Primary Objective

The primary objective is to compare the radiographic progression-free survival (rPFS) of apalutamide in combination with abiraterone acetate (AA) plus prednisone or prednisolone (AAP) and AAP in subjects with chemotherapy-naïve mCRPC.

1.1.2. Secondary Objectives

The secondary objectives of this study are:

- To characterize the safety profile of apalutamide in combination with AAP
- To characterize the population pharmacokinetics (PK) of apalutamide and abiraterone

1.1.3. Other Objectives

The other objectives of this study are:

- To explore the relationship between PK and pharmacodynamics (PD) of apalutamide and abiraterone
- To evaluate exploratory biomarkers predictive of response and resistance in subjects when treated with apalutamide in combination with AAP compared with AAP
- To assess the effect on patient-reported outcomes (PROs) in this study population when treated with apalutamide in combination with AAP compared with AAP
- To evaluate other endpoints of clinical relevance including additional assessments of pain, objective response, time to symptomatic skeletal-related event (SSRE), and PSA response
- To evaluate medical resource utilization information (MRU)

1.2. Trial Design

This is a randomized, double-blind placebo-controlled, multinational, multicenter Phase 3 study to determine if subjects with chemotherapy-naïve mCRPC will benefit from the addition of apalutamide to AAP compared with AAP. Subjects will continue ADT (in this study, GnRHa or surgical castration). Approximately 960 subjects who meet all the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio to receive apalutamide and AAP or matching placebo and AAP. Subjects will be stratified by the presence or absence of visceral metastases, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) grade of 0 or 1, and region (European Union [EU], North America [United States/Canada], and Rest of World [ROW]). The study will consist of a Screening Phase; a

Treatment Phase, and a Followup Phase. The study is anticipated to end approximately 84 months after the first subject is randomized. A study design scheme is provided in protocol Figure 2.

A treatment cycle is defined as 28 days. Treatment will continue until disease progression, unacceptable toxicity, death or the sponsor terminates the study. Subjects must discontinue study drugs with documented unequivocal clinical progression (protocol Section 10.2). If the subject has radiographic progression, but not unequivocal clinical progression, and alternate treatment is not initiated, the subject may continue on study treatment at the investigator's discretion.

After discontinuing study drug, subjects will be contacted every 3 months (protocol Section 9.1.5) until death or termination of the study. In addition to survival follow up, analgesic use, SSREs, ECOG PS, and subsequent therapy for prostate cancer up to and including chemotherapy will be collected. Patient-reported outcomes (PROs) questionnaires will also be administered every 3 months for up to 12 months after treatment discontinuation.

Subjects will be monitored for safety during the Screening and Treatment Phases and up to 30 days after the last dose of study drug. Adverse events, including clinically significant laboratory abnormalities reported as AEs, will be graded and summarized using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. Dose modification guidelines will be provided.

1.3. Statistical Hypotheses for Trial Objectives

The primary hypothesis of the study is that apalutamide in combination with AAP compared with AAP will demonstrate improved rPFS and an acceptable safety profile in subjects with chemotherapy-naïve mCRPC. The statistical hypothesis is listed as follows:

H_0: The rPFS distributions of the combination group (apalutamide+AAP), $S_A(t)$, and that of the control group (Placebo+AAP), $S_P(t)$, are equal:

$S_A(t) = S_P(t)$, for all $t > 0$

H_1: The rPFS distributions are not equal for at least one time point t:

$S_A(t) \neq S_P(t)$, for some $t > 0$

where rPFS is defined as the time from the date of randomization to the date of radiographic progression or death, whichever occurs first. Radiographic progression for primary endpoint will be based on the investigator's assessment of soft tissue lesion using computed tomography (CT)/magnetic resonance imaging (MRI) per response evaluation criteria in solid tumors (RECIST 1.1)[1] and bone lesion progression on bone scans per modified Prostate Cancer Working Group 2 (PCWG2)[2].

1.4. Sample Size Justification

This study is designed to provide sufficient power (approximately CCI) to detect a hazard ratio (HR) of C in the secondary endpoint of OS based on an assumed median OS of CCI for the control group (AAP). The assumption for OS is a HR of C, a CCI risk reduction in death. This represents an improvement of CCI (CCI versus CCI) in the median time to death in the treatment group of apalutamide plus AAP compared with the control group of AAP alone. Under the assumption that the failure distribution of OS follows an exponential distribution with a constant HR, approximately CC death events will be required to detect the assumed HR at a maximum two-sided significance level of

0.05, with enrollment duration of approximately [redacted] (approximately 960 subjects) and additional follow-up of [redacted] to reach the total number of events. The median time of OS in the control group of AAP alone and the enrollment projection are assumed based on the observation in the COU-AA-302 study. See Section 5.3 for detail statistical procedure use in the adjustment of the significance level for OS.

It is assumed that the failure distribution of the primary endpoint, rPFS follows an exponential distribution with a constant hazard rate. The assumption for rPFS is a hazard ratio of [redacted], a [redacted]% risk reduction of experiencing radiographic progression or death. This represents an improvement in the median time to radiographic progression or death of approximately [redacted] longer in the treatment group of apalutamide plus AAP than in the control group of AAP alone. Based on simulation to account for the correlation between rPFS and OS, it is estimated that approximately [redacted] rPFS events would be required to provide at least [redacted]% power in detecting a hazard ratio (HR) of [redacted] (median rPFS of [redacted] for the control group [AAP] versus [redacted] for the treatment group [apalutamide and AAP]) at a two-sided significance level of 0.05 under the assumption of a positive correlation between rPFS and OS (r = [redacted]). The median time of rPFS in the control group of AAP alone and the correlation between rPFS and OS are assumed based on the observation in the COU-AA-302 study. The same enrollment assumptions as described for OS are assumed.

1.5. Randomization and Blinding

1.5.1. Randomization

Subjects who meet all the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio to receive apalutamide and AAP or matching placebo and AAP using permuted block randomization. Subjects will be stratified by:

- Visceral metastases (Presence vs. absence)
- ECOG performance status (Grade of 0 or 1)
- Region (EU, NA, and ROW)

The countries included in each region are listed as below. NA: US and Canada; EU: Belgium, France, Germany, Italy, Netherlands, Spain, and UK; ROW: Australia, Korea, China, Japan, South Africa, Russia, Mexico, Brazil, and Argentina.

1.5.2. Blinding

This study is a double blind study. All subjects and study team members associated with the study conduct are to remain blinded to treatment group assignment until the time of database lock and unblinding of the study. Unblinding during the study can only happen in the case of a safety or a medical emergency, or for conducting data review by the IDMC as outlined in the IDMC charter.

2. GENERAL ANALYSIS DEFINITIONS

Study Day: For safety, study day will be calculated in reference to the date of first dose. Study Day 1 corresponds to the date the subject receives first dose of study drug. For Efficacy analysis, Study day will be calculated in reference to the date of randomization.

Cycle: For the purpose of the study, a treatment cycle is defined as 28 days. Subjects will begin taking study drug on Day 1 of Cycle 1.

Baseline Value: Unless otherwise specified, the baseline value will be defined as the closest measurement prior to the first dose of study drug. Change from baseline will be defined as (post-baseline value – baseline value).

Treatment Duration: Treatment duration will be defined as the duration of time from the date of the first dose of study drug to the date of last dose of study drug.

Time to event: Time to event calculations will be defined as the time from randomization to the date of the event of interest. Time to event or duration of event endpoints will be based on the actual date of the event, not visit number or visit label.

2.1. Visit Windows

The Treatment Phase will begin at Cycle 1 Day 1 of treatment and will continue until study drug is discontinued. Subjects should start study drug within 72 hours after randomization. Visits for each cycle will have a ±2 day window.

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. The last available value collected prior to the first dose of study drug will be used as the baseline value.

Study Day will be used in the analysis of safety data. The protocol allows a 72-hour window (3 calendar days) between randomization and the first dose; all efficacy analyses on time-to-event endpoints will consider the date of randomization as Day 1.

2.2. Pooling Algorithm for Analysis Centers

There is no plan for pooling the centers (study sites) for efficacy or safety analyses, unless analysis by site is warranted.

2.3. Analysis Sets

The following analysis sets will be used for this study:

Intent-to-Treat (ITT) Population: The ITT population includes all randomized subjects and will be classified according to their assigned treatment group, regardless of the actual treatment received. Subject disposition and efficacy analyses will be performed on data from the ITT population.

Safety Population: The safety population includes all subjects who received at least 1 dose of study drug as actually treated.

Patient-report Outcomes Population [PRO]: The PRO population includes all randomized subjects who completed at least the baseline assessment of the BPI-SF, FACT-P or EQ-5D-5L questionnaires. All time-to-event analysis will be based on ITT population.

Population Pharmacokinetics Populations [PK]: The PK population includes all randomized subjects who have at least 1 PK sample collected.

Biomarker Population: All randomized subjects who have at least 1 biomarker sample collected.

2.4. Definition of Subgroups

In order to assess the consistency of treatment benefit with respect to the primary efficacy endpoint of rPFS and the secondary endpoint of OS, additional univariate analyses will be performed for the following important subgroups:

- Baseline ECOG performance status (0, 1)
- Presence of visceral metastases (yes, no)
- Baseline Brief Pain Inventory-Short Form (BPI-SF) Question 3 (worst pain in the last 24 hours) score (0 to ≤1, >1 to ≤3, >3)
- Bone metastasis only at entry (yes, no)
- Number of bone lesions at baseline (<=10 vs. >10)
- Age (< 65, ≥65, ≥75)
- Baseline PSA above median (yes, no)
- Baseline LDH above median (yes, no)
- Baseline ALP above median (yes, no)
- Geographic region (EU, NA, ROW)

Subgroup analysis of selected countries will be performed for regional regulatory filing purpose.

3. INTERIM ANALYSIS AND INDEPENDENT DATA MONITORING COMMITTEE REVIEW

3.1. Interim Analysis

3.1.1. Futility Analysis

A non-binding futility analysis using an intermediate endpoint, the prostate-specific antigen (PSA) 90% decline rate (PSA90), is planned when approximately CC subjects have been treated for at least C cycles. The PSA90 is defined as ≥ 90% maximum decrease in PSA from baseline. Under the assumption of a correlation between PSA90 and OS of C observed in the COU-AA-302 study, a clinically meaningful improvement from CCI decline rate in the control group to CCI in the treatment group of apalutamide plus AAP, and a type II error rate of approximately CC, CC subjects will be required. The study may be considered futile if the p-value obtained from a chi-square test is CCI. The purpose of this analysis is to provide an early look at PSA90 to ensure that the combination of apalutamide plus AAP has sufficient antitumor activity compared with AAP. This futility analysis will not be used to substantiate an efficacy claim.

A non-binding futility analysis using rPFS will be implemented after observing CCI (CC events) of the total number of required CC events. The study may be considered futile if the estimated hazard ratio (HR) from Cox proportional-hazard model is greater than C. The probability of stopping under null hypothesis is CCI, and the probability of stopping under alternative hypothesis is CC.

Non-binding futility analyses are also being implemented for the OS endpoint (see Section 5.3, Table 2).

3.1.2. Interim Analysis

There will be no interim analysis of the primary rPFS endpoint.

Two interim analyses and one final analysis are planned for the OS endpoint. CCI

(see Section 5.3 for more details).

3.2. Independent Data Monitoring Committee (IDMC)

An IDMC will be commissioned for the study to perform regular safety review and the planned interim analyses. The IDMC will review the safety data when the first 60 subjects who have completed at least 1 cycle of treatment.

The IDMC will review the progress of the study and cumulative masked (ie, A vs B instead of actual treatment designation) safety data on a periodic basis as well as serve as the primary reviewer of the efficacy analyses.

Complete details regarding the composition and governance of the IDMC will be outlined in the IDMC Charter.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

The following parameters will be summarized by treatment group and overall using the ITT population:

- Age, sex, race, ethnicity, weight, height
- Baseline ECOG performance status
- Baseline PSA value
- Baseline Hemoglobin value
- Baseline Lactate Dehydrogenase value
- Baseline Alkaline Phosphatase value
- Baseline Testosterone value
- Average of 7-day BPI-SF Pain Score (Q3) leading to Cycle 1 Day 1 (with minimum 1 day)
- Baseline Analgesic Usage Score
- Time from Initial Diagnosis to First Dose
- Tumor Stage at Diagnosis
- Lymph Node Stage at Diagnosis
- Gleason Score at Initial Diagnosis

- Extent of Disease

4.2. Disposition Information

Subject enrollment and disposition will be summarized by treatment group. The summary of subject disposition will display the number of subjects screened, the number of subjects who screen failed, the number of subjects randomized, and the number of subjects in the ITT, safety, and population PK populations. The summary will also include the number and percent of subjects who are ongoing in the treatment and who discontinued from treatment and reason for discontinuation.

4.3. Treatment Compliance and Extent of Exposure

The safety population will be used to summarize drug exposure, treatment compliance, and dose modifications by treatment group.

Treatment duration will be defined as the duration from the date of the first dose of study drug to the date of last dose of study drug. The number of tablets taken will be calculated based on the number of tablets dispensed at the study visits minus the number of returned tablets.

The percent overall treatment compliance will be defined as the number of tablets taken during the study divided by the expected number of tablets, multiplied by 100. Each subject should be taking a maximum of 8 tablets of study drug (excluding prednisone) per day while on the study. A subject's expected number of tablets will be calculated as the number of assigned tablets per day multiplied by treatment duration.

Subjects with at least one dose modification and the reason for the dose modification will be summarized by treatment group.

4.4. Protocol Deviations

Protocol deviations and eligibility deviations will also be summarized by treatment group. Protocol deviations will be reviewed on a case-by-case basis and assessed if they are considered major deviations for this study. The final list will be complied prior to database lock. The major protocol deviations may include, but are not limited to, the following:

- Deviation from inclusion/exclusion criteria that may affect efficacy endpoints
- Major study drug dosing errors or dose modifications that are not within the protocol specifications that may compromise subject safety or efficacy assessments.
- Administration of prohibited concomitant medication during the course of the study treatment period
- Any other deviation that impacts subject safety

4.5. Prior and Concomitant Medications

Prior and concomitant medications, other than study treatment, taken prior to starting study treatment and those administered during the study will be summarized by treatment group. Medications are considered concomitant if taken during the treatment period (within 30 days of the last study drug dose). Medications will be summarized by WHO Drug therapeutic class and generic medication name.

4.6. Subsequent Anti-cancer Therapies

Subsequent therapies received after discontinuation of study treatment will be summarized by treatment arm in the overall population as well as by geographic region.

The following imputation rule will be used for missing start dates for subsequent therapies:

a. If all parts of the start date are missing, the date will be imputed with the date after the discontinuation date.
b. In the case where only the start day of therapy is missing, it will be replaced by the day after the discontinuation date if the therapy starts in the same month and year as the discontinuation date. Otherwise, it will be replaced by the first of the month.

If both the start day and month of therapy are missing, the start day and month will be replaced by the day and month of the date after the discontinuation date if the therapy and the discontinuation occur in the same year; otherwise, it will be replaced by 1st of January.

5. EFFICACY

This section outlines the planned analyses of the primary and secondary efficacy, and other endpoints of the study

Efficacy analyses will be performed in the ITT population, incorporating the randomization stratification factors as documented on the electronic case report form (eCRF) from the interactive web response system (IWRS), unless otherwise specified. All continuous variables will be summarized using number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized with count and percentage.

Time-to-event endpoints will be summarized using the Kaplan-Meier method[5] and displayed graphically where appropriate. Median event times and two-sided 95% confidence interval (CI) for each treatment group will be provided. Stratified Cox proportional-hazard models will be used to estimate the HR and its 95% CI. The stratification factors to be used in the model are presence or absence of visceral metastases, ECOG performance status, and region.

The testing for the time-to-event endpoints will be based on the stratified log rank test; non-stratified log rank test will be performed as a sensitivity analysis, as appropriate. Multivariate Cox regression analysis, adjusting for important selected prognostic factors, will be performed as supportive analyses for rPFS and OS. The details of including prognostic factors can be found in Section 5.2.4 and additional exploratory analysis can be found in Section 5.3.3.

The proportional hazard assumption will be assessed graphically by plotting log (-log [estimated survival distribution function]) against log (survival time). The resulting graphs should have approximately parallel lines when the assumption holds. If the proportional hazards assumption is reasonably met, then the HR will be used as an estimate of treatment effect. If the proportional hazards assumption is violated, then the inference remains statistically valid for testing equality in survival distributions, but treatment effect will only be estimated using the median time to event in each treatment group.

Endpoints with binary outcome (e.g., objective response rate) will be summarized by descriptive statistics (count and percentage) by the treatment group. The relative risk (treatment: control) will be reported along with the corresponding two-sided 95% CI. The response rates between two treatment groups will be

compared by using the chi-square test; Fisher's exact test may be used if the expected counts in some of the cells are less than 5.

5.1. Analysis Specifications

5.1.1. Level of Significance

In general, a two-sided significance level of $\alpha = 0.05$ will be used for all hypothesis testing and all confidence intervals will be calculated on the two-sided 95% confidence level, unless otherwise specified.

5.1.2. Data Handling Rules

In general, no imputation method is planned for handling missing or incomplete data unless specified otherwise for a specific endpoint. Sensitivity analyses with censoring rules may be conducted if warranted and will be documented in the clinical study report.

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

a. If all parts of the date are missing, the date will not be imputed.

b. In the case where 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 date of the month.

c. 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.

d. 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 both the stop day and month of an event are missing, the stop day and month will be replaced by the stop day and month of study treatment if the event and the stop of the treatment occur in the same year; otherwise, it will be replaced by 31st of December.

5.2. Primary Endpoint of rPFS

5.2.1. Definition

The primary efficacy endpoint is radiographic progression-free survival (rPFS), based on the imaging assessments by the investigator, is defined as the time from the date of randomization to the date of first documentation of radiographic progressive disease or death due to any cause, whichever occurs first.

Radiographic progression in this study is defined as the time from randomization to the occurrence of one of the following:

- A subject is considered to have progressed by bone scan if:
  - The first bone scan with ≥2 new lesions compared with baseline is observed <12 weeks from randomization and is confirmed by a second bone scan taken ≥6 weeks later showing ≥2 additional new lesions (a total of ≥4 new lesions compared with baseline);

  - The first bone scan with ≥ 2 new lesions compared with baseline is observed ≥12 weeks from randomization and the ≥2 new lesions are verified on the next bone scan ≥6 weeks later (a total of ≥ 2 new lesions compared with baseline).

- Progression of soft tissue lesions measured by computed tomography (CT) or magnetic resonance imaging (MRI) as defined in modified RECIST 1.1 criteria.

Subjects that withdraw from the study (i.e., withdrawal of consent, lost to follow-up) or receive new systemic anti-cancer therapy without documented disease progression will be censored on the date of the last tumor assessment. Subjects with no evidence of radiographic progressive disease or death will be censored on the date of the last tumor assessment. If there was no tumor assessment performed after the baseline visit, the subject will be censored on the date of randomization. Key censoring rules are summarized as shown in Table 1. More detailed censoring rules are documented in Data Presentation Specifications (DPS).

Table 1: Key censoring Rule

Scenario	Censoring rule
No tumor assessment at Baseline or No tumor assessment after Baseline	Censored on the date of randomization
Subjects who are lost to follow-up or withdraw from study	Censored on the date of the last tumor assessment
Subjects who receive new systemic anti-cancer therapy prior to documented disease progression or death	Censored on the date of the last tumor assessment prior to the start of the new systemic anti-cancer therapy
Subjects with no evidence of radiographic progressive disease or death	Censored on the date of the last tumor assessment
Subjects who miss ≥2 consecutive planned radiographic scans or has ≥2 consecutive unreadable scans before progression or death	Censored on the date of the last tumor assessment before the missed/unreadable scans

5.2.2. Analysis Methods

The primary analysis for the comparison of the survival distributions of rPFS between two treatment groups will be carried out using the stratified log rank test at a two-sided significance level of 0.05. If the number of events required for the primary analysis of rPFS and the first interim analysis of OS occur approximately at the same time, the primary analysis of rPFS will be performed at the time of the first interim analysis of OS. Otherwise, the timing of the primary analysis of rPFS may be adjusted taking into consideration the number of death events.

Non-stratified log rank test will be performed as a sensitivity analysis. Stratified Cox proportional-hazard model will be used to obtain the HR and its 95% confidence interval.

5.2.3. Audit Plan

In this study, the primary efficacy endpoint of rPFS is based on the investigators' radiographic evaluation of the disease. To confirm that the investigator or local site evaluation (LE) is not biased in favor of the experimental arm, an audit plan based on the NCI method (Dodd et.al., Biometrics) [6] will be implemented. This plan includes a subset of subjects randomly selected for a blinded independent central review (BICR).

The goal of the audit method by Dodd et al is to provide confidence that the local site evaluation of any treatment effect for rPFS is a true estimate and unlikely to be affected by investigator bias. Assuming an observed investigator-assessed HR for rPFS of 0.5-0.75, an audit size of approximately 60% of all randomized subjects is recommended by Dodd et.al. (Biometrics 2011)[6] and Zhang (2013)[8]. Therefore approximately 590 subjects will be randomly selected for BICR. All randomized subjects who have {baseline CT/MRI scan and at least one post-baseline CT/MRI scan} OR {baseline bone scan and at least one post-baseline bone scan} will be eligible for the random sample generation.

All scans will be collected and stored in a central location so that a valid audit can be performed using independent centralized review of blinded radiographic scans. Assuming a compelling and clinically meaningful investigator-assessed treatment effect size is present, based on the Independent Data Monitoring Committee (IDMC) review and recommendation, the upper limit of the 2-sided 95% confidence interval for the overall estimated log HR by LE based on the audited subset can be estimated by Equation (3) of Dodd et al. Specifically, the estimated overall log HR by LE is expressed as

$$\tilde{\theta}_c = \hat{\theta}_{CA} + \hat{\rho}\sqrt{\delta}(1-\delta)\sqrt{\frac{\hat{V}_{CA}}{\hat{V}_L}}(\hat{\theta}_{L\bar{A}} - \hat{\theta}_{LA})$$

where, δ is the proportion of available audit subjects out of the total randomized subjects. $\hat{\theta}_{CA}$ is the log HR) based on BICR assessed rPFS related datasets that are audited. $\hat{\theta}_{LA}$ is the log (HR) based on investigator's assessed rPFS related datasets that are audited. $\hat{\theta}_{L\bar{A}}$ is log (HR) based on the investigator's assessed rPFS related datasets that are not audited. $\hat{V}_L$ is the variance estimate of log HR based on the overall investigator's assessed rPFS related datasets. The $\hat{\rho}$ is correlation coefficient between $\hat{\theta}_{CA}$ and $\hat{\theta}_{LA}$ that will be estimated using bootstrap method with 6000 samples.

Let γ_c be the upper bound of one-sided (1-α/2) CI for $\tilde{\theta}_c$, and CIF be the clinical irrelevance factor. Based on a minimally relevant improvement in rPFS, it is set that CIF = log(1) = 0 for a hazard ratio of 1 for the proposed audit plan. If this upper limit of the overall estimated log HR by BICR is below 0 or the overall estimated HR by BICR is below 1, then the concordance of the estimates by LE and BICR will be confirmed. Kaplan-Meier methodology will be used to compare the rPFS curves derived from LE and BICR of the audited subset of patients to demonstrate no evidence of bias.

IDMC will review the audit findings and make recommendations. The audit analysis will be coordinated through the independent SSG statistician for the IDMC review. Therefore, all investigators, study team, and the central reviewer will remain blinded to treatment assignment until the IDMC reviews the audit findings and confirms that no bias is present in the investigator review. If bias is considered present, a complete-case of BICR will be considered.

A sensitivity audit analysis will be performed using PhRMA method (Amit et.al., EJC 2011)[7]. The method can be found in Attachment 2.

5.2.4. Other Analyses related to Primary Endpoint

Subgroup Analysis

To assess the consistency of treatment benefit with respect to the primary efficacy endpoint of rPFS within the important subgroups defined in Section 2.4, a univariate non-stratified proportional hazard model will be fitted to evaluate the treatment effect within each subgroup, the hazard ratio and 95% confidence interval will be estimated. Forest plots will also be provided.

Multivariate Analysis

To evaluate the treatment effect when controlling for clinically meaningful factors at baseline, multivariate Cox regression analysis, adjusting for important selected prognostic factors, will be performed as supportive analysis, if appropriate. The adjusted hazard ratio and its 95% confidence interval for treatment and each factor will be provided. The following baseline covariates may be considered for inclusion in the model:

- Visceral metastases (IWRS: presence, absence)
- ECOG performance status at randomization (IWRS: 0, 1)
- PSA (continuous)
- Lactate dehydrogenase
- Alkaline phosphatase
- Hemoglobin
- Bone metastasis only (yes, no)
- Age

Clinical Progression

As an exploratory analysis, Time from rPFS to clinical progression (CP) may be summarized by treatment arm if sufficient number of subjects reaches CP during the study. Clinical Progression is defined in Section 5.4.2:

Other Analysis

The number of patients who remained on study drug beyond radiographic progression and the duration that they remained on study drug may be summarized by treatment arm if sufficient number of subjects belong to this category.

5.3. Secondary Endpoints

The analyses of the secondary endpoints will be performed at the time of the first interim analysis of OS.

CCI [redacted]

CCI [redacted]

[redacted]

- CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

The above procedure will control the familywise type I error rate at 0.05 [5].

CCI [redacted]

[redacted]

5.3.1. Definition

- Overall survival (OS) is defined as the time from randomization to the date of death from any cause. Subjects who are alive at the time of the analysis will be censored on the last known date that they were alive.

- Time to chronic opioid use (defined as administration of additional opioid analgesics lasting for ≥ 3 weeks for oral; or for ≥ 7 days for non-oral formulation) is defined as the time from randomization to the first date of chronic opioid use. Subjects who did not meet the definition of chronic opioid use at the time of the analysis will be censored on the last known date with no chronic opioid use.
- Time to initiation of cytotoxic chemotherapy is defined as the time from randomization to the date of initiation of cytotoxic chemotherapy. Subjects who did not initiate cytotoxic chemotherapy at the time of the analysis will be censored on the last known alive date.
- Time to pain progression is a composite endpoint, defined as the time from the date of randomization to the first date a subject experiences: A. {an increase by 2 points from baseline in the BPI-SF worst pain intensity score (BPI3) observed at 2 consecutive evaluations ≥ 3 weeks apart}, or B. {initiation of chronic opioids as defined in Time to chronic opioid use above}, whichever occurs first.

  Given the fact that BPI-SF will be implemented during the 7-day period leading to each assessment cycle (including Day 1 of the cycle), non-missing daily BPI3 pain scores from the 7-day collection with minimum of 1 day entries is averaged to be evaluated if an increase by 2-point has occurred.

  Subjects with no pain progression at the time of analysis will be censored at the last known date of no progression. All sensitivity analyses for this endpoint are included in a separate SAP for PRO analysis.

For all these time-to-events endpoints, subjects with no on-study assessment or no baseline assessment will be censored on the date of randomization. Additionally, sensitivity analyses will be performed for time to chronic opioid use and time to pain progression endpoints, the initiation of anti-cancer subsequent therapy will be used to censor the event after the therapy.

5.3.2. Analysis Methods

The testing of these secondary efficacy endpoints will be based on the stratified log rank test. Secondary efficacy endpoints will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. Cox proportional hazard models will be used to estimate the HR and its 95% confidence interval.

5.3.3. Additional Analysis for OS

The following sensitivity analyses for the OS may be carried out as appropriate if it is deemed useful to aid in the interpretation of the results.

Subgroup Analysis

To assess the consistency of treatment benefit with respect to the primary efficacy endpoint of rPFS within the important subgroups defined in Section 2.4, a univariate non-stratified proportional hazard model will be fitted to evaluate the treatment effect within each subgroup, the hazard ratio and 95% confidence interval will be estimated. Forest plots will also be provided.

Examination of overall survival may be performed to compare patients who received a concurrent androgen receptor inhibitor and abiraterone with patients who received abiraterone followed by enzalutamide after discontinuation of study treatment. This is to evaluate the possibility of reduced efficacy of enzalutamide after abiraterone failure, the issue of whether concomitant abiraterone + 2nd generation antiandrogen is superior to a sequential approach (abiraterone followed by enzalutamide in the U.S.).

Multivariate Analysis

Multivariate analysis of OS adjusting for baseline prognostic factors will be performed similarly as rPFS outlined in Section 5.2.5. The adjusted hazard ratio and its 95% confidence interval for treatment and each factor will be provided. The results may be used to support the findings obtained from the primary analysis.

Sensitivity Analysis for OS

A large number of subjects are expected to receive subsequent anti-cancer therapies after discontinuing study treatment, the following analyses may be used, if appropriate, in estimating the true treatment effect on OS:

- Inverse Probability Censoring Weighted (IPCW) log-rank test as described by Cole and Hernan[9]
- Using a time-dependent Cox regression; the HR prior to receiving subsequent anti-cancer therapy and after will be estimated, the associated 95% CI will be calculated.

5.4. Other Efficacy Analyses

5.4.1. Definition

Other efficacy endpoints are defined in Table 3.

Table 3: Other Endpoints

Endpoint	Description	Analysis Population
Time to deterioration of ECOG PS	Primary Analysis: Defined as the time from randomization to the date of deterioration in ECOG PS grade (increase by at least 1 grade from baseline with confirmation at least 4 weeks apart). Sensitivity Analysis: the deterioration in ECOG PS grade is defined as the following: from 0 or 1 increase to 2 or above; or from 2 increase to 3.	ITT Population
Time to symptomatic skeletal-related event (TTSSRE)	The time from randomization to first occurrence of one of the following: • Use of external beam radiation therapy (EBRT) to relieve skeletal symptoms • The occurrence of new symptomatic bone fractures (cancer-related: vertebral or non-vertebral) • The occurrence of tumor-related spinal cord compression • Need for tumor-related orthopedic surgical intervention Subjects who have no symptomatic skeletal-related event (SSRE) at the time of analysis will be censored at the last known on-study date of no SSRE.	ITT Population
Objective response rate	Objective response rate defined as the proportion of subjects with measurable disease achieving a complete or partial response according to modified RECIST 1.1.	Subjects with measurable disease at Baseline

Table 3: Other Endpoints

Endpoint	Description	Analysis Population
Duration of response	Duration of response in subjects with measurable disease (based on modified RECIST 1.1) is defined from the time of documented response to the first date of documented progression. Subjects who have not been administered with cytotoxic chemotherapy at the time of analysis will be censored on the last known date of no cytotoxic chemotherapy.	Subjects with CR or PR
Health related-Quality of Life (HRQOL)	The patient-reported outcomes will include the following: • BPI-SF: worst pain intensity score (Item 3), pain interference score (combining Items 9a-9g), and average pain (average of Items 3-6) that are based on average of 7-day diary. • FACT-P: FACT-P total score, each subscale score (PWB, SFWB, EWB, FWB, FACT-G, PCS), TOI, PRS, and FAPSI-8. • EQ-5D-5L: 5 domain levels and VAS score; Health Utility Index (HUI). See PRO SAP for the PRO endpoint definition and analysis methods.	ITT Population
Time to analgesic progression	The time from randomization to the first date of an increase in analgesic usage score of one level increase from baseline observed at 2 consecutive evaluation ≥4 weeks apart. Subjects with no analgesic progression at the time of analysis will be censored on the last known date the subject was known to have not progressed.	ITT Population
Time to PSA progression	The time from randomization to the first date of documented PSA progression per PCWG2 criteria. Subjects with no PSA progression at the time of analysis will be censored on the last known date with no progression.	ITT Population
PSA response Rate	Proportion of subjects achieving a PSA decline of ≥50% according to PCWG2 criteria.	ITT Population
Progression-free survival on first subsequent therapy (PFS2)	PFS2 is defined as time from randomization to the date of first progression (radiographic, clinical, or PSA progression) on the first subsequent therapy or death from any cause, whichever occurs first	ITT population

Table 3: Other Endpoints

Endpoint	Description	Analysis Population
Time to clinical progression	A composite endpoint is defined as time from randomization to first occurrence of one of the following: 1. deterioration in ECOG PS to grade 3; 2. need to initiate any of the following: a. alternative anti-cancer therapy (systemic), b. the use of external beam radiation therapy for tumor related symptoms c. the need for tumor-related surgical intervention/procedure; d. the need for chronic opioid analgesics (per protocol definition); e. cancer-related symptomatic events of clear clinical significance. If no event was observed, subject will be censored at the last known alive date. In addition, a sensitivity analysis excluding the component of deterioration of ECOG performance status from the composite endpoint will be performed.	ITT population

5.4.2. Analysis Methods

Analyses of the other endpoints (except for HRQOL measures) will be performed on the ITT population, unless otherwise specified. Time-to-event endpoints and endpoints with binary outcome will be carried out as described above. HRQOL measures related endpoints, and analysis strategies are described in Section 5.4.3 below.

5.4.3. Patient Reported Outcome (PRO)

A separate statistical analysis plan will be provided for PRO data.

6. SAFETY

6.1. Adverse Events

Subjects will be assessed for adverse events (AEs) at each monthly clinic visit while on the study. Adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 and coded to preferred term and system organ class (SOC) using the MedDRA version 20.0.

All AEs reported during the AE reporting period (inclusive of the 30-day post last dose of study drug period) will be considered as treatment-emergent adverse events and will be summarized by treatment group as treated using all subjects in the safety population.

For each treatment group, adverse event incidence rates will be summarized with frequency and percentage by SOC and preferred term, with all subjects treated in that treatment group as the denominator, unless otherwise specified. In addition, AE incidence rates will also be summarized by severity and relationship to study drug. Treatment-related AEs are those judged by the Investigator to be at least possibly related to the blinded study drug. Subjects with multiple occurrences of events will only

be counted once at the maximum severity to study drug for each preferred team, SOC, and overall. Deaths that occur within 30 days after the last dose of study drug are defined as on-study deaths.

Summary tables of the following AEs will be provided:

- Overall summary of AEs: the number and percentage of subjects who experienced any AE, Grade 3/4 AEs, any serious adverse event (SAE), any treatment-related AE, treatment related Grade 3/4 AE, any treatment-related SAE, AE leading to treatment discontinuation, related AE leading to treatment discontinuation, AE leading to death, related AE leading to death, and all deaths within 30 days of last dose
- All AEs by SOC and preferred term (for all AEs and for most frequent AEs (reported in ≥ 5% of subjects))
- All AEs by SOC, preferred term, and toxicity grade
- All AEs by decreasing frequency of preferred term
- Grades 3 or 4 AEs by SOC and preferred term
- Treatment-related AEs by SOC and preferred term
- Treatment-related AEs by SOC, preferred term, and toxicity grade
- Treatment-related Grades 3 or 4 AEs by SOC and preferred term (for all Grades 3 and 4 AEs and for Grades 3 and 4 most frequent AEs (reported ≥ 1% of subjects))
- AEs that led to study drug discontinuation by SOC and preferred term. Study drug discontinuation will be determined from the End of Treatment CRF (where reason for termination is "Adverse Event") and the specific AE will be determined from the AE CRF page (where action taken is "Withdrawn from Study")
- AEs that led to study drug discontinuation by SOC, preferred term, and toxicity grade
- All SAEs by SOC and preferred term
- All SAEs by SOC, preferred term, and toxicity grade
- Deaths will be summarized by time period (on-study vs. during follow-up) and cause of death.

The incidence of AEs of special interest will be summarized by category and preferred term. Adverse Events of Special Interest for apalutamide + AAP include:

- Seizure
- Fall (relationship to syncope or dizziness will be assessed)
- Hypothyroidism
- Skin Rash
- Fracture (relationship to medical history or adverse event of osteoporosis or osteopenia will be assessed along with relationship of AE of change in weight and use of bone targeted agents at doses for treatment of either osteoporosis or metastatic disease that were initiated prior to or following the event)
- Osteoporosis/Osteopenia excluding fracture
- Rhabdomyolysis/Myopathy
- Cardiac disorders (ischaemic heart disease, arrhythmia, cardiac failure, and other cardiac disorders)

- Hepatotoxicity
- Allergic alveolitis
- Hypertension
- Hypokalemia
- Fluid retention/oedema

Note that fall is a single preferred term, all other categories are comprised of a group of preferred terms. A listing of preferred terms that comprise the groupings are provided in Attachment 1.

The AEs of clinical importance will be summarized by category and preferred term. Adverse events of clinical importance include: Diabetes and Cognitive Deficits, which were identified based on previous experience with apalutamide. A listing of the single preferred terms that comprise the groupings are provided in Attachment 1.

Subject listings of all Grades 3 or 4 AEs, all SAEs, AEs that led to study drug discontinuation, and all deaths will be provided as well.

Narratives will be written for the following subjects in the final clinical study report:

- Deaths within 30 days of the last dose of study drug
- Subjects who have serious adverse event
- Subjects who discontinue study drug due to adverse events
- Subjects who experience AEs of special interest of seizure (any grade)
- Other treatment-emergent AEs of special interest (grade 3 or higher) including skin rash, fractures, fall, and hypothyroidism
- Grade 3 or higher major adverse cardiovascular events (MACE) to include ischemic heart disease, cardiac failure, cerebrovascular disease, and arrhythmias.

6.2. Clinical Laboratory Tests

Only data collected by the central laboratory will be summarized. Local laboratory data collected during study for the purposes of planning treatment administration, dose modification, or monitoring adverse events, will not be summarized.

Normal ranges will be used to identify values that are outside the normal ranges and abnormal laboratory results will be graded according to the NCI CTCAE Version 4.03.

A shift summary of baseline grade vs worst post-baseline CTCAE grade will be presented, as appropriate for selected parameters. For each laboratory parameter, the baseline laboratory value will be defined as the last laboratory value collected on or prior to the date of the first dose of study drug.

A listing of subjects who develop toxicities of Grade ≥ 3 will be provided for each lab parameter.

Subjects meeting lab criteria for eDISH (Evaluation of Drug Induced Serious Hepatotoxicity) will be listed. eDISH is defined as 1) Elevated ALT or AST at any time. That is, max (ALT/ULN) >3 or max (AST /ULN) >3. 2) Elevated TBL at any time. That is, max (TBL/ULN) >=2.

6.3. Vital Signs and Physical Examination Findings

Baseline vital sign (temperature, blood pressure (systolic and diastolic), respiration rate, and heart rate) will be summarized by treatment group. Only blood pressure and body weight are reported during treatment phase. Subjects with markedly abnormalities in blood pressure as compared to baseline will be summarized according to the following categories defined below.

Parameter	Criteria for Markedly Abnormality
Systolic Blood Pressure	Absolute result < 90 mmHg and decrease from baseline > 20 mmHg
	Absolute result > 160 mmHg and increase from baseline > 20 mmHg
Diastolic Blood Pressure	Absolute result < 50 mmHg and decrease from baseline > 10 mmHg
	Absolute result > 100 mmHg and increase from baseline > 10 mmHg
Weight (kg)a	5 - < 10% weight loss from baseline
	10 - < 20% weight loss from baseline
	>= 20% weight loss from baseline

6.4. Electrocardiogram

Electrocardiograms (ECGs) (12-lead) will only be recorded at screening, and no QT data are collected. Abnormalities reported at screening will be summarized.

7. PHARMACOKINETICS

Pharmacokinetic assessment (trough PK samples) will be per protocol. Pre-dose blood samples (up to 1 hour prior to on-site study drugs administration) will be drawn as described in the Laboratory Manual on Day 1 of Cycles 1, 2, 3, 4, 5 and 6.

Analyses on PK data will be conducted and reported separately.

8. BIOMARKERS

A pre-defined biomarker signature based on the mRNA expression of component genes such as (FLH1, MT1E, SF1 and STARD4) will be evaluated. For each of the subjects with the biomarker sample collected and evaluated, expression status of the biomarker signature (i.e. Positive/Negative) will be assigned. If adequate data is available, efficacy analysis (including but may not be limited to: rPFS, time to PSA progression, overall survival, PSA response rate, and objective response rate) will be performed within the biomarker signature positive and biomarker signature negative subgroups comparing apalutamide plus AAP versus AAP alone.

Other exploratory biomarker analysis may also be performed to assess the association of the rest of the biomarkers with clinical response or time-to-event endpoints using appropriate statistical methods, (such as analysis of variance [ANOVA], categorical or survival models), depending on the endpoints. Analyses may be performed within and between each treatment group. Other clinical covariates (such as baseline tumor characteristics and patient demographics) may also be included in the model. Results of these exploratory analyses will be presented in separate technical reports.

9. MEDICAL RESOUURCE UTILIZATION

Medical resource utilization will be descriptively summarized by treatment group. This report will be prepared separately and will not be a part of the clinical study report.

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Attachment 1: Audit Analysis Using Amit's Method

To confirm that the investigator review is not biased in favor of the experimental arm for primary analysis of rPFS, a sensitivity audit analysis will be performed based on the publication of Amit et al [7].

Based on the 590 subjects randomly selected for BICR, the audit will use calculations of early discrepancy rates (EDR) and late discrepancy rates (LDR) for each treatment group to determine whether bias is present in the investigator assessments. For this study, bias will be considered present in the investigator review if the EDR in the experimental arm is lower than EDR in the control arm, or LDR in the experimental arm is higher than LDR in the control arm. Specifically, Table 4 shows the agreement between Blinded Independent Central Review and Investigator Review.

Table 4: Blinded Independent Central Review versus Investigator Review of Disease Progression

	Blinded Independent Central Review	
	PD	No PD
Investigator PD	$a = a1 + a2 + a3$	b
No PD	c	d

$a1$: number of agreements on timing and occurrence of PD.
$a2$: number of times investigator declares PD later than Central Review.
$a3$: number of times investigator declares PD earlier than Central Review.

The early discrepancy rate (EDR) of the investigator review is defined as:

$$EDR = \frac{b + a_3}{a + b}$$

The late discrepancy rate (LDR) of the investigator review is defined as:

$$LDR = \frac{c + a_2}{b + c + a_2 + a_3}$$

Note the EDR and LDR represent the frequency with which the investigator review declares progression earlier than independent review (EDR) and the frequency with which the investigator review declares progression later than independent review (LDR).

Bias will be considered present in the investigator review if

EDR (experimental arm) < EDR (control arm)
indicating the EDR in the experimental arm is lower than EDR in the control arm,

or

LDR (experimental arm) > LDR (control arm)
indicating LDR in the experimental arm is higher than LDR in the control arm.

The final determination of EDR and LDR for each treatment arm and interpretation of the findings will be coordinated by the independent SSG statistician for IDMC. Therefore, all

investigators, Company personnel, and the central reviewer will remain blinded to treatment assignment until the IDMC reviews the audit findings.

Attachment 2: Adverse Events of Special Interest or Clinical importance

The search criteria of adverse event(s) of interest (AEOI) are based on adverse event preferred terms from MedDRA Version 20.0 dictionary.

Most categories are based on a MedDRA SMQ but if one does not exist a compilation of terms that reflect the event will be proposed for extraction and analysis of the data. Each of these events is defined below:

Adverse Event of Special Interest Category=Seizure	
Search Criteria Category= Selected PTs	
2-Hydroxyglutaric aciduria	Hypocalcaemic seizure
Acquired epileptic aphasia	Hypoglycaemic seizure
Acute encephalitis with refractory, repetitive partial seizures	Hyponatraemic seizure
Alcoholic seizure	Idiopathic generalised epilepsy
Amygdalohippocampectomy	Lafora's myoclonic epilepsy
Aspartate-glutamate-transporter deficiency	Lennox-Gastaut syndrome
Atonic seizures	Migraine-triggered seizure
Atypical benign partial epilepsy	Molybdenum cofactor deficiency
Aura	Myoclonic epilepsy
Automatism epileptic	Myoclonic epilepsy and ragged-red fibres
Autonomic seizure	Narcolepsy
Baltic myoclonic epilepsy	Partial seizures
Benign rolandic epilepsy	Partial seizures with secondary generalisation
Biotinidase deficiency	Petit mal epilepsy
CSWS syndrome	Polymicrogyria
Change in seizure presentation	Post stroke epilepsy
Clonic convulsion	Post stroke seizure
Complex partial seizures	Post-traumatic epilepsy
Convulsion prophylaxis	Postictal headache
Convulsions local	Postictal paralysis
Convulsive threshold lowered	Postictal psychosis
Corpus callosotomy	Postictal state
Deja vu	Preictal state
Double cortex syndrome	Psychomotor seizures
Dreamy state	Schizencephaly
Drop attacks	Seizure
Drug withdrawal convulsions	Seizure anoxic

Epilepsy	Seizure cluster
Epileptic aura	Seizure like phenomena
Epileptic psychosis	Severe myoclonic epilepsy of infancy
Febrile convulsion	Simple partial seizures
Febrile infection-related epilepsy syndrome	Status epilepticus
Foaming at mouth	Sudden unexplained death in epilepsy
Focal dyscognitive seizures	Temporal lobe epilepsy
Frontal lobe epilepsy	Tongue biting
Generalised non-convulsive epilepsy	Tonic clonic movements
Generalised tonic-clonic seizure	Tonic convulsion
Glucose transporter type 1 deficiency syndrome	Tonic posturing
Hemimegalencephaly	Topectomy
Hyperglycaemic seizure	Uncinate fits
Adverse Event of Special Interest Category=Skin rash	
Search Criteria Category= Selected PTs	
Acquired epidermolysis bullosa	Noninfective conjunctivitis
Acute generalised exanthematous pustulosis	Oculomucocutaneous syndrome
Administration site hypersensitivity	Oral mucosal blistering
Administration site rash	Oral mucosal exfoliation
Administration site recall reaction	Oral papule
Administration site urticaria	Oropharyngeal blistering
Application site rash	Papule
Blau syndrome	Paraneoplastic rash
Blister	Pemphigoid
Blister rupture	Pemphigus
Bullous impetigo	Penile exfoliation
Butterfly rash	Perineal rash
Catheter site rash	Pogosta disease
Conjunctivitis	Rash
Corneal exfoliation	Rash erythematous
Cutaneous vasculitis	Rash follicular
Dermatitis bullous	Rash generalised
Dermatitis exfoliative	Rash macular
Dermatitis exfoliative generalised	Rash maculo-papular
Drug eruption	Rash maculovesicular
Drug reaction with eosinophilia and systemic symptoms	Rash morbilliform

Epidermal necrosis	Rash papular
Epidermolysis	Rash papulosquamous
Epidermolysis bullosa	Rash pruritic
Eruptive pseudoangiomatosis	Rash pustular
Erythema multiforme	Rash rubelliform
Exfoliative rash	Rash scarlatiniform
Eyelid rash	Rash vesicular
Familial cold autoinflammatory syndrome	Sea bather's eruption
Fixed drug eruption	Skin erosion
Genital rash	Skin exfoliation
Genital ulceration	Skin necrosis
HLA-B*1502 assay positive	Skin reaction
HLA-B*5801 assay positive	Skin swelling
Hyper IgD syndrome	Staphylococcal scalded skin syndrome
Hypopharyngeal synechiae	Stevens-Johnson syndrome
Implant site rash	Stoma site rash
Incision site rash	Stomatitis
Infusion site rash	Symmetrical drug-related intertriginous and flexural exanthema
Injection site rash	Systemic lupus erythematosus rash
Instillation site rash	Tongue exfoliation
Lip exfoliation	Toxic epidermal necrolysis
Lupus miliaris disseminatus faciei	Toxic skin eruption
Medical device site rash	Urticaria
Mouth ulceration	Urticaria papular
Mucocutaneous rash	Vaccination site rash
Mucocutaneous ulceration	Vaginal exfoliation
Mucosa vesicle	Vaginal ulceration
Mucosal erosion	Vascular access site rash
Mucosal exfoliation	Vessel puncture site rash
Mucosal necrosis	Viral rash
Mucosal ulceration	Vulval ulceration
Nikolsky's sign	Vulvovaginal rash
Nodular rash	Vulvovaginal ulceration
Adverse Event of Special Interest Category=Hypothyroidism	
Search Criteria Category= Selected PTs (SMQ)	

Anti-thyroid antibody	Secondary hypothyroidism
Anti-thyroid antibody positive	Silent thyroiditis
Atrophic thyroiditis	Tertiary hypothyroidism
Autoimmune hypothyroidism	Thyroglobulin absent
Autoimmune thyroid disorder	Thyroglobulin decreased
Autoimmune thyroiditis	Thyroid atrophy
Blood thyroid stimulating hormone increased	Thyroid hemiagenesis
Butanol-extractable iodine decreased	Thyroid hormone replacement therapy
Congenital hypothyroidism	Thyroid therapy
Congenital thyroid disorder	Thyroidectomy
Free thyroxine index decreased	Thyroiditis
Generalised resistance to thyroid hormone	Thyroiditis acute
Hashimoto's encephalopathy	Thyroiditis chronic
Hypothyroidic goitre	Thyroiditis fibrous chronic
Hypothyroidism	Thyroiditis subacute
Iodine uptake decreased	Thyroxin binding globulin increased
Myxoedema	Thyroxine decreased
Myxoedema coma	Thyroxine free decreased
Polyglandular autoimmune syndrome type II	Thyroxine therapy
Polyglandular autoimmune syndrome type III	Transient hypothyroxinaemia of prematurity
Post procedural hypothyroidism	Tri-iodothyronine decreased
Primary hypothyroidism	Tri-iodothyronine free decreased
Protein bound iodine decreased	Tri-iodothyronine uptake increased
Reverse tri-iodothyronine decreased	
Adverse Event of Special Interest Category=Fall	
Search Criteria Category= Selected PTs	
Fall	
Adverse Event of Special Interest=Fracture	
Search Criteria Category= Selected PTs	
Acetabulum fracture	Hand fracture
Ankle fracture	Hip fracture
Atypical femur fracture	Humerus fracture
Atypical fracture	Ilium fracture
Avulsion fracture	Impacted fracture
Cervical vertebral fracture	Internal fixation of fracture

Chance fracture	Jaw fracture
Clavicle fracture	Limb fracture
Closed fracture manipulation	Loss of anatomical alignment after fracture reduction
Comminuted fracture	Lower limb fracture
Complicated fracture	Lumbar vertebral fracture
Compression fracture	Multiple fractures
Costal cartilage fracture	Open fracture
Craniofacial fracture	Open reduction of fracture
Elevation skull fracture	Open reduction of spinal fracture
Epiphyseal fracture	Osteochondral fracture
External fixation of fracture	Osteoporotic fracture
Facial bones fracture	Patella fracture
Femoral neck fracture	Pelvic fracture
Femur fracture	Periprosthetic fracture
Fibula fracture	Pubis fracture
Foot fracture	Radius fracture
Forearm fracture	Rib fracture
Fracture	Sacroiliac fracture
Fracture debridement	Scapula fracture
Fracture delayed union	Skull fracture
Fracture displacement	Skull fractured base
Fracture malunion	Spinal compression fracture
Fracture nonunion	Spinal fracture
Fracture of clavicle due to birth trauma	Spinal fusion fracture
Fracture of penis	Sternal fracture
Fracture pain	Stress fracture
Fracture reduction	Surgical fixation of rib fracture
Fracture treatment	Thoracic vertebral fracture
Fractured coccyx	Tibia fracture
Fractured ischium	Torus fracture
Fractured maxilla elevation	Traumatic fracture
Fractured sacrum	Ulna fracture
Fractured skull depressed	Upper limb fracture
Fractured zygomatic arch elevation	Wrist fracture
Greenstick fracture	
Adverse Event of Special Interest Category=Ischaemic Heart Disease	

Search Criteria Category= Selected PTs	
Acute coronary syndrome	Electrocardiogram ST segment depression
Acute myocardial infarction	Electrocardiogram ST segment elevation
Angina pectoris	Electrocardiogram ST-T segment abnormal
Angina unstable	Electrocardiogram ST-T segment depression
Anginal equivalent	Electrocardiogram ST-T segment elevation
Arteriogram coronary abnormal	Electrocardiogram T wave abnormal
Arteriosclerosis coronary artery	Electrocardiogram T wave inversion
Arteriospasm coronary	Exercise electrocardiogram abnormal
Blood creatine phosphokinase MB abnormal	Exercise test abnormal
Blood creatine phosphokinase MB increased	External counterpulsation
Blood creatine phosphokinase abnormal	Haemorrhage coronary artery
Blood creatine phosphokinase increased	Infarction
Cardiac stress test abnormal	Ischaemic cardiomyopathy
Cardiopulmonary exercise test abnormal	Kounis syndrome
Computerised tomogram coronary artery abnormal	Microvascular coronary artery disease
Coronary angioplasty	Myocardial hypoxia
Coronary arterial stent insertion	Myocardial infarction
Coronary artery bypass	Myocardial ischaemia
Coronary artery disease	Myocardial necrosis
Coronary artery dissection	Myocardial necrosis marker increased
Coronary artery embolism	Myocardial reperfusion injury
Coronary artery insufficiency	Myocardial stunning
Coronary artery occlusion	Papillary muscle infarction
Coronary artery reocclusion	Percutaneous coronary intervention
Coronary artery restenosis	Periprocedural myocardial infarction
Coronary artery stenosis	Post procedural myocardial infarction
Coronary artery thrombosis	Postinfarction angina
Coronary bypass thrombosis	Prinzmetal angina
Coronary endarterectomy	Scan myocardial perfusion abnormal
Coronary no-reflow phenomenon	Silent myocardial infarction
Coronary ostial stenosis	Stress cardiomyopathy
Coronary revascularisation	Stress echocardiogram abnormal
Coronary vascular graft occlusion	Subclavian coronary steal syndrome
Dissecting coronary artery aneurysm	Subendocardial ischaemia
ECG electrically inactive area	Troponin I increased
ECG signs of myocardial infarction	Troponin T increased

ECG signs of myocardial ischaemia	Troponin increased
Electrocardiogram Q wave abnormal	Vascular graft occlusion
Electrocardiogram ST segment abnormal	
Adverse Event of Special Interest Category=Cardiac Failure	
Search Criteria Category= Selected PTs	
Acute left ventricular failure	Dyspnoea paroxysmal nocturnal
Acute pulmonary oedema	Ejection fraction decreased
Acute right ventricular failure	Heart transplant
Artificial heart implant	Hepatic vein dilatation
Atrial natriuretic peptide abnormal	Hepatojugular reflux
Atrial natriuretic peptide increased	Jugular vein distension
Brain natriuretic peptide abnormal	Left ventricular dysfunction
Brain natriuretic peptide increased	Left ventricular failure
Cardiac asthma	Low cardiac output syndrome
Cardiac cirrhosis	Lower respiratory tract congestion
Cardiac failure	Myocardial depression
Cardiac failure acute	N-terminal prohormone brain natriuretic peptide abnormal
Cardiac failure chronic	N-terminal prohormone brain natriuretic peptide increased
Cardiac failure congestive	Neonatal cardiac failure
Cardiac failure high output	Nocturnal dyspnoea
Cardiac index decreased	Obstructive shock
Cardiac output decreased	Oedema due to cardiac disease
Cardiac resynchronisation therapy	Orthopnoea
Cardiac ventriculogram abnormal	Pulmonary congestion
Cardiac ventriculogram left abnormal	Pulmonary oedema
Cardiac ventriculogram right abnormal	Pulmonary oedema neonatal
Cardio-respiratory distress	Radiation associated cardiac failure
Cardiogenic shock	Right ventricular dysfunction
Cardiomegaly	Right ventricular failure
Cardiopulmonary failure	Stroke volume decreased
Cardiorenal syndrome	Systolic dysfunction
Cardiothoracic ratio increased	Venous pressure increased
Central venous pressure increased	Venous pressure jugular abnormal
Chronic left ventricular failure	Venous pressure jugular increased
Chronic right ventricular failure	Ventricular assist device insertion

Cor pulmonale	Ventricular dysfunction
Cor pulmonale acute	Ventricular dyssynchrony
Cor pulmonale chronic	Ventricular failure
Diastolic dysfunction	Wall motion score index abnormal
Dilatation ventricular	
Adverse Event of Special Interest Category=Arrhythmia	
Search Criteria Category= Selected PTs	
Accelerated idioventricular rhythm	Palpitations
Arrhythmia supraventricular	Parasystole
Atrial fibrillation	Rebound tachycardia
Atrial flutter	Respiratory sinus arrhythmia magnitude abnormal
Atrial flutter with 1:1 atrioventricular conduction	Respiratory sinus arrhythmia magnitude decreased
Atrial parasystole	Respiratory sinus arrhythmia magnitude increased
Atrial tachycardia	Retrograde p-waves
Bradycardia	Rhythm idioventricular
Cardiac arrest	Sinus tachycardia
Cardiac death	Sudden cardiac death
Cardiac fibrillation	Sudden death
Cardiac telemetry abnormal	Supraventricular extrasystoles
Cardio-respiratory arrest	Supraventricular tachyarrhythmia
Chronotropic incompetence	Supraventricular tachycardia
ECG P wave inverted	Syncope
Electrocardiogram P wave abnormal	Tachycardia
Electrocardiogram RR interval prolonged	Tachycardia paroxysmal
Electrocardiogram U-wave abnormality	Torsade de pointes
Electrocardiogram abnormal	Ventricular arrhythmia
Electrocardiogram ambulatory abnormal	Ventricular extrasystoles
Electrocardiogram change	Ventricular fibrillation
Electrocardiogram repolarisation abnormality	Ventricular flutter
Heart rate abnormal	Ventricular parasystole
Heart rate decreased	Ventricular pre-excitation
Heart rate increased	Ventricular tachyarrhythmia
Junctional ectopic tachycardia	Ventricular tachycardia
Loss of consciousness	
Clinical Importance Category=Diabetes	

Search Criteria Category= Selected PTs	
ACQUIRED LIPOATROPHIC DIABETES	GLYCOSYLATED HAEMOGLOBIN INCREASED
BLOOD 1,5-ANHYDROGLUCITOL DECREASED	HYPERGLYCAEMIA
BLOOD GLUCOSE INCREASED	HYPERGLYCAEMIC HYPEROSMOLAR NONKETOTIC SYNDROME
DIABETES COMPLICATING PREGNANCY	HYPERGLYCAEMIC SEIZURE
DIABETES MELLITUS	HYPERGLYCAEMIC UNCONSCIOUSNESS
DIABETES MELLITUS INADEQUATE CONTROL	HYPEROSMOLAR HYPERGLYCAEMIC STATE
DIABETES WITH HYPEROSMOLARITY	IMPAIRED FASTING GLUCOSE
DIABETIC ARTERITIS	INSULIN RESISTANCE
DIABETIC COMA	INSULIN RESISTANCE SYNDROME
DIABETIC HEPATOPATHY	INSULIN RESISTANT DIABETES
DIABETIC HYPERGLYCAEMIC COMA	INSULIN-REQUIRING TYPE 2 DIABETES MELLITUS
DIABETIC HYPEROSMOLAR COMA	KETOACIDOSIS
DIABETIC KETOACIDOSIS	KETONURIA
DIABETIC KETOACIDOTIC HYPERGLYCAEMIC COMA	KETOSIS
DIABETIC METABOLIC DECOMPENSATION	LATENT AUTOIMMUNE DIABETES IN ADULTS
FRUCTOSAMINE INCREASED	METABOLIC SYNDROME
FULMINANT TYPE 1 DIABETES MELLITUS	MONOGENIC DIABETES
GESTATIONAL DIABETES	NEONATAL DIABETES MELLITUS
GLUCOSE TOLERANCE IMPAIRED	PANCREATOGENOUS DIABETES
GLUCOSE TOLERANCE IMPAIRED IN PREGNANCY	TYPE 1 DIABETES MELLITUS
GLUCOSE URINE PRESENT	TYPE 2 DIABETES MELLITUS
GLYCOSURIA	TYPE 3 DIABETES MELLITUS
GLYCOSURIA DURING PREGNANCY	URINE KETONE BODY PRESENT
Clinical Importance Category=Cognitive Deficits	
Search Criteria Category= Selected PTs	
Amnesia	Disturbance in attention
Cognitive disorder	Memory impairment
Adverse Event of Special Interest/Clinical Importance Category=Other Cardiac Disorders	
Search Criteria Category= Selected PTs	
Atrioventricular block	Electrocardiogram QT prolonged
Atrioventricular block first degree	Hypertrophic cardiomyopathy

Bundle branch block left	Left ventricular hypertrophy
Cardiac disorder	Long QT syndrome
Cardiomyopathy	Metabolic cardiomyopathy
Cardiomyopathy acute	Mitral valve disease
Cardiomyopathy alcoholic	Non-obstructive cardiomyopathy
Chest pain	Restrictive cardiomyopathy
Conduction disorder	Sinus arrhythmia
Congestive cardiomyopathy	Sinus bradycardia
Cytotoxic cardiomyopathy	Sinus node dysfunction
Diabetic cardiomyopathy	Viral cardiomyopathy
Electrocardiogram QT interval abnormal	Wandering pacemaker
Adverse Event of Special Interest Category=Osteoporosis/Osteopenia excluding Fracture	
Search Criteria Category= Selected PTs	
BONE METABOLISM BIOCHEMICAL MARKER INCREASED	Kyphosis
Body height abnormal	N-telopeptide urine increased
Body height below normal	Osteocalcin increased
Body height decreased	Osteopenia
Bone density abnormal	Osteoporosis
Bone density decreased	Osteoporosis postmenopausal
Bone formation decreased	Osteoporosis prophylaxis
Bone formation test abnormal	Post-traumatic osteoporosis
Bone loss	Pyridinoline urine increased
Bone metabolism disorder	Resorption bone increased
Bone resorption test abnormal	Senile osteoporosis
C-telopeptide increased	Spinal deformity
Deoxypyridinoline urine increased	TARTRATE-RESISTANT ACID PHOSPHATASE DECREASED
Hip arthroplasty	Vertebral body replacement
Hip surgery	Vertebroplasty
Kyphoscoliosis	Wrist surgery
Adverse Event of Special Interest Category=Rhabdomyolysis or Myopathy	
Search Criteria Category= Selected PTs	
Muscle necrosis	Myoglobinuria
Myoglobin blood increased	Myopathy

Myoglobin blood present	Myopathy toxic
Myoglobin urine present	NECROTISING MYOSITIS
Myoglobinaemia	Rhabdomyolysis
Adverse Event of Special Interest Category=Hypertension	
Search Criteria Category= Selected PTs	
Accelerated hypertension	Hypertensive cardiomegaly
Aldosterone urine abnormal	Hypertensive cardiomyopathy
Aldosterone urine increased	Hypertensive crisis
Angiotensin I increased	Hypertensive emergency
Angiotensin II increased	Hypertensive encephalopathy
Angiotensin converting enzyme increased	Hypertensive heart disease
Blood aldosterone abnormal	Hypertensive nephropathy
Blood aldosterone increased	Labile blood pressure
Blood catecholamines abnormal	Labile hypertension
Blood catecholamines increased	Malignant hypertension
Blood pressure abnormal	Malignant hypertensive heart disease
Blood pressure ambulatory abnormal	Malignant renal hypertension
Blood pressure ambulatory increased	Maternal hypertension affecting foetus
Blood pressure diastolic abnormal	Mean arterial pressure increased
Blood pressure diastolic increased	Metabolic syndrome
Blood pressure fluctuation	Metanephrine urine abnormal
Blood pressure inadequately controlled	Metanephrine urine increased
Blood pressure increased	Neurogenic hypertension
Blood pressure management	Non-dipping
Blood pressure orthostatic abnormal	Norepinephrine abnormal
Blood pressure orthostatic increased	Norepinephrine increased
Blood pressure systolic abnormal	Normetanephrine urine increased
Blood pressure systolic increased	Orthostatic hypertension
Catecholamines urine abnormal	PAGE KIDNEY
Catecholamines urine increased	Pre-eclampsia
Diastolic hypertension	Prehypertension
Diuretic therapy	Procedural hypertension
Eclampsia	Pseudoaldosteronism
Ectopic aldosterone secretion	Renal hypertension
Ectopic renin secretion	Renal sympathetic nerve ablation
Endocrine hypertension	Renin abnormal

Epinephrine abnormal	Renin increased
Epinephrine increased	Renin-angiotensin system inhibition
Essential hypertension	Renovascular hypertension
Gestational hypertension	Retinopathy hypertensive
HELLP syndrome	SUPINE HYPERTENSION
HYPERTENSIVE CEREBROVASCULAR DISEASE	Secondary aldosteronism
HYPERTENSIVE END-ORGAN DAMAGE	Secondary hypertension
Hyperaldosteronism	Systolic hypertension
Hypertension	Tyramine reaction
Hypertension neonatal	Withdrawal hypertension
Hypertensive angiopathy	
Adverse Event of Special Interest Category=Fluid Retention or Oedema	
Search Criteria Category= Selected PTs	
Administration site joint effusion	Injection site swelling
Administration site oedema	Instillation site oedema
Administration site swelling	Joint effusion
Amyloid related imaging abnormalities	Joint swelling
Application site joint effusion	Lipoedema
Application site joint swelling	Local swelling
Application site oedema	Localised oedema
Application site swelling	Lymphoedema
Ascites	Medical device site joint effusion
Bone marrow oedema	Medical device site joint swelling
Bone marrow oedema syndrome	Mouth swelling
Bone swelling	Muscle oedema
Brain oedema	Muscle swelling
Bronchial oedema	Myocardial oedema
COMPRESSION GARMENT APPLICATION	Non-cardiogenic pulmonary oedema
Capillary leak syndrome	OROPHARYNGEAL OEDEMA
Catheter site oedema	Oedema
Cerebral oedema management	Oedema due to renal disease
Cervix oedema	Oedema mucosal
Compression stockings application	Oedema neonatal
Cytotoxic oedema	Oedema peripheral
Effusion	Oedematous kidney
Elephantiasis nostras verrucosa	Oesophageal oedema

Extensive swelling of vaccinated limb	PERINEPHRIC COLLECTION
Fluid overload	PERINEPHRIC OEDEMA
Fluid retention	Pelvic fluid collection
Gallbladder oedema	Pericardial effusion
Gastrointestinal oedema	Peripheral oedema neonatal
Generalised oedema	Peripheral swelling
Gestational oedema	Pleural effusion
Gravitational oedema	Prevertebral soft tissue swelling of cervical space
Heat oedema	Puncture site oedema
Hydraemia	Reexpansion pulmonary oedema
Hydrothorax	Retroperitoneal effusion
Hypervolaemia	Retroperitoneal oedema
Hypoosmolar state	Scleroedema
Implant site oedema	Skin oedema
Implant site swelling	Skin swelling
Incision site oedema	Spinal cord oedema
Incision site swelling	Subdural effusion
Infusion site joint effusion	Swelling
Infusion site joint swelling	Testicular swelling
Infusion site oedema	Vaccination site joint effusion
Infusion site swelling	Vaccination site joint swelling
Injection site joint swelling	Vasogenic cerebral oedema
Injection site oedema	Visceral oedema
Adverse Event of Special Interest Category=Hepatotoxicity	
Search Criteria Category= Selected PTs	
5'nucleotidase increased	Hepatitis acute
ACUTE ON CHRONIC LIVER FAILURE	Hepatitis cholestatic
Abnormal faeces	Hepatitis chronic active
Acute graft versus host disease in liver	Hepatitis chronic persistent
Acute hepatic failure	Hepatitis fulminant
Acute yellow liver atrophy	Hepatitis toxic
Alanine aminotransferase abnormal	Hepatobiliary disease
Alanine aminotransferase increased	Hepatobiliary scan abnormal
Allergic hepatitis	Hepatocellular foamy cell syndrome
Ammonia abnormal	Hepatocellular injury
Ammonia increased	Hepatomegaly

Anorectal varices	Hepatopulmonary syndrome
Anorectal varices haemorrhage	Hepatorenal failure
Aspartate aminotransferase abnormal	Hepatorenal syndrome
Aspartate aminotransferase increased	Hepatosplenomegaly
Asterixis	Hepatotoxicity
Autoimmune hepatitis	Hyperammonaemia
BILIARY DYSPEPSIA	Hyperbilirubinaemia
BILIRUBIN EXCRETION DISORDER	Hypercholia
BILIRUBIN URINE PRESENT	Hypertransaminasaemia
BILIRUBIN URINE PRESENT	Hypoalbuminaemia
BIOPSY GALLBLADDER ABNORMAL	INTESTINAL VARICES HAEMORRHAGE
Bacterascites	Icterus index increased
Bile culture positive	Intestinal varices
Bile duct pressure increased	Intrahepatic portal hepatic venous fistula
Bile output abnormal	Ischaemic hepatitis
Bile output decreased	Jaundice
Bile output increased	Jaundice cholestatic
Biliary ascites	Jaundice extrahepatic obstructive
Biliary cirrhosis	Jaundice hepatocellular
Biliary cirrhosis primary	Kayser-Fleischer ring
Biliary fibrosis	LIVER DIALYSIS
Bilirubin conjugated abnormal	LIVER FUNCTION TEST DECREASED
Bilirubin conjugated increased	LIVER FUNCTION TEST INCREASED
Bilirubin excretion disorder	Leucine aminopeptidase increased
Bilirubinuria	Limy bile syndrome
Biopsy bile duct abnormal	Liver and small intestine transplant
Biopsy liver abnormal	Liver disorder
Blood alkaline phosphatase abnormal	Liver function test abnormal
Blood alkaline phosphatase increased	Liver induration
Blood bilirubin abnormal	Liver injury
Blood bilirubin increased	Liver iron concentration abnormal
Blood bilirubin unconjugated increased	Liver iron concentration increased
Blood cholinesterase abnormal	Liver operation
Blood cholinesterase decreased	Liver palpable
Bromosulphthalein test abnormal	Liver sarcoidosis
CHILD-PUGH-TURCOTTE SCORE ABNORMAL	Liver scan abnormal
COMPUTERISED TOMOGRAM LIVER ABNORMAL	Liver tenderness

Child-Pugh-Turcotte score increased	Liver transplant
Cholaemia	Lupoid hepatic cirrhosis
Cholangiogram abnormal	Lupus hepatitis
Cholecystogram intravenous abnormal	MODEL FOR END STAGE LIVER DISEASE SCORE ABNORMAL
Cholecystogram oral abnormal	MODEL FOR END STAGE LIVER DISEASE SCORE INCREASED
Cholestasis	Minimal hepatic encephalopathy
Cholestatic liver injury	Mitochondrial aspartate aminotransferase increased
Cholestatic pruritus	Mixed liver injury
Chronic graft versus host disease in liver	Molar ratio of total branched-chain amino acid to tyrosine
Chronic hepatic failure	NON-ALCOHOLIC FATTY LIVER
Chronic hepatitis	NON-CIRRHOTIC PORTAL HYPERTENSION
Coma hepatic	Nodular regenerative hyperplasia
Computerised tomogram liver	Non-alcoholic steatohepatitis
Cryptogenic cirrhosis	Ocular icterus
Deficiency of bile secretion	Oedema due to hepatic disease
Diabetic hepatopathy	Oesophageal varices haemorrhage
Drug-induced liver injury	PORTAL HYPERTENSIVE COLOPATHY
Duodenal varices	PORTAL SHUNT PROCEDURE
Endoscopic retrograde cholangiopancreatography abnormal	Parenteral nutrition associated liver disease
Endoscopy biliary tract abnormal	Perihepatic discomfort
Faeces pale	Peripancreatic varices
Foetor hepaticus	Periportal oedema
Galactose elimination capacity test abnormal	Peritoneal fluid protein abnormal
Galactose elimination capacity test decreased	Peritoneal fluid protein decreased
Gallbladder palpable	Peritoneal fluid protein increased
Gallbladder varices	Peritoneovenous shunt
Gamma-glutamyltransferase abnormal	Pneumobilia
Gamma-glutamyltransferase increased	Portal fibrosis
Gastric variceal injection	Portal hypertension
Gastric variceal ligation	Portal hypertensive enteropathy
Gastric varices	Portal hypertensive gastropathy
Gastric varices haemorrhage	Portal shunt
Glutamate dehydrogenase increased	Portal tract inflammation
Graft versus host disease in liver	Portal vein cavernous transformation
Granulomatous liver disease	Portal vein dilatation

Guanase increased	Portal vein flow decreased
HEPATIC STEATO-FIBROSIS	Portal vein pressure increased
Haemorrhagic ascites	Portopulmonary hypertension
Hepaplastin abnormal	Radiation hepatitis
Hepaplastin decreased	Renal and liver transplant
Hepatectomy	Retinol binding protein decreased
Hepatic artery flow decreased	Retrograde portal vein flow
Hepatic atrophy	Reye's syndrome
Hepatic calcification	Reynold's syndrome
Hepatic cirrhosis	SPLENORENAL SHUNT
Hepatic congestion	SPLENORENAL SHUNT PROCEDURE
Hepatic encephalopathy	Small-for-size liver syndrome
Hepatic encephalopathy prophylaxis	Spider naevus
Hepatic enzyme abnormal	Splenic varices
Hepatic enzyme decreased	Splenic varices haemorrhage
Hepatic enzyme increased	Spontaneous intrahepatic portosystemic venous shunt
Hepatic failure	Steatohepatitis
Hepatic fibrosis	Stomal varices
Hepatic fibrosis marker abnormal	Subacute hepatic failure
Hepatic fibrosis marker increased	Total bile acids increased
Hepatic function abnormal	Transaminases abnormal
Hepatic hydrothorax	Transaminases increased
Hepatic hypertrophy	Ultrasound biliary tract abnormal
Hepatic infiltration eosinophilic	Ultrasound liver abnormal
Hepatic lesion	Urine bilirubin increased
Hepatic mass	Urobilinogen urine decreased
Hepatic necrosis	Urobilinogen urine increased
Hepatic pain	Varices oesophageal
Hepatic sequestration	Varicose veins of abdominal wall
Hepatic steatosis	WHITE NIPPLE SIGN
Hepatic vascular resistance increased	X-ray hepatobiliary abnormal
Hepatitis	Yellow skin
Adverse Event of Special Interest Category=Hypokalemia	
Search Criteria Category= Selected PTs	
Blood potassium	Blood potassium decreased
Blood potassium abnormal	Hypokalaemia

Adverse Event of Special Interest Category=Allergic alveolitis	
Search Criteria Category= Selected PTs	
Allergic alveolitis	