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STATISTICAL ANALYSIS PLAN

Protocol EZH-1101

CELLO-1: A Phase 1b/2 Open-Label Study Evaluating Tazemetostat in Combination with Enzalutamide or Abiraterone/Prednisone in Chemotherapy Naïve Subjects with Metastatic Castration Resistant Prostrate Cancer

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Version 2.0

29 September 2023

STATISTICAL ANALYSIS PLAN FOR EZH-1101

SIGNATURE PAGE

The undersigned have reviewed this plan and find it meets the protocol requirements for the reporting of this study.

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MODIFICATION HISTORY

After approval of version 1.0 of the statistical analysis plan, subsequent versions should be documented below with a brief description of the change from the previous version, as well as, the rationale for the change.

Version, Date	Made by	Brief Description of Change and Rationale
V1.1, 10 SEP 2022	PPD	• In Section 8.4.1, regarding rPFS definition and associated censoring rules, a footnote is added to clarify that (i) the PD for bone lesion is determined by two or more new bone lesions compared to baseline bone scan per PCWG3 and the two scans (i.e., the confirmatory scan is required for bone disease progression) should be at least 6 weeks apart from each other; (ii) the PD for soft tissue lesion is determined based on CT or MRI per RECIST 1.1 where no confirmatory scan is required for soft tissue disease progression. • Appendix C is added to provide details for the determination of radiographic PD in both bone and soft tissue defined by the criteria in Section 8.4.1. This detailed information helps the programmers to write SAS codes in determining PD to calculate rPFS. • In Section 8.5.6, the more detailed description of ECG measures and markedly abnormal criteria is added for clarification. • Some editorial updates are made, accordingly, per protocol amended from version 5 to version 6.
V1.2 01 Apr 2023	PPD	In Section 8.4.1, the censoring rules associated rPFS have been updated.
V2.0 29 Sep 2023	PPD	• Updated list of abbreviations and definitions of terms table • In Section 1, stated results of biomarkers analysis will be in separate CSR. • In Section 2.2, listed changes to analysis from protocol • In Section 3, listed all objectives and removed endpoints. • In section 6, 1) added screened population in Phase 1b and 2 portion; 2) removed FACT-P population in Phase 1b; 3) In phase 1b, changed the population used for protocol deviations, demographics, other baseline characteristics and efficacy analyses to safety analysis population; 4) clarify in phase 1b, treatment group or dose level can be used for the summary. • In section 7.2, clarified baseline definition in phase 2 that if a subject's first assessment occurs after randomization but prior to the first dose, this assessment will be used as the baseline. • In section 7.4, per protocol added "in phase 2 portion, secondary efficacy endpoints will only be compared between treatment groups only if the primary endpoint (rPFS) achieves statistical significance at an overall alpha level of 0.05.". • Moved section 7.5 common conventions to appendix F. • In Section 8.1, adjusted the wording in disposition summary. • In Section 8.2, 1) clarified PD to be summarized on the safety population in phase 1b part and ITT population in phase 2 part; 2) removed Inc/Exc criteria list • In Section 8.3.1, 1) added age group (65-75 years, and 75+ years); 2) added BSA and removed height and weight. • In Section 8.3.2, 1) update tumor stage category to I-III and IV; 2) added PSA at baseline (<=10, 10-20, >20 ng/ml); 3) change tumor stage at initial diagnosis to tumor stage at study entry; 4) change

Version, Date	Made by	Brief Description of Change and Rationale
		time since initial diagnosis to time since last disease progression prior to enrollment • In Section 8.3.3, 1) updated the section name to Prior Cancer Related Procedures; 2) specify the WHO Drug Dictionary and MedDRA version • In Section 8.3.3 and Section 8.3.4, surgical history was moved to Section 8.3.3 and removed from Section 8.3.4 • In Section 8.4, clarified FACT-P population to be used in FACT-P analysis. • In Section 8.4.1, 1) added "rPFS will be programmatically derived based on investigator assessments and Blinded Independent Central Review (BICR) separately."; 2) clarified new anticancer treatment include systemic therapy and/or radiotherapy in Table 1; 3) added "If subjects had subsequent anti-cancer therapy, missing 2 consecutive scheduled tumour assessments and withdrawal of study consent or lost to follow-up on same date, censored reason will be assigned in the order of 2 consecutive scheduled tumour assessments > anti-cancer therapy > withdrawal of study consent or lost to follow-up." in Table 1; 4) correct significance level to 0.025 (one sided); 5) add a swim plot for phase1b • In Section 8.4.2, removed duplicated wording. • In Section 8.4.2.1, 1) updated PSA $\geqslant$ 2 to PSA $\geqslant$ 1 for subject at baseline; 2) add a swim plot for phase1b • In Section 8.4.2.2, 1) updated "for subjects who did not have a decline in PSA value by Week 17" to "for subjects who did not have a decline in PSA value beyond 12 weeks); 2) updated Table 2; 3) add KM plot • In Section 8.4.2.3, 1) updated the censoring rule and removed Table 3; 2) add KM plot • In Section 8.4.2.4, 1) clarified the date of first dose of study drug will be used in phase 1b; 2) update censoring rule "TTNT will be censored at the last subsequent treatment assessment date or date of randomization (phase 2)/date of first dose of study drug (phase 1b), whatever come later if the subject did not receive subsequent treatment."; 3) add KM plot • In Section 8.4.2.5, 1) clarified the date of first dose of study drug will be used in phase 1b; 2) added DOR; 3) added "ORR will be calculated based on investigator and central imaging assessment separately."; 4) added "The ORR will be summarized by treatment arm and the associated 95% CI will be estimated using the Clopper Pearson method.". • In Section 8.4.2.6, updated DCR definition • In Section 8.4.2.7, removed duplicate wording and clarify the stat test to be used for treatment comparison. • In Section 8.4.2.8, 1) added FACT-P instructions, missing data handling rule, analysis visit window and clarified the endpoints; 2) stated SWB, EWB, PCS, Total FACT-P score will be analyzed in this study • In Section 8.4.3, 1) added additional subgroup variables; 2) removed subgroups in ORR and a swim plot showing AE-V7 and NEPC; 3) added "If there are less than 5 events across treatment groups per subgroup level, analysis within that level will be omitted." • In Section 8.4.4, 1) added BPI-SF instructions, analysis visit window and clarify the endpoint; 2) updated PSA90 same as

Version, Date	Made by	Brief Description of Change and Rationale
		PSA50; 3) analyses of other exploratory endpoints not listed in the SAP are removed and might be specified in a separate document. • In Section 8.5.3, 1) added MedDRA version to 23.1 or higher; 2) removed "Adverse events with CTCAE Grade 5 or outcome of death are excluded from AE summary tables and summarized under death related tables"; 3) add TEAEs leading to death in the AE summary; 4) updated the death reason in death summary • In Section 8.5.4, 1) added "A scatter plot of ALT versus total bilirubin, both expressed as multiples of upper limit of normal range, will be produced. The scatter plot will be repeated for AST versus total bilirubin."; 2) remove analysis of RBC and cardiac biomarkers • In Section 8.5.10, remove ECHO and MUGA listing • In Section 8.6, clarified that complete details of the analysis of the PK parameters will be specified in a separate PK analysis plan. • In Section 8.7, updated references • Added appendix B FACT-P, appendix C BPI-SF and appendix D EQ-5D-5L

TABLE OF CONTENTS

SIGNATURE PAGE 2
MODIFICATION HISTORY 3
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 9
1. INTRODUCTION 12
2. OVERALL STUDY DESIGN 12
2.1. General Description 12
2.2. Changes to Analysis from Protocol 15
3. STUDY OBJECTIVES 15
3.1. Primary Objectives 15
3.2. Secondary Objectives: 16
3.3. Exploratory Objectives 17
4. INTERIM ANALYSIS 18
5. SAMPLE SIZE DETERMINATION 18
6. ANALYSIS POPULATIONS 19
6.1. Phase 1b/Phase 2 Analysis Populations 19
6.2. Phase 1b Analysis Populations 19
6.3. Phase 2 Analysis Populations 19
7. DEFINITIONS AND CONVENTIONS 20
7.1. Study Day 20
7.2. Baseline 20
7.3. Multicenter Studies 20
7.4. Multiple Comparisons/Multiplicity 20
7.5. Missing Data 20
7.6. Unscheduled Visits 21
7.7. Statistical Analysis Software 21
8. STATISTICAL ANALYSIS 21
8.1. Disposition of Subjects 21
8.2. Protocol Deviations 22
8.3. Demographics and Other Baseline Characteristics 22
8.3.1 Demography and Other Baseline Disease Characteristics 22
8.3.2 Tumor Diagnosis 23
8.3.3 Prior Cancer Related Procedures 23
8.3.4 Medical History 23

8.4. Efficacy Analyses 23
8.4.1 Analysis of Primary Efficacy Endpoint 23
8.4.2 Analysis of Secondary Efficacy Endpoints 25
8.4.2.1. PSA50 25
8.4.2.2. Time to PSA Progression (TTPP) 26
8.4.2.3. Time to First Skeletal-Related Event (SRE) 26
8.4.2.4. Time to Initiation of the next systemic Treatment (TTNT) for prostate cancer 26
8.4.2.5. Best Overall Response (BOR) and Objective Response Rate (ORR) 27
8.4.2.6. Disease Control Rate (DCR) at 6 months 27
8.4.2.7. Circulation Tumor Cells (CTCs) 27
8.4.2.8. FACT-P (Phase 2 only) 28
8.4.3 Subgroup Analyses 30
8.4.4 Analysis of Exploratory Endpoints 31
8.5. Safety Analyses 32
8.5.1. General Considerations 32
8.5.2. Study Drug Exposure 32
8.5.3. Adverse Events 34
8.5.4. Laboratory Values 35
8.5.5. Vital Signs 36
8.5.6. Electrocardiograms (ECGs) 37
8.5.7. Physical Examination 38
8.5.8. Prior and Concomitant Medications and Procedures 38
8.5.9. Subsequent Anticancer Therapy 38
8.6. Pharmacokinetic Analysis 38
8.7. References 39
APPENDIX A. ALGORITHMS FOR HANDLING PARTIAL DATES 40
APPENDIX B. FACT-P (VERSION 4.0) 42
APPENDIX C. BPI-SF (2009 CHARLES S. CLEELAND) 50
APPENDIX D. EQ-5D-5L (VERSION 3.0) 53
APPENDIX E. DETERMINATION OF RADIOGRAPHIC DISEASE PROGRESSION DEFINED BY THE CRITERIA 56
APPENDIX F. COMMON CONVENSIONS 57

LIST OF TABLES

Table 1: Date of Event or Censoring for rPFS 24
Table 2: Date of Event or Censoring for TTPP 26
Table 3: Vital Signs and Abnormality Criteria 37
Table 4: ECG Measures and Markedly Abnormal Criteria 38
Table 5: Treatment-emergent Adverse Events 40
Table 6: Prior and Concomitant Medications 40
Table 7: Determination of Radiographic Evidence of Disease Progression 56

LIST OF FIGURES

Figure 1: Study Schema 15
Figure 2: Post Week 9 Bone Scan Assessment Flow Diagram 58

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALT	alanine aminotransferase
AR	androgen receptor
AR-V7	androgen-receptor splice variant 7
AST	aspartate aminotransferase
BICR	blinded independent central review
BID	twice daily
BOR	best overall response
BPI	brief pain inventory
BPI-SF	brief pain inventory-short form
BSA	body surface area
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CR	compete response
CRF	case report form
CSR	clinical study report
CTC	circulation tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EWB	emotional well-being
EZH2	enhancer of zeste homologue-2
EQ-5D-5L	EuroQol 5-Dimension 5-Level questionnaire
FACT-P	Functional Assessment of Cancer Therapy - Prostrate
FWB	functional well-being
HLGT	high-level group term
HR	heart rate
HUI	health utilities index
HRQL	health related quality of life
INR	international normalized ratio
ITT	Intent-to-treat
KM	Kaplan-Meier
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities

MMRM	mixed-effects model for repeated measures
nmCRPC	nonmetastatic castration-resistant prostate cancer
NCI	National Cancer Institute
NE	not evaluable
NEPC	neuroendocrine prostate cancer
ORR	objective response rate
PBMC	peripheral blood mononuclear cell
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PCS	prostate cancer
PFS	progression-free survival
PD	progressive disease
PK	pharmacokinetics
PKAP	Pharmacokinetics analysis plan
PR	partial response
PSA	prostate-specific antigen
PSA50	the percentage of participants who had a PSA decline of at least 50% from baseline
PSA90	the percentage of participants who had a PSA decline of at least 90% from baseline
PT	partial thromboplastin
PTT	partial thromboplastin time
PWB	physical well-being
QTcF	QT interval corrected by Fridericia's formula
RECIST	response evaluation criteria in solid tumors
rPFS	radiographic progression-free survival
REML	restricted maximum likelihood
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAF	safety analysis populaton
SAP	statistical analysis plan
SD	stable disease
SI	standardized using International System of Units
SOC	system organ class
SRE	skeletal-related event
SWB	social/family well-being
TDD	time to definitive deterioration
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event

TTNT	time to initiation of the next systemic treatment
TTPP	time to PSA progression
TOI	Trial Outcome Index
VAS	visual analogue scale
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the planned analyses, excluding pharmacokinetics and pharmacodynamics, to be included in the Clinical Study Report for the phase 1b/2 Protocol EZH-1101. This SAP is based on Amendment 6 of the protocol, dated on 31 August 2022. This plan should be read in conjunction with the study protocol and the electronic case report forms (eCRFs). This SAP must be approved prior to database lock.

A separate analysis plan document will be developed for pharmacokinetic and pharmacodynamics data analysis. Results of the analyses of pharmacokinetic and pharmacodynamics parameters and biomarkers will be presented in separate clinical study report (CSR).

2. OVERALL STUDY DESIGN

2.1. General Description

This is a 2-part, global, multi-center, open-label, randomized phase 1b/2, active-controlled safety and efficacy study of oral administration of tazemetostat in combination with enzalutamide or abiraterone/prednisone (phase 1b) and tazemetostat in combination with enzalutamide versus enzalutamide alone (phase 2) in asymptomatic or mildly symptomatic subjects with progressive, metastatic castration-resistant prostate cancer (mCRPC) who have not received chemotherapy for mCRPC and who: for phase 1b, are either previously untreated with a second generation androgen inhibitor (abiraterone, enzalutamide, or apalutamide) or progressed on a second generation androgen inhibitor (abiraterone, enzalutamide, or apalutamide); or for phase 2, previously progressed on abiraterone. The phase 1b portion of this study was designed to determine the recommended phase 2 dose (RP2D) of tazemetostat in combination with either enzalutamide or abiraterone/prednisone, based on safety, tolerability, pharmacokinetic, pharmacodynamic, and efficacy profiles. The study design is displayed in Figure 1.

Phase 1b:

The following paragraphs describe the plan for the phase 1b dose escalation and RP2D determination portion of the study, which has been completed. The RP2D of tazemetostat when administered in combination with enzalutamide was established as 1200 mg twice daily (BID).

The phase 1b part of the study comprised dose escalation to determine the RP2D for the phase 2 part and to establish the safety profile of the combination of tazemetostat with enzalutamide or abiraterone/prednisone. The selection of therapy depends on which agent the subjects were previously treated with and progressed on prior to enrollment into the study. Subjects who were previously treated with enzalutamide and/or apalutamide will receive tazemetostat in combination with abiraterone/prednisone. Similarly, subjects who were previously treated with abiraterone/prednisone will receive tazemetostat in combination with enzalutamide. Subjects who are previously untreated with either enzalutamide or abiraterone/prednisone were equally distributed in both dose escalation arms of the phase 1b part of the study.

In the phase 1b part of the study, there were 3 different tazemetostat dose levels planned to be tested in combination with abiraterone/prednisone and 5 different tazemetostat dose levels planned to be tested in combination with enzalutamide. Dose escalation was performed using a modified 3+3 design consisting of a planned maximum of approximately 24 evaluable

subjects (7 for the combination with abiraterone/prednisone and 13 for the combination with enzalutamide, and up to 4 additional subjects in the event of a DLT). Dose escalations began at 400 mg tazemetostat twice daily, followed by 600 mg tazemetostat twice daily, followed by 800 mg tazemetostat twice daily, as tolerated according to occurrence of DLTs, as defined in the protocol). For the enzalutamide combination only, dose escalation could further proceed to 1200 mg twice daily followed by 1600 mg twice daily, as tolerated. For both enzalutamide and abiraterone/prednisone, prescribed doses as recommended by the respective package inserts are to be used throughout the study.

For phase 1b dose escalation purposes, DLTs were assessed during the first cycle. After completion of cycle 1 of each combination (tazemetostat with enzalutamide or tazemetostat with abiraterone/prednisone), all available safety data were reviewed jointly by the Sponsor and Investigators and the decision to proceed to the next dose cohort was made.

For each combination therapy, the following dose escalation procedure was followed (all dose levels of tazemetostat noted here are given twice daily):

- A single subject was to be enrolled at the 400 mg dose level. If the subject did not experience a DLT, then dose escalation would proceed to the next level of 600 mg. If the subject did experience a DLT, the study would stop for this combination therapy.
- At the 600 mg dose-escalated level, 3 subjects were to be enrolled. If no subjects experienced a DLT at the 600 mg level, then dose escalation would proceed to the next level of 800 mg. If 1 subject experienced a DLT at 600 mg, then the 600 mg dose level would be expanded by 3 additional subjects; if there were no additional DLTs at the 600 mg level (i.e., no more than 1 DLT in 6 subjects), then dose escalation would proceed to the 800 mg level. If, however, 2 or more subjects out of the first 3 or 6 subjects enrolled at 600 mg experienced a DLT, then the next lower, previously tested dose of 400 mg would be expanded by 2 additional subjects for a total of 3 subjects. If no additional DLTs were observed at the 400 mg dose level, then 400 mg would be evaluated for suitability as the RP2D. If 1 DLT was observed at the 400 mg dose level, 3 additional subjects would be enrolled; 400 mg would be evaluated for suitability as the RP2D if no further DLTs occur. Otherwise, the study for this combination therapy would stop.
- At the 800 mg dose-escalated level, 3 subjects were to be enrolled. If no subjects experienced a DLT at the 800 mg level, then for the abiraterone/prednisone combination, 800 mg would be evaluated for suitability as the RP2D. If 1 subject experienced a DLT at 800 mg, then the 800 mg dose level would be expanded by 3 additional subjects; if there were no additional DLTs at the 800 mg level (no more than 1 DLT in 6 subjects), then for the abiraterone/prednisone combination, 800 mg would be evaluated for suitability as the RP2D.
- If another DLT was observed after expansion to 6 subjects at 800 mg (2 out of 6), then 600 mg would be evaluated for suitability as the RP2D.
- For the enzalutamide combination only, if none of the first 3 subjects or no more than 1 of 6 subjects experienced a DLT at the 800 mg dose level, then dose escalation would proceed to the next level of 1200 mg. At the 1200 mg dose-escalated level, 3 subjects would be enrolled. If no subjects experienced a DLT at the 1200 mg level, then dose escalation would proceed to the next level of 1600

mg. If 1 subject experienced a DLT at 1200 mg, then the 1200 mg dose level would be expanded by 3 additional subjects; if there were no additional DLTs at the 1200 mg level (i.e., no more than 1 DLT in 6 subjects), then dose escalation would proceed to the 1600 mg level. If, however, 2 or more subjects out of the first 3 or 6 subjects enrolled at 1200 mg experienced a DLT, then the next lower, previously tested dose of 800 mg would be evaluated for suitability as the RP2D.

- For the enzalutamide combination only, at the 1600 mg dose-escalated level, 3 subjects were to be enrolled. If no subjects experienced a DLT at the 1600 mg level, then 1600 mg would be evaluated for suitability as the RP2D. If 1 subject experienced a DLT at 1600 mg, then the 1600 mg dose level would be expanded by 3 additional subjects; if there were no additional DLTs at the 1600 mg level (i.e., no more than 1 DLT in 6 subjects), then 1600 mg would be evaluated for suitability as the RP2D. If, however, 2 or more subjects out of the first 3 or 6 subjects enrolled at 1600 mg experienced a DLT, then the next lower, previously tested dose of 1200 mg would be evaluated for suitability as the RP2D.

Seven subjects were enrolled in the abiraterone/prednisone combination dose escalation arm and 14 subjects were enrolled in the enzalutamide combination dose escalation arm. Determination of the RP2D was informed by all available information, including pharmacokinetic (PK) parameters and the overall safety and tolerability of each combination. The RP2D of tazemetostat when administered in combination with enzalutamide was established as 1200 mg twice daily. Any available AR splice variant expression status (i.e., AR-V7) and neuroendocrine (small cell NEPC) status data were also evaluated before proceeding to phase 2.

Now that the RP2D for tazemetostat in combination with enzalutamide has been established, subjects with mCRPC previously treated with abiraterone/prednisone will be enrolled and randomized 1:1 in the phase 2 part of the study to receive either tazemetostat with enzalutamide or enzalutamide alone.

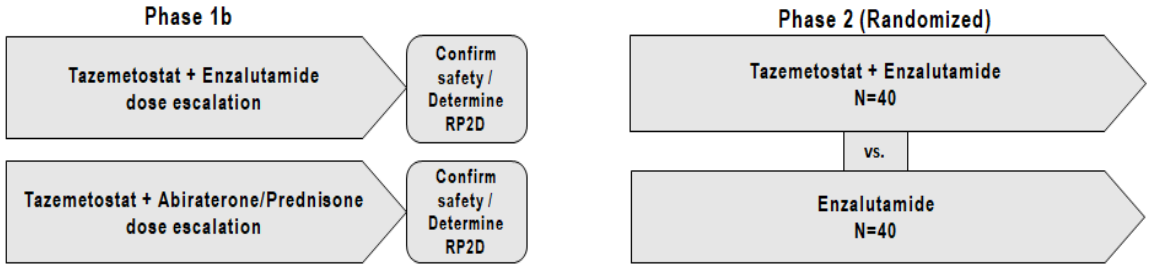
Subjects treated in the phase 1b part of the study who did not experience a DLT may continue in the study after cycle 1 on the combination regimen at the assigned dose until progression or occurrence of unacceptable toxicity. For subjects who had been assigned to the enzalutamide combination in phase 1b, the dose of tazemetostat may be increased to the RP2D after consultation with the Medical Monitor.

Phase 2:

The phase 2 part of the study will include an open-label, 2-arm randomized component. Approximately 80 chemotherapy naive, qualified subjects with mCRPC who were previously treated with abiraterone/prednisone will be enrolled and randomized 1:1 to receive either tazemetostat combined with enzalutamide (using the newly established RP2D of 1200 mg orally twice daily when given in combination with enzalutamide) as determined in phase 1b part of the study or enzalutamide alone. All subjects will receive treatment in 28-day cycles.

Total study enrollment will be approximately 104 subjects in the trial to assess combination therapy (up to approximately 24 subjects in phase 1b; 80 subjects in randomized phase 2). Study duration will be approximately 12 months for phase 1b and approximately [redacted] months for phase 2, for a total study duration of approximately 50 months.

Figure 1: Study Schema



Key Objectives of Phase 1b and Phase 2 to Assess Combination Therapy:

- Phase 1b: Safety, pharmacokinetics, anti-tumor activity in subjects with mCRPC previously treated and untreated with second generation anti-androgens. Determine RP2D. Sample size: maximum of approximately 24 (7 for the abiraterone/prednisone combination and 13 for the enzalutamide combination, and up to 4 additional subjects in the event of a DLT).
- Phase 2 Primary Objective: rPFS. Sample size: 80
- Phase 1b/2 Secondary Objectives: PSA50, TTPP, time to first SRE, ORR and BOR, DCR, time to new treatment, CTC, CTC 30% reduction, and (for phase 2 only) FACT-P FWB and PCS subscales and TDD.
- Total sample size: approximately 104

Abbreviations: CTC = circulating tumor cells; DCR = disease control rate; DLT = dose-limiting toxicity; FACT-P = Functional Assessment of Cancer Therapy – Prostate; FWB = Functional Well-being; mCRPC = metastatic castration-resistant prostate cancer; ORR = objective response rate; PCS = Prostate Cancer Subscale; PSA = prostate specific antigen; RP2D = recommended phase 2 dose; rPFS = radiographic progression-free survival; SRE = skeletal-related event; TDD = time to definitive deterioration; TTPP = time to PSA progression.

2.2. Changes to Analysis from Protocol

The following changes in the SAP are not in protocol amendment (31 August 2022):

- Screened population is added in Phase 1b/2.
- In phase 1b, the population used for protocol deviations, demographics, other baseline characteristics as well as efficacy analyses is changed to safety analysis population.
- Disease control rate at 6 months is re-defined in Section 8.4.2.6
- In PSA50, the minimum PSA value at baseline is changed to ≥ 1 ug/L (1 ng/mL) per PCWG3. Same change is in PSA90.
- In time to PSA progression (TTPP), for subjects who did not have a decline in PSA value, the time frame is changed from “by 17 weeks” to “beyond 12 weeks” per PCWG3.
- In subgroup analysis, remove a swim lane plot showing AR-V7 and NEPC status.
- In FACT-P analysis, a second analysis using a pattern mixture model is removed.

3. STUDY OBJECTIVES

3.1. Primary Objectives

Phase 1b:

- To determine the safety and tolerability of each of the combinations (tazemetostat with enzalutamide or tazemetostat with abiraterone/prednisone).

- To select RP2Ds for each combination treatment based on PK and pharmacodynamic parameters as well as efficacy and the overall tolerability of each of the combinations (tazemetostat with enzalutamide or tazemetostat with abiraterone/prednisone).

Phase 2:

- To determine the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone, as assessed by radiographic progression-free survival (rPFS) according to Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria for progression in bone or in soft tissue (the latter by Response Evaluation Criteria in Solid Tumors 1.1 [RECIST 1.1]).

3.2. Secondary Objectives:

Phase 1b and Phase 2:

- To determine the benefit of combining tazemetostat with enzalutamide or abiraterone/prednisone (in phase 1b) and the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone (in phase 2) as assessed by:
  - Prostate-specific antigen (PSA)50 (PSA50), defined as the percentage of subjects with a ≥50% decline of PSA from baseline at any time on study for subjects with a baseline PSA ≥2.0 ug/L (ng/mL) per PCWG3 criteria.
  - Objective Response Rate (ORR) and best overall response (BOR) in soft tissue per RECIST 1.1 guidelines.
  - Disease control rate (DCR; no radiographic progression per PCWG3 criteria, and no unequivocal clinical progression or death) at 6 months on treatment.
  - Time to first skeletal-related event (SRE) per PCWG3.
  - Time to initiation of the next systemic treatment (TTNT) for prostate cancer.
  - Time to PSA progression (TTPP), as defined as the duration from baseline to the day of PSA progression per PCWG3 criteria in months.
  - Reduction in circulating tumor cells (CTC) from a state of having a detectable number of CTCs to having an undetectable number of CTCs.
  - CTC response rate, defined as the percentage of subjects with a ≥30% reduction in CTC number from baseline.
- To further evaluate the safety and tolerability of the combination of tazemetostat with enzalutamide.
- To assess the PK of tazemetostat when administered in combination with enzalutamide (phases 1b and 2) and abiraterone/prednisone (phase 1b only) and the PK of enzalutamide (phases 1b and 2) and abiraterone (phase 1b only) when administered in combination with tazemetostat.

Phase 2 Only:

- To determine the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide only on quality of life (QoL) as assessed be changes

from baseline in FACT-P Functional Well-being subscale (FWB) and Prostate Cancer Subscale (PCS) scores over the course of the study

- To determine the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone to QoL as assessed by time to definitive deterioration (TDD) in functional status and in prostate symptoms as assessed by the FACT-P FWB and PCS scores, respectively.

3.3. Exploratory Objectives

Phase 1b Only:

- To evaluate the rate of pain progression relative to the time of screening at 6 months using the Brief Pain Inventory (BPI)-Short Form (-SF) for tazemetostat in combination with enzalutamide or abiraterone/prednisone.

Phase 2 Only:

- To evaluate the rate of pain progression relative to baseline at each post-baseline time point using the BPI-SF for tazemetostat in combination with enzalutamide versus enzalutamide alone.
- To determine the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone to QoL as assessed by changes from baseline in the FACT-P domains: Emotional, Social, and Physical Well-being over the course of the study.
- To determine the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone to QoL as assessed by changes from baseline in EQ-5D-5L visual analogue scale (VAS) and Health Utilities Index (HUI) scores over the course of the study.

Phase 1b and 2:

- To determine the benefit of tazemetostat in combination with enzalutamide or abiraterone/prednisone (in phase 1b) and the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone (in phase 2) as assessed by PSA90.
- To determine the benefit of tazemetostat in combination with enzalutamide or abiraterone/prednisone (in phase 1b) and the benefit of combining tazemetostat with enzalutamide when compared to enzalutamide alone (in phase 2) as assessed by ctDNA burden.
- To assess the pharmacodynamic modulation of enhancer of zeste homologue-2 (EZH2) activity by tazemetostat by measuring H3K27me3 levels in paired pre- and on-treatment tumor biopsies, including biopsies taken at disease progression (in phase 2 only in responders), that may be obtained from the phase 1b and phase 2 portions of the study.
- To assess genetic and molecular characteristics of responders as compared to non-responders, including mutational status of selected genes and gene expression signatures in tumor biopsies taken pre-treatment, on drug treatment (at cycle 2 day 1), and at disease progression (only in responders).

- To assess the genetic and molecular characteristics of responders as compared to non-responders, including the mutational status in pre- and on-treatment tumor biopsies and ctDNA in liquid biopsies. Expression profiling signatures of NEPC and AR signaling in pre- and on-treatment tumor biopsies will also be determined. AR-V7 and NEPC status (morphologically) and, possibly, selected neuroendocrine marker(s) will be determined in CTCs from liquid biopsies taken at baseline. Neuroendocrine status will also be determined in baseline serum samples using serum biomarker neuron-specific enolase (NSE) collected pre-dosing.
- To compare concordance of genetic and molecular characteristics in tumor and liquid biopsy samples.
- To assess immunological endpoints in tumor biopsy samples, including the number and activation/exhaustion status of CD8+ and regulatory T-cell subtypes and other immune cells in tumor infiltrates from tumor biopsies taken pre-treatment, on drug treatment (at cycle 2 day 1), and at disease progression (only in responders). Also, to investigate circulating immune cell sub-populations isolated from PBMCs taken pre-treatment, on drug treatment (at cycle 2 day 1), and at disease progression (only in responders) to determine the impact of drug treatment on immune cell numbers, antigen presentation, and immune cell activation status.

4. INTERIM ANALYSIS

Not applicable to this study.

5. SAMPLE SIZE DETERMINATION

Phase 1b

The sample size is not based on statistical considerations. A maximum of 24 subjects will be enrolled.

Phase 2

The Phase 2 sample size calculation was performed based on the primary endpoint of rPFS. To compare the combination of tazemetostat with enzalutamide to enzalutamide alone, [redacted] rPFS events from a total of 74 total subjects (37 per arm) will provide approximately [redacted] power for the analysis of rPFS, with a 2-sided total type I error of 0.05 to reject the null hypothesis that there is no difference in rPFS between the two arms. To account for the approximate [redacted] dropout, the sample size will increase to 80 (40 per arm).

The sample size assumes that the combination of tazemetostat with enzalutamide will prolong rPFS by [redacted] (hazard ratio [HR] = [redacted]) from [redacted] months for enzalutamide to [redacted] months, with [redacted] of subjects lost to follow-up over a [redacted]-month enrollment period, a 9-month follow-up period (a total follow-up time of 18 months, tmax = 18), and a total phase 2 study duration of approximately [redacted] months. (The critical boundary to achieve statistical significance for the final rPFS logrank testing between two arms is HR=[redacted] or [redacted] months of improvement in rPFS.)

6. ANALYSIS POPULATIONS

6.1. Phase 1b and Phase 2 Analysis Populations

Screened Population:

The Screened Population consists of all subjects who signed the inform consent form. The Screened population will be used in summaries of primary reasons of screen failure.

Safety Analysis Population (SAF):

The Safety Population is defined as all subjects who have received any dose of the study drugs. The safety population will be used for protocol deviations, demographics, other baseline characteristics, efficacy analyses in phase 1b portion, and safety analysis in phase 1b and 2 portion. Subjects will be analyzed according to the assigned dose level for the respective dose escalation cohort or actually received treatment in phase 1b portion and actually received treatment in Phase 2 portion.

Pharmacokinetic (PK) Population:

The PK population will include all subjects in the Safety Population who have at least one post-dose sample collected to allow estimation of the PK parameters. The PK population will be used for PK data analysis.

6.2. Phase 1b Analysis Populations

Enrolled Population:

The Enrolled Population consists of all subjects in the phase 1b part who signed the inform consent form and were not screen failures. The enrolled population will be used in summaries of disposition of subjects.

Dose-Limiting Toxicity (DLT) Population:

The DLT population will consist of evaluable subjects in the dose escalation cohorts who received at least 80% of planned study drug during cycle 1. Subjects will be analyzed according to the assigned dose level for the respective dose escalation cohort.

6.3. Phase 2 Analysis Populations

Intent-to-treat (ITT) Population:

The ITT population is defined as all subjects who are randomized into the trial. The ITT population will be used for summaries of disposition of subjects, protocol deviations, demographics and other baseline characteristics as well as efficacy analysis. Subjects will be analyzed according to the treatment arm to which they were randomized.

FACT-P Population:

The FACT-P population will include all subjects in the ITT population who complete an evaluable FACT-P questionnaire at baseline and ≥1 post-baseline visit. An evaluable questionnaire will have sufficient items completed to allow calculation of ≥1 FACT-P subscale.

7. DEFINITIONS AND CONVENTIONS

7.1. Study Day

Study day will be calculated in reference to the first dose date of study drug/randomization as follows:

- assessment date/event date – first dose date of study drug/randomization + 1 if the assessment date or event date ≥ first dose date/randomization date.
- assessment date/event date – first dose date of study drug/randomization if the assessment date or event date < first dose date/randomization date.

For phase 1b, the first dose date of study drug will be used in the calculations; for Phase 2, the date of randomization will be used in the calculations.

Under the convention specified above, there will be no Study Day 0.

7.2. Baseline

Baseline is defined as:

- the last value recorded for a variable prior to or on the date the subject received the first dose of study drug in the Phase 1b part, and
- the last value recorded for a variable prior to or on the date of randomization in the Phase 2 part. If a subject's first assessment occurs after randomisation but prior to the first dose, this assessment will be used as the baseline.

Baseline will be determined separately for each laboratory analyte.

7.3. Multicenter Studies

The center effect will not be considered for this study. All centers will be pooled together.

7.4. Multiple Comparisons/Multiplicity

In phase 2 portion, secondary efficacy endpoints will only be compared between treatment groups only if the primary endpoint (rPFS) achieves statistical significance at an overall alpha level of 0.05.

7.5. Missing Data

Unless noted otherwise, missing data will not be imputed. All analyses will be based on observed data only. The effective sample size at each assessment visit will be based on the total number of subjects with non-missing data for the parameter of interest at that visit.

Missing or partially missing start or end dates for adverse events (AEs) and medications will be imputed based on the conventions described in Appendix A. The purpose of the imputation for AEs is to determine if an AE with an incomplete date is treatment-emergent, as defined in Section 8.5.3. Similarly, the purpose of the imputation for medications is to determine if a medication with an incomplete date was given concomitantly with study drug, as defined in Section 8.5.8.

Missing or partially missing dates for initial disease diagnosis will be imputed. If the month and year of the diagnosis are provided but the day is missing, the missing day is imputed as 15. If only the year is provided, then the missing month and day are imputed as July 1st for the calculation.

7.6. Unscheduled Visits

In general, for by-visit summaries, data will be presented based on the visit number and corresponding visit name (i.e., name of planned clinical encounter). Visit windowing will not be used for handling unscheduled visits. Instead, all unscheduled visits will be assigned a visit name of "Unscheduled". Unscheduled visits will be included in all data listings and will contribute to the derivation of best- or worst-case values where required.

The visit number for unscheduled visits will be assigned by adding 0.01 to the visit number of the previously scheduled visit to facilitate chronological sorting. As an example, if an unscheduled visit occurs after Study Day 1, where the visit number is "1", the unscheduled visit will have visit number of "1.01".

7.7. Statistical Analysis Software

All statistical analyses for this study will be performed using SAS® version 9.4 or higher (SAS® Institute Inc., Cary NC).

8. STATISTICAL ANALYSIS

All data will be summarized by assigned dose level in the Phase 1b part and by planned treatment group per randomization in the Phase 2 part. In addition, where appropriate, a total column might be included to summarize subjects across dose levels/treatment groups. Summaries of continuous variables will present the number of subjects included in the analysis (N), the mean and standard deviation (SD), the median, the minimum, and the maximum statistics. Counts and percentages will be presented for summaries of categorical variables.

For Phase 1b, disposition of subjects, protocol deviations, demographics and other baseline characteristics will be summarized on the SAF population by assigned dose level.

For Phase 2, disposition of subjects, protocol deviation, demographics and other baseline characteristics will be summarized on the ITT population by planned treatment group per randomization.

8.1. Disposition of Subjects

Phase 1b:

The number of subjects screened, primary reason of screen failure, enrolled and not enrolled will be summarized by screened population.

Subject disposition, including reasons for treatment and study withdrawal as well as Country and site will be summarized and listed based on the SAF population.

A subject listing indicating analysis population and country/site of enrollment will be presented for the SAF population.

Phase 2:

The number of subjects screened, screened but not randomized and associated reason will be summarized by screened population.

The number of subjects in each population defined in Section 6 will be summarized on the ITT population by randomized treatment group. Similarly, the number of subjects randomized also will be summarized by country and site. Subjects in the randomized population but not in the safety population will be counted in a 'Not Treated' for table summaries on the ITT population.

A subject listing indicating analysis population and country of enrollment will be presented for the ITT population.

Subject disposition, including reasons for treatment and study withdrawal, will be summarized and listed based on the ITT population.

8.2. Protocol Deviations

Protocol deviations will be identified and reported by the process described in the current version of the study Protocol Deviation Plan. The number and percentage of subjects with major protocol deviations will be tabulated on the safety population by category in phase 1b part and ITT population in phase 2 part.

All major protocol deviations will be listed by subject.

8.3. Demographics and Other Baseline Characteristics

Baseline characteristics of subjects will be summarized for the following factors:

- demography and baseline disease characteristics
- cancer related history
- prior cancer treatments (radiotherapy or surgery)
- medical history

8.3.1 Demography and Other Baseline Disease Characteristics

The following variables will be summarized to describe the demographics and other baseline disease characteristics at enrollment/randomization:

- Age summarized as a continuous variable in years relative to the date informed consent is signed. Age will also be summarized categorically based on the following age groups:18 to < 65 years , ≥ 65 years (65 to <75 years, and ≥75 years)
- race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Not Reported)
- ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported)
- baseline body surface area (BSA) (m2)
- baseline Eastern Cooperative Oncology Group (ECOG) performance status.

8.3.2 Tumor Diagnosis

The following variables will be summarized to describe tumor diagnosis:

- tumor histology at study entry
- stage of disease at study entry (I–III, IV, unknown)
- time since last disease progression prior to enrollment (years)
- metastatic disease (yes, no)
- PSA at baseline (<=10, >10-20, >20 ng/ml).

8.3.3 Prior Cancer Related Procedures

The following variables will be summarized to characterize the extent of prior cancer related procedures:

- Prior anti-cancer therapy (yes, no)
- Prior radiotherapy (yes, no)
- Prior cancer-related surgery (yes, no)
- Number of regimens of prior anti-cancer therapy
- Number of prior surgeries
- Site of radiotherapy
- Prior hormonal agent (Enzalutamide only, Abiraterone only, both).

Reported terms for prior cancer treatments will be coded using the World Health Organization (WHO) Drug Dictionary Global B3 Sep2019 and will be listed for each subject, and the numbers of subjects who received each treatment will be summarized according to generic drug name.

Prior surgical terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v23.1 or higher in use at the time of the analysis and summarized by the MedDRA high-level group term (HLGT) and preferred term (PT).

8.3.4 Medical History

Medical history will be coded using the MedDRA v23.1 or higher and presented by system organ class (SOC) and PT.

8.4. Efficacy Analyses

All efficacy analysis will be performed by dose level/ treatment group on the SAF population for the phase 1b part and by treatment group on the ITT population or FACT-P (for FACT-P analysis) for the phase 2 part.

8.4.1 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is rPFS. The rPFS of tazemetostat in combination with enzalutamide will be compared to the rPFS of enzalutamide alone.

Radiographic PFS (rPFS) is defined as the time from date of randomization (phase 2)/date of first dose of study drug (phase 1b) to the first objective evidence of radiographic progression using RECIST 1.1 (soft tissue) and PCWG3 (bone), or death from any cause, whichever occurs first. In cases where the progressive disease (PD) or death has not occurred, the censoring rules provided in Table 1 below will be applied. rPFS will be programmatically derived based on investigator assessments and Blinded Independent Central Review (BICR) separately.

The determination of radiographic PD in both bone and soft tissue defined by the criteria is listed in Appendix E . Note that the PD for bone lesion is determined by two or more new bone lesions on bone scan per PCWG3 criteria (i.e., the appearance of two or more new bone lesions on bone scan) and the two scans (i.e., the confirmatory scan is required for bone disease progression) should be at least 6 weeks apart from each other; the PD for soft tissue lesion is determined based on CT or MRI per RECIST 1.1 criteria and no confirmatory scan is required for soft tissue disease progression.

Table 1: Date of Event or Censoring for rPFS

No.	Scenario	Date of Event (PD/Death) or Censoring	Event (PD/Death) or Censored
1	Death between adequate assessment visits or death before first radiographic assessment	Date of death	Event
2	No post-baseline radiographic assessment and death occurred prior to the first planned radiological assessment	Date of death	Event
3	Progression documented between scheduled visits	Date of assessment of progression[1]	Event
4	No baseline radiographic assessment	Date of first dose (phase 1b part) or date of randomization (phase 2 part)	Censored
5	No post-baseline radiographic assessment	Date of first dose (phase 1b part) or date of randomization (phase 2 part)	Censored
6	New anticancer treatment including systemic therapy and/or radiotherapy started or cancer-related surgery documented prior to documented disease progression or death [2]	Date of last adequate radiographic assessment on or prior to starting anti-cancer therapy or having cancer-related surgery	Censored
7	No progression (or death) and no new anticancer treatment or no cancer-related surgery documented	Date of last adequate radiographic assessment	Censored
8	Two or more consecutive missing scheduled assessments (with 1 week window) followed by progression or death	Date of last adequate radiographic assessment prior to missed assessments	Censored
9	Lost to follow-up or withdraw from study	Date of last adequate radiographic assessment	Censored

PD = progressive disease; rPFS = radiological progression-free survival.
[1] The earliest of (i) Date of radiographic assessment showing new lesion (if progression from bone or soft tissue is based on new lesion); or (ii) Date of radiographic assessment showing unequivocal progression from bone or soft tissue in non-target lesions, or (iii) Date of last radiographic assessment of target lesions (if progression from bone or soft tissue is based on increase in sum of the target lesion measurements)
[2] If PD and subsequent anti-cancer therapy occur on the same day, assume the progression was documented first, e.g., outcome is progression and the date is the date of the assessment of progression). If anti-cancer therapy is started prior to any assessments, censoring date should be the date of Study Day 1.
*If subjects had subsequent anti-cancer therapy, missing 2 consecutive scheduled tumour assessments and withdrawal of study consent or lost to follow-up on same date, censored reason will be assigned in the order of 2

consecutive scheduled tumour assessments > anti-cancer therapy > withdrawal of study consent or lost to follow-up.

The primary analysis of rPFS for tazemetostat in combination with enzalutamide, compared with enzalutamide treatment alone will be based upon at least the first [redacted] rPFS events observed. A log-rank test will be used to compare tazemetostat in combination with enzalutamide to enzalutamide treatment alone at the significance level of 0.025 (one-sided). Conventionally, HRs with corresponding 2-sided 95% CIs will be estimated using the Cox proportional hazards model. Graphical methods like K-M curves will be used to assess the Cox proportional hazards model assumptions.

rPFS will also be summarized descriptively using the Kaplan-Meier (KM) method. The KM estimate along with the corresponding 95% CI will be calculated using the Brookmeyer and Crowley method and will be provided for the median. The event-free rate with corresponding 95% CI will be calculated using Greenwood's formula and will be provided at 4 months, 8 months, 12 Months, and 18 months. Median follow-up for rPFS will be estimated according to the KM estimate of potential follow-up [Schemper, 1996]. The KM cures will also be provided.

rPFS will be calculated as follows:

- For phase 2, rPFS (months) = (Event or Censoring Date – Date of Randomization + 1) / 30.4375.
- For phase 1b, rPFS (months) = (Event or Censoring Date – Date of 1st Dose of Study Drug + 1) / 30.4375.

The rPFS will be censored at the time of analysis using the censoring rules provided in Table 1. If a subject meets more than one of these conditions, then the scenario that occurs first will be used for analysis.

A swim plot showing rPFS in months will be provided for phase 1b.

Refer also to Section 8.4.3 for subgroup analyses for this endpoint.

8.4.2 Analysis of Secondary Efficacy Endpoints

In the phase 2 portion of the study, comparisons between treatment groups for the secondary endpoints will occur only if the primary endpoint of rPFS achieves statistical significance at an alpha level of 0.05.

For phase 1b, the analysis of the secondary efficacy endpoints will take place at the end of the phase 1b. For the phase 2 part, the analysis of the secondary efficacy endpoints will take place at the time of the final analysis for rPFS, i.e., when [redacted] rPFS events have been observed.

8.4.2.1. PSA50

PSA50 is defined as the percentage of subjects with a ≥ 50% reduction of PSA from baseline at any time on study for subjects with PSA ≥ 1 ug/L (1 ng/mL) at baseline per PCWG3 criteria. Confirmed PSA response is defined as ≥50% reductions in PSA from baseline to post-baseline PSA result, with a consecutive assessment that also has a 50% decrease from baseline, conducted at least 3 weeks later required to confirm the PSA response. If a consecutive value meets the response criteria but is obtained within 3 weeks and the next assessment also meets response criteria and is taken after 3 weeks, then the initial response is considered as confirmed response as well. However, a subject with missing PSA value is considered as non-responder. PSA50 will be calculated by dose level/treatment group for subjects with PSA ≥ 1 ug/L at the baseline assessment (cycle 1 day 1 predose) and at least 1 post baseline assessment. A Cochran-

Mantel- Haenszel mean score test will be used to compare the response rates between tazemetostat in combination with enzalutamide and enzalutamide treatment alone. A swim plot showing PSA50 and PSA90 versus treatment duration will be provided for phase 1b.

8.4.2.2. Time to PSA Progression (TTPP)

TTPP is defined as the duration from date of randomization (phase 2)/date of first dose of study drug (phase 1b) to the date of first PSA progression per PCWG3 criteria in months. PSA progression is defined as a ≥25% increase and an absolute increase of ≥ 2 µg/L (2 ng/mL) above the nadir (or baseline value for subjects who did not have a decline in PSA value beyond 12 weeks). This increase must be confirmed by a second consecutive assessment conducted at least 3 weeks later. The date of confirmed PSA progression is the date of the initial ≥25%. For those subjects without confirmed PSA progression at the time of the analysis, they will be right censored following the rules provide in Table 2 below. A log-rank test will be used to compare TTPP between tazemetostat in combination with enzalutamide and enzalutamide treatment alone. TTPP is per PCWG3 criteria and is calculated in months. The KM curves of the two treatment arms with HR will be plotted.

Table 2: Date of Event or Censoring for TTPP

Situation	Date of Event or Censoring	Censored
No baseline or post-baseline PSA assessment	Date of First Dose (phase 1b) or Randomization (phase 2)	Yes
No confirmed PSA progression	Last PSA assessment date	Yes
Subject had a confirmed PSA progression	Date of first observation of PSA progression	No
Confirmed PSA progression after two or more consecutive missed PSA assessments (with 1 week window)	Date of last PSA assessment before missed assessments	Yes

8.4.2.3. Time to First Skeletal-Related Event (SRE)

Time to first SRE (per PCWG3 criteria) is defined as the time from date of randomization (phase 2)/date of first dose of study drug (phase 1b) to the date of first SRE. An SRE is defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression. Patients who have not experienced any of the above conditions will be censored at time of death, time of last AE assessment or date of randomization (phase 2)/date of first dose of study drug (phase 1b), whichever came later.

A log-rank test will be used to compare time to SREs between tazemetostat in combination with enzalutamide and enzalutamide treatment alone. The KM curves of the two treatment arms with HR will be plotted.

8.4.2.4. Time to Initiation of the next systemic Treatment (TTNT) for prostate cancer

TTNT is defined as the time from date of randomization (phase 2)/date of first dose of study drug (phase 1b) to date of first documented administration of systemic treatment for prostate cancer. TTNT will be censored at the last study treatment assessment date or date of

randomization (phase 2)/date of first dose of study drug (phase 1b), whichever come later if the subject did not receive subsequent treatment.

A log-rank test will be used to compare time to initiation of subsequent treatment between tazemetostat in combination with enzalutamide and enzalutamide treatment alone. The KM curves of the two treatment arms with HR will be plotted.

8.4.2.5. Best Overall Response (BOR) and Objective Response Rate (ORR)

Best overall response (BOR) for each subject (CR, PR, SD, progressive disease (PD), or not evaluable (NE)) occurring between the date of randomization (phase 2)/date of first dose of study drug (phase 1b) and the date of documented disease progression or the date of subsequent therapy will be determined based on PCWG3 criteria and RECIST 1.1 guidelines. BOR will be summarized showing the number and percentage of subjects in each response category. ORR is defined as the proportion of subjects with BOR of CR or PR. ORR will be calculated based on investigator and BICR assessment separately.

Only subjects with measurable soft tissue disease at screening (i.e., at least 1 target lesion per RECIST 1.1) will be included in this analysis. The ORR will be summarized by treatment arm and the associated 95% CI will be estimated using the Clopper Pearson method. A Cochran-Mantel-Haenszel test will be used to compare ORR between tazemetostat in combination with enzalutamide and enzalutamide treatment alone.

Duration of response (DoR) is defined as the time of initial response (CR or PR) until radiographic progression using RECIST 1.1 and PCWG3 guidelines or death from any cause. DoR will be calculated as follows:

DOR (months) = (Progression/Death/Censoring Date – Response Start Date + 1) / 30.4375

Subjects who do not have documented radiographic progression or death will be censored following the same rules as rPFS specified in Table 1 DOR will be analyzed using the same approach as rPFS.

8.4.2.6. Disease Control Rate (DCR) at 6 months

Disease control rate (DCR) at 6 months (i.e. 24 weeks) is defined as the proportion of patients with measurable soft tissue disease at baseline who had BOR of CR or PR and remaining on the study without progression at 23 weeks or with a duration of SD for at least 23 weeks after of randomization (phase 2)/first dose (phase 1b) using overall imaging-based response assessed by RECIST 1.1 (soft tissue) and PCWG-3 criteria (bone). DCR was reported by investigator-assessment.

A Cochran-Mantel-Haenszel test will be used to compare DCR between tazemetostat in combination with enzalutamide and enzalutamide treatment alone, and the corresponding p-value will be provided. Also, the 95% CI will be provided for each treatment group and for the difference in proportion between the two treatment groups, using the Clopper-Pearson exact method.

8.4.2.7. Circulation Tumor Cells (CTCs)

In subjects who enter the study with a detectable number of CTCs, the rate of CTC reduction to zero is the proportion of subjects who convert to an undetectable number of CTCs. CTC response is defined as a ≥30% reduction in CTCs from baseline in subjects who enter the study

with a detectable number of CTCs. The rate of CTC reduction to zero and the CTC response rate for tazemetostat in combination with enzalutamide will be compared with those for enzalutamide treatment alone using the Cochran-Mantel-Haenszel test. The 95% CI will be estimated using Clopper-Pearson exact method.

8.4.2.8. FACT-P (Phase 2 only)

Analyses of FACT-P will be carried out on FACT-P population.

The instrument descriptions and scoring algorithms are detailed in Appendix B. The questionnaire will be administered, at baseline, Cycle 3, 5, every 3 cycles starting from Cycle 7 and Post-treatment visits.

The following outcome measures can be calculated from the FACT-P questionnaire, the resulting value is the total score for the associated questions or scaled scores:

- Physical well-being subscale (PWB) (Questions GP1 to GP7)
- Social/family well-being subscale (SWB) (Questions GS1 to GS7)
- Emotional well-being subscale (EWB) (Questions GE1 to GE6)
- Functional well-being subscale (FWB) (Questions GF1 to GF7)
- Prostate cancer subscale (PCS) (Questions C2, C6, P1 to P8, BL2 and BL5)
- Total Functional Assessment of Cancer Therapy- General (FACT-G) score, sum of PWB, SWB, EWB and FWB
- Trial Outcome Index (TOI), sum of PWB, FWB and PCS
- Functional Assessment of Prostate Cancer Symptoms Index 6 (FAPSI-6) (Questions
- P1 to P3, GP1, C2 and GE6)
- Total FACT-P score (sum of scores of all the sub-scales)

In this study, only SWB, EWB, PCS, Total FACT-P score will be analyzed.

Items to be reversed

- Each question in the FACT-P questionnaires has a choice of 5 responses, “Not at all”, “A little bit”, “Somewhat”, “Quite a bit” and “Very much”. The scores range from 0 (“Not at all”) to 4 (“Very much”) for positively phrased questions. Negatively phrased questions have a reverse scoring, from 0 (“Very much”) to 4 (“Not at all”). This results in a consistent approach, where higher scores indicate a better quality of life.
- Note, questions that are reversed (via subtraction of the response from 4) are: GP1-7, GE1, GE3-6, C2, P1-3, P6-P8 and BL2.

Missing data

As per the functional assessment of chronic illness (FACIT) scoring guidelines (Cella et al 1993, Cella et al 1994, Esper et al 1997),

- More than 80% of questions in a questionnaire must be completed for the questionnaire to have the FACT-P total score evaluable. If 80% or less of

questions are completed, the FACT-P total scores will not be calculated. Similarly, FACT-G total score and and TOI score require more than 80% of the relevant questions to be completed for the score to be evaluable.

- For each domain (PWB, SWB, EWB, FWB and PCS) if more than 50% of the items were answered (e.g., a minimum of 4 of 7 items, 4 of 6 items, etc), the subscale score will be calculated by multiplying the sum of subscale by the number of items in the subscale, then dividing by the number of items actually answered:
- Subscale score= (sum of item scores x N of items in subscale)/ N of items answered
- If at least 50% of the domain items are missing, that domain will be treated as missing and thus NE. The total score for each variable (FACT-G, FACT-P TOI and FACT-P Total) is then calculated as the sum of the un-weighted prorated scores. If a domain score is NE, any health related quality of life (HRQL) variable which these domains contribute to is also termed NE. For example, for the FACT-P TOI variable, if PWB is NE at a visit, the FACT-P TOI variable is also NE at this visit. Also, the FACT-P total score cannot be computed if any of the domain scores is NE.

Analysis Visit Window

For summaries of PRO data, assessments will be assigned to calculated visit windows (4 weeks per cycle, details in Study Protocol Table 8). The time windows will be exhaustive so that data recorded at any timepoint have the potential to be summarized. Inclusion within the visit window will be based on the actual date and not the intended date of the visit. The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls half-way between the two visits. If there is more than one value per subject within an assessment window then the closest to the planned study day value should be summarised, or the earlier in the event the values are equidistant from the planned study day. The value at a given timepoint will be missing if no assessment was reported within the specified assessment window around the planned study day.

All PRO instruments will be listed separately by treatment arm and subject.

Descriptive summary and Change from baseline

FACT-P results including subscale and total scores will be summarized at each visit by treatment arm using the number of subjects with non-missing data (n), mean, standard deviation, median, minimum and maximum. Change from baseline will be summarized using the same statistics. Change from baseline in the FACT-P results will be analyzed using mixed-effects model for repeated measures (MMRM). Restricted maximum likelihood (REML) estimation will be used. The model will include treatment, visit and treatment by visit interaction as explanatory variables and the baseline score as a covariate. An unstructured covariance matrix will be used to model the within-subject error and the Kenward-Roger approximation will be used to estimate the degrees of freedom. The mean change from baseline will be summarized and plotted by treatment group. Least square mean, standard error and 95% CI of treatment difference will be presented.

Percent of subjects with deterioration of FACT-P SWB, EWB, PCS, total FACT-P score

Subjects will be defined as having each FACT-P subscale or total score deterioration, if they experience a decrease of ≥ 3 points in subscale score or ≥ 10 points in total FACT-P score at any post-baseline visits compared with baseline.

The percentage of subjects with deterioration at post-baseline visits will be summarized by the treatment arm. The difference between two treatments, and the associated 95% CI and p-value based on the Cochran- Mantel-Haenszel (CMH) test will be calculated.

Time to definitive deterioration (TDD) of FACT-P SWB, EWB, PCS, Total FACT-P score

Time to deterioration in each FACT-P subscale score or total score is defined as the interval from the date of randomization until the date of the first clinically meaningful deterioration (i.e. 3 points or more decline for subscale score, 10 points or more decline for total score) that is confirmed at a subsequent visit at least 3 weeks apart with no improvement in between the visits (except if it was the patient's last available assessment) or death (by any cause) in the absence of a clinically meaningful deterioration, regardless of whether the patient discontinues study drug(s) prior to the deterioration. Death will be included as an event only if it occurs within 2 HRQL assessment visits from the last available HRQL assessment. For patients who receive a subsequent anti-cancer therapy, data will only be included until the start date of the subsequent anti-cancer therapy.

Number and percent of subjects with deterioration and censored will be summarized by treatment arm.

Time to deterioration will be estimated by KM methodology. Treatment arms will be compared using a log rank test and the estimated HR from Cox regression analysis will be presented to summarise the effect of tazemetostat in combination with enzalutamide. Estimates of median time to deterioration and HR will be presented with corresponding 95% CIs. KM based rates of being alive without deterioration at 3, 6, 9, 12, and 18 months will be estimated and associated two-sided 95% CIs will be provided. The KM curves of the two treatment arms with HR will be plotted.

8.4.3 Subgroup Analyses

Subgroup analysis will be performed for rPFS by following variables:

- age (<65 years, >=65 years)
- race (Asian, American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander, White, not reported, Other)
- baseline ECOG
- stage of disease at initial diagnosis (I–III, IV, unknown)
- metastatic site (bone only, visceral: lung or liver, other)
- PSA at baseline (<=10, 10-20, >20 ng/ml)
- AR-V7 status (negative, positive)
- NEPC status (negative, positive).

If there are less than 5 events across treatment groups per subgroup level, analysis within that level will be omitted.

8.4.4 Analysis of Exploratory Endpoints

Note: Any other exploratory endpoints listed in the protocol but not in this SAP will be specified in separate analysis plan documents.

BPI-SF

The BPI-SF will be used to assess the impact of pain on daily life. The BPI-SF comprises a total of 15 items measuring 2 domains: pain severity (intensity) and pain interference. The instrument descriptions and scoring algorithms are detailed in Appendix C.

The BPI-SF pain severity domain/subscale consists of 4 items (#3, #4, #5, and #6) that assess pain at its "worst," "least," "average," and "now" (current pain) respectively on an 11-point numeric rating scale (NRS) ranging from 0=No pain to 10=Pain as bad as you can imagine. Pain severity subscale or composite score from all the 4 items will be calculated as a mean score where all items must be non-missing.

Same analysis visit window as FACT-P will be applied in BPI-SF.

Rate of pain progression at 6 months (phase 1b)

In phase 1b, the rate of pain progression, defined as the proportion of subjects with an increase of ≥30% from the time of screening in the average of BPI pain intensity item scores (items 3, 4, 5, and 6) at 6 months, will be used to assess tazemetostat in combination with enzalutamide and tazemetostat in combination with abiraterone/prednisone. The BPI scores will be summarized descriptively at time of screening, at 3 months, and at 6 months.

Pain progression rates and associated 95% CIs are calculated for each arm. The difference in the response rates between two treatments, and the associated 95% CI and p-value based on the CMH test will be calculated.

Rate of pain progression (phase 2)

In phase 2, the rate of pain progression, defined as the proportion of subjects with an increase of ≥30% from baseline in the average of BPI pain intensity item scores (items 3, 4, 5, and 6) at each post-baseline time point, will be used to compare tazemetostat in combination with enzalutamide to enzalutamide treatment alone. The BPI scores will be summarized descriptively at time of baseline and at each post-baseline time point.

Pain progression rates and associated 95% CIs are calculated for each arm. The difference in the response rates between two treatments, and the associated 95% CI and p-value based on the Cochran-Mantel-Haenszel (CMH) test will be calculated.

Change from baseline at post-baseline visits

Change from baseline in the BPI-SF mean severity score will be analyzed using same approach as FACT-P.

PSA90 (phase 1b and phase 2)

PSA90 is defined as the percentage of subjects with a ≥ 90% reduction of PSA from baseline at any time on study for subjects with PSA ≥ 1 ug/L (1 ng/mL) at baseline per PCWG3 criteria. Confirmed PSA90 response is defined as ≥90% reductions in PSA from baseline to post-baseline PSA result, with a consecutive assessment that also has a 90% decrease from baseline, conducted at least 3 weeks later required to confirm the PSA response. If a consecutive value meets the response criteria but is obtained within 3 weeks and the next assessment also meets

response criteria and is taken after 3 weeks, then the initial response is considered as confirmed response as well. However, a subject with missing PSA value is considered as non-responder. PSA90 will be calculated by treatment group for subjects with PSA ≥ 1 ug/L (1 ng/mL) at the baseline assessment (cycle 1 day 1 predose) and at least 1 post baseline assessment. A Cochran-Mantel- Haenszel mean score test will be used to compare the response rates between tazemetostat in combination with enzalutamide and enzalutamide treatment alone.

FACT-P (phase 2)

The details of FACT-P scoring are specified in Section 8.4.2.8. For exploratory objectives, scores will be summarized descriptively over the course of the study by treatment group, with emphasis on the following FACT-P domains: Emotional, Social, and Physical Well-being subscale. The analyses will be conducted on the FACT-P population.

The analyses approaches are detailed in Section 8.4.2.8.

EQ-5D-5L (phase 2)

The instrument descriptions and scoring algorithms are detailed in Appendix D.

EQ-5D-5L VAS and index value will be summarized and analyzed using the same method as above FACT-P. Standard EQ-5D-5L value set from US will be applied to generate index value. EQ-5D-5L descriptive system will also be summarized by presenting the frequency and proportion of each level for each dimension by visit and by treatment arm.

8.5. Safety Analyses

8.5.1. General Considerations

Safety analyses will be conducted using the Safety population as defined in Section 6. In general, safety data from the phase 1b part will be tabulated by assigned dose levels/actual treatment groups and overall. The data from the phase 2 will be tabulated by actual treatment group and overall. For all analyses, subjects who receive a dose modification will be retained and analyzed in the treatment group of their original assignment. For certain presentations, such as laboratory analyses and vital signs, data will be presented for the Safety population.

Data from the phase 1b and the phase 2 will be presented separately.

8.5.2. Study Drug Exposure

Study drug exposure may be summarized for the phase 1b by assigned dose level.

Study drug exposure and compliance in the randomized phase 2 will be summarized and listed for the Safety population.

The following summaries of overall drug exposure will be presented:

- Duration of exposure (weeks) = [(last dose date of study drug – first dose date of study drug) + 1]/7. Except for the first and last dose dates, this calculation is not adjusted for periods where dosing is interrupted, or dose is recorded as 0.
- Total number of cycles
- Number of cycles by category
- Numbers of subjects requiring dose reductions, treatment interruption or treatment discontinuation in response to AEs (based on action taken for reported AEs)

The following summaries of tazemetostat drug exposure will be presented:

- Duration of exposure (weeks) = [(last dose date of study drug – first dose date of study drug) + 1]/7. Except for the first and last dose dates, this calculation is not adjusted for periods where dosing is interrupted or dose is recorded as 0.
- Total number of cycles
- Total amount of study drug taken (mg)
- Average dose intensity (mg BID/day) = total amount of study drug taken (mg) / [2 * planned duration of exposure (days)]
- Numbers of subjects requiring dose reductions, treatment interruption or treatment discontinuation in response to AEs (based on action taken for reported AEs)
- Percentage study drug taken = 100% * Average dose intensity (mg BID/day) / MTD or RP2D(mg BID/day)

The following summaries of abiraterone drug exposure will be presented

- Duration of exposure (weeks) = [(last dose date of study drug – first dose date of study drug) + 1]/7. Except for the first and last dose dates, this calculation is not adjusted for periods where dosing is interrupted or dose is recorded as 0.
- Total number of cycles
- Total amount of study drug taken (mg)
- Average dose intensity (mg /day) = total amount of study drug taken (mg) / [planned duration of exposure (days)]
- Numbers of subjects requiring dose reductions, treatment interruption or treatment discontinuation in response to AEs (based on action taken for reported AEs)
- Percentage study drug taken = 100% * Average dose intensity (mg/day) / 1000 mg/day

The following summaries of prednisone drug exposure will be presented

- Duration of exposure (weeks) = [(last dose date of study drug – first dose date of study drug) + 1]/7. Except for the first and last dose dates, this calculation is not adjusted for periods where dosing is interrupted or dose is recorded as 0.
- Total number of cycles
- Total amount of study drug taken (mg)
- Average dose intensity (mg BID/day) = total amount of study drug taken (mg) / [2*planned duration of exposure (days)]
- Numbers of subjects requiring dose reductions, treatment interruption or treatment discontinuation in response to AEs (based on action taken for reported AEs)
- Percentage study drug taken = 100% * Average dose intensity (BID/day) / 10 mg BID/day

The following summaries of enzalutamide drug exposure will be presented

- Duration of exposure (weeks) = [(last dose date of study drug – first dose date of study drug) + 1]/7. Except for the first and last dose dates, this calculation is not adjusted for periods where dosing is interrupted or dose is recorded as 0.
- Total number of cycles
- Total amount of study drug taken (mg)
- Average dose intensity (mg /day) = total amount of study drug taken (mg) / [planned duration of exposure (days)]
- Numbers of subjects requiring dose reductions, treatment interruption or treatment discontinuation in response to AEs (based on action taken for reported AEs)
- Percentage study drug taken = 100% * Average dose intensity (mg/day) / 160 mg/day

Exposure will be summarized separately by treatment group for the first six cycles and for subsequently cycles.

8.5.3. Adverse Events

Summary tables will be provided for all reported treatment-emergent AEs (TEAEs), defined as AEs that started or worsened in severity on or after the date of the first dose of study drug (Study Day 1) through 30 after the end of study drug, or prior to initiation of another investigational agent or cytotoxic chemotherapy. Missing or partially missing start and end dates for AEs and SAEs will be handled according to the conventions described in Table 5 in Appendix A. For cases in which it is not possible to ascertain treatment-emergence, the event will be classified as treatment-emergent.

The reported AE term will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 or higher. The severity of each AE will be graded by the Investigator based on version 5.0 of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). If a severity grading scale does not exist for an AE, the Investigator will classify the severity as mild, moderate, severe, life-threatening/debilitating, or fatal based on the criteria described in the study protocol. The causal relationship between the occurrence of an AE and study drug will be judged by the Investigator as “related” or “not related”.

AEs will be summarized by dose level and/or treatment arm and based on the number and percentage of subjects experiencing events by MedDRA system organ class and preferred term. If a subject experiences repeat episodes of the same AE (as defined by the MedDRA system organ class and preferred term), then the event with the highest reported severity grade and the strongest causal relationship to study drug will be used for purposes of the incidence tabulations.

Tabular summaries will be provided for treatment-emergent AEs and will be summarized as follows:

- All TEAEs
- TEAEs with ≥ 10% incidence overall based on PT
- TEAEs of grade 3 or 4
- Treatment-related TEAEs

- Treatment-related TEAEs of grade 3 or 4
- TEAEs leading to dose interruption
- TEAEs leading to dose reduction
- TEAEs leading to discontinuation of study drug
- Treatment-emergent serious adverse events (TESAEs)
- Treatment-related treatment emergent SAEs
- TEAEs of special interest
- TEAEs leading to death

Additionally, separate listings of SAEs, TEAEs leading to discontinuation of study drug, and TEAEs leading to dose modification (reductions and/or interruption) will be provided. A listing of TEAEs of special interest described in the protocol Section 12.2.1.6 will be provided.

Subject deaths will be summarized and listed as follows:

- Summary and listing of subjects who died during and till 30 days after last dose of study drug
- Summary and listing of subjects who died during and till 30 days after last dose of study drug with treatment-related TEAEs
- Summary and listing of subjects who died after 30 days after the last dose of study drug with treatment-related AEs

The summary and listing will include the reason for death:

- Any AE (by MedDRA preferred Term)
  - Any treatment related TEAE
  - Any treatment not related TEAE
- Progressive Disease
- Other

8.5.4. Laboratory Values

Blood samples for the following clinical laboratory tests were collected and analyzed for safety:

- Hematology: Hemoglobin, hematocrit, WBC, differential blood count with ANC, platelet count.
- Serum chemistries: alkaline phosphatase, alanine aminotransferase (ALT) , aspartate aminotransferase (AST), direct bilirubin, total bilirubin, blood urea nitrogen, creatinine, bicarbonate, albumin, calcium, magnesium, glucose, phosphorus, total protein, and triglycerides.
- Coagulation: partial thromboplastin (PT), partial thromboplastin time (PTT), aPTT, and international normalized ratio (INR).

- Urinalysis: glucose, blood, protein, and pH.

Clinical laboratory samples were processed at the clinical site or at an affiliated local laboratory facility. For purposes of analysis and reporting, laboratory values will be standardized using International System of Units (SI).

Laboratory values that are reported using a nonnumeric qualifier (e.g., less than [<] or greater than [>] sign), the reported numeric value will be used for analysis without the qualifier.

Whenever defined, laboratory values will be assigned toxicity grades based on version 5.0 of the CTCAE. For some laboratory tests, these criteria may include qualifying definitions (e.g., clinical AE and/or requirement for concomitant medication) in addition to the specific laboratory value used for the definition of the toxicity grades. For such tests, the qualifying definitions will not be used for the assignment of toxicity grades.

The maximum or "worst" change in each laboratory value occurring during treatment will be assessed by means of shift tables showing the number and proportion of subjects with directional shifts in CTCAE toxicity grades relative to the baseline toxicity grade. For laboratory variables without CTCAE toxicity grades (such as thyroid function), similar tables will be constructed showing shifts to outside (above or below) the local laboratory normal range relative to baseline.

Hematology, serum chemistry, and coagulation values will be summarized by dose level and/or treatment arm in a descriptive manner by calculating the mean, standard deviation, median, and range of the following values that are derived for each subject:

- baseline value
- minimum post-baseline value and corresponding change from baseline
- maximum post-baseline value and corresponding change from baseline
- last post-baseline value and corresponding change from baseline
- shift from baseline toxicity grade to worst post-baseline toxicity grade

A scatter plot of ALT versus total bilirubin, both expressed as multiples of upper limit of normal range, will be produced. The scatter plot will be repeated for AST versus total bilirubin.

The baseline value will be determined using the convention described in Section 7.2 . Lab shift tables from baseline value to worst post-baseline value based on CTCAE toxicity grades will also be provided.

8.5.5. Vital Signs

The following vital signs were measured following the initiation of study drug:

- systolic and diastolic blood pressures (mm Hg)
- heart rate (beats per minute)
- body temperature (degrees Celsius)

Each of these vital signs will be summarized descriptively by calculating the mean, standard deviation, median, and range (minimum and maximum) of the following values that are derived for each subject:

- baseline value

- minimum post-baseline value and corresponding change from baseline
- maximum post-baseline value and corresponding change from baseline
- last post-baseline value and corresponding change from baseline

In addition, summaries of heart rate, temperature, systolic blood pressure, and diastolic blood pressure will be based on markedly abnormal criteria defined in Table 3 below:

Table 3: Vital Signs and Abnormality Criteria

Vital Sign	Abnormal Criteria
Heart rate (bpm)	< 60 bpm > 100 bpm
Temperature (ºC)	≤ 35 ºC ≥ 38 ºC
Systolic blood pressure (mmHg)	120-139 mmHg, inclusive (CTCAE grade 1) 140–159 mm Hg, inclusive (CTCAE grade 2) ≥ 160 mmHg (CTCAE Grade 3)
Diastolic blood pressure (mmHg)	80–89 mmHg, inclusive (CTCAE grade 1) 90–99 mm Hg, inclusive (CTCAE grade 2) ≥ 100 mmHg (CTCAE grade 3)

Incidence of abnormal worst-case values will be presented. For heart rate and temperature, both high and low values will be presented separately such that subjects can be counted in both categories. Abnormal vital sign values will be flagged as such on the vital signs listing.

The baseline value will be determined using the convention described in Section 7.2 .

8.5.6. Electrocardiograms (ECGs)

Categorical analyses of the QTcF interval data across time points will be performed using shifts from baseline for the number and percentage of subjects meeting or exceeding the following threshold values: > 450 msec, > 480 msec, > 500 msec. Additionally, the number and percentage of subjects with QTcF interval increases from baseline > 30 msec and > 60 msec will be summarized by dose level and/or treatment arm.

The following summaries will be provided for 12-lead ECG measurements listed above:

- 12-lead ECG values and changes from baseline (and changes from pre-dose) by planned visit
- Shift from baseline to worst post-baseline in QTcF status categorized as markedly abnormal or not (defined in the table below)

- Number and percentage of subjects whose worst-case changes from baseline in QTcF measurements meet markedly abnormal criteria (described in the table below).

Table 4: ECG Measures and Markedly Abnormal Criteria

QTcF Measure	Markedly Abnormal Criteria
Observed	450–480 msec, inclusive [CTCAE grade 1] 481–500 msec, inclusive [CTCAE grade 2] > 500 msec [CTCAE grade 3 or higher]
Change from Baseline	31–60 msec, inclusive, increase from baseline >60 msec increase from baseline

The listings will include the individual ECG values, the calculated averages, and other information collected from the 12-lead ECG. QTcF measures meeting the markedly abnormal criteria as defined in the table above will be flagged on the listing.

8.5.7. Physical Examination

Physical examination results will be listed by subject.

8.5.8. Prior and Concomitant Medications and Procedures

- Prior medications will include medications which stopped prior to the first dose of study drug.
- Concomitant medications are defined as medications that were started prior to first dose of study drug or at any time after the start of first dose of study drug and stopped prior to the discontinuation of study drug.

Medications with missing or partially missing start or end dates will be handled according to the conventions described in Table 6 in Appendix A. If it cannot be determined whether a medication was a prior medication due to partial medication start or end dates, the medication will be considered concomitant.

The reported medication term will be coded using the World Health Organization (WHO) Drug Dictionary in effect at the time of the analysis. The number and percentage of subjects taking concomitant medications will be summarized by dose level/treatment group and generic name, sorted in decreasing order of frequency. All reported prior and concomitant medications will be listed by subject.

Concomitant procedures will be displayed in subject listing format.

8.5.9. Subsequent Anticancer Therapy

The number and percentage of subjects taking subsequent anticancer therapy during the study and the type of subsequent anticancer therapy (chemotherapy, targeted therapy, immunotherapy radiation, and other) will be tabulated by treatment group.

All subsequent anticancer therapy will be listed by subject.

8.6. Pharmacokinetic Analysis

All pharmacokinetic analyses will be performed based on the PK population.

Complete details of the analysis of the PK parameters will be specified in a separate PK analysis plan (PKAP).

8.7. References

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APPENDIX A. ALGORITHMS FOR HANDLING PARTIAL DATES

Table 5: Treatment-emergent Adverse Events

START DATE	STOP DATE	ACTION
Known	Known/Partial/Missing	If start date < study drug start date, then not TEAE If start date >= study drug start date and < end of treatment + 30 days then TEAE If start date > end of treatment + 30 daysthen not TEAE
Partial, but known components show that it cannot be on or after study drug start date	Known/Partial/Missing	Not TEAE
Partial, could be on or after study drug start date	Known	If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, then not TEAE If stop date >= study drug start date, then TEAE
	Missing	Assumed TEAE

Table 6: Prior and Concomitant Medications

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study drug start date, assign as prior If stop date >= study drug start date and start date <= end of treatment + 30 days, assign as concomitant If stop date >= study drug start date and start date > 30 days after the end of treatment, assign as post-treatment
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date and start date <= end of treatment + 30 days , assign as concomitant If stop date >= study drug start date and start date > 30 days after the end of treatment, assign as post-treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment + 30 days, assign as concomitant If start date > 30 days after the end of treatment, assign as post-treatment

START DATE	STOP DATE	ACTION
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date and start date <= end of treatment + 30 days, assign as concomitant If stop date >= study drug start date and start date > 30 days after the end of treatment, assign as post-treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date and start date <= end of treatment + 30 days, assign as concomitant If stop date >= study drug start date and start date > 30 days after the end of treatment, assign as post-treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment + 30 days, assign as concomitant If start date > 30 days after the end of treatment, assign as post-treatment
Missing	Known	If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant Cannot be assigned as post-treatment
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date >= study drug start date, assign as concomitant Cannot be assigned as post-treatment
	Missing	Assign as concomitant

APPENDIX B. FACT-P (VERSION 4.0)

Below is a list of statements that other people with your illness have said are important.

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GS1	I feel close to my friends.....	0	1	2	3	4
GS2	I get emotional support from my family.....	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness.....	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.* ☐					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4

GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4

BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4

Scoring Guidelines

Instructions: 1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. Add subscale scores to derive total scores (TOI, FACT-G & FACT-P).
5. **The higher the score, the better the QOL.**

Subscale	**Item Code**	**Reverse item?**		**Item response**	**Item Score**
PHYSICAL	GP1	4	-	_____	=_____
WELL-BEING	GP2	4	-	_____	=_____
(PWB)	GP3	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-28	GP5	4	-	_____	=_____
	GP6	4	-	_____	=_____
	GP7	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**PWB subscale score**

SOCIAL/FAMILY WELL-BEING (SWB)	GS1	0	+	_____	=_____
	GS2	0	+	_____	=_____
	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
Score range: 0-28	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____**=SWB subscale score**

EMOTIONAL WELL-BEING (EWB)	GE1	4	-	_____	=_____
	GE2	0	+	_____	=_____
	GE3	4	-	_____	=_____
	GE4	4	-	_____	=_____
Score range: 0-24	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 6: _____
Divide by number of items answered: _____**=EWB subscale score**

FUNCTIONAL WELL-BEING (FWB)	GF1	0	+	_____	=_____
	GF2	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
Score range: 0-28	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**FWB subscale score**

Subscale	**Item Code**	**Reverse item?**		**Item response**	**Item Score**
PROSTATE CANCER SUBSCALE (PCS)	C2	4	-	_____	=_____
	C6	0	+	_____	=_____
	P1	4	-	_____	=_____
	P2	4	-	_____	=_____
	P3	4	-	_____	=_____
Score range: 0-48	P4	0	+	_____	=_____
	P5	0	+	_____	=_____
	P6	4	-	_____	=_____
	P7	4	-	_____	=_____
	BL2	4	-	_____	=_____
	P8	4	-	_____	=_____
	BL5	0	+	_____	=_____

Sum individual item scores:_____
Multiply by 12: _____
Divide by number of items answered: _____=**PC Subscale score**

To derive a FACT-P Trial Outcome Index (TOI):
Score range: 0-104

_____ + _____ + _____ =_____=**FACT-P TOI**
(**PWB** score) (**FWB** score) (**PCS** score)

To Derive a FACT-G total score:
Score range: 0-108

_____ + _____ + _____ + _____=_____=**FACT-G Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score)

To Derive a FACT-P total score:
Score range: 0-156

_____ + _____ + _____ + _____ + _____ =_____=**FACT-P Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score) (**PCS** score)

APPENDIX C. BPI-SF (2009 CHARLES S. CLEELAND)

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: ____

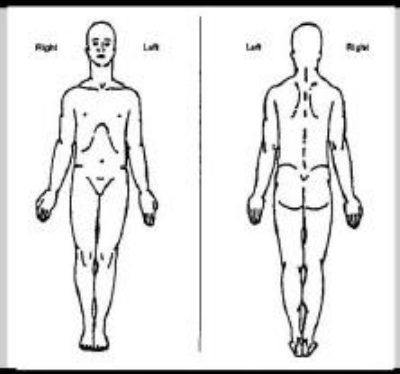
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

Scoring Guidelines:

Pain Severity Score = mean of items 3-6 (pain at its worst, pain at its least, pain on the average, pain for right now)

Pain Interference Score = mean of items 9A-9G (interference of pain with: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life).

APPENDIX D. EQ-5D-5L (VERSION 3.0)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES (*e.g. work, study, housework, family or leisure activities*)

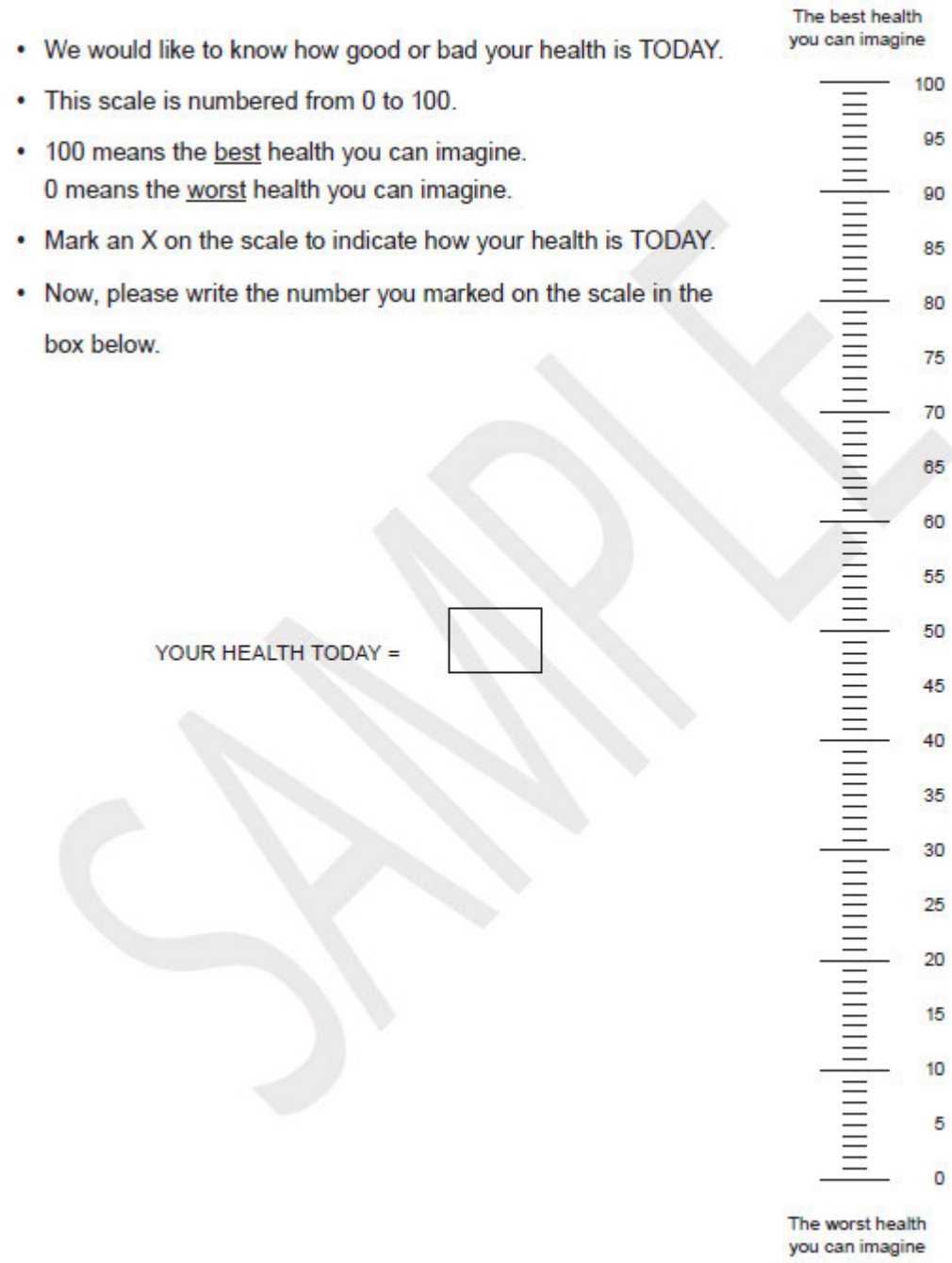
I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑



EuroQol/EQ-5D is a standardized, reliable and validated instrument to measure quality of life. It consists of the EQ-5D descriptive system and the EQ Visual Analogue scale (EQ VAS).

The EQ-5D 5 level version (EQ-5D-5L) descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: level 1 (no problems), level 2 (slight problems), level 3 (moderate problems), level 4 (severe problems), and level 5 (extreme problems).

A total of 3125 health states are possible. Each state is referred to in terms of a 5-digit code. For example, state 11111 indicates no problem on any of the 5 dimensions, while state 12345 indicates no problems with mobility, slight problems with self-care, moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression. There should be only one response for each dimension and missing values will be coded as 9. If 2 levels are selected for a dimension, the dimension will be treated as missing.

The health state can be summarized to be a single number (5-digit code), or represented by a single summary number (index value), which reflects how good or bad a health state is according to the preferences of the general population of a country/region.

An EQ-5D summary index is derived by applying a formula that attaches values (weights) to each of the levels in each dimension. The index is calculated by deducting the appropriate weights from 1, the value for full health (i.e. state 11111). The collection of index values (weights) for all possible EQ-5D health states is called a value set. Most EQ-5D value sets have been obtained from a standardized valuation exercise, in which a representative sample of the general population in a country/region is asked to place a value on EQ-5D health states.

The EQ VAS records the subject's self-rated health state on a 100-point vertical, visual analogue scale (0 = worst imaginable health state; 100 = best imaginable health state).

APPENDIX E. DETERMINATION OF RADIOGRAPHIC DISEASE PROGRESSION DEFINED BY THE CRITERIA

The documentation required for the determination of radiographic disease progression in both bone and soft tissue is listed in Table 7, and a flow diagram for assessment of bone scans to declare disease progression in bone per PCWG3 after the week 9 scan is provided in Figure 2 . Tumor assessments will be performed every 8 weeks for the first 6 months and then every 12 weeks thereafter, starting after cycle 7 until radiographic disease progression is seen.

Table 7: Determination of Radiographic Evidence of Disease Progression

Date Progression Detected (Visit)[a]	Criteria for Progression	Criteria for Confirmation of Progression (requirement and timing)	Criteria for Documentation of Disease Progression on Confirmatory Scan
Week 9 (Cycle 3 Day 1 [±7 days])	Bone lesions; 2 or more new lesions compared to **baseline** bone scan by PCWG3	Timing: at least 6 weeks after progression identified or at week 17 visit[b].	Two or more new bone lesions on bone scan (compared to week 9 scan).
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1	No confirmatory scan required for soft tissue disease progression.	n/a
Week 17 (Cycle 5 Day 1 [±7 days])	Bone lesions: Two or more new lesions on bone scan compared to week 9 bone scan.	Timing: at least 6 weeks after progression identified or at week 25 visit. Required for bone lesions observed on bone scan[b].	Persistent[c] or increase in number of bone lesions on bone scan compared to week 9 scan.
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1.	No confirmatory scan required for soft tissue disease progression.	n/a
Week 25 (Cycle 7 Day 1 [±7 days]) or later	Bone lesions: Two or more new lesions compared to week 9 bone scan.	Timing: at least 6 weeks after progression identified. Required for bone lesions observed on bone scan[b].	Persistent[c] or increase in number of lesions on bone scan compared to week 9 scan.
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST 1.1.	No confirmatory scan required for soft tissue disease progression.	n/a

Abbreviations: CT = computed tomography; RECIST = Response Evaluation Criteria in Solid Tumors; MRI = magnetic resonance imaging; n/a = not applicable; PCWG3 = Prostate Cancer Clinical Trials Working Group 3.

[a] Progression detected by bone scan at an unscheduled visit either prior to week 9 or between scheduled visits will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan.

[b] Confirmation must occur at the next available scan.

[c] For confirmation, at least two of the lesions first identified as new must be present at that next available scan (confirmation scan).

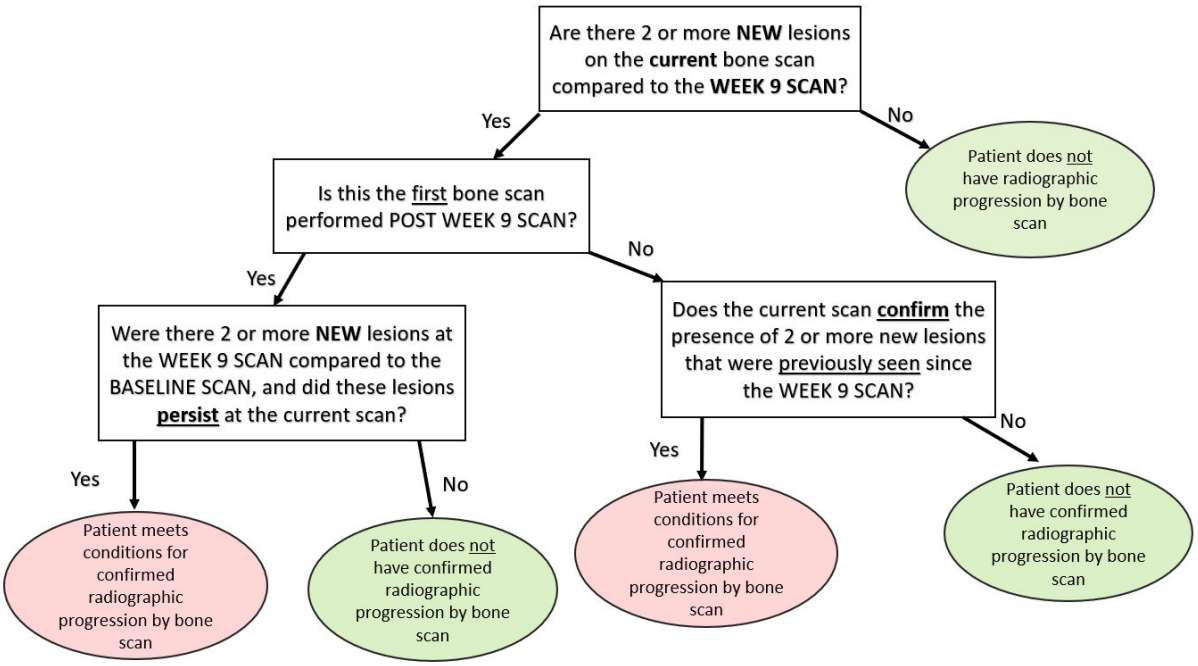
APPENDIX F. COMMON CONVENSIONS

- 1 pound = 0.454 kg
- 1 inch = 2.54 cm
- 1 year = 365.25 days. Year is calculated as (days / 365.25) and will be rounded up to 1 significant digit for purposes of presentation
- 1 month = 30.4375 days. Month is calculated as (Days / 30.4375) and will be rounded up to 1 significant digit for purposes of presentation
- Body mass index (BMI) calculated as [weight (kg)/height $(m)^2$]
- Dates, time, and date/time fields will be displayed in data listings in ISO 8601 formats
- Change from baseline = Value at Visit X – Baseline Value
- Percent change from baseline = 100 × (Value at Visit X – Baseline Value) / Baseline Value
- Data from all centers will be pooled for analyses.
- Confidence Interval (CI) will be presented as 2-sided 95% CI.
- Safety data will not be imputed except for incomplete dates associated with AEs and medications (rules in Appendix A) and missing severity or relationship (rules in Section <X.Y>).
- Missing response data will be handled as described in Section 8 .
- Summary statistics will include the number and percentage of subjects in each category for discrete variables and the number of observations (available data), mean, median, standard deviation (SD), minimum, and maximum for continuous variables.
- When the denominator includes subjects with missing values, a “missing” category may be added for completeness and displayed last in the category summary.
- Time-to-event statistics will include the median, , provided they are estimable.
- In summary tables of continuous variables (except for weight, height and BMI), the minimum and maximum values will be displayed to the same number of decimal places as the raw data; all mean, median, and percentile values will be formatted to one more decimal place than the measured value. SD values will be formatted to two more decimal places than the measured value, unless otherwise specified. The maximum number of decimal places is 3 and values will be truncated to 3 decimal places in situations where there are more than 3 decimal places. Wherever possible data will be decimal aligned. For weight, height and BMI, only one decimal place will be kept for summary results (except N).
- All percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form XX.X (XX.X%).
- Post Baseline Duration in days = end date – start date + 1 (divide by 7 to convert to weeks, divide by 30.4375 to convert to months, and divide by 365.25 to convert to years; round result to 1 decimal place).

- Listings typically will be sorted by study phase, study treatment, subject identification number (concatenated site and subject number), visit, date, and time, if collected.
- P-values, if applicable, will be presented to 3 decimal places. If the rounded result is a value of 1.000, it will be displayed as > 0.999.

Any date in the listings will use the *date9.* format, for example, 07MAY2002.

Figure 2: Post Week 9 Bone Scan Assessment Flow Diagram



Note: Progression detected by bone scan at an unscheduled visit after week 9 will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the diagram.

Study films (CT/MRI and bone scan) should be read on-site using PCWG3 and RECIST 1.1 guidelines and also be submitted in a digital format for a blinded independent central radiology review.