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Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for A Phase I, Open-Label, Dose-Finding Study of GSK2636771 Administered in Combination with Enzalutamide (Xtandi) in Male Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC)
Compound Number	:	GSK2636771
Effective Date	:	03-MAR-2020

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 2013N172718_04.
- This RAP is intended to describe the safety, efficacy and pharmacokinetic analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

RAP Author(s):

Author	Date
Lead PPD Statistician (Oncology, Clinical Statistics)	
Co-Authors PPD Clinical Pharmacology Manager (Oncology, CPMS)	17-FEB-2020
PPD Clinical Biomarker Lead (Oncology, Biomarkers)	17-FEB-2020

RAP Team Review Confirmations (Method: E-mail)

Reviewer	Date
PPD Clinical Development Director (Oncology)	17-FEB-2020
PPD Principal Programmer/Analyst (Oncology, Clinical Programming)	18-FEB-2020

Clinical Statistics and Clinical Programming Line Approvals (Method: Pharma TMF eSignatures)

Approver	Date
PPD Senior Statistics Director (Oncology, Clinical Statistics)	e-signature
PPD Programming Manager (Oncology, Clinical Programming)	e-signature

TABLE OF CONTENTS

PAGE

1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol 200331:

Revision Chronology:		
2013N172718_00	22-May-2014	Original
2013N172718_01	08-Sep-2014	Amendment 1 incorporates changes to Section 5.2, Permanent Discontinuation of Study Treatment(s) for clarification as requested by the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom.
2013N172718_02	26-Feb-2015	Amendment 2 incorporates changes to list of authors and primary medical monitor (contact information) due to changes in personnel assignment within GSK; list of abbreviations was revised appropriately based upon addition/deletion of abbreviated terms used throughout the protocol; Time and Events Tables were revised for clarification of assessments and procedures to be performed and to reflect changes made throughout the body of the protocol.
2013N172718_03	24-Jun-2016	Amendment 3 incorporates changes to update the risk assessment section and to include additional requirements for monitoring of renal events following an INDSR report for Acute Renal Failure in a subject enrolled in this study. In addition, it was clarified that subjects with disease progression defined by PSA progression alone or for the worsening of an isolated disease site that is not clinically significant are not required to discontinue treatment in the study. Separate definitions for disease progression as a study endpoint and disease progression mandated by the protocol to result in a subject being withdrawal from treatment is clarified. Optional pharmacodynamics paired biopsies as well as clarifications around biomarker assessments were added to the Time and Events tables for the Dose Escalation and Dose Expansion Phases. Additional language was added to clarify that the decision to terminate the Dose Expansion Phase will take into account all relevant factors, including but not solely based upon the statistical methodology and futility criterion. Other minor clarifications and corrections of inadvertent errors were also added.
2013N172718_04	27-Jan-2017	Amendment 4 was completed to include additional requirements for monitoring of events related to calcium results, including revisions to the Table & Events to clarify additional laboratory testing requirements; clarification of secondary clinical activity endpoints and update to associated statistical section(s); revision of clinical activity population allowing the combination of dose escalation and dose

Revision Chronology:		
		expansion populations; revision of dose escalation and dose expansion wording to allow multiple dose levels in dose expansion to establish RP2D after dose expansion phase; adjustment to Week 12 visit window and clarification for Week 12 assessment timing; revision to reflect current indication for enzalutamide throughout; clarification of study populations; clarification of bone progression definition. Other minor clarifications and corrections of inadvertent errors were also added.

All data displays (Tables, Figures & Listings) will use the term "Subject" which reflects CDISC and GSK Data Display Standards terminology.

1.1. RAP Amendments

Revision chronology:

RAP Section	**Amendment Details**
Reporting and Analysis Plan_200331_Final_V1 [02-Dec-2019]	
Reporting and Analysis Plan_200331_Amendment_Final_V1	
7.2.	Removed references to PCWG2 modification of RECIST since it was not required in the protocol. • Removed the text "PCWG2 modified" prior to "RECIST" throughout the section. • Removed the text "Additional requirement (per PCWG2) that progression at first assessment be confirmed by a second scan 6 or more weeks later" from the RECIST response (at 16 weeks) in Table 2.
7.2.1.2.	• Added the following text to Table 4 to clarify the definition of Bone Response (at week 12): "This algorithm assumes subjects had bone lesions identified via bone scan at baseline. For subjects without bone lesions identified via Bone Scan at baseline, the confirmed and unconfirmed bone responses are set to missing."
7.2.1.3.	• Removed the following text from the RECIST response as was not required in the protocol: "with the added PCWG2 requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later."
7.2.1.4.	• Added additional 12 scenarios to Table 5 to clarify the Overall Response at week 12.These scenarios take into account subjects with no baseline bone lesions identified via bone scan.
7.3.1.	• Removed the text "PCWG2 modified" prior to "RECIST" throughout the section as was not required in the protocol.
9.2.1.1.	• Clarified the description of the how the secondary objectives will be displayed.
13.12.9., 13.12.10., 13.12.14.	• Added clarifying text to the titles of the PK tables/figures/listings

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol amendment 4 (Dated: 27-Jan-2017) are outlined in Table 1. These exploratory endpoints were unlikely to provide any additional information to what would be provided by the other endpoints.

Table 1 Exploratory Endpoints Removed from Protocol Defined Analysis Plan

Protocol		Reporting & Analysis Plan	
objective	**endpoint**	**Statistical Analysis Plan**	**Rationale for Changes**
• Evaluation of biomarkers in CTCs that may predict response to combination	• AR expression, PTEN FISH and other genomic evaluations in CTCs	• removed	• analysis not performed since no response was identified
• Evaluation of tumor tissue to explore explanation for the mechanism of resistance to combination therapy	• Based on analysis of DNA, RNA and proteins from tumour tissue obtained at time of progression after initially responding to combination therapy	• removed	• paired biopsies were not obtained
• To determine pharmacodynamic effects of drug treatment	• RNA/protein analysis of pre/post treatment tumour biopsies	• removed	• paired biopsies were not obtained

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To assess the safety and tolerability of GSK2636771 + enzalutamide administered orally once daily continuously in subjects with mCRPC.	• AEs, SAEs, DLTs, and changes in laboratory values, ECGs, and vital signs (BP, temperature and heart rate)
• To determine the RP2D of orally administered GSK2636771 + enzalutamide in subjects with mCRPC.	• Safety and tolerability as assessed by AEs, SAEs, DLTs, and changes in laboratory values, ECGs, and vital signs (BP, temperature and heart rate)

Objectives	Endpoints
• To evaluate lack of progression in the dose expansion subjects with mCRPC by rate of subjects who do not progress for 12 weeks	• Non-Progressive Disease (Non-PD) rate for 12 weeks according to PCWG2 criteria (either by RECIST 1.1, or progression in bone or PSA progression with accompanying progression by RECIST 1.1 or bone scan when baseline radiological or bone disease present or PSA progression if no other baseline disease).
Secondary Objectives	**Secondary Endpoints**
• To evaluate the clinical activity of oral GSK2636771 + enzalutamide in the treatment of mCRPC (PTEN deficient)	• PSA50 response rate defined as the percent of subjects achieving PSA50 at 12 weeks or thereafter (PSA50 is ≥50% decrease in PSA from baseline) • Objective Response Rate (ORR) defined as complete response (CR) rate plus partial response (PR) rate per RECIST 1.1 • Time to PSA progression according to PCWG2 criteria • Time to radiological progression according to PCWG2 criteria (either by RECIST 1.1, PSA progression and/or progression in bone) • Radiological progression free survival (rPFS) per RECIST1.1 and/or bone scans
• To determine the effect of GSK2636771 on enzalutamide PK following repeat-dose oral administration.	• Plasma concentrations of enzalutamide and N-desmethyl enzalutamide.
• To determine the PK of GSK2636771 in the presence of enzalutamide.	• Blood GSK2636771 concentrations.
Exploratory Objectives	**Exploratory Endpoints**
• To determine the frequency of PTEN deficiency in subjects with mCRPC	• Frequency of PTEN-deficient mCRPC reported in subjects based on pre-screened tumours
• To determine the mechanism of PTEN deficiency	• PTEN deletion, mutation or promoter methylation
• To identify additional biomarkers (DNA, RNA or protein based) in tumour or in circulation that may predict response to oral GSK2636771 + enzalutamide	• Response prediction biomarkers based on analysis of DNA, RNA, and proteins from surrogate tissues (e.g., cfDNA) and/or tumour tissue
• To determine the effect of enzalutamide with GSK2636771 on the kinetics of tumour growth	• Longitudinal tumour size measurements; serum PSA levels, change from baseline in CTCs

Objectives	Endpoints
• Evaluation of biomarkers in CTCs that may predict response to combination	• AR expression, PTEN FISH and other genomic evaluations in CTCs
• Evaluation of tumour tissue to explore explanation for the mechanism of resistance to combination therapy	• Based on analysis of DNA, RNA and proteins from tumour tissue obtained at time of progression after initially responding to combination therapy
• To determine pharmacodynamic effects of drug treatment	• RNA/protein analysis of pre/post treatment tumour biopsies

2.3. Study Design

<table>
<tr><th colspan="2">Overview of Study Design and Key Features</th></tr>
<tr><td>Design Features</td><td>

Dose Escalation Phase of the study is to determine the maximum tolerated dose (MTD) and select a recommended dose for Dose Expansion Phase or a recommended Phase 2 dose (RP2D) based on the safety, pharmacokinetic, and pharmacodynamic profiles observed after combination therapy of GSK2636771 and enzalutamide. Any cohort may be expanded up to 12 subjects in order to collect adequate data on safety, PD or PK.
Dose Expansion Phase: This phase of the study will evaluate the long-term safety of the combination treatment as well as the 12-week non-progressive disease (PD) rate of the combination treatment in subjects with mCPRC. To confirm dose(s) identified during dose escalation, multiple dose levels of GSK2636771 in combination with enzalutamide may be examined during dose expansion, with each dose level cohort enrolling up to 20 subjects.

</td></tr>
<tr><td>Dosing</td><td>The planned starting dose of study treatment will be GSK2636771 300 mg orally once daily in combination with enzalutamide 160 mg orally once daily. Participants will begin combination therapy only after completing a 14-day run-in period of enzalutamide monotherapy 160 mg orally once daily. Dose escalations will be performed in Dose Escalation Phase and dose adjustments are allowed to address tolerability and safety issues.
<table>
<tr><th>Cohort</th><th>N</th><th>GSK2636771</th><th>Enzalutamide</th></tr>
<tr><td>-1</td><td>3 - 6</td><td>200 mg once daily</td><td>160 mg once daily</td></tr>
<tr><td>1</td><td>3 - 6</td><td>300 mg once daily</td><td>160 mg once daily</td></tr>
<tr><td>2</td><td>3 - 6</td><td>400 mg once daily</td><td>160 mg once daily</td></tr>
</table>
</td></tr>
<tr><td>Treatment Assignment</td><td>

This is a non-randomized open-label study.

</td></tr>
<tr><td>Interim Analysis</td><td>

No formal interim analyses will be performed at Dose Escalation Phase. Available safety data will be reviewed and summarized on an ongoing basis. Review of preliminary safety data from all available dose cohorts will be performed in each study treatment combination before starting a new dose cohort and before selecting a dose level for expansion.
Futility will be evaluated when there is adequate enrolment; this analysis may occur using the combination of the dose escalation and dose expansion population.

</td></tr>
</table>

2.4. Statistical Hypotheses / Statistical Analyses

No formal statistical hypothesis will be tested during dose escalation phase. All analyses will be descriptive and exploratory.

For dose expansion phase, the 12-week non-PD rate will be tested using the predictive probability design by Lee and Liu (Lee, 2008). The null and alternative hypotheses for the non-PD rate are as follows:

H0: $p \leq 5.0\%$
HA: $p > 30\%$.

This hypothesis will be tested using a combination of data provided in both the dose escalation and dose expansion phases.

3. PLANNED ANALYSES

3.1. Interim Analyses

3.1.1. Dose Escalation Phase

In the Dose Escalation Phase, available safety data will be reviewed and summarized on an ongoing basis. Review of preliminary safety data from all available dose cohorts will be performed in each study treatment combination before starting a new dose cohort and before selecting a dose level for expansion. Safety will be reviewed on an ongoing basis by the Safety Monitoring Team, composed of study investigators and key GSK personnel including the medical monitor, study manager, and study statistician.

3.1.2. Dose Expansion Phase

After the initial 10 subjects become evaluable at a dose level using a combination of dose escalation and dose expansion subjects, 12-week non-PD rate will be reviewed on an ongoing basis and the number of responses observed will be compared with the stopping rules provided below.

3.2. Final Analyses

The final planned primary and secondary analyses will be performed after the completion of the following sequential steps:

1. All participants have completed or withdrawn from the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Screened	• This population will consist of all subjects who were screened for PTEN status and enrolment of study	• Summary of study eligibility and PTEN status
All Treated Safety	• This population will consist of all subjects who receive at least one dose of GSK2636771 or Enzalutamide.	• Safety
All Treated Clinical Activity	• This population will consist of all subjects who received at least one dose of GSK2636771.	• Clinical Activity
Modified All Treated Clinical Activity	• This population will consist of all subjects in All Treated Clinical Activity who were treated at the same dose as the dose expansion cohort and have been on study drug for at least 12 weeks or have discontinued study treatment due to disease progression, died, or withdrawn for any reason.	• Evaluation of non-PD rate
All Evaluable Subjects	• This population will consist of all subjects from All Treated Clinical Activity Population who have at least one post-dose disease assessment and have been exposed to study drug for at least 12 weeks or have progressed or have died or have withdrawn from the study for any reason	• Dose Escalation & Expansion futility analyses
PK Concentration Population	• This population will consist of all subjects in the All Treated Safety Population for whom a blood sample for pharmacokinetics is obtained, analysed, and was measurable.	• Listing, summary, and figures of PK concentration
Biomarker Population	• This population will consist of subjects in the All Treated Safety Population for whom a sample was obtained and analyzed for biomarkers	• PTEN deletion and gene mutation • CTC conversion

NOTES :

- Please refer to Appendix 12: List of Data Displays which details the population to be used for each display being generated.

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

- Data will be reviewed prior to freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Participants will be listed and summarized based on their treatment group initially assigned regardless of any dose modifications that may occur following treatment initiation.

Treatment Group Descriptions				
RandAll NG		**Data Displays for Reporting**		
Code	**Description**	**Description**	**Data Display**	**Order in TLF**
A	Enzalutamide	Run-in Enzalutamide	Run-in Enza	1
B	GSK2636771 + Enzalutamide	GSK2636771 200mg/ Enzalutamide 160mg Escalation	GSK 200mg / Enza 160mg Escalation	2
		GSK2636771 200mg/ Enzalutamide 160mg Expansion	GSK 200mg / Enza 160mg Expansion	3
		GSK2636771 200mg/ Enzalutamide 160mg Overall	GSK 200mg / Enza 160mg Overall	4
		GSK2636771 300mg/ Enzalutamide 160mg Escalation	GSK 300mg / Enza 160mg Escalation	5
		GSK2636771 400mg/ Enzalutamide 160mg Escalation	GSK 400mg / Enza 160mg Escalation	6

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest GSK2636771 pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first GSK2636771 dose and used as baseline.

For laboratory data, baseline will be the latest non-missing pre-dose value from central lab. If no central lab value is available, the latest non-missing pre-dose value from local lab will be used. If there are multiple assessments on the same day, the mean will be used as the baseline value.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.3. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
13.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
13.5	Appendix 5: Data Display Standards & Handling Conventions
13.6	Appendix 6: Derived and Transformed Data
13.7	Appendix 7: Reporting Standards for Missing Data
13.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the All Treated Safety population, unless otherwise specified.

Study population analyses including analyses of subject's disposition, demographic and baseline characteristics, protocol deviations, substance use, past and current medical conditions, disease characteristics at initial diagnosis and at screening, prior and follow-up anti-cancer therapy, cancer-related surgical procedures, concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 12: List of Data Displays.

6.1.1. Disposition of Subjects

A summary of the number of subjects in each of the dosing groups/phases will be provided. A listing of subjects excluded from analysis populations will also be provided.

A summary of subject status and reason for study withdrawal will be provided. This display will show the number and percentage of subjects who withdrew from the study, including primary reasons for study withdrawal. Reasons for study withdrawal will be presented in the order they are displayed in the eCRF.

A summary of study treatment status will be provided. This display will show the number and percentage of subjects who are completed or discontinued study treatment and a summary of the primary reasons for discontinuation of study treatment. Reasons for study treatment discontinuation will be presented in the order they are displayed in the eCRF. A listing of study treatment discontinuation will be generated. The listing will include last dose date and reasons for study treatment discontinuation as well as study part of discontinuation.

A table of study eligibility information will be provided based on All Pre-screened and Screened population. Number of subjects who were pre-screened for PTEN status and/or screened for enrolment, reasons of failure, subjects PTEN status etc. will be presented.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics (e.g. age, race, ethnicity, sex, baseline height, and baseline body weight) will be summarized and listed. In addition, age will also be categorized and summarized by two groups of categories, <18, 18-64, 65-74, >74 and <18-64, 65-84; >=85 for Development Safety Update Report and Europe Clinical Trial Registry disclosure, respectively. The count and percentage will be computed for sex and ethnicity.

Race and racial combinations will be summarized and listed.

Medical conditions will be summarized by past and current categories.

Disease history and characteristics (primary tumor type, lesion status, time since initial diagnosis in weeks, stage at initial diagnosis and screening, time since last progression in weeks) will be listed. Separate summaries of disease characteristics at initial diagnosis and screening will be provided.

Prior anti-cancer therapy will be coded using GSK Drug coding dictionary, then summarized by type of therapy and listed. A listing of prior anti-cancer therapy will show the relationship between Anatomical Therapeutic Chemical (ATC) Level 1, Ingredient, and verbatim text.

A summary of prior anti-cancer therapies will be provided. The number of lines of prior anti-cancer therapies and radiotherapy will be tabulated. Number of subjects who received Enzalutamide before or after chemotherapy will be provided. Summary of cancer-related surgeries will be produced. A summary of the best response to the most recent prior anti-cancer therapy will also be provided.

Substance use, including smoking history and alcohol use, will also be summarized and listed.

6.1.3. Treatment Compliance

A listing of planned and actual treatments will be produced including number of tablets prescribed per day and total number of tablets dispensed.

In addition, summaries of study treatment exposure by Enzalutamide run in and combination treatment with GSK2636771 and dose modifications (e.g. number of dose reductions, number of dose interruptions) will further characterize compliance.

6.1.4. Concomitant Medications

Concomitant medications will be coded using GSK Drug coding dictionary, summarized, and listed. The summary of concomitant medications will show the number and percentage of subjects taking concomitant medications by Ingredient. Multi-ingredient products will be summarized by their separate ingredients rather than as a combination of ingredients.

In the summary of concomitant medications, each subject is counted once within each unique ingredient. For example, if a subject takes Amoxycillin on two separate occasions, the subject is counted only once under the ingredient “Amoxycillin”. In the summary of concomitant medications, the ingredients will be summarized by the base only, using CMBASECD and CMBASE.

A summary of the relationship between concomitant medications and reasons of the medications will be generated.

Blood products or blood supportive care products will be listed.

6.1.5. Subsequent Anti-Cancer Therapies

The number and percentage of subjects that received chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radioactive therapy, small molecule targeted therapy, radiotherapy and cancer-specific surgery as post study treatment (see Section 13.4.1 for definition) anti-cancer therapy will be summarized. Time from study treatment discontinuation to the first post study anti-cancer therapy will also be included in this summary table.

Follow-up anti-cancer therapy will be coded using GSK Drug coding dictionary, then summarized by ingredient. A listing of the type of follow-up anti-cancer therapy received (chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radioactive therapy, small molecule targeted therapy, radiotherapy and cancer-specific surgery and details of the anticancer therapy for each subject will be provided.

7. EFFICACY ANALYSES

7.1. Overview of Planned Efficacy Analyses

The primary efficacy analyses will be based on the All Treated Clinical Activity Population, unless otherwise specified, and all summaries and data listings will use treatment labels as specified in Section 5.1. All summaries will be presented by dose, and overall.

7.2. Primary Efficacy Analyses

This analysis is to determine whether the 12-week non-PD rate is greater than 5%. The 12-week non-PD rate is defined as the percentage of subjects without progression (non-PD) at Week 12 as determined from PSA results, radiographic assessment per RECIST 1.1, and bone scan (see Section 7.2.1.4 for algorithm details). The PSA and bone scan results recorded at week 12 will be used for the evaluation of 12-week non-PD rate. Radiological assessments (CT/MRI) of target and non-target lesions at week 16 (instead of week 12) will be considered for the evaluation of week 12 non-PD rate since there were no week 12 radiological assessments scheduled for subjects during the study.

The disease progression is defined by 1 or more of the following criteria:

- PSA progression alone if no other baseline disease
- PSA progression according to the PCWG2 criteria with accompanying progression by RECIST 1.1 or bone scan for subjects with soft tissue baseline disease
- Bone progression on bone scan according to the PCWG2 criteria [measured by bone scan]
- Radiographic progression in soft tissue or bone by RECIST 1.1 for subjects with baseline disease.

The components of the 12 week non-PD rate primary efficacy endpoint are defined in Table 2. Additional details on these endpoints and composite 12-week non-PD rate are provided in Section 7.2.1 through Section 7.2.4.

Table 2 Components of the 12 week Non-PD Rate

Primary Efficacy endpoint	Definition
PSA Response (at 12 weeks)	**Progression Definition (per PCWG2)*:** • *If there has been a decline from baseline:* time from start of therapy to first PSA increase that is ≥25% and ≥2 ng/mL in absolute value from the nadir, and which is confirmed by a second value 3 or more weeks later (i.e., a confirmed rising trend) at least 12 weeks after the start of combination treatment • *If there has NOT been a decline from baseline:* time from start of therapy to first PSA increase that is ≥25% and ≥2 ng/mL in absolute value from the baseline value, determined at least 12 weeks after start of combination treatment • See Section 7.2.1 for additional details on response
Bone Response (at 12 weeks)	**Progression Definition (per PCWG2)*:** The appearance of ≥2 new lesions, and, for the first reassessment only, a confirmatory bone scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions. The date of progression is the date of the first scan that shows a minimum of 2 additional new lesions. • See Section 7.2.2 for additional details on response.
RECIST Response (at 16 weeks)	**Progression Definition (per RECIST v1.1)*:** At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 mm. The date of PD is the date of the first scan that shows progression. Progression is also defined as unequivocal progression in non-target lesions or identification of unequivocal new lesions. • See Section 7.2.3 for additional details on response.

*[**Scher**, 2008]

7.2.1. Endpoint / Variables

7.2.1.1. PSA Response (at week 12)

Determination of PSA response at week 12 is based on PCWG2 criteria. The algorithm is outlined in the Table 3. The response is categorized into progression (PD), non-PD, or not evaluable (NE).

Table 3 Assessment of PSA Response

Visit				
Week 8 (or any visit < 12 weeks)	**Week 12***	**Week 16 (or visit ≥3 weeks after week 12)**	**Response (Confirmed)**	**Response (unconfirmed)**
PSA less than baseline	PSA increase that is ≥25% and ≥2 ng/mL in absolute value from the nadir (or week 8 visit)	PSA ≥ week 12 visit	PD	PD
PSA NOT less than baseline	PSA increase that is ≥25% and ≥2 ng/mL in absolute value from the baseline	Any	PD	PD
Missing	PSA increase that is ≥25% and ≥2 ng/mL in absolute value from the baseline	PSA ≥ week 12 visit	PD	PD
PSA less than baseline	PSA increase that is ≥25% and ≥2 ng/mL in absolute value from the nadir	Results present, PSA < week 12 value (rising trend not confirmed by PSA)	Non-PD	PD
PSA less than baseline	PSA increase that is <25% or <2 ng/mL in absolute value from the nadir	Any	Non-PD	Non-PD
PSA NOT less than baseline or is missing	PSA increase that is <25% or <2 ng/mL in absolute value from the baseline	Any	Non-PD	Non-PD
PSA less than baseline	PSA increase that is ≥25% and ≥2 ng/mL in absolute value from the nadir (or week 8 visit)	missing	NE	PD
Missing	PSA increase that is ≥25% and ≥2 ng/mL in absolute value from the baseline	PSA < week 12 visit	Non-PD	PD
Missing	PSA increase that is ≥25% and ≥2 ng/mL in absolute value from the	missing	NE	PD

Visit				
Week 8 (or any visit < 12 weeks)	**Week 12***	**Week 16 (or visit ≥3 weeks after week 12)**	**Response (Confirmed)**	**Response (unconfirmed)**
	baseline			
Results available at week 8 and 12 but do not meet PD definition		Any	Non-PD	Non-PD
If conditions above not met		Any	NE	NE

* 12 week visit window is defined as follows: If visit occurred under amendment 3, use 78 days ± 3 days; if visit occurred under amendment 4, use window of 78 days + 5 days.

Note: PSA response of "Any" includes scenarios where results are present and/or missing.

7.2.1.2. Bone Response (at week 12)

The determination of bone response at week 12 is based on PCWG2 criteria for bone progression (Table 2). The algorithm defining the response is outlined in Table 4. The response is categorized into progression (PD), non-PD, not evaluable (NE), and missing.

Table 4 Bone Response Algorithm (based on bone scan results) +

First post-baseline bone scan prior to 12 weeks?	Week 12 visit*	Secondary Assessment (at least 6 weeks after week 12 visit)	Bone Response (confirmed)	Bone Response (unconfirmed)
No	≥ 2 new lesions	≥ 2 new lesions	PD	PD
No	≥ 2 new lesions	< 2 new lesions	non-PD	PD
No	< 2 new lesions	≥ 2 new lesions	non-PD	Non-PD
No	< 2 new lesions	< 2 new lesions	non-PD	Non-PD
No	not done/missing	Any	Not Evaluable	Not Evaluable
No	≥ 2 new lesions	not done/missing	Not Evaluable	PD
No	< 2 new lesions	any	Non-PD	Non-PD
No	Not done/missing	any	Not Evaluable	Not Evaluable
No	not done/missing	not done/missing	Not Evaluable	Not Evaluable
Yes	≥ 2 new lesions	Any (confirmation not required since first bone scan was prior to 12 weeks)	PD	PD

First post-baseline bone scan prior to 12 weeks?	Week 12 visit*	Secondary Assessment (at least 6 weeks after week 12 visit)	Bone Response (confirmed)	Bone Response (unconfirmed)
Yes	< 2 new lesions	Any	non-PD	Non-PD
Yes	not done/missing	Any	Not Evaluable	Not Evaluable

* 12 week visit window is defined as follows: If visit occurred under amendment 3, use 78 days ± 3 days; if visit occurred under amendment 4, use window of 78 days + 5 days.

+This algorithm assumes subjects had bone lesions identified via bone scan at baseline. For subjects without bone lesions identified via Bone Scan at baseline, the confirmed and unconfirmed bone responses are set to missing.

7.2.1.3. RECIST Response

The determination of confirmed (and unconfirmed) radiographic response (PR, CR, and PD) at week 12 is based on RECIST v1.1 criteria (Table 1). The algorithm is well defined in the RECIST guidelines (Eisenhauer, 2009). Categories for response include: PD, non-PD (CR, PR, SD, or non-CR/non-PD), NE, and missing (only if no baseline measurable/non-measurable lesions present). The unconfirmed response will also be assessed.

According to PCWG2 criteria, radiological response at week 12 for subjects with baseline disease will be determined by RECIST 1.1 criteria assessed 12 weeks following initiation of GSK2636771 and enzalutamide combination treatment. Since CT/MRI tumour assessments were not scheduled at week 12, the week 16 assessments or the closest unscheduled CT/MRI assessment after week 12 will be used for week 12 RECIST response evaluation.

7.2.1.4. Overall Response (at week 12)

The overall response at week 12 will be used to determine the 12-week non-PD rate. Table 5 provides the algorithm for the derivation of the overall response assessed at 12 weeks post treatment for subjects with or without measurable disease at baseline.

Table 5 Algorithm for Overall Response at Week 12

Measurable/Non-Measurable Disease Identified at baseline?	RECIST Response (RECIST 1.1)	Bone Response at Week 12	PSA Response at Week 12	Overall Response at Week 12 (PD/non-PD/NE)
Yes	PD	PD	PD	PD
Yes	PD	PD	Non-PD	PD
Yes	PD	PD	NE	PD
Yes	PD	Non-PD	PD	PD

Measurable/Non-Measurable Disease Identified at baseline?	RECIST Response (RECIST 1.1)	Bone Response at Week 12	PSA Response at Week 12	Overall Response at Week 12 (PD/non-PD/NE)
Yes	PD	Non-PD	Non-PD	PD (via target lesion)
Yes	PD	Non-PD	NE	PD (via target lesions)
Yes	PD	NE (missing data)	PD	PD
Yes	PD	NE (missing data)	Non-PD	PD (via target lesions)
Yes	PD	NE (missing data)	NE	PD (via target lesions)
Yes	PD	no baseline bone lesions	PD	PD
Yes	PD	no baseline bone lesions	Non-PD	PD (via target lesions)
Yes	PD	no baseline bone lesions	NE	PD (via target lesions)
Yes	Non-PD	PD	PD	PD
Yes	Non-PD	PD	Non-PD	PD
Yes	Non-PD	PD	NE	PD
Yes	Non-PD	Non-PD	PD	Non-PD
Yes	Non-PD	Non-PD	Non-PD	Non-PD
Yes	Non-PD	Non-PD	NE	Non-PD
Yes	Non-PD	NE (missing data)	PD	NE
Yes	Non-PD	NE (missing data)	Non-PD	NE
Yes	Non-PD	NE (missing data)	NE	NE
Yes	Non-PD	no baseline bone lesions	PD	Non-PD
Yes	Non-PD	no baseline bone lesions	Non-PD	Non-PD
Yes	Non-PD	no baseline bone lesions	NE	Non-PD
Yes	NE	PD	PD	PD
Yes	NE	PD	Non-PD	PD
Yes	NE	PD	NE	PD
Yes	NE	Non-PD	PD	NE
Yes	NE	Non-PD	Non-PD	NE
Yes	NE	Non-PD	NE	NE
Yes	NE	NE (missing data)	PD	NE
Yes	NE	NE (missing data)	Non-PD	NE
Yes	NE	NE (missing data)	NE	NE
Yes	NE	no baseline bone	PD	NE

Measurable/Non-Measurable Disease Identified at baseline?	RECIST Response (RECIST 1.1)	Bone Response at Week 12	PSA Response at Week 12	Overall Response at Week 12 (PD/non-PD/NE)
		lesions		
Yes	NE	no baseline bone lesions	Non-PD	NE
Yes	NE	no baseline bone lesions	NE	NE
No	-	PD	PD	PD
No	-	PD	Non-PD	PD
No	-	PD	NE	PD
No	-	Non-PD	PD	PD
No	-	Non-PD	Non-PD	non-PD
No	-	Non-PD	NE	non-PD
No	-	NE (missing data)	PD	PD
No	-	NE (missing data)	Non-PD	Non-PD
No	-	NE (missing data)	NE	NE
No	-	no baseline bone lesions	PD	PD
No	-	no baseline bone lesions	Non-PD	Non-PD
No	-	no baseline bone lesions	NE	NE

Note: "-" = "missing response"

For subjects without measurable/non-measurable disease in baseline, the overall response will be determined on PSA response alone.

Subjects with unknown or missing responses will be treated as having PD (i.e., subjects with NE will be included in the denominator but will not be included in the numerator when calculating the percentage of non-PD).

7.2.2. Summary Measure

12 week Non-PD Rate

The number and percentage of participants with the non-PD will be summarized by dose. The corresponding exact 95% Confidence Interval (CI) will also be provided. Subjects with unknown or missing response will be treated as having PD (i.e., subjects with NE will be included in the denominator when calculating the percentage of non-PD).

7.2.3. Population of Interest

The primary efficacy analyses will be based on the All Treated Clinical Activity population, unless otherwise specified. All summaries will be presented by dose, and

overall. The full details of data listings, tables, and figures are presented in Appendix 12: List of Data Displays.

7.2.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.3. Secondary Efficacy Analyses

7.3.1. Endpoint / Variables

PSA and RECIST 1.1 response data will be reported. Subjects with unknown or missing response data, including those who withdraw from the study without an assessment, will be treated as non-responders (i.e., they will be included in the denominator when calculating the percentage). No imputation will be performed for missing lesion assessment or PSA response data. An exact 95% CI will be computed for the PSA50 response rate and RECIST 1.1 confirmed response rate.

Due to the small sample size in the 400 mg cohort (n=2), the radiographic Progression Free Survival (rPFS), time to PSA progression, and time to radiological progression for this cohort will not be summarized separately, however, it will be included in the overall summary. The cohort will also be included in the associated listings.

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK data standards and statistical principles.

Secondary Efficacy Endpoint	Definition	Analysis / Display

PSA50 Response Rate	defined as proportion of subjects with a decrease of ≥50% in the PSA concentration from the baseline PSA value determined at least 12 weeks after start of treatment until last post-treatment follow-up visit or initiation of new anti-cancer therapy and confirmed after 3 or more weeks by an additional PSA evaluation.	• Confirmed and unconfirmed PSA changes will be categorized as follows: decline >=50%, PSA increase >=25% (PSA progression per PCWG2), No significant PSA change, and Not Evaluable.
		  • Confirmed and unconfirmed PSA50 response rate will be reported by dose level along with the exact 95% confidence interval.
		  • See Section 13.6.3 for algorithm details.
		• Waterfall plots will be presented that show the maximum percentage of change in PSA from baseline.
		• Spider plots will be presented to show percent change in PSA from baseline over time

Best Overall Response	defined as the best confirmed/unconfirmed response	• Confirmed and unconfirmed best overall response will be reported

Secondary Efficacy Endpoint	Definition	Analysis / Display
(BOR)	(Complete Response [CR] > Partial Response [PR] > Stable Disease [SD] [or non-CR/non-PD] > Progressive Disease [PD] > Not Evaluable [NE]) from combination treatment start date until disease progression or initiation of new anti-cancer therapy, whichever is earlier, as assessed by the investigator per RECIST 1.1 Criteria.	○ To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after first dose at a minimum interval of 56 days • RECIST 1.1 criteria requires that progression at first assessment be confirmed by a second scan 6 or more weeks later •
Objective Response Rate (ORR)	defined as the percentage of subjects with a confirmed complete response (CR) or a partial response (PR) as the BOR, as assessed by the investigator per RECIST 1.1 criteria.	• The number and types of responses, as outlined in RECIST 1.1, will be listed and summarized separately, as appropriate. The investigator observed ORR, confirmed and unconfirmed, will be reported at the interim and final analysis for each cohort specified in treated dose, if data warrant. The estimates along with 95% exact confidence interval (CI) will be provided. • Subjects with unknown or missing response will be treated as non-responders, i.e. these subjects will be included in the denominator when calculating the percentage.
Radiographic Progression-free survival (rPFS)	defined as the interval of time (in weeks) between the date of first dose of GSK2636771 and the earlier of the date of disease progression as assessed by the investigator per RECIST 1.1 criteria and the date of death due to any cause. Determination of dates of PFS events and dates for censoring are described in Table 6	• The date of disease progression will be defined as the earliest date of disease progression as assessed by the investigator using RECIST 1.1 criteria or progression on bone scan. • RECIST 1.1 criteria requires that progression at first assessment be confirmed by a second scan 6 or more weeks later. If no scans are available after the first assessment, the subject should be censored on the date of their first assessment. • See Table 1, Bone Response, for definition of progression on bone scan. Bone progression at first assessment requires confirmation by a second scan 6 or more weeks later that shows a minimum of 2 or more additional new lesions. If no second scan is available, the subject should be censored on the date of their first assessment. • rPFS will be summarized by dose level using Kaplan-Meier quantile estimates along with 2-sided 95% CIs.
Time to PSA	defined as the time from combination study treatment start	• See Table 1 for definition of PSA progression per

Secondary Efficacy Endpoint	Definition	Analysis / Display
progression	until the first PSA progression (confirmed if there has been a PSA decline from baseline)	PCWG2. • Time to PSA progression will be summarised using Kaplan-Meier methods (plots and summarize table on medians and quartiles) by dose level.

Time to radiological progression	defined as the time from combination study treatment start until the first radiological progression by RECIST 1.1 and/ or confirmed bone progression.	• The date of disease progression will be defined as the earliest date of disease progression as assessed by the investigator using RECIST 1.1 criteria or progression on bone scan.
		  • RECIST 1.1 criteria requires that progression at first assessment be confirmed by a second scan 6 or more weeks later. If no scans are available after the first assessment, the subject should be censored on the date of their first assessment.
		  • See Table 1, Bone Response, for definition of progression on bone scan. Bone progression at first assessment by bone scan requires confirmation by a second bone scan 6 or more weeks later that shows a minimum of 2 or more additional new lesions. If no second scan is available, the subject should be censored on the date of their first assessment.
		• Time to radiological progression will be summarised using Kaplan-Meier methods (plots and summary table on medians and quartiles) by dose level.

Table 6 Censoring Rules for rPFS Analysis

Censoring Rules		
Scenario	**Date of Event (Progression/Death) or Censoring**	**Event (Progression/Death) or Censoring**
No adequate baseline tumour assessments (MRI/CT or Bone Scan) and the subject has not died	First Dose Date	Censored
No post-baseline tumour assessments and the subject has not died (if the subject has died follow the rules for death indicted at the bottom of the table)	First Dose Date	Censored
Progression documented between scheduled visits	Date of assessment of progression[1]	Event
With adequate post-baseline assessment and no progression (*or death*)	Date of last 'adequate' assessment of response[2]	Censored
No adequate post-baseline assessment before start of new anticancer therapy	First dose date	censored
With adequate post-baseline assessment and new anticancer treatment started (prior to documented disease progression).	Date of last 'adequate' assessment of response[2] *(on or prior to starting anti-cancer therapy)*	Censored
Death before first PD assessment (or Death at baseline or prior to any adequate assessments)	Date of death	Event
Death between adequate assessment visits	Date of death	Event
Death or progression after more than one missed visit	Date of last 'adequate' assessment of response[2] *(prior to missed assessments)):* Since the disease assessment is every 8 weeks, a window of 119 days (16 weeks + 3-day window) will be used to determine whether there is extended time without adequate assessment. If the time difference between PD/death and last adequate disease assessment is more than 119 days, PFS will be censored at the last adequate disease assessment prior to PD/death.	Censored

NOTES :

[1] The earliest of (i) Date of radiological assessment showing new lesion (if progression is based on new lesion); or (ii) Date of radiological assessment showing unequivocal progression in non-target lesions, or (iii) Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)

[2] An adequate assessment is defined as an assessment where the response is CR, PR, or SD.

[3] If PD and New 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 adequate assessments, censoring date should be the date of randomization.

7.3.2. Summary Measure

PSA50 Response Rate

The proportion of subjects with a decrease of ≥50% in the PSA concentration from the baseline PSA value will be categorized as follows: decline >=50%, PSA increase >=25% (PSA progression per PCWG2), No significant PSA change, and Not Evaluable.

Confirmed and unconfirmed PSA50 response rate will be reported by dose level and overall along with the exact 95% confidence interval. See Section 13.6.3 for algorithm details.

ORR

The number and percentage of participants with the BOR in the following response categories at [timepoint] will be summarized by dose and overall: CR, PR, overall response (CR+PR), SD or Non-CR/Non-PD, PD and NE. The corresponding exact 95% CI for ORR will also be provided. Participants with unknown or missing responses will be treated as non-responders, i.e., these participants will be included in the denominator when calculating percentages of response.

Time to PSA Progression

Time to progression will be summarized descriptively by dose (200 mg and 300 mg doses only) and overall using median(s) and quartiles in the subset of subjects with PSA progression.

Time to Radiological Progression

Time to progression at will be summarized descriptively by dose (200 mg and 300 mg doses only) and overall using median(s) and quartiles in the subset of subjects with radiological progression.

Radiological Progression Free Survival (rPFS)

The distribution of PFS for each dose (200 mg and 300 mg doses only) and overall will be estimated using the Kaplan-Meier method. The median, 25th and 75th percentiles of PFS will be estimated and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method (1982). PFS rate and corresponding 95% CI will also be estimated from the Kaplan-Meier analysis.

7.3.3. Population of Interest

The secondary efficacy analyses will be based on the All Treated Clinical Activity population, unless otherwise specified.

7.3.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.3.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed. No additional statistical analysis will be performed.

8. SAFETY ANALYSES

8.1. Overview of Planned Analyses

The safety analyses will be based on the All Treated Safety population, unless otherwise specified, and all summaries and data listings will use treatment labels as specified in Section 5.1. All summaries will be presented by Enzalutamide run-in, combination treatment by dose level, and combination total.

Details of data displays are presented in Appendix 12: List of Data Displays

8.2. Extent of Exposure

Dose intensity: Average daily dose on study, cumulative dose of the combination treatment will be summarised with mean, median, standard deviation, minimum, and maximum. The cumulative duration of exposure to the combination treatment in weeks (from first day to last day of treatment plus 1 day) will also be summarised.

Reductions, escalations, and interruptions will be summarised by number of modifications and reasons for modifications for Enzalutamide and GSK2636771 separately. The summaries of dose modifications will be provided only if the data warrant. All the dose reductions, dose escalations and dose interruptions will be listed separately.

8.3. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. Details on treatment emergent AEs are provided in Section 13.4.2. Dose modifications (, dose interruptions, dose reductions and dose escalations) and Dose limiting toxicity (DLT) will also be summarized and listed according to GSK Oncology Data Standards.

In addition, a trellis display of subject profiles will be produced that displays individual subject data for renal function tests (correct calcium, magnesium, phosphorous, creatinine, PTH) over time within the same panel for all subjects, along with information regarding age, bone metastasis at baseline, denosumab received within 6 months prior to study, denosumab received during study.

The full details of the planned displays are provided in Appendix 12: List of Data Displays.

8.4. Adverse Events of Special Interest (AESI) Analyses

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting. The list is below:

- Hypocalcaemia
- Increase in Creatinine

8.5. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Haematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 12: List of Data Displays.

8.6. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. LVEF and Performance status will be summarized and listed based on GSK Oncology Data Standard. The details of the planned displays are presented in Appendix 12: List of Data Displays.

8.6.1. Deaths and Serious Adverse Events

All deaths will be summarised based on the number and percentage of subjects. This summary will classify subjects by time of death relative to the last dose of medication (>30 days or ≤30 days) and primary cause of death (disease under study, SAE related to study treatment, or other). A supportive listing will be generated to provide subject-specific details on subjects who died.

All SAEs will be tabulated based on the number and percentage of subjects who experienced the event. The summary table will be displayed in descending order of total incidence by Preferred Term only.

SAEs will also be summarized by maximum toxicity grade. Relevant serious adverse events will be displayed by preferred term and will be sorted in descending order based on total incidence in each treatment group.

SAEs are included in the listing of all adverse events. Separate supportive listings with subject-level details will be generated for

- Fatal SAEs
- Non-Fatal SAEs.

8.7. Pregnancies

A listing of pregnancies will be generated if there was any female partner of the male subjects become pregnant during the study.

9. PHARMACOKINETIC ANALYSES

Pharmacokinetic analysis will be the combined responsibility of GSK Clinical Pharmacology Modelling and Simulation Department and GSK Discovery Biometrics and Clinical Statistics.

The merge of PK concentration data, randomisation and eCRF data will be performed by Clinical Statistics (Programmer).

9.1. Primary Pharmacokinetic Analyses

There were no primary pharmacokinetic endpoints defined in the objectives for this study.

9.2. Secondary Pharmacokinetic Analyses

9.2.1. Endpoint / Variables

9.2.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 13.5.3 Reporting Standards for Pharmacokinetic).

Concentration-time data for GSK2636771, enzalutamide and N-desmethyl enzalutamide from the Dose Escalation Phase will be listed and summarized. In addition, concentration-time figures will be presented.

The following secondary objectives will be displayed graphically:

- The PK of enzalutamide and N-desmethyl enzalutamide following repeat-dose oral administration with and without GSK2636771, and
- The PK of GSK2636771 in the presence of enzalutamide.

9.2.2. Population of Interest

The pharmacokinetic (PK) analyses will be based on the PK Concentration population, unless otherwise specified.

9.2.3. Statistical Analyses / Methods

No formal statistical analysis will be performed.

10. BIOMARKER ANALYSES

10.1. Exploratory Biomarker Analyses

10.1.1. Endpoint / Variables

10.1.1.1. Circulating Tumour Cells

CTC response rate will be performed, which is defined as percent of subjects having favourable (CTC <5/7.5 mL of blood) at nadir, if baseline is unfavourable (CTC≥5/7.5mL of blood). Conversions from baseline number of CTCs using the CellSearch platform in blood samples will be summarized and listed as part of this RAP.

If data warrant, additional analysis of CTC will be discussed as part of a RAP supplement; i) Analysis of baseline CTC with clinical outcome (time on treatment and PSA changes

10.1.1.2. Frequency of PTEN loss and Mechanism of PTEN Loss

The frequency of PTEN loss is defined as the proportion of subjects that were tested by central PTEN testing that were identified as PTEN-deficient. The number of tumour biopsy samples with a Histo-score (H score) of 30 and less will be compared with the total number of tumour biopsy samples that were analysed by central PTEN testing to evaluate the frequency of PTEN loss in mCRPC for this study.

The H-Score of all enrolled subjects will be compared to molecular sequencing of tumour biopsy sample to understand the mechanism(/s) of PTEN loss.

10.1.1.3. Mutational Analysis of Tumour Biopsy Sample

Mutational analysis of screening tumour biopsy samples will be analysed to understand gene mutations of mCRPC subjects enrolled in this study and to evaluate the frequency of PTEN homozygous loss. Gene mutations include, small nuclear variant (SNV), copy number variation (gene deletion and gene amplification) and gene fusions.

10.1.2. Summary Measure

1. CTC response rate is defined as any conversion from ≥5 at baseline to <5 over the course of the study. Data will be presented as a single line in a table, for each subject.
2. PTEN:
    a. Frequency of PTEN loss by PTEN IHC (H-Score ≤ 30) in all screened subjects.
    b. Homozygous or heterozygous PTEN loss based on Foundation Medicine analysis
3. Heatmap representation of all SNV, CNV, gene fusion and indels of genes in the 475 gene panel from Foundation Medicine (n=16 subjects).

10.1.3. Population of Interest

The exploratory biomarker analyses will be based on the All Screened and/or Biomarker population, unless otherwise specified.

10.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 10.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

11. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

For this study no on treatment biopsy samples were obtained for Pharmacodynamic analysis. Therefore, no PD analysis can be done for this study.

If data warrant, the pharmacokinetic / pharmacodynamic relationship of GSK2636771 administered in Male Subjects with Metastatic Castration-Resistant Prostate Cancer (mCRPC) may be explored. The influence of subject demographics and baseline characteristics, including disease activity in this population will be investigated.

Further details of PK/PD analyses will be described under a separate RAP. Results of the PK/PD analyses may be included in a report separate from the clinical study report (CSR).

12. REFERENCES

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13. APPENDICES

13.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

13.1.1. Exclusions from Per Protocol Population

No exclusions are noted.

13.2. Appendix 2: Schedule of Activities

13.2.1. Protocol Defined Schedule of Events

Table 7 Time and Events Table for Dose Escalation Phase

See following page.

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200331

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**	**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression[31]**	**Post-Treatment Follow-Up Visit[28]**	**Extended Follow-Up Visits[29]**	**Post-Extended Follow-Up /EOS Visit[30]**
		Day -14 to Day -1	Day 1 to Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Week 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window				*+1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	*+5days Week 12 only; ±3 days for all other visits*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Clinical Assessments													
Informed Consent	X[3]	X[4]											
Demographics	X												
Medical History		X											
Determination of PTEN Deficiency Status	M[5]												
Safety Assessments													
ECOG PS		X		X		X	X	X	Week 8 and then Q8wks	X	X		X
Physical Exam		X		X					Week 8 and then Q8wks		X		X
Height[8]		X											
Weight		X		X					Week 8 and then Q8wks		X		X
Vital Signs[9]		X		X	X	X	X	X	X		X		X
12-Lead ECG[10]		X[6]					X		Week 8 and then Q8wks		X		X
ECHO/MUGA		X[6,7]		As clinically indicated									
AE Monitoring			Continuous							X[11]	X[11]		
Concomitant Medications		X	Continuous								X		

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200331

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**	**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression[31]**	**Post-Treatment Follow-Up Visit[28]**	**Extended Follow-Up Visits[29]**	**Post-Extended Follow-Up /EOS Visit[30]**
		Day -14 to Day -1	Day 1 to Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Week 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window				*+1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	*+5days Week 12 only; ±3 days for all other visits*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Laboratory Assessments[12]													
Hematology/ Clinical Chemistry		X[6]		X	X	X	X	X	X		X		X
Ionized Calcium		X[6]		X[33]	X	X	X	X	X		X		X
Vitamin D[34]		X[6]					X				X		X
Coagulation: PT, PTT, INR		X[6]		X			X						
Liver function Tests		X[6]		X	X	X	X	X	X		X		X
Urinalysis[13] Urine Microscopy[13] UPC[14]		X[6]		X			X		X		X		X
Urine Electrolytes[15]		X[6]		X[33]		X	X		Week 8 and then Q8wks		X		
Parathyroid Hormone				X	As clinically indicated[16]								
Bone Markers[35]				X				X	Weeks 12 and 24		X		X
PSA and LDH[32]		X[6]		X					X	X	X		X
Serum Testosterone		X[6]									X		X
PK Assessments													
PK Blood Sampling[17]								X	Weeks 8 and 12				

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200331

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**	**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression[31]**	**Post-Treatment Follow-Up Visit[28]**	**Extended Follow-Up Visits[29]**	**Post-Extended Follow-Up /EOS Visit[30]**
		Day -14 to Day -1	Day 1 to Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Week 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window				*+1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	*+5days Week 12 only; ±3 days for all other visits*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Disease Assessments[18]													
CT scan or MRI[19]		X[6,7]							Week 8 and then Q8wks to Week 48; then Q12wks	X		X	
Chest X-ray or Chest CT scan		X[6,7]											
Bone Scan[20]		X[6,7]							Week 12 and then Q12wks	X		X	
Biomarker Assessments													
CTC – Janssen[21]		X		X			X		Weeks 8, 16, 24, and 32	X			
CTC – EPIC[22]		X							Week 8 only	X			
Predictive Biomarker: Tumor Tissue[23]				X									
Progression Tumor Biopsy[24]										X			
Tumor Biopsies for Pharmacodynamics[24]			X (Day 14)		X[24]								
cfDNA/RNA/Soluble Markers[25]		X		X			X		Weeks 8, 16, 24, and 32	X			

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200331

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**	**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression**[31]	**Post-Treatment Follow-Up Visit**[28]	**Extended Follow-Up Visits**[29]	**Post-Extended Follow-Up /EOS Visit**[30]
		Day -14 to Day -1	Day 1 to Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Week 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window				*+1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	*+5days Week 12 only; ±3 days for all other visits*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Biomarker Assessments *continued*													
Blood Sample for Genetic Research[26]				X									
Study Treatments[27]													
Enzalutamide			Continuous	Continuous									
GSK2636771				Continuous									

Abbreviations: AE, adverse event; cfDNA, circulating-free tumor DNA; CT, computed tomography; CTC, circulating tumor cells; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOS, End of Study; HbA1C, hemoglobin A1C; INR, international normalization ratio; M, mandatory; MRI, magnetic resonance imaging; MUGA, multigated acquisition scan; O, optional; PD, pharmacodynamics; PK, pharmacokinetics; PS, performance status; PSA, prostate-specific antigen; PT, prothrombin time; PTEN, phosphatase and tensin homolog; PTH, parathyroid hormone; PTT, partial thromboplastin time; Q4wks, every 4 weeks; Q8wks, every 8 weeks; Q12wks, every 12 weeks; UPC, urine:protein:creatinine; Wk(s), week(s)

1. **Study Assessments:** All assessments may be performed more frequently if clinically appropriate. Assessments scheduled on days of dosing should be completed prior to the administration of study treatments, unless otherwise specified
2. **Study Assessments:** Assessments throughout the study are calendar based starting from Week 1, Day 1 of the Combination Treatment Period (the first dose of combination treatment). Dose interruptions should not alter the assessment schedule for any subsequent treatment period.
3. **Pre-Screening Informed Consent:** Separate pre-screening informed consent must be obtained prior to initiation of any pre-screening procedures or assessments.
4. **Screening Informed Consent:** Informed consent must be obtained prior to initiation of any screening procedures or assessments..
5. **PTEN Deficiency Status (Mandatory):** Tumor tissue samples (archived or fresh tumor tissue obtained by pre-treatment biopsy) will be collected to determine PTEN deficiency status of the tumor by the designated central laboratory. Refer to the SRM for details about the number of slides to be submitted, preparation, handling and shipping. Results of

the PTEN deficiency testing from the central laboratory only will be used to determine if the subject is eligible to continue Screening. Only subjects with PTEN deficient tumor based on central laboratory testing results will be screened. **Any remaining tumor tissue may be used for other predictive biomarker analyses** if consent has been obtained.

6. **Screening:** When possible, screening assessments that require imaging, ECG, ECHO/MUGA, or laboratory studies should be performed AFTER PTEN status has been determined.
7. **Screening:** All screening assessments must be completed and all entry criteria must be met prior to assessments on Day 1 of Enzalutamide Run-In Period. EXCEPTION: ECHO/MUGA must be completed within 28 days of enrollment (Day 1 of Enzalutamide Run-In Period), and disease assessment must be completed within 28 days (35 days if MRI is used) prior to enrollment (Day 1 of the Enzalutamide Run-In Period).
8. **Height** is only measured at Screening**.**
9. **Vital Signs:** Blood pressure, temperature and heart rate will be measured. Vital signs may be measured more frequently if clinically warranted.
10. **ECG:** A single 12-lead ECG is to be performed ***before*** vital signs are measured and any blood draws, if assessments are planned at the same nominal time point.
11. **AE Monitoring:** Continued monitoring of AEs applies only to ongoing events at time of treatment discontinuation.
12. **Laboratory Assessments:** Refer to Section 8.6.6 in protocol for list of specific laboratory tests to be performed. Assessments may be performed within 24 hrs prior to scheduled visit (liver function tests and urine tests for UPC may be performed up to 72 hrs prior to a scheduled visit) to ensure availability of results.
13. **Urinalysis and Urine Microscopy:** Urinalysis and urine microscopy will be performed at the time points indicated. Assessments may be performed within 24 hrs prior to a scheduled visit to ensure availability of results.
14. **UPC:** Urine sample for UPC is to be collected at the time points indicated. Perform UPC with the first morning urine specimen (if possible) when urine dipstick protein ≥2+. Urine samples for UPC may be collected up to 72 hrs prior to a scheduled visit to ensure that results are available at time of visit. If the urine sample collected at Screening is contaminated with other bodily fluids, UPC will not be determined and subject will remain eligible for the study.
15. **Urine Electrolytes:** Urine samples will be obtained at Screening, pre-dose on Day 1 (Week 1), Day 3 OR Day 4, Day 15 (Week 3), Day 22 (Week 4) of the Combination Treatment Period, Week 8 and then every 8 weeks (± 3 days) thereafter during the Treatment Continuation Period, and at the post-treatment follow-up visit to determine urine electrolytes (magnesium, phosphorus and calcium) and urine creatinine.
16. **Parathyroid Hormone (PTH):** Assessment of PTH will be performed if a Grade 2 or higher hypocalcemia or hypophosphatemia is reported.
17. **PK Blood Sampling: Day 14 (Enzalutamide Run-In Period):** Plasma samples for analysis of enzalutamide and N-desmethyl enzalutamide will be collected at pre-dose and 0.5, 1, 2, 3, 4, and 6 hrs post-dose on Day 14 of Enzalutamide Run-In Period, the day prior to administration of the first dose of combination study treatment (GSK2636771 and enzalutamide). **Week 5, Day 29 (Treatment Continuation Period):** Blood and plasma samples for analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected at pre-dose and 0.5, 1, 2, 3, 4, and 6 hrs post-dose. Actual date and time of sample collection and dosing of study treatments must be recorded. Explanations are required for any deviations of more than 5 minutes from the planned time during the first 2 hrs and for deviations of more than 20 minutes from the planned time for samples collected at 3 hrs up to 6 hrs post-dose. **Week 8 and Week 12 (Treatment Continuation Period):** Blood and plasma samples for analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected pre-dose only.
18. **Disease Assessments:** Disease assessments at Screening must be performed within 28 days prior to enrollment (Day 1 of the Enzalutamide Run-In Period), or within 35 days prior to enrollment (Day 1 of the Enzalutamide Run-In Period if disease assessment is performed by MRI, to identify target and non-target lesions.
19. **CT scan or MRI:** Scans should be performed at Screening, Week 8 and then every 8 weeks (±7 days) during the first 48 weeks of the Treatment Continuation Period and then every 12 weeks (±7 days) thereafter in the Treatment Continuation Period, and at the time of disease progression. All confirmatory scans are to be performed within 4 weeks (±3 days) of a CR or PR. If a subject discontinues treatment for reasons other than disease progression, disease assessments should continue every 3 months until disease progression, initiation of new anti-cancer treatment, subject withdrawal of consent, or death.
20. **Bone Scan:** A bone scan is required for all subjects at Screening. For subjects without bone disease at baseline, subsequent bone scans should be performed as clinically indicated. Subjects with bone metastases at baseline should have a bone scan performed at Week 12 and then every 12 weeks (±7 days) thereafter in the Treatment

Continuation Period, or as clinically indicated, and at the time of disease progression**.** If a subject discontinues treatment for reasons other than disease progression, bone scans should continue every 3 months until disease progression, initiation of new anti-cancer treatment, subject withdrawal of consent, or death.

21. **CTC-Janssen:** Whole blood samples will be obtained at Screening; pre-dose on Day 1 (Week 1) and Day 22 (Week 4) of the Combination Treatment Period; pre-dose on Day 1 of Weeks 8, 16, 24 and 32 of the Treatment Continuation Period; and at time of disease progression.
22. **CTC-EPIC:** Whole blood samples will be obtained at Screening, pre-dose on Day 1 of Week 8 of the Treatment Continuation Period, and at the time of disease progression for protein and genomic analysis.
23. **Predictive Biomarkers Tumor Tissue:** For subjects enrolled into the study, additional slides of tumor tissue samples will be collected and submitted to the designated laboratory for analysis once a subject has received their first dose of GSK2636771 on Week 1, Day 1 of the Combination Treatment Period. Tumor tissue may be obtained from archived tissue samples or fresh tumor tissue submitted for the PTEN testing. If additional tumor tissue is not available, no new biopsy procedure is required for predictive biomarker analysis. Refer to the SRM for details about the number of slides to be submitted, preparation, handling and shipping.
24. **Tumor Biopsies for PD and progression**: These biopsies are optional and may be undertaken in select cases upon agreement with the investigator and when consent is provided by the subject. For pharmacodynamic biomarker analyses, fresh tissue biopsies would be collected between Day 12 of the Enzalutamide Run-in Period and Week 1/Day 1, prior to any treatment with GSK2636771, and 2-4 hours post dose between Days 8 and 15 of the Combination Treatment Period (post-treatment). For subjects who consent to the optional progression biopsy, a fresh tumor biopsy should be completed if the subject initially responded to combination treatment and then progressed.
25. **cfDNA/RNA/Soluble Markers:** Plasma samples will be obtained from collected blood samples at Screening, pre-dose on Weeks 1, 4, 8, 16, 24, and 32 of the Combination Treatment Period, and at the time of treatment discontinuation due to disease progression. Plasma will be analyzed for genomic changes in the circulating tumor DNA, RNA, and soluble markers.
26. **Genetic Research:** A 6-mL blood sample should be collected after Screening, preferably on Week 1, Day 1 of the Combination Treatment Period, if informed consent has been obtained for genetic research.
27. **Study Treatment:** Enzalutamide monotherapy should be taken once daily during the Enzalutamide Run-In Period. Enzalutamide will be self-administered in the clinic on Day 14 of the Enzalutamide Run-In Period. GSK2636771 and enzalutamide will be administered in the clinic on Week 1, Day 1 of the Combination Treatment Period and on days when blood, plasma, and/or urine samples are collected for analysis of PK, CTC, and/or urine electrolytes.
28. **Post-Treatment Follow-Up Visit:** ***ONLY*** subjects who withdraw during the Enzalutamide Run-In Period or withdraw from study treatment ***due to*** disease **progression** (see Section 5.2 in protocol) **should have a post-treatment follow-up visit conducted within approximately 30 days (-2/+7 days) of last dose of study treatment(s). If a subject is unable t**o return to the clinic due to hospitalization, site staff is encouraged to call subject for assessment of AEs.
29. **Extended Follow-Up Visits:** Subjects who withdraw from study treatment ***without*** disease progression should be contacted every 3 months (±14 days) until disease progression, death, withdrawal of consent, or subject is lost to follow-up. Contact may include a clinic visit, a telephone contact, or an e-mail. The initiation of any new anti-cancer treatments and date of last contact should be documented.
30. **Post-Extended Follow-Up/EOS Visit:** ***ONLY*** subjects who discontinue the Extended Follow-Up Visits should have a Post-Extended Follow-Up/EOS Visit performed.
31. Subjects are not required to discontinue treatment on the basis of PSA progression alone or for the worsening of an isolated disease site that is not clinically significant (see Section 5.2 in protocol)
32. When collected as part of the routine standard of care for a subject, LDH will be reported.
33. Complete clinical chemistries laboratory assessments at Week1/Day 1 and **again on either Day 3 or Day 4**. The Day 3 or Day 4 assessments can be completed at a local laboratory and does **not** require a clinic visit. The hematology panel does NOT need to be collected on Day 3/ Day.4. Review of these labs must occur before Week 2, Day 1 visit.
34. Includes assessments for 25-OH D and 1,25-OH2 D.
35. Includes urine and blood and/or serum samples. Must be collected at the same time of day (±1 hour) to eliminate diurnal effects, and after fasting. See SRM for additional details on the specific assessments and sample collection.

Table 8 Time and Events Table for Dose Expansion Phase

See following page.

CONFIDENTIAL

200331

Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**	**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression[31]**	**Post-Treatment Follow-Up Visit[28]**	**Extended Follow-Up Visits[29]**	**Post-Extended Follow-Up /EOS Visit[30]**
		Day -14 to Day -1	Day 1 to Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Week 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window				*+1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	*+5days Week 12 only; ±3 days for all other visits*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Clinical Assessments													
Informed Consent	X[3]	X[4]											
Demographics	X												
Medical History		X											
Determination of PTEN Deficiency Status	M[5]												
Safety Assessments													
ECOG PS		X		X		X	X	X	Week 8 and then Q8wks	X	X		X
Physical Exam		X		X					Week 8 and then Q8wks		X		X
Height[8]		X											
Weight		X		X					Week 8 and then Q8wks		X		X
Vital Signs[9]		X		X	X	X	X	X	X		X		X
12-Lead ECG[10]		X[6]					X		Week 8 and then Q8wks		X		X
ECHO/MUGA		X[6,7]		As clinically indicated									
AE Monitoring			Continuous							X[11]	X[11]		
Concomitant Medications		X	Continuous								X		

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Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**	**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression**[31]	**Post-Treatment Follow-Up Visit**[28]	**Extended Follow-Up Visits**[29]	**Post-Extended Follow-Up /EOS Visit**[30]
		Day -14 to Day -1	Day 1 to Day 14	Wk 1, Day 1	Wk 2, Day 8	Wk 3, Day 15	Wk 4, Day 22	Week 5, Day 29	Week 8 and every 4 weeks thereafter			Every 3 months	
Visit Window				*+1 day*	*±1 day*	*±1 day*	*±1 day*	*±1 day*	*+5days Week 12 only; ±3 days for all other visits*	*+1 day*	*-2/+7 days*	*±14 days*	*±3 days*
Laboratory Assessments[12]													
Haematology/ Clinical Chemistry		X[6]		X	X	X	X	X	X		X		X
Ionized Calcium		X[6]		X[33]	X	X	X	X	X		X		X
Vitamin D[34]		X[6]					X				X		X
Coagulation: PT, PTT, INR		X[6]		X			X						
Liver function Tests		X[6]		X	X	X	X	X	X		X		X
Urinalysis[13] Urine Microscopy[13] UPC[14]		X[6]		X			X		X		X		X
Urine Electrolytes[15]		X[6]		X[33]		X	X		Week 8 and then Q8wks		X		
Parathyroid Hormone				X	As clinically indicated[16]								
Bone Markers[35]				X				X	Weeks 12 and 24		X		X
PSA and LDH[32]		X[6]		X					X	X	X		X
Serum Testosterone		X[6]									X		X
PK Assessments													
PK Blood Sampling[17]								X	Weeks 8 and 12				

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Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**	**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression[31]**	**Post-Treatment Follow-Up Visit[28]**	**Extended Follow-Up Visits[29]**	**Post-Extended Follow-Up /EOS Visit[30]**
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Disease Assessments[18]													
CT scan or MRI[19]		X[6,7]							Week 8 and then Q8wks to Week 48; then Q12wks	X		X	
Chest X-ray or Chest CT scan		X[6,7]											
Bone Scan[20]		X[6,7]							Week 12 and then Q12wks	X		X	
Biomarker Assessments													
CTC – Janssen[21]		X		X			X		Weeks 8, 16, 24, and 32	X			
CTC – EPIC[22]		X							Week 8 only	X			
Predictive Biomarker: Tumor Tissue[23]				X									
Progression Tumor Biopsy[24]										X			
Tumor Biopsies for Pharmacodynamics[24]			X (Day 14)		X[24]								
cfDNA/RNA/Soluble Markers[25]		X		X			X		Weeks 8, 16, 24, and 32	X			

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Study Assessments[1,2]	**Pre-Screening**	**Screening**	**Enzalutamide Run-In Period**	**Combination Treatment Period** *(DLT Reporting Period)*				**Treatment Continuation Period**		**Time of Discontinuation of Treatment due to Disease Progression**[31]	**Post-Treatment Follow-Up Visit**[28]	**Extended Follow-Up Visits**[29]	**Post-Extended Follow-Up /EOS Visit**[30]
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Biomarker Assessments *continued*													
Blood Sample for Genetic Research[26]				X									
Study Treatments[27]													
Enzalutamide			Continuous	Continuous									
GSK2636771				Continuous									

Abbreviations: AE, adverse event; cfDNA, circulating-free tumor DNA; CT, computed tomography; CTC, circulating tumor cells; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOS, End of Study; HbA1C, hemoglobin A1C; INR, international normalization ratio; M, mandatory; MRI, magnetic resonance imaging; MUGA, multigated acquisition scan; O, optional; PD, pharmacodynamics; PK, pharmacokinetics; PS, performance status; PSA, prostate-specific antigen; PT, prothrombin time; PTEN, phosphatase and tensin homolog; PTH, parathyroid hormone; PTT, partial thromboplastin time; Q4wks, every 4 weeks; Q8wks, every 8 weeks; Q12wks, every 12 weeks; UPC, urine:protein:creatinine; Wk(s), week(s)

1. **Study Assessments:** All assessments may be performed more frequently if clinically appropriate. Assessments scheduled on days of dosing should be completed prior to the administration of study treatments, unless otherwise specified
2. **Study Assessments:** Assessments throughout the study are calendar based starting from Week 1, Day 1 of the Combination Treatment Period (the first dose of combination treatment). Dose interruptions should not alter the assessment schedule for any subsequent treatment period.
3. **Pre-Screening Informed Consent:** Separate pre-screening informed consent must be obtained prior to initiation of any pre-screening procedures or assessments.
4. **Screening Informed Consent:** Informed consent must be obtained prior to initiation of any screening procedures or assessments..
5. **PTEN Deficiency Status (Mandatory):** Tumor tissue samples (archived or fresh tumor tissue obtained by pre-treatment biopsy) will be collected to determine PTEN deficiency status of the tumor by the designated central laboratory. Refer to the SRM for details about the number of slides to be submitted, preparation, handling and shipping. Results of

the PTEN deficiency testing from the central laboratory only will be used to determine if the subject is eligible to continue Screening. Only subjects with PTEN deficient tumor based on central laboratory testing results will be screened. **Any remaining tumor tissue may be used for other predictive biomarker analyses** if consent has been obtained.

6. **Screening:** When possible, screening assessments that require imaging, ECG, ECHO/MUGA, or laboratory studies should be performed AFTER PTEN status has been determined.
7. **Screening:** All screening assessments must be completed and all entry criteria must be met prior to assessments on Day 1 of Enzalutamide Run-In Period. EXCEPTION: ECHO/MUGA must be completed within 28 days of enrollment (Day 1 of Enzalutamide Run-In Period), and disease assessment must be completed within 28 days (35 days if MRI is used) prior to enrollment (Day 1 of the Enzalutamide Run-In Period).
8. **Height** is only measured at Screening**.**
9. **Vital Signs:** Blood pressure, temperature and heart rate will be measured. Vital signs may be measured more frequently if clinically warranted.
10. **ECG:** A single 12-lead ECG is to be performed ***before*** vital signs are measured and any blood draws, if assessments are planned at the same nominal time point.
11. **AE Monitoring:** Continued monitoring of AEs applies only to ongoing events at time of treatment discontinuation.
12. **Laboratory Assessments:** Refer to Section 8.6.6 in protocol) for list of specific laboratory tests to be performed. Assessments may be performed within 24 hrs prior to scheduled visit (liver function tests and urine tests for UPC may be performed up to 72 hrs prior to a scheduled visit) to ensure availability of results.
13. **Urinalysis and Urine Microscopy:** Urinalysis and urine microscopy will be performed at the time points indicated. Assessments may be performed within 24 hrs prior to a scheduled visit to ensure availability of results.
14. **UPC:** Urine sample for UPC is to be collected at the time points indicated. Perform UPC with the first morning urine specimen (if possible) when urine dipstick protein ≥2+. Urine samples for UPC may be collected up to 72 hrs prior to a scheduled visit to ensure that results are available at time of visit. If the urine sample collected at Screening is contaminated with other bodily fluids, UPC will not be determined and subject will remain eligible for the study.
15. **Urine Electrolytes:** Urine samples will be obtained at Screening, pre-dose on Day 1 (Week 1), Day 3 OR Day 4, Day 15 (Week 3), Day 22 (Week 4) of the Combination Treatment Period, Week 8 and then every 8 weeks (± 3 days) thereafter during the Treatment Continuation Period, and at the post-treatment follow-up visit to determine urine electrolytes (magnesium, phosphorus and calcium) and urine creatinine.
16. **Parathyroid Hormone (PTH):** Assessment of PTH will be performed if a Grade 2 or higher hypocalcemia or hypophosphatemia is reported.
17. **PK Blood Sampling: Week 5, Day 29 (Treatment Continuation Period):** Blood and plasma samples for analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected at pre-dose and 1, 2, and 3 hrs post-dose if a morning clinic visit is scheduled, or at approximately 5 to 6, 6 to 7, and 7 to 8 hrs post-dose if an afternoon clinic visit is scheduled. Actual date and time of sample collection and dosing of study treatments must be recorded. Explanations are required for any deviations of more than 5 minutes from the planned time during the first 2 hrs and for deviations of more than 20 minutes from the planned time for samples collected at 3 hrs up to 8 hrs post-dose. **Week 8 and Week 12 (Treatment Continuation Period):** Blood and plasma samples for analysis of GSK2636771, enzalutamide and N-desmethyl enzalutamide will be collected pre-dose only.
18. **Disease Assessments:** Disease assessments at Screening must be performed within 28 days prior to enrollment (Day 1 of the Enzalutamide Run-In Period), or within 35 days prior to enrollment (Day 1 of the Enzalutamide Run-In Period if disease assessment is performed by MRI, to identify target and non-target lesions.
19. **CT scan or MRI:** Scans should be performed at Screening, Week 8 and then every 8 weeks (±7 days) during the first 48 weeks of the Treatment Continuation Period and then every 12 weeks (±7 days) thereafter in the Treatment Continuation Period, and at the time of disease progression. All confirmatory scans are to be performed within 4 weeks (±3 days) of a CR or PR. If a subject discontinues treatment for reasons other than disease progression, disease assessments should continue every 3 months until disease progression, initiation of new anti-cancer treatment, subject withdrawal of consent, or death.
20. **Bone Scan:** A bone scan is required for all subjects at Screening. For subjects without bone disease at baseline, subsequent bone scans should be performed as clinically indicated. Subjects with bone metastases at baseline should have a bone scan performed at Week 12 and then every 12 weeks (±7 days) thereafter in the Treatment

Continuation Period, or as clinically indicated, and at the time of disease progression**.** If a subject discontinues treatment for reasons other than disease progression, bone scans should continue every 3 months until disease progression, initiation of new anti-cancer treatment, subject withdrawal of consent, or death.

21. **CTC-Janssen:** Whole blood samples will be obtained at Screening; pre-dose on Day 1 (Week 1) and Day 22 (Week 4) of the Combination Treatment Period; pre-dose on Day 1 of Weeks 8, 16, 24 and 32 of the Treatment Continuation Period; and at time of disease progression.
22. **CTC-EPIC:** Whole blood samples will be obtained at Screening, pre-dose on Day 1 of Week 8 of the Treatment Continuation Period, and at the time of disease progression for protein and genomic analysis.
23. **Predictive Biomarkers Tumor Tissue:** For subjects enrolled into the study, additional slides of tumor tissue samples will be collected and submitted to the designated laboratory for analysis once a subject has received their first dose of GSK2636771 on Week 1, Day 1 of the Combination Treatment Period. Tumor tissue may be obtained from archived tissue samples or fresh tumor tissue submitted for the PTEN testing. If additional tumor tissue is not available, no new biopsy procedure is required for predictive biomarker analysis. Refer to the SRM for details about the number of slides to be submitted, preparation, handling and shipping.
24. **Tumor Biopsies for PD and progression**: These biopsies are optional and may be undertaken in select cases upon agreement with the investigator and when consent is provided by the subject. For pharmacodynamic biomarker analyses, fresh tissue biopsies would be collected between Day 12 of the Enzalutamide Run-in Period and Week 1/Day 1, prior to any treatment with GSK2636771, and 2-4 hours post dose between Days 8 and 15 of the Combination Treatment Period (post-treatment). For subjects who consent to the optional progression biopsy, a fresh tumor biopsy should be completed if the subject initially responded to combination treatment and then progressed..
25. **cfDNA/RNA/Soluble Markers:** Plasma samples will be obtained from collected blood samples at Screening, pre-dose on Weeks 1, 4, 8, 16, 24, and 32 of the Combination Treatment Period, and at the time of discontinuation of treatment due to disease progression. Plasma will be analyzed for genomic changes in the circulating tumor DNA, RNA, and soluble markers.
26. **Genetic Research:** A 6-mL blood sample should be collected after Screening, preferably on Week 1, Day 1 of the Combination Treatment Period, if informed consent has been obtained for genetic research.
27. **Study Treatment:** Enzalutamide monotherapy should be taken once daily during the Enzalutamide Run-In Period. Enzalutamide will be self-administered in the clinic on Day 14 of the Enzalutamide Run-In Period. GSK2636771 and enzalutamide will be administered in the clinic on Week 1, Day 1 of the Combination Treatment Period and on days when blood, plasma, and/or urine samples are collected for analysis of PK, CTC, and/or urine electrolytes.
28. **Post-Treatment Follow-Up Visit:** ***ONLY*** subjects who withdraw during the Enzalutamide Run-In Period or withdraw from study treatment ***due to*** disease progression see Section 5.2 in protocol) should have a post-treatment follow-up visit conducted within approximately 30 days (-2/+7 days) of last dose of study treatment(s). If a subject is unable to return to the clinic due to hospitalization, site staff is encouraged to call subject for assessment of AEs.
29. **Extended Follow-Up Visits:** Subjects who withdraw from study treatment ***without*** disease progression should be contacted every 3 months (±14 days) until disease progression, death, withdrawal of consent, or subject is lost to follow-up. Contact may include a clinic visit, a telephone contact, or an e-mail. The initiation of any new anti-cancer treatments and date of last contact should be documented.
30. **Post-Extended Follow-Up/EOS Visit:** ***ONLY*** subjects who discontinue the Extended Follow-Up Visits should have a Post-Extended Follow-Up/EOS Visit performed.
31. These assessments should be completed at the time of disease progression that leads to discontinuation of treatment. Subjects are not required to discontinue treatment on the basis of PSA progression alone or for the worsening of an isolated disease site that is not clinically significant (see Section 5.2 in protocol).
32. When collected as part of the routine standard of care for a subject, LDH will be reported.
33. Complete clinical chemistries laboratory assessments at Week1/Day 1 and **again on either Day 3 or Day 4**. The Day 3 or Day 4 assessments can be completed at a local laboratory and does **not** require a clinic visit. The hematology panel does NOT need to be collected on Day 3/ Day.4. Review of these labs must occur before Week 2, Day 1 visit.
34. Includes assessments for 25-OH D and 1,25-OH2 D.
35. Includes urine and blood and/or serum samples. Must be collected at the same time of day (±1 hour) to eliminate diurnal effects, and after fasting. See SRM for additional details on the specific assessments and sample collection

13.3. Appendix 3: Assessment Windows

13.3.1. Definitions of Assessment Windows for Analyses

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
Primary/Secondary Efficacy	For patients seen at week 12 under protocol amendment 1-3	Week 12 ± 3 days	78-3 days	78 + 3 days	Week 12
Primary/Secondary Efficacy	For patients seen at week 12 under protocol amendment 4	Week 12 + 5 days	78 days	78+5 days	Week 12

13.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

13.4.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	End Date < Combination Treatment Start Date
Post-Treatment	Start Date > Stop Date of GSK2636771 For interim analyses when subjects are still on treatment, Study Treatment Stop Date will be imputed following rules specified in Section 13.7.2.1.
Concomitant	Any medication that is not a prior or post -treatment

NOTES:

- Please refer to Section 13.7.2.1: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

13.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date or missing &: ○ Treatment Start Date≤ AE Start Date AE start data is missing

NOTES:

- Treatment start date refers to the time the first dose of enzalutamide is administered on Day 1 of the Enzalutamide Run-In Period
- Treatment stop date refers to the date of discontinuation of study treatments(s)
- If the treatment stop date is missing, then the AE will be considered to be On-Treatment.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

13.5. Appendix 5: Data Display Standards & Handling Conventions

13.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: US1SALX00259
HARP Compound	: arprod\gsk2636771\mid200331\
Analysis Datasets	
• Analysis datasets will be created according to IDSL standard.	
Generation of RTF Files	
• RTF files will be generated for all tables	

13.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include subject level listings in the main body of the GSK Clinical Study Report. All subject level listings should be in the modular appendices as ICH or non-ICH listings

Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.

Unscheduled Visits
• Unscheduled visits will not be included in summary tables and/or figures. For worst-case analysis, unscheduled visits will be included. • All unscheduled visits will be included in listings.

Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

13.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to [Insert document name]. Note: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PK File	Not applicable.
NONMEM/PK/PD File	Not applicable.

13.6. Appendix 6: Derived and Transformed Data

13.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time window (as per Section 13.3.1), the value closest to the target day for that window will be used. If values are the same distance from the target, then the mean will be taken. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day for Safety

• Calculated as the number of days from First Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Date ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

Study Day for Efficacy

• Calculated as the number of days from First Dose Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Date ≥ First Dose Date → Study Day = Ref Date – First Dose Date + 1

Change from Baseline
• Change from Baseline = Post-Baseline Visit Value – Baseline • % Change from Baseline= 100 x (Post-Baseline Visit Value – Baseline) / Baseline • Maximum Increase/Decrease from Baseline = maximum (Increase/Decrease from Baseline) • If either the Baseline or Post-Baseline Visit Value is missing, Change from Baseline and % Change from Baseline is set to missing
Date of Response
• For post-baseline disease assessments, the date of response (PR or better) is assigned to the latest date of disease assessments; for other response categories (SD or Non-CR/Non-PD, NE, PD), the date of response is assigned to the earliest date of disease assessments.
Date of New Anti-Cancer Therapy
• Derived as the earliest date of new anti-cancer therapy, radiotherapy (where applicable) or cancer-related surgical procedure (where applicable). Missing or partial dates will be imputed for derivation of new anti-cancer therapy following rules specified in Section 13.7.2.1.

13.6.2. Study Population

Treatment Compliance
• Treatment compliance will be calculated based on the formula: **Treatment Compliance = Number of Actual Doses / (Planned Treatment Duration in Days * Frequency)** • Frequency is 2 for BID and 1 for QD. Treatment compliance could be greater than 100% if there are events of overdose. Cumulative compliance (since Day 1) at each visit will be calculated. • Planned Treatment Duration is defined as the time from start of study treatment until treatment end date.
Extent of Exposure
• Missing treatment stop date will be imputed following rules specified in Section 13.7.2.1. • Daily Oral Drugs o Extent of exposure will be calculated for each treatment component o Number of days of exposure (duration on study treatment) to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – Treatment Start Date + 1** o Participants who were assigned a treatment but did not report a treatment start date will be categorised as having zero days of exposure. o The cumulative dose will be based on the formula: **Cumulative Dose = Sum of (Number of Days x Total Daily Dose)** • If there are any treatment breaks during the study, exposure data will be adjusted accordingly.
Time since Initial Diagnosis
• Calculated as the number of [Days] from the Date of Initial Diagnosis: o [Randomization/First Dose Date] = Missing → Elapse Time = Missing o Date of Initial Diagnosis = Completely/partially Missing → Elapse Time = Missing o Otherwise → Elapse Time = [Randomization/First Dose Date] – Date of Initial Diagnosis + 1

13.6.3. Efficacy

PSA response (including PSA50 response)
• Using the following algorithm, the following 4 categories will be created: o [PSA] Decline>=50% from baseline [confirmed/unconfirmed] (PSA50) o No significant PSA change o PSA Progression (PSA increase >=25% from baseline) o Not Evaluable • **For at least 12 weeks PSA:** for visits under amendment 3, use week 12 ± 3 days; for visits under amendment 4, use week 12 + 5 days
PSA Response Algorithm – PSA50 unconfirmed
• **Step 1:** Within identified population define PSA Analysis Set • If there is no post-baseline PSA visit with a non-missing result, output to [Not Evaluable] • If there is no baseline PSA, output to [Not Evaluable] • Output rest to [PSA evaluable Analysis Set] • **Step 2:** within [PSA evaluable Analysis Set] create two subsets • If any post-baseline visit PSA < baseline output to subset I (decline from baseline) • Else if the visit is post-baseline output to Subset II (no decline from baseline)

PSA response (including PSA50 response)

- **Step 3.** Under Subset I:
  - For each subject retain the response flag (urspflg). Find the first visit PSA <= 0.5*baseline, add urspflg (unconfirmed PSA response flag) =1; output to [Decline>=50% from baseline (unconfirmed]
  - Else output to [temp set 1]

  - Among [temp set 1], find nadir (lowest PSA value at this or any earlier visit through baseline) Retain nadir for each subject.
    - PSA >=1.25*nadir and (PSA-nadir)>=2ng/mL, add uprgflg (unconfirmed PSA progression flag)=1
    - If PSA >=1.25*nadir and (PSA-nadir)≥ 2ng/mL is confirmed by a second PSA value obtained >=21 days (3 weeks) from the initial increase, add cprgflg (confirmed PSA progression flag)=1
  - If progression is confirmed [sum(uprgflg,cprgflg)=2] output to [PSA progression]
  - Else output to [No significant PSA change]

- **Step 4.** Under Subset II
  - If any visit >=XX days (12 weeks) PSA >= 1.25*baseline and abs(increase from baseline) >=2ng/mL output to [PSA progression] (no confirmation required).
  - Else output to [No significant PSA change]

PSA Response Algorithm – PSA50 Confirmed
NOTE: Steps are very similar to unconfirmed PSA50 with differences indicated in Red.

- **Step 1:** Within identified population define PSA Analysis Set
  - If there is no post-baseline PSA visit with a non-missing result, output to [Not Evaluable]
  - If there is no baseline PSA, output to [Not Evaluable]
  - Output rest to [PSA evaluable Analysis Set]

- **Step 2:** within [PSA evaluable Analysis Set] create two subsets
  - If any post-baseline visit PSA < baseline output to subset I (decline from baseline)
  - Else if the visit is post-baseline output to Subset II (no decline from baseline)

- **Step 3.** Under Subset I:
  - For each subject retain the response flags (urspflg and crspflg). Find the first visit PSA <= 0.5*baseline, add urspflg (unconfirmed PSA response flag) =1;
  - Find the second visit PSA <= 0.5*baseline, if this visit time is >=21 days (3 weeks) from the first visit, add crspflg (confirmed PSA response flag)=1
  - If the response is confirmed (urspflg+crspflg)=2, output to [Decline>=50% from baseline (confirmed]
  - Else output to [temp set 1]

  - Among [temp set 1], find nadir (lowest PSA value at this or any earlier visit through baseline) Retain nadir for each subject.
    - PSA >=1.25*nadir and (PSA-nadir)>=2ng/mL, add uprgflg (unconfirmed PSA progression flag)=1
    - If PSA >=1.25*nadir and (PSA-nadir)≥ 2ng/mL is confirmed by a second PSA value obtained >=21 days (3 weeks) from the initial increase, add cprgflg (confirmed PSA progression flag)=1

PSA response (including PSA50 response)

• If progression is confirmed [sum(uprgflg,cprgflg)=2] output to [PSA progression]
• Else output to [No significant PSA change]
 	
• **Step 4.** Under Subset II
  • If any visit >=XX days (12 weeks) PSA >= 1.25*baseline and abs(increase from baseline) >=2ng/mL output to [PSA progression] (no confirmation required).
  • Else output to [No significant PSA change]

13.6.4. Safety

Adverse Events
AE'S OF Special Interest
• Hypocalcaemia • Increase in Creatinine
Duration of AE

• Calculated as the number of [days] from AE Start Date to AE Stop Date:
  • AE Start Date = Missing → Elapse Time = Missing
  • AE Stop Date = Missing → Elapse Time = Missing
  ○ Otherwise → Elapsed Time = AE Stop Date – AE Start Date + 1

ECHO/MUGA
• Change from Baseline for cardiac data, e.g., Left Ventricular Ejection Fraction (LVEF), will be calculated based on the same modality (ECHO or MUGA) throughout the study for each subject. Post-baseline assessments with a different cardiac scan modality will not be used to calculate change from Baseline.

13.7. Appendix 7: Reporting Standards for Missing Data

13.7.1. Premature Withdrawals

Element	Reporting Detail
General	Subject study completion (i.e. as specified in the protocol) was defined as below: • A subject will be considered to have completed the study if the subject dies or otherwise progresses during the study treatment or post-treatment follow-up period. All other subjects will be considered to have withdrawn from the study. • Withdrawn subjects were not replaced in this study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

13.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated using a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

13.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings. • Partial dates for AE recorded in the CRF will be imputed using the following conventions:

Missing start day	• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month. • Else if study treatment start date is not missing: o If month and year of start date = month and year of study treatment start date then ▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month. ▪ Else set start date = study treatment start date. o Else set start date = 1st of month.

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<tr><td>Missing start day and month</td><td>• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1.
• Else if study treatment start date is not missing:
○ If year of start date = year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1.
▪ Else set start date = study treatment start date.
○ Else set start date = January 1.</td></tr>
<tr><td>Missing stop day</td><td>Last day of the month will be used.</td></tr>
<tr><td>Missing stop day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
<tr><td>Concomitant Medications/ Medical History/ Blood Supportive Products</td><td>• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month.
• Else if study treatment start date is not missing:
○ If month and year of start date = month and year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month.
▪ Else set start date = study treatment start date.
○ Else set start date = 1st of month.</td></tr>
<tr><td>Missing start day and month</td><td>• If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = January 1.
• Else if study treatment start date is not missing:
○ If year of start date = year of study treatment start date then
▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1.
▪ Else set start date = study treatment start date.
• Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year)</td></tr>
<tr><td>Missing end day and month</td><td>A '31' will be used for the day and 'Dec' will be used for the month.</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
<tr><td>New Anti-Cancer</td><td>Start dates for follow-up anti-cancer therapy, radiotherapy (where applicable), and surgical procedures (where applicable) will be imputed in order to define event and censoring rules for</td></tr>
</table>

Element	Reporting Detail

Therapy/ Radiotherapy/ Surgical Procedures for Efficacy Evaluation (e.g., response rate, time to event)	progression-free survival, response rate, or duration of response (i.e. start date for new anti-cancer therapy). Dates will only be imputed when a month and year are available, but the day is missing. The following rules will be used to impute the date when partial start dates are present on anti-cancer therapy, radiotherapy, and/or surgical procedures dataset[s]:
	
	• Completely missing start dates will remain missing, with no imputation applied;
	• Partial start dates will be imputed using the following convention:
	  • If both month and day are missing, no imputation will be applied;
	  • If only day is missing:
	  ○ If the month of partial date is the same as the month of last dosing date, minimum of (last dosing date + 1, last day of the month) will be used for the day;
	  ○ If the month of partial date is the same as the month of last disease assessment and the last disease assessment is PD, minimum of (last date of disease assessment + 1, last day of the month) will be used for the day;
	  ○ If both conditions above are met, the later date will be used for the day;
	  ○ Otherwise, a '01' will be used for the day;
	• Completely or partial missing end dates will remain missing, with no imputation applied;

Treatment end date	• If there is more than one study treatment, imputation of missing treatment end date will be applied to all applicable treatments following rules below and treatment end date is the latest treatment end date across all study treatments.
	For daily oral treatment
	
	• In general, completely missing end dates are not imputed, with the following exceptions for imputation of missing treatment end date at interim analyses.
	• For imputation of missing exposure end date at an interim analysis when subjects are still on treatment, the following conventions will be applied:
	  ○ If the missing end date is in the last exposure record, the earliest of: the date of the data cut-off, the date of withdrawal from the study, or the death date will be used
	  ○ If the missing end date is not in the last exposure record, treatment start date for the record will be used
	• The imputed treatment end date will be used to calculate cumulative dose and duration of treatment as specified in Section 13.6.2. For non-continual treatment

13.8. Appendix 8: Values of Potential Clinical Importance

13.8.1. Laboratory Values

To identify laboratory values of potential clinical importance, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.0) will be used to assign grades for laboratory parameters including clinical chemistry, haematology, liver function tests, QTc (Bazett's or Fridericia's) values, vital signs (heart rate, blood pressure, temperature) and LVEF.

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern. The laboratory reference ranges will be provided on the listings of laboratory data. Clinical laboratory test results outside of the reference range will be flagged in the listings.

For laboratory data which are not listed in the NCI CTCAE v4.0, a summary of values outside the normal range will be provided.

13.8.2. ECG and Vital Signs

For ECG and vital signs, the most updated IDSL standard up to the RAP effective date will be followed.

13.9. Appendix 9: Population Pharmacokinetic (PopPK) Analyses

Population PK analysis will be done under a separate RAP and reported outside of the CSR.

13.10. Appendix 10: Pharmacokinetic / Pharmacodynamic Analyses

PK/PD analyses will be done under a separate RAP and reported outside of the CSR.

13.11. Appendix 11: Abbreviations & Trade Marks

13.11.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AR	Androgen receptor
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
AUC(0-t)	Area under the concentration-time curve from zero over the dosing interval
AUC(0-τ)	Area under the concentration-time curve from zero to the last quantifiable blood or plasma concentration
BID	Twice daily
BOR	Best Overall Response
BP	Blood pressure
cfDNA	Circulating-free tumor DNA
CI	Confidence Interval
CL/F	Oral clearance
Cmax	Maximum observed concentration
CNV	Copy Number Variant
CPMS	Clinical Pharmacology Modeling & Simulation
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTC	Circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
DBR	Database Release
DBF	Database Freeze
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DP	Decimal Places
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOS	End of Study
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FISH	Fluorescent in situ hybridization
GSK	GlaxoSmithKline
ICH	International Conference on Harmonization
IDSL	International Data Standards Library

Abbreviation	Description
IHC	Immunohistochemistry
INDSR	Investigational New Drug Safety Report
INR	International Normalized Ratio
ka	Absorption rate constant
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
M	Mandatory
mCRPC	Metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MHRA	Medicines and Healthcare Products Regulatory Agency
mL	Milliliter
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
N, n	Number
NCI	National Cancer Institute
NE	Not evaluable
O	Optional
ORR	Objective Response Rate
PCWG2	Prostate Cancer Working Group 2
PD	Pharmacodynamic or progressive disease
PI3Kβ	Phosphoinositide 3-kinase beta
PK	Pharmacokinetic
PR	Partial response
PopPK	Population Pharmacokinetic
PS	Performance Status
PSA	Prostate-specific antigen
PSA50	Prostate-specific antigen decrease from baseline ≥50%
PT	Prothrombin time
PTEN	Phosphatase and tensin homolog
PTH	Parathyroid hormone
PTT	Partial thromboplastin time
Q4wks	Every 4 weeks
Q8wks	Every 8 weeks
Q12wks	Every 12 weeks
QD	Every day
QTc	Corrected QT interval
QTcB	QT interval corrected by Bazett's formula
QTcF	QT interval corrected by Fridericia's formula
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase II dose
rPFS	Radiological progression free survival

Abbreviation	Description
SAC	Statistical Analysis Complete
SAE	Serious adverse event(s)
SBP	Systolic blood pressure
SD	Stable disease or standard deviation
SNV	Small Nuclear Variant
SRM	Study Reference Manual
SRT	Safety Review Team
Tmax	Time of occurrence of maximum observed concentration
TMF	Trial Master File
UPC	Urine protein to creatinine
US	United States
V/F	Oral volume of distribution
Wk(s)	Week(s)

13.11.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
NONMEM
SAS
WinNonlin

13.12. Appendix 12: List of Data Displays

13.12.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.n	1.1 to 1.n
Efficacy	2.1 to 2.n	2.1 to 2.n
Safety	3.1 to 3.n	3.1 to 3.n
Pharmacokinetic	4.1 to 4.n	4.1 to 4.n
Biomarker	5.1 to 5.n	5.1 to 5.n
Section	**Listings**	
ICH Listings;	1 to x	
Other Listings	y to z	

13.12.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 13: Example Mock Shells for Data Displays

Section	Figure	Table	Listing
Study Population		POP_T1	
Efficacy		EFF_T1, EFF_T2, EFF_T3	EFF_L1, EFF_L2
Safety			
Pharmacokinetic			
Biomarker	BIO_F1		BIO_L1, BIO_L2, BIO_L3
Non-ICH			NICH_L1

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

13.12.3. Deliverables

Delivery [Priority] [1]	Description
SAC [X]	Final Statistical Analysis Complete

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort

13.12.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	All Treated Safety	ES8	Summary of Subject Status and Reason for Study Withdrawal	ICH E3, FDAAA, EudraCT	SAC
1.2.	All Treated Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3	SAC
1.3.	All Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	EudraCT/Clinical Operations; for all subjects screened;	SAC
1.4.	All Treated Safety	NS1	Summary of Number of Participant by Country and Site ID	EudraCT/Clinical Operations	SAC
1.5.	All Screened	POP_T1	Summary of Study Eligibility in Screening	/arenv/arprod/gsk2636771/p3b115717/sac/drivers/t_elig_prescn.sas	SAC
Protocol Deviation					
1.6.	All Treated Safety	DV1	Summary of Important Protocol Deviations	ICH E3	SAC
Population Analysed					
1.7.	All Treated Safety	SP1A	Summary of Study Population	IDSL	SAC
Demographic and Baseline Characteristics					
1.8.	All Treated Safety	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.9.	All Treated Safety	DM11	Summary of Age Ranges	EudraCT (<18-64, 65-84; >=85); DSUR (<18,18-64, 65- 74, >=75)	SAC
1.10.	All Treated Safety	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT; include all races and race details	SAC
1.11.	All Treated Safety	MH1	Summary of Past Medical Conditions	ICH E3	SAC
1.12.	All Treated Safety	MH1	Summary of Current Medical Conditions	ICH E3	SAC
1.13.	All Treated Safety	CM8	Summary of Concomitant Medications	ICH E3	SAC
Exposure and Treatment Compliance					
1.14.	All Treated Safety	EX1	Summary of Exposure to Study Treatment	ICH E3	SAC
1.15.					
1.16.	All Treated Safety	COMP1	Summary of Overall Compliance Based on Exposure		SAC
Disease Characteristics					
1.17.	All Treated Safety	DC1	Summary of Disease Characteristics at Initial Diagnosis	ICH E3 ; See Table 1.4 from /arenv/arprod/gsk2636771/mid200331/ dsur_2018_01/drivers/t_dischar_init.sas	SAC
1.18.	All Treated Safety	DC2	Summary of Disease Characteristics at Screening	See Table 1.5 from /arenv/arprod/ gsk2636771/mid200331/	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
				dsur_2018_01/drivers/ t_dischar_scr.sas add Time on Enza prior study,	
1.19.	All Treated Safety	LA1	Summary of Disease Burden at Baseline	ICH E3	SAC
Anti-Cancer Therapy					
1.20.	All Treated Safety	AC2	Summary of Prior Anti-Cancer Therapy	IDSL; add "Enzalutamide received prior to chemotherapy", “Enzalutamide received following chemotherapy”	SAC
1.21.	All Treated Safety	CM1	Summary of Pre-Treatment Dictionary Coded Anti-Cancer Therapy	IDSL	SAC
1.22.	All Treated Safety	CM1	Summary of Post-Treatment Dictionary Coded Anti-Cancer Therapy	IDSL	SAC
1.23.	All Treated Safety	AC3	Summary of Number of Prior Anti-Cancer Therapy Regimens	IDSL; include Biologic, chemotherapy, hormonal, immunotherapy, radioactive therapy, and small molecule targeted therapy along with radiotherapy and surgery	SAC
1.24.	All Treated	AC4	Summary of Best Response to Prior Enzalutamide Therapy		SAC
1.25.	All Treated Safety	AC4	Summary of the Most Recent Best Response to Prior Anti-Cancer Therapies	IDSL; By therapies	SAC
1.26.	All Treated Safety	FAC1	Summary of Post-Treatment Anti-Cancer Therapy	IDSL; include Biologic, chemotherapy, hormonal, immunotherapy, radioactive therapy, and small molecule targeted therapy along with radiotherapy and	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
				surgery	
Surgical and Medical Procedures					
1.27.	All Treated Safety	OSP1	Summary of Prior Cancer-Related Surgical Procedures	IDSL, include follow-up surgeries separately if present	SAC
Substance Use					
1.28.	All Treated Safety	SU1	Summary of Substance Use	IDSL, include Smoking history and alcohol use	SAC

13.12.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.1.	Modified All Treated Clinical Activity	EFF_T1	Summary of Confirmed and Unconfirmed Non-PD Response Rate at 12 Weeks (PCWG2 Criteria)	Include 95% exact confidence interval	SAC
2.2.	All Treated Clinical Activity	RE1a	Summary of Investigator-Assessed Best Response (RECIST 1.1 Criteria) (Confirmed) for Subjects with Target Lesion and/or Non-Target Lesion at Baseline	Including response without confirmation; (see Table 2.006 present_2016_1 reporting effort)	SAC
2.3.	All Treated Clinical Activity	RE1a	Summary of Investigator-Assessed Best Response (RECIST 1.1 Criteria) (Unconfirmed) for Subjects with Target Lesion and/or Non-Target Lesion at Baseline	Including response with confirmation; (see Table 2.007 from present_2016_1 reporting effort)	SAC
2.4.	All Treated Clinical Activity	EFF_T2	Summary of PSA50 Response for All Subjects (Confirmed)	Including response with confirmation (see Table 2.008 from present_2016_1 reporting effort), provide overall results and results stratified by measurable vs. non-measurable disease at baseline	SAC
2.5.	All Treated Clinical Activity	EFF_T2	Summary of PSA50 Response for All Subjects (Unconfirmed)	Including response without confirmation (see Table 2.009 from present_2016_1 reporting effort), provide overall results and results stratified by measurable vs. non-measurable disease at baseline	SAC
2.6.	All Treated Clinical Activity	TTE1	Summary of Time to PSA progression (PCWG2 criteria)	Add footnote indicating 400 mg cohort not summarized individually due to small sample size (n=2)	SAC
2.7.	All Treated Clinical Activity	TTE1	Summary of Time to radiological progression (PCWG2 criteria)	Add footnote indicating 400 mg cohort not summarized individually due to small sample size (n=2)	SAC
2.8.	All Treated Clinical Activity	TTE1	Summary of Investigator-Assessed Radiological Progression-Free Survival (PCWG2 Criteria)	Add footnote indicating 400 mg cohort not summarized individually due to small sample size (n=2)	SAC

13.12.6. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.1	All Treated Clinical Activity		Waterfall Plot of Maximum Reduction in PSA Values by Dose	arenv/arprod/gsk2636771/mid200331/present_2018_01/drivers/f_water_psa.sas	SAC
2.2	All Treated Clinical Activity	OLB12B	Mean Change (95% CI) Change from Baseline in PSA by Time and Treatment		SAC
2.3	All Treated Clinical Activity		Spider Plot of Percent Change from Baseline in PSA values by Dose	arenv/arprod/gsk2636771/mid200331/present_2018_01/drivers/f_spider_psa_1.sas	SAC
2.4	All Treated Clinical Activity		Waterfall Plot of Maximum Reduction in Target Lesion Diameter by Dose	arenv/arprod/gsk2636771/mid200331/present_2018_01/drivers/f_delta_p1.sas	SAC
2.5	All Treated Clinical Activity		Spider Plot of Percent Change from Baseline in Target Lesion Diameter by Dose	arenv/arprod/gsk2636771/mid200331/present_2018_01/drivers/f_spider_nmc_2.sas	SAC
2.6	All Treated Clinical Activity	OEX12	Swimming Lane Plot of Duration of Study Treatment by Dose	One panel for each cohort; add labels of PR, PSA PD, Radiological PD, clinical PD, DLT, AEs leading to dose reduction/interruption etc.	SAC
2.7	All Treated Clinical Activity	TTE10	Graph of Kaplan Meier Investigator-Assessed Radiological Progression-Free Survival Curves by dose	Do not summarize results for the 400 mg cohort	SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.8	All Treated Clinical Activity	TTE10	Graph of Kaplan Meier Investigator-Assessed Radiological Progression-Free Survival Curves (overall)	400 mg included in overall summary	SAC
2.9	All Treated Clinical Activity	TTE10	Graph of Kaplan Meier Curves for Time to PSA Progression by dose	Do not summarize results for the 400 mg cohort	SAC
2.10	All Treated Clinical Activity	TTE10	Graph of Kaplan Meier Curves for Time to PSA Progression (overall)	400 mg included in overall summary	SAC
2.11	All Treated Clinical Activity	TTE10	Graph of Kaplan Meier Curves for Time to Radiological Progression by dose	Do not summarize results for the 400 mg cohort	SAC
2.12	All Treated Clinical Activity	TTE10	Graph of Kaplan Meier Curves for Time to Radiological Progression (overall)	400 mg included in overall summary	SAC

13.12.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	All Treated Safety	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term	ICH E3	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.2.	All Treated Safety	AE3	Summary of Common (>=5%) Adverse Events by Overall Frequency	ICH E3	SAC
3.3.	All Treated Safety	AE3	Summary of Common (>=5%) Grade 2-4 Adverse Events by Overall Frequency	ICH E3	SAC
3.4.	All Treated Safety	AE3	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Grade	ICH E3	SAC
3.5.	All Treated Safety	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term and Maximum Grade	FDAAA, EudraCT ‘	SAC
3.6.	All Treated Safety	AE3	Summary of Common (>=5%) Drug-Related Grade 2-4 Adverse Events by Overall Frequency	ICH E3	SAC
3.7.	All Treated Safety	OAE07	Summary of All Adverse Events by Maximum Grade		SAC
3.8.	All Treated Safety	OAE07	Summary of Adverse Events Related to Study Treatment by Maximum Grade		SAC
3.9.	All Treated Safety	AE3	Summary of Adverse Events Leading to Dose Reductions	By preferred term	SAC
3.10.	All Treated Safety	AE3	Summary of Adverse Events Leading to Dose Escalations	By preferred term	SAC
3.11.	All Treated Safety	AE3	Summary of Adverse Events Leading to Dose Interruptions	By preferred term	SAC
Adverse Events of Special Interest					
3.12.	All Treated Safety	ESI1	Summary of Characteristics of Hypocalcaemia		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.13.	All Treated Safety	ESI2a	Summary of Onset and Duration of the First Occurrence of Hypocalcaemia		SAC
3.14.	All Treated Safety	OAE01	Summary of Hypocalcaemia by Maximum Grade	by AESI and preferred term	SAC
3.15.	All Treated Safety	AE17	Summary of Exposure Adjusted Incidence Rate for Hypocalcaemia by Maximum Grade		SAC
3.16.	All Treated Safety	ESI1	Summary of Characteristics of Increase in Creatinine		SAC
3.17.	All Treated Safety	ESI2a	Summary of Onset and Duration of the First Occurrence of Increase in Creatinine		SAC
3.18.	All Treated Safety	OAE01	Summary of Increase in Creatinine by Maximum Grade	by AESI and preferred term	SAC
3.19.	All Treated Safety	AE17	Summary of Exposure Adjusted Incidence Rate for Increase in Creatinine by Maximum Grade		SAC
Serious and Other Significant Adverse Events					
3.20.	All Treated Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT	SAC
3.21.	All Treated Safety	AE3	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment by Preferred Term		SAC
3.22.	All Treated Safety	AE3	Summary of Serious Adverse Events by Maximum Grade	By preferred term	SAC
3.23.	All Treated Safety	AE3	Summary of Drug Related Serious Adverse Events by Maximum Grade	By preferred term	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.24.	All Treated Safety	AE3	Summary of Fatal Adverse Events	If there are < 5 fatal AEs, only provide listing.	SAC
3.25.	All Treated Safety	AE3	Summary of Drug Related Fatal Adverse Events	If there are < 5 fatal AEs, only provide listing.	SAC
3.26.	All Treated Safety	AE3	Summary of Non-Serious Drug-Related Adverse Events by Overall Frequency		SAC
3.27.	All Treated Safety	AE3	Summary of Serious Drug-Related Adverse Events by Overall Frequency		SAC
Deaths					
3.28.	All Treated Safety	DTH1A	Summary of Deaths	IDSL; report time to death from last dose in weeks	SAC
3.29.	All Treated Safety	AE5	Summary of Cardiovascular Events by maximum Grade	See Section 8.6.1 for details.	SAC
Laboratory: Chemistry					
3.30.	All Treated Safety	LB1	Summary of Chemistry Changes from Baseline	ICH E3; include PSA, serum testosterone, and PTH, ionized calcium, vitamin D (total D, D1, D2, and D3), Serum Bone Markers (osteocalcin, Bone Specific Alk Phos, Serum N-telopeptide)	SAC
3.31.	All Treated Safety	LB1	Summary of Percent Changes in Chemistry from Baseline	include PSA, serum testosterone, and PTH, ionized calcium, vitamin D (total D, D1, D2, and D3), Serum Bone Markers (osteocalcin, Bone Specific Alk Phos, Serum N-telopeptide)	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.32.	All Treated Safety	OLB9C	Summary of Worst Case Chemistry Results by Maximum Grade Increase Post-Baseline Relative to Baseline	ICH E3; by visit summary rows are not needed	SAC
3.33.	All Treated Safety	OLB11B	Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	SAC
Laboratory: Haematology					
3.34.	All Treated Safety	LB1	Summary of Haematology Changes from Baseline	ICH E3; include PT, PTT, and INR	SAC
3.35.	All Treated Safety	LB1	Summary of Percent Changes in Haematology from Baseline	include PT, PTT, and INR	SAC
3.36.	All Treated Safety	OLB9C	Summary of Worst Case Haematology Results by Maximum Grade Increase Post-Baseline Relative to Baseline	ICH E3; by visit summary rows are not needed	SAC
3.37.	All Treated Safety	OLB11B	Summary of Worst Case Haematology Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	SAC
Laboratory: Urinalysis					
3.38.	All Treated Safety	LB1	Summary of Urine Concentration Changes from Baseline	ICH E3; include Urine Bone Marker (Urine C-telopeptide),	SAC
3.39.	All Treated Safety	LB1	Summary of Percent Changes in Urine Concentration from Baseline	include Urine Bone Marker (Urine C-telopeptide),	SAC
3.40.	All Treated Safety	OUR1B	Summary of Worst Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline	ICH E3	
Laboratory: Hepatobiliary (Liver)					
3.41.	All Treated Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	IDSL	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.42.	All Treated Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL	SAC
ECG					
3.43.	All Treated Safety	EG1	Summary of ECG Findings	IDSL	SAC
3.44.	All Treated Safety	OECG1B	Summary of Maximum Fridericia's QTc Values Post-Baseline Relative to Baseline by Category	IDSL	SAC
3.45.	All Treated Safety	EG2	Summary of Change from Baseline in ECG values by Visit	IDSL	SAC
3.46.	All Treated Safety	OECG2B	Summary of Maximum Increase in Fridericia's QTc Values Post-Baseline Relative to Baseline by Category	IDSL	SAC
Vital Signs					
3.47.	All Treated Safety	VS1	Summary of Change from Baseline in Vital Signs	ICH E3	SAC
3.48.	All Treated Safety	OVT2B	Summary of Worst Case Vital Signs Results by Maximum Grade Increase Post-Baseline Relative to Baseline	IDSL	SAC
3.49.	All Treated Safety	OVTB	Summary of Worst Case Vital Signs Results Relative to Normal Range Post-Baseline Relative to Baseline	IDSL	SAC
LVEF					
3.50.	All Treated Safety	OLVEF1A	Summary of Left Ventricular Ejection Fraction (%) Absolute Change from Baseline	IDSL; Add "(%) Absolute" in title; remove column "LVEF (%)"	SAC
Dose Modifications					
3.51.	All Treated Safety	ODMOD1	Summary of Dose Reductions of GSK2636771	ICH E3	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.52.	All Treated Safety	ODMOD1	Summary of Dose Escalations of GSK2636771	ICH E3	SAC
3.53.	All Treated Safety	ODMOD2	Summary of Dose Interruptions of GSK2636771	ICH E3	SAC
3.54.	All Treated Safety	ODMOD1	Summary of Dose Reductions of Enzalutamide	ICH E3	SAC
3.55.	All Treated Safety	ODMOD1	Summary of Dose Escalations of Enzalutamide	ICH E3	SAC
3.56.	All Treated Safety	ODMOD2	Summary of Dose Interruptions of Enzalutamide	ICH E3	SAC
Dose Limiting Toxicity (DLT)					
3.57.	All Treated Safety	DL1	Summary of Dose-Limiting Toxicities during the Determinative Period	ICH E3	SAC
Performance Status					
3.58.	All Treated Safety	PS1A	Summary of ECOG Performance Status	ICH E3	SAC
3.59.	All Treated Safety	PS4A	Summary of Change in ECOG Performance Status from Baseline		SAC

13.12.8. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.1.	All Treated Safety	AE10	Plot of Common (>=5%) Adverse Events	IDSL	SAC
Laboratory					
3.2.	All Treated Safety	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin	IDSL	SAC
3.3.	All Treated Safety	LB11	Figure of LFT Patient Profiles for Possible Hy's Law Subjects by Dose	If there are subjects with liver events	SAC
3.4.	All Treated Safety	LB7	Summary of change from Baseline in Calcium values by Dose (Hypocalcaemia, hypophosphatemia, creatinine increase)		SAC
ECG					
3.5.	All Treated Safety	OECG4	Fridericia's QTc Shifts from Baseline to Worst-case Post Baseline	IDSL	SAC

13.12.9. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration					
4.1.	PK concentration	PK01	Summary of GSK2636771 (in the presence of enzalutamide) Plasma Pharmacokinetic Concentration-Time Data by dose	IDSL	SAC
4.2.	PK concentration	PK01	Summary of Enzalutamide Plasma Pharmacokinetic Concentration-Time Data by Dose (with and without GSK2636771)	IDSL	SAC
4.3.	PK concentration	PK01	Summary of N-desmethyl enzalutamide Plasma Pharmacokinetic Concentration-Time Data by Dose (with and without GSK2636771)	IDSL	SAC

13.12.10. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK					
4.1.	PK concentration	PK16a	Individual GSK2636771 (in the presence of enzalutamide) Concentration-Time Plots (Linear and Semi-log) - Dose Escalation Phase only	IDSL	SAC
4.2.	PK concentration	PK17	Mean GSK2636771 (in the presence of enzalutamide) Concentration-Time Plots (Linear and Semi-log) by Dose - Dose Escalation Phase only	IDSL	SAC
4.3.	PK concentration	PK18	Median GSK2636771 (in the presence of enzalutamide) Concentration-Time Plots (Linear and Semi-log) by Dose - Dose Escalation Phase only	IDSL	SAC
4.4.	PK concentration	PK16a	Individual Enzalutamide Concentration-Time Plots (Linear and Semi-log) - Dose Escalation Phase only (with and without GSK2636771)	IDSL	SAC
4.5.	PK concentration	PK17	Mean Enzalutamide Concentration-Time Plots (Linear and Semi-log) by Dose- Dose Escalation Phase only (with and without GSK2636771)	IDSL	SAC
4.6.	PK concentration	PK18	Median Enzalutamide Concentration-Time Plots (Linear and Semi-log) by Dose- Dose Escalation Phase only (with and without GSK2636771)	IDSL	SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.7.	PK concentration	PK16a	Individual N-desmethyl enzalutamide Concentration-Time Plots (Linear and Semi-log) - Dose Escalation Phase only (with and without GSK2636771)	IDSL	SAC
4.8.	PK concentration	PK17	Mean N-desmethyl enzalutamide Concentration-Time Plots (Linear and Semi-log) by Dose- Dose Escalation Phase only (with and without GSK2636771)	IDSL	SAC
4.9.	PK concentration	PK18	Median N-desmethyl enzalutamide Concentration-Time Plots (Linear and Semi-log) by Dose- Dose Escalation Phase only (with and without GSK2636771)	IDSL	SAC
4.10.	PK Concentration	PK19	Mean enzalutamide and GSK2636771 (by dose) Concentration-Time Plots (with and without GSK2636771)	Plot GSK2636771 concentrations by dose	SAC
4.11.	PK Concentration	PK19	Mean N-desmethyl enzalutamide and GSK2636771 (by dose) Concentration-Time Plots (with and without GSK2636771)	Plot GSK2636771 concentrations by dose	SAC

13.12.11. Biomarker Tables

Biomarker: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.1	Biomarker	BIO_T1	Summary of Conversion (>5 cells/mL dropping to ≤5 cells/mL) from Baseline in CTCs by Visit		SAC
5.2	All Screened	BIO_T2	Summary of Frequency of PTEN Loss (H-Score ≤ 30) at Screening		SAC
5.3	Biomarker	BIO_T3	Categorization of PTEN loss by Sequencing (homozygous vs heterozygous)		SAC

13.12.12. Biomarker Figures

Biomarker: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.1	Biomarker	BIO_F1	Heatmap Display of 2 or More Gene Alterations by Subject		SAC

13.12.13. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	All Enrolled	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC
2.	All Treated Safety	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC
3.	All Treated Safety	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH E3	SAC
4.	All Treated Safety	TA1	Listing of Planned and Actual Treatments	IDSL	SAC
Protocol Deviations					
5.	All Treated Safety	DV2	Listing of Important Protocol Deviations	ICH E3	SAC
6.	All Treated Safety	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC
Populations Analysed					
7.	All Treated Safety	SP3	Listing of Participants Excluded from Any Population	ICH E3	SAC
Demographic and Baseline Characteristics					
8.	All Treated Safety	DM2	Listing of Demographic Characteristics	ICH E3	SAC
9.	All Treated Safety	DM9	Listing of Race	ICH E3	SAC
Prior and Concomitant Medications					
10.	All Treated Safety	CP_CM3	Listing of Concomitant Medications	IDSL	SAC
Exposure and Treatment Compliance					

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
11.	All Treated Safety	OEX3A	Listing of Exposure to Enzalutamide	ICH E3	SAC
12.	All Treated Safety	OEX3A	Listing of Exposure to GSK2636771		SAC
13.	All Treated Safety	COMP2	Listing of Study Treatment Compliance		SAC
14.	All Treated Safety	ODMOD10a	Listing of Dose Reductions		SAC
15.	All Treated Safety	ODMOD10a	Listing of Dose Escalations		SAC
16.	All Treated Safety	ODMOD11a	Listing of Dose Interruptions		SAC
Response					
17.	Modified All Treated Clinical Activity	EFF_L1	Listing of Overall Unconfirmed Response at Week 12	List all data used for Table 2.1 by cohort and subject – see Listing 2.010 from reporting effort present_2016_1	SAC
18.	Modified All Treated Clinical Activity	EFF_L1	Listing of Overall Confirmed Response at Week 12	List all data used for Table 2.1 by cohort and subject – see Listing 2.010 from reporting effort present_2016_1	SAC
19.	All Treated Clinical Activity	LA2	Listing of Investigator Assessed Target Lesion Assessments (RECIST 1.1 Criteria)		SAC
20.	All Treated Clinical Activity	LA3	Listing of Investigator-Assessed Non-Target Lesion Assessments (RECIST 1.1 Criteria)		SAC
21.	All Treated Clinical Activity	LA4	Listing of Investigator -Assessed New Lesions (RECIST 1.1 Criteria)		SAC
22.	All Treated Clinical Activity	RE5	Listing of Investigator -Assessed Tumour Responses(RECIST1.1 Criteria)	Include with and without confirmation in same listing	SAC
23.	All Treated Clinical Activity	OLB7	Listing of Subject PSA Value by Visit/Week		SAC
24.	All Treated Clinical Activity	LA2	Listing of Subject Bone Scan Results by Visit/Week	Use lesion dataset where lsorgcd=BE	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
25.	All Treated Clinical Activity	TTE9	Listing of Time to PSA Progression		SAC
26.	All Treated Clinical Activity	TTE9	Listing of Time to Radiological Progression		SAC
27.	All Treated Clinical Activity	TTE9	Listing of Radiographic Progression-Free Survival		SAC
Adverse Events					
28.	All Treated Safety	AE8	Listing of All Adverse Events	ICH E3	SAC
29.	All Treated Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC
30.	All Treated Safety	AE2	Listing of Relationship Between System Organ Class, Preferred Terms and Verbatim Text	IDSL	SAC
Serious and Other Significant Adverse Events					
31.	All Treated Safety	AE8	Listing of Fatal Serious Adverse Events	ICH E3	SAC
32.	All Treated Safety	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3	SAC
33.	All Treated Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC
34.	All Treated Safety	AE8	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment	ICH E3	SAC
35.	All Treated Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study	ICH E3	SAC
Dose Limiting Toxicities					
36.	All Treated Safety	DL3	Listing of Dose-Limiting Toxicities (DLTs) During the Determinative Period		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Deaths					
37.	All Treated Safety	DTH3	Listing of Deaths	ICH E3	SAC
Hepatobiliary (Liver)					
38.	All Treated Safety	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events	IDSL	SAC
39.	All Treated Safety	SU2	Listing of Substance Use for Participants with Liver Stopping Events	IDSL	SAC
All Laboratory					
40.	All Treated Safety	LB5A	Listing of All Laboratory Data for Participants with Any Value Outside Normal Range	ICH E3; include PSA, serum testosterone, parathyroid hormone, PT, PTT, INR	SAC
41.	All Treated Safety	LB5A	Listing of All Bone Biomarker Laboratory Data	Include ionized calcium, vitamin D (total D, D1, D2, and D3), Urine Bone Marker (Urine C-telopeptide), Serum Bone Markers (osteocalcin, Bone Specific Alk Phos, Serum N-telopeptide)	SAC
42.	All Treated Safety	LB14	Listing of Laboratory Data with Character Results	ICH E3	SAC
43.	All Treated Safety	UR2A	Listing of Urinalysis Data for Participants with Any Value of Potential Clinical Importance	ICH E3	SAC
ECG					
44.	All Treated Safety	EG3	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance	IDSL	SAC
45.	All Treated Safety	EG5	Listing of All ECG Findings for Participants with an Abnormal ECG Finding	IDSL	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
46.	All Treated Safety	OECG5A	Listing of Fridericia's QTc Values of Potential Clinical Importance		SAC
Vital Signs					
47.	All Treated Safety	OVT7A	Listing of Vital Signs with Values of Potential Clinical Importance		SAC
Performance Status					
48.	All Treated Safety	PS5A	Listing of Performance Status		SAC

13.12.14. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Disease Characteristics					
49.	All Treated Safety	DC3	Listing of Disease Characteristics at Initial Diagnosis		SAC
50.	All Treated Safety	DC4	Listing of Disease Characteristics at Screening		SAC
51.	All Treated Safety	MD2	Listing of Metastatic Disease at Screening		SAC
52.	All Treated Safety	MH2	Listing of Current and Past Medical Conditions	Only required is conditions are not MedDRA coded	SAC
Anti-Cancer Therapy					
53.	All Treated Safety	AC6	Listing of Prior Anti-Cancer Therapy		SAC
54.	All Treated Safety	AC7	Listing of Prior Anti-Cancer Radiotherapy		SAC
55.	All Treated Safety	AC6	Listing of Follow-up Anti-Cancer Therapy		SAC
56.	All Treated Safety	AC7	Listing of Follow-up Anti-Cancer Radiotherapy		SAC
Surgical Procedures					
57.	All Treated Safety	OSP3	Listing of Prior/Post-Treatment Cancer Related Surgical Procedures		SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Substance Use					
58.	All Treated Safety	SU2	Listing of Substance Use		SAC
Responses					
59.	All Treated Clinical Activity	RE6	Listing of Subjects with Progressive Disease Based on Clinical Assessment		SAC
LVEF					
60.	All Treated Safety	OLVEF2A	Listing of Left Ventricular Ejection Fraction Results	Option	SAC
PK					
61.	PK Concentration	PK07	Listing of GSK2636771 (in the presence of enzalutamide) Pharmacokinetic Concentration-Time Data by Dose	IDSL	SAC
62.	PK Concentration	PK07	Listing of Enzalutamide Pharmacokinetic Concentration-Time Data by Dose	IDSL	SAC
63.	PK Concentration	PK07	Listing of N-desmethyl enzalutamide Pharmacokinetic Concentration-Time Data by Dose	IDSL	SAC
Other					
64.	All Treated Safety	NICH_L1	Listing of Subjects Received Blood Product or Blood Supportive Care	Including all data in BLDPROD dataset	SAC
65.	All Treated Safety		Listing of Circulating Tumour Cells (CTC) Concentrations	arenv/arprod/gsk2636771/p3b115717/sac/drivers/t_ctc.sas; add column indicating whether there have been conversion to < 5 cells/7.5mL from week 1.	SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
66.	All Treated Safety	OLIVER5	Listing of Liver Chemistry Assessments for Subjects with Liver Signal/Events		SAC
67.	All Treated Safety	PREG1a	Listing of Pregnancies	update for partners who became pregnant	SAC

13.13. Appendix 13: Example Mock Shells for Data Displays

Data Display Specification will be made available on request