Clinical Study Protocol	
Study Intervention	Saruparib (AZD5305)
Study Code	D9721C00002
Version	5.0
Date	11 September 2024

EU CT Number	2023-503691-25-00
IND Number	162254

An Open-label, Randomised, Phase I, Multi-centre Study to Investigate the Biological Effects of Saruparib (AZD5305) Alone, Darolutamide Alone, and in Combination Given Prior to Radical Prostatectomy in Men with Newly Diagnosed Prostate Cancer (ASCERTAIN)

Sponsor Name: AstraZeneca AB

Legal Registered Address: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifier Number:

EU CT Number: 2023-503691-25-00
IND Number: 162254

This protocol has been subject to a peer review according to AstraZeneca Standard procedures. The protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Standard - Bioethics and in compliance with prevailing laws and regulations.

Version Scope: Global

Brief Title: A Study to Investigate the Biological Effects of Saruparib (AZD5305) Alone, Darolutamide Alone, and in Combination Given Prior to Radical Prostatectomy in Men with Newly Diagnosed Prostate Cancer (ASCERTAIN)

Study Phase: I

Acronym: ASCERTAIN

Study Clinical Lead Name and Contact Information will be provided separately.

Study Clinical Lead is responsible for the clinical integrity of the study (for example, the study physician or scientist).

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 4	11 September 2024
Amendment 3	31 January 2024
Amendment 2	12 September 2023
Amendment 1	25-May-2023
Original Protocol	02-Mar-2023

Amendment 4 (11 September 2024)

The Clinical Study Protocol (CSP) version 4.0, 31 January 2024, has been amended to reduce the Schedule of Assessment (SoA) burden on patients and make the CSP more patient centric. Additional edits were made to include clarifications and to align with the sponsor's protocol authoring requirements for early development oncology studies.

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Throughout	Minor typographic edits	To provide clarity and improve consistency	Non-substantial
Synopsis, Table 1 SoA for Study Treatment Arms, and Table 2 SoA for No-treatment Arm, Section 4.1 Overall Design, and Section 8.4.1 Time Period and Frequency of Collection	The post-surgery follow-up visit is expected to happen 7 to 90 days after surgery. Study visit was re-named in the protocol. The time window for this visit was amended to state 7 to 90 days	Provide flexibility to sites	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Table 1 SoA for Study Treatment Arms	The time window for the Day 15 visit was amended to ±3 days. The Day 15 and Day before RP assessments can be combined in the same visit if the visit window allows. In this instance, all assessments required for Day 15 and the Day before RP must be performed on the single visit Blood sample collection for PK and pharmacodynamic assessments was no longer required on Day 15 Blood sample collection for PK and pharmacodynamic assessments was updated to specify that this should be on Day 21 if there are no RP delays or on the Day of the RP visit and collected before surgery Changes were made to the footnote to provide additional clarity for sites and additional information on blood sampling for the genomic research as already included in Appendix D The numbering of footnotes was adjusted as needed	Provide flexibility to sites	Substantial
Table 1 SoA for Study Treatment Arms, and Table 2 SoA for No-treatment Arm	Screening window was amended to Day 28 to Day -1 and footnote was amended to state that certain assessments conducted at Screening may be re-used for the Day 1 visit rather than repeat the test provided these assessments are conducted within 7 days of Day 1	Provide flexibility to sites and clarity to sites	Not substantial
Synopsis, Table 1 SoA for Study Treatment Arms, Schema (Figure 1), and Section 4.1 Overall Design	The footnote on radical prostatectomy (RP) on Day 22 was updated to specify that participants should undergo RP the next day if feasible to minimise any delays between stopping treatment and RP	To provide clarity to sites	Non-substantial
Synopsis and Section 6.6.7 Safety Data Monitoring Committee	Updates were made to specify that the SDMC will review safety data when available and that biomarker data at the time of the SDMC meeting may also be presented	To provide clarity to sites	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 4.4 End-of-Study Definition	Statement added that a participant is considered to have completed the study if they have completed all phases of the study including the post-surgery follow-up visit	To provide clarity to sites and align with latest Sponsor template	Non-substantial
Section 5.1 Inclusion Criteria and Section 6.8.1 Concomitant Therapy (Table 11 Prohibited Concomitant Medications)	The requirement for patients taking warfarin (coumarin derivatives) to switch to low-molecular weight heparin before study entry was removed. Participants unable to switch may participate in the study; however, it is recommended that International Normalisation Ratio (INR) is monitored frequently Table 11 was also updated to include this change	To provide flexibility to sites	Substantial
Section 5.1 Inclusion Criteria	The criterion related to informed consent for the Optional Genetic Research was amended so that it was clear that this is an optional informed consent	To provided clarity to sites	Non-substantial
Section 6.6.4 Dose Modification Guidelines for Darolutamide and Appendix G3 (Table 20 and Table 21)	Details from the Toxicity Management guidelines (TMG) were added to the protocol. Participants were to discontinue study treatment if ALT or AST rise to > 3 × ULN with monitoring continued until ALT and/or AST returns to baseline or normal values. The phrasing in Table 20 and Table 21 in Appendix G3 was updated	To provided clarity to sites	Substantial
Section 6.8.1 Concomitant Therapy	Formatting amendment from a bullet point and 'Note' added as medications administered as standard of care during surgery do not need reporting	To provided clarity to sites	Non-substantial
Section 8.5.1 Collection of Samples for Pharmacokinetics (Table 17 PK/Blood for PD [PAR] Timepoints [Study Treatment Arms])	Blood sample collection for PK and pharmacodynamic assessments was no longer required on Day 15 The follow-up visit after surgery was renamed for consistency Footnotes were amended for consistency with changes to the SoA	For consistency and to provide clarity to sites	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Appendix A	European Union (EU) safety reporting requirements were updated to add the CTR SUSAR statement as the study is expected to continue beyond 30 January 2025. The wording on personal data breaches and data retention was updated as per the latest template. The web address for the site where the clinical study will be described was updated	To align with latest EU safety reporting requirements and the Sponsor's updated template	Non-substantial
Appendix B AEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Minor updates were made to the wording as per the latest CSP template	To align with the Sponsor's updated template	Non-substantial

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
γH2Ax	Gamma-histone 2AX (Ser139)
ADT	Androgen deprivation therapy
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase/Transaminase
AML	Acute myeloid leukaemia
AR	Androgen receptor
AST	Aspartate Aminotransferase/Transaminase
BCR	Binding Corporate Rules
BCRP	Breast cancer resistance protein
BID	Twice daily
BP	Blood pressure
BRCA	Breast cancer gene
CFR	Code of Federal Regulations
CHIP	Clonal Haematopoiesis of Indeterminate Potential
CI	Confidence interval
CRF	Case Report Form
CRO	Contract Research Organisation
CTCAE	Common Terminology Criteria for Adverse Events
CSP	Clinical Study Protocol
CSR	Clinical Study Report
ctDNA	Circulating tumour DNA
CVS	Cardiovascular
CYP	Cytochrome P450
DCO	Data cut-off
DDI	Dose-dependent interaction
DDR	DNA damage repair response
DILI	Drug Induced Liver Injury
DUS	Disease Under Study
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU CT	EU Clinical Trial

Abbreviation or special term	Explanation
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
HBS	Human Biological Sample(s)
HepB	Hepatitis B
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCP	Healthcare professional
HCV	Hepatitis C virus
HR	Heart rate
HRD	Homologous recombination deficient
HRR	Homologous recombination repair
HRRm	Homologous recombination repair gene mutation
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalised Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
LRV	Lower reference value
mCRPC	Metastatic castration-resistant prostate cancer
mCSPC	Metastatic castration-sensitive prostate cancer
MDS	Myelodysplastic syndrome
mRNA	Messenger RNA
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NHA	New hormonal agents
NIMP	Non-investigational Medicinal Product
NOAC	Non-vitamin K antagonist oral anticoagulants
NYHA	New York Heart Association
OATP	Organic anion transporting polypeptides

Abbreviation or special term	Explanation
QD	Once daily
OS	Overall survival
PAR	Poly (adenosine diphosphate–ribose)
PARP	Poly (adenosine diphosphate ribose) polymerase
PARPi	Inhibitor of poly (adenosine diphosphate ribose) polymerase
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PFS	Progression-free survival
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic(s)
PSA	Prostate-specific antigen
QTcF	QT interval with Fridericia's correction
RP2D	Recommended Phase 2 Dose
rPFS	Radiographic progression-free survival
RNA	Ribonucleic acid
RP	Radical prostatectomy
RTSM	Randomisation and Trial Supply Management
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SDMC	Safety and Data Monitoring Committee
SoA	Schedule of Activities
TBL	Total Bilirubin
TdP	Torsades de Pointes
TMG	Toxicity management guidelines
TPV	Third party vendor
TV	Target value
ULN	Upper Limit of Normal
USPI	United States Prescribing Information

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

An Open-label, Randomised, Phase I, Multi-centre Study to Investigate the Biological Effects of Saruparib (AZD5305) Alone, Darolutamide Alone, and in Combination Given Prior to Radical Prostatectomy in Men with Newly Diagnosed Prostate Cancer (ASCERTAIN)

Brief Title:

A Study to Investigate the Biological Effects of Saruparib (AZD5305) Alone, Darolutamide Alone, and in Combination Given Prior to Radical Prostatectomy in Men with Newly Diagnosed Prostate Cancer (ASCERTAIN)

Regulatory Agency Identifier Number:

EU CT Number:
IND Number: 162254

Rationale:

ASCERTAIN, is a Phase I, open-label, randomised, multi-centre study to investigate the mechanism of action of saruparib, previously known as AZD5305, or darolutamide alone, or when given in combination to patients with localised unfavourable-intermediate risk/high risk/very high risk prostate cancer who are eligible for curative radical prostatectomy.

Saruparib is a novel PARPi that has the unique properties to potently and selectively inhibit and trap PARP1. In biochemical assays, saruparib has an IC_{50} against the PARP1 recombinant enzyme of 3.6 nM, with a > 2-log-fold selectivity for PARP1 against PARP2 and any of the other members of the PARP family (Illuzzi et al 2021, Johannes et al 2021, Leo and Johannes, 2021). All currently approved PARPi are almost equipotent in targeting PARP1 and PARP2 (2 members of the PARP family). Recent literature reports suggest that inhibition of only PARP1 is required for the anti-proliferative effect (Murai et al 2012), and that PARP2 has been shown in animal models to play a key role in the survival of haematopoietic stem progenitor cells (Farrés et al 2013; Farrés et al 2015). These observations suggest that inhibition and trapping of PARP2, a feature shared by all the current approved PARPi, is not needed for anticancer effects, and is hypothesised to be a potential contributor to haematological toxicity observed in patients. For these reasons, saruparib may have improved therapeutic index with less toxicities compared with currently approved PARPi. Saruparib is currently being developed as an oral therapy, both as a monotherapy and in combination with chemotherapy and antibody drug conjugates.

Despite recent emerging data suggesting that combining a PARPi and NHA can further improve survival benefit for patients with metastatic prostate cancer, the mechanisms behind this combination benefit are not fully understood. A significant improvement in rPFS was demonstrated when olaparib was added to abiraterone acetate + ADT compared with abiraterone acetate alone for both men with mCRPC who had previously received docetaxel (Clarke et al 2018) and those who had not received a prior line of systemic therapy (Clarke et al 2022), irrespective of HRRm status. Moreover, the TALAPRO-2 study of talazoparib + enzalutamide in patients with mCRPC has recently shown a statistically significant and clinically meaningful improvement in rPFS compared with placebo + enzalutamide (Agarwal et al 2023).

While recent clinical data demonstrate the benefit of combining these 2 treatments, there is a lack of detailed understanding on the mechanism of action for combining a PARPi with an NHA, and the availability of non-clinical models is limited in prostate cancer, especially in the early disease setting. This window of opportunity clinical trial, ASCERTAIN, was designed to further elucidate the mechanism of action behind the benefit of combining NHA + PARPi. Demonstrating a mechanism of action in clinical samples would further support the use of this combination therapy in clinical practice. Moreover, it is hypothesised that by sparing PARP2, saruparib may offer a more efficacious and less toxic cancer treatment in the combination settings compared with currently approved PARPi.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the effects of study treatment on γH2AX change in participants with localised prostate cancer	• Fold change in % γH2AX positive cells from baseline value in tumour samples
Secondary	
• To assess the safety and tolerability of study treatment in participants with localised prostate cancer	• Incidence and severity of AEs/SAEs per CTCAE v5.0 • Changes from baseline in laboratory findings, vital signs, and ECGs
• To assess the impact of study treatment on surgical feasibility in participants with localised prostate cancer	• Number of participants undergoing planned surgery • Reasons and number of participants requiring treatment-related and non-treatment related delays of surgery and delays > 7 days from scheduled day
• To assess the effects of study treatment on Ki-67 change in participants with localised prostate cancer	• Change in Ki-67 % positive cells from baseline in tumour samples

γH2AX = gamma-histone 2AX (Ser139); AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; SAE = serious adverse event.

For exploratory objectives and endpoints, see Section 3 of the protocol.

Overall Design Synopsis:

This is an open-label, randomised, Phase I, multi-centre study in newly diagnosed patients with localised prostate cancer who have unfavourable-intermediate risk/high risk/very high risk disease and are eligible for curative radical prostatectomy.

The study will be conducted at approximately 15 centres in approximately 6 countries.

Patients diagnosed with primary prostate cancer who are scheduled for curative radical prostatectomy will be recruited. Recruitment procedures are conducted according to local country and site-specific regulations. Participants will be allocated to either treatment (up to 100 biomarker evaluable patients) or to no-treatment (up to 20 biomarker evaluable patients) arms prior to receiving surgery.

Allocation to treatment or no-treatment arms would be decided by the participant and Investigator during screening.

Following the screening visit, eligible participants who consented to treatment will be randomised to receive one of the following 3 study treatments:

Saruparib (up to 40 biomarker evaluable patients),

Darolutamide (up to 20 biomarker evaluable patients) or,

Saruparib + darolutamide (up to 40 biomarker evaluable patients).

Darolutamide dose will be 600 mg BID. Saruparib dose will be 60 mg QD.

For treatment arms, Day 1 is the start of treatment and treatment should be started as soon as possible and no later than 3 days after randomisation. Participants randomised to treatment arms will receive continuous study treatment for 21 days unless unacceptable toxicity occurs, or the participant withdraws consent. Following the 21 days of study treatment, participants should undergo radical prostatectomy on Day 22 (if no surgical delays). If there are radical prostatectomy delays due to reasons not related to the study procedures/toxicities, participants can receive up to a maximum of 28 days of study treatment and participants should undergo radical prostatectomy the next day if feasible but no later than 7 days after the last dose of the study treatment. In case of unforeseen circumstances, treatment pauses to accommodate the new surgery date can be agreed with the medical monitor and it is preferable that participants receive a minimum of 7 days of study treatment prior to receiving radical prostatectomy.

For the no-treatment arm, Day 1 is defined as participant allocation date with no study treatment to be taken by the participants in this arm. Radical prostatectomy should be performed as per local practice.

Participants will be randomised to saruparib: darolutamide: saruparib + darolutamide at a 2:1:2 ratio until the total number of planned biomarker evaluable patients per treatment arm has been achieved.

Brief Summary:

The purpose of this study is to measure biological effects with either saruparib tablets taken alone, darolutamide tablets taken alone, and saruparib and darolutamide tablets taken together, in participants with newly diagnosed prostate cancer who will undergo surgery to remove the prostate.

Study details include:

- The study duration will vary. The post-surgery follow-up visit is expected to happen 7 to 90 days after surgery.
- The treatment duration will be up to a maximum of 28 days.
- There will be 6 visits in total. These include visits at screening, Day 1, Day 15, day before surgery, day of surgery, and follow-up after surgery.

Disclosure Statement: This is an open-label, randomised, Phase I, multi-centre study with 4 arms.

Number of Participants:

Up to a maximum of 100 participants will be randomised to study intervention and up to a maximum of 20 will be allocated to the no-treatment arm, such that approximately 120 biomarker evaluable patients complete the study.

Study Arms and Duration:

Participants will be randomised in a 2:1:2 basis to receive 21 days of: 1) saruparib (up to 40 biomarker evaluable patients), 2) darolutamide (up to 20 biomarker evaluable patients) or 3) saruparib + darolutamide (up to 40 biomarker evaluable patients), followed by surgery as per standard of care in all treatment arms.

Participants will self-administer saruparib orally at 60 mg QD following the SDMC decision. Participants will self-administer darolutamide orally at a total dose of 1200 mg; administered as 600 mg taken BID orally with food.

Participants in the no-treatment arm (up to 20 biomarker evaluable patients) will not receive any study treatment but will have surgery as per standard of care.

Data Monitoring / Other Committee: Yes

An SDMC will decide on the starting dose of saruparib prior to recruitment of the first

participant based on emerging data from ongoing saruparib studies. During the study conduct, the SDMC will undertake review of safety data when approximately 10 participants across the treatment arms have completed the Day before RP visit and radical prostatectomy. Additionally, the SDMC will review the safety data when data are available for 25 and 50 participants, respectively, in the study treatment arms together with available safety data from the no-treatment arm. Available biomarker data at the time of the SDMC meetings may also be presented. Based on the SDMC outcome, the study design may change, including revision on tumour sample requirement or randomisation ratio, with a protocol amendment.

Statistical Methods

Analysis of Primary/Secondary Endpoints

γH2AX/Ki-67

Fold change in % γH2AX positive cells (as primary endpoint) and % Ki-67 positive cells (as secondary endpoint) in tumour samples will be listed and summarised appropriately by each treatment arm, based on the biomarker evaluable analysis set.

Safety and Tolerability

Safety and tolerability (secondary endpoint) will be assessed in terms of AEs/SAEs. These variables will be collected for all participants enrolled. All safety analyses will be performed on the safety analysis dataset, defined as participants who received at least one dose of treatment and all participants in the no-treatment arm. For all endpoints, the data will be summarised and/or listed according to the treatment received.

Surgical Feasibility

Surgical feasibility (secondary endpoint) will be assessed in terms of rate of participants with radical prostatectomy as planned. The rate and reasons of treatment-related and non-treatment related delays of surgery and delays > 7 days from scheduled day, will be captured.

Definition of Biomarker Evaluable Patients

A total of up to 120 participants may be randomised or allocated across 4 arms (randomisation N = 100: saruparib, darolutamide, saruparib + darolutamide, or allocation N = 20: no-treatment arm). Patients will be considered biomarker evaluable if they have:

(a) completed at least 75% of the assigned study treatment in each treatment arm (eg, minimum 16 days of treatment out of 21 days),
(b) or who have been assigned to the no-treatment arm, and;

(c) whose tumour samples are biomarker evaluable for γH2AX analysis, as defined in the Pathology Manual.

Recruitment may continue after 120 patients enrolled based on SDMC reviews to monitor the number of biomarker evaluable patients. Non-biomarker evaluable patients may be replaced.

Sample Size Determination

The sample size is based on the primary endpoint, assessment of fold change in % γH2AX positive cells, and 120 biomarker evaluable patients required to fully evaluate all planned arms. A Fisher's Exact test with a 10% 2-sided level will have 80% power to detect a 30% difference between the 2 group proportions (for saruparib and saruparib + darolutamide) when the sample size in each group is 40.

Interim Analyses

Two interim analyses are planned for the study.

A quality check will be conducted after approximately 25 participants have been recruited, completed the radical prostatectomy, and analysed to assess the proportion of biomarker evaluable participants. The review will also include participants in the no-treatment arm.

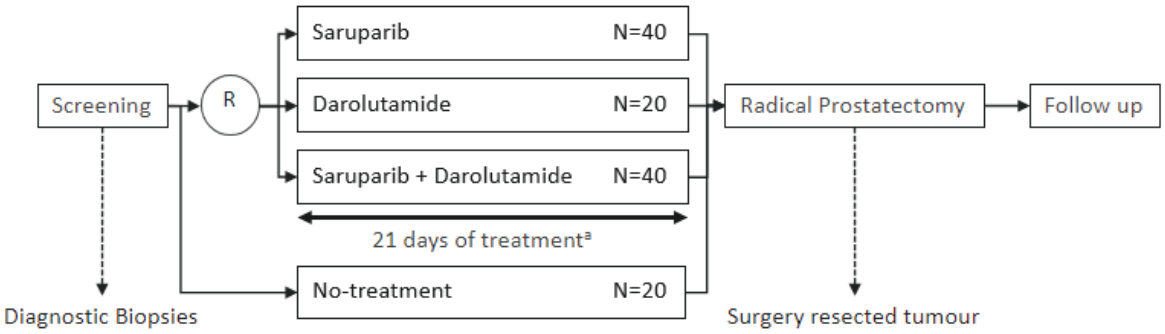
An interim analysis for futility is planned based on biomarker response (proportion of participants with % γH2AX positive cells ≥ 2-fold change) and will be triggered when approximately half (~50 participants) of the participants in the randomised arms are biomarker evaluable. The decision criteria here will be applied to the saruparib and saruparib + darolutamide arms individually, which are expected to exhibit biomarker activity. It is expected that the darolutamide alone and no-treatment arms alone will observe < 2-fold changes in responses.

This is an exploratory study and in addition to the decision points the quality of the biopsies will be monitored on an ongoing basis during the study.

1.2 Schema

A schema of the study design is presented in Figure 1.

Figure 1 Study Design



[a] Participants should undergo radical prostatectomy on Day 22 (if no surgical delays). Participants can continue study treatment for a maximum of 28 days in total if there are radical prostatectomy delays due to reasons not related to the study procedures/toxicities. In such a case, participants should undergo radical prostatectomy the next day if feasible but no later than 7 days after the last dose of the study treatment.

1.3 Schedule of Activities

The schedules of activities are presented for the study treatment arms (Table 1) and the no-treatment arm (Table 2).

1.3.1 Randomised Treatment Arms

Table 1 Schedule of Activities for the Study Treatment Arms

Visit number	Screening	Day 1	Day 15[a]	Day before RP [b, c]	Day of RP [d]	Post-surgery follow-up	See details in section
Window	**-28 to -1**		**± 3**	**-3**	**See footnote [d]**	**7 to 90**	
Clinical assessments [b]							
Inclusion/exclusion criteria	X						5
Informed consent	X						8.1
Demographic and medical history	X						8.1
Physical examination	X	As clinically indicated				X	8.3.1
ECOG PS	X	As clinically indicated				X	8.3.2
Height	X						8.1
Weight	X					X	8.1
Vital signs	X	X [e]	X [e]	X [e]		X	8.3.3
ECG	X [e]	X [e, f]	X [e]			X	8.3.4
Concomitant medications	X	X	X	X		X	6.8.1
AEs	X	X	X	X		X	8.4
Laboratory assessments [b]							
Haematology, coagulation and chemistry	X	X [e, g]	X [e]	X [e]		X	8.3.5
Total serum testosterone level	X			X			8.3.5
Pharmacokinetics							
Plasma saruparib PK (for saruparib and saruparib + darolutamide arms) [h]		X		X [c]			8.5.1

Table 1 Schedule of Activities for the Study Treatment Arms

Visit number	Screening	Day 1	Day 15[a]	Day before RP [b, c]	Day of RP [d]	Post-surgery follow-up	See details in section
Window	**-28 to -1**		**± 3**	**-3**	**See footnote [d]**	**7 to 90**	
Plasma darolutamide PK (for darolutamide and saruparib + darolutamide arms) [h]		X		X [c]			8.5.1
Disease evaluation							
Diagnostic mpMRI	X (optional)						8.2
mpMRI				X (optional)			8.2
PSA	X [i]	X [g]		X		X	8.6.2.1
Diagnostic tumour biopsy (FFPE)	X						8.8.2.1
Diagnostic tumour biopsy (fresh frozen)	X (optional) [i]						8.8.2.2
Prostatectomy tumour sample (FFPE)					X		8.8.3
Prostatectomy tumour sample (fresh frozen)					X		8.8.3
Prostatectomy non-tumour sample (fresh frozen)					X (optional)		8.8.3
Blood for germline HRR status	X [i]						8.8.6
Blood sample for CHIP	X [i]						8.8.6
Blood for pharmacodynamic samples (PAR)	X [i]	X		X [c]		X	8.6.2
ctDNA	X [i]	X [e, g]	X [e]	X [c, e]		X	8.8.5
Blood biomarker samples (eg, immune markers and proteomics)	X [i]	X [e, g]	X [e]	X [c, e]		X	8.8.4
Urine for exploratory research	X [i]	X [g]	X	X		X	8.8.1
Optional Genomics Initiative							
Genomics initiative blood sample	X (optional) [j]						8.7

Table 1 Schedule of Activities for the Study Treatment Arms

Visit number	Screening	Day 1	Day 15[a]	Day before RP [b, c]	Day of RP [d]	Post-surgery follow-up	See details in section
Window	**-28 to -1**		**± 3**	**-3**	**See footnote [d]**	**7 to 90**	
Randomisation	X						6.3
Study treatment (one of the following)							
Saruparib		X [k]					6.1.1.1
Darolutamide		X [k]					6.1.1.2
Saruparib + darolutamide		X [k]					6.1.1.1 6.1.1.2

[a] Day 15 and Day before RP assessments can be combined in the same visit if visit window allows. In this instance, **all** assessments required for Day 15 and Day before RP must be performed on the single visit.

[b] If participants receive treatment for more than 21 days additional safety monitoring will be performed on the Day before RP, as clinically indicated.

[c] Blood for PK/pharmacodynamic assessments will be collected on the Day before RP visit, which is Day 21 if there are no RP delays or on the Day of the RP visit. If collected on the Day of RP visit, collection to be performed before surgery.

[d] Participants should undergo RP on Day 22 (if no surgical delays). Participants can continue study treatment for maximum of 28 days in total if there are RP delays due to reasons not related to the study procedures/toxicities. In such a case, participants should undergo RP the next day if feasible but no later than 7 days after the last dose of the study treatment.

[e] Assessment/sample to be collected pre-dose.

[f] Triplicate ECGs should be done at screening and Day 1. At all other time points, a single ECG will be obtained.

[g] If conducted within 7 days, the screening blood samples can be used for Day 1.

[h] Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and AstraZeneca, eg, for urgent safety reasons, and this may be reflected as a protocol deviation.

[i] Assessment/sample to be taken preferably only after the participant's eligibility for the study has been confirmed, where possible.

[j] The blood sample for this genomic research will be obtained from the participants at screening (after eligibility has been confirmed) or Day 1 pre-dose. If for any reason the sample is not drawn at screening or Day 1, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics research during the study.

[k] Dosing as per dosing schedule.

AE = adverse event; CHIP = Clonal Haematopoiesis of Indeterminate Potential; ctDNA = circulating tumour DNA; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed and paraffin-embedded; HRR = homologous recombination repair; mpMRI = Multiparametric MRI; PAR = Poly adenosine diphosphate ribose; PK = pharmacokinetic(s); PS = performance status; PSA = prostate-specific antigen; RP = radical prostatectomy.

1.3.2 No-treatment Arm

Table 2 Schedule of Activities for the No-treatment Arm

Visit days	Screening	RP	Post-surgery follow-up	
Window	-28 to -1	See footnote [a]	7 to 90	See details in section
Clinical assessments				
Inclusion/exclusion criteria	X			5
Informed consent	X			8.1
Demographic and medical history	X			8.1
Physical examination	X		X	8.3.1
ECOG PS	X		X	8.3.2
Height	X			8.1
Weight	X		X	8.1
Vital signs	X		X	8.3.3
ECG (single)	X			8.3.4
Concomitant medications	X		X	6.8.1
AEs	X		X	8.4
Laboratory assessments				
Haematology, coagulation and chemistry	X		X	8.3.5
Total serum testosterone level	X	X [b, c]		8.3.5
Biomarker assessments				
PSA	X [d]	X [b, c]	X	8.6.2.1
Diagnostic tumour biopsy (FFPE)	X			8.8.2.1
Diagnostic tumour biopsy (fresh frozen)	X (optional) [d]			8.8.2.2
Prostatectomy tumour sample (FFPE)		X		8.8.3
Prostatectomy tumour sample (fresh frozen)		X		8.8.3
Prostatectomy non-tumour sample (fresh frozen)		X (optional)		8.8.3
Blood for germline HRR status	X [d]			8.8.6
Blood sample for CHIP	X [d]			8.8.6
ctDNA	X [d]	X [b, c]	X	8.8.5
Blood biomarker samples (eg, immune markers and proteomics)	X [d]		X	8.8.4
Urine for exploratory research	X [d]	X [b, c]	X	8.8.1
Optional genomics initiative				
Genomics initiative blood sample	X (optional) [e]			8.7

[a] Perform RP at the timing as per local practice.

[b] Sample to be taken on the day of RP (-3 day). If collected on the day of RP, collection to be performed before surgery.
[c] If conducted within 7 days, the screening blood samples can be used for Day 1.
[d] Assessment/sample to be taken preferably only after the participant's eligibility for the study has been confirmed, where possible.
[e] The blood sample for this genomic research will be obtained from the participants at screening (after eligibility has been confirmed) or Day 1 pre-dose. If for any reason the sample is not drawn at screening or Day 1, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics research during the study.

AE = adverse event; CHIP = Clonal Haematopoiesis of Indeterminate Potential; ctDNA = circulating tumour DNA; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FFPE = formalin-fixed and paraffin-embedded; HRR = homologous recombination repair; PS = performance status; PSA = prostate-specific antigen; RP = radical prostatectomy.

2 INTRODUCTION

ASCERTAIN, is an open-label, randomised, Phase I, multi-centre study to investigate the mechanism of action of saruparib, previously known as AZD5305, or darolutamide alone, or when given in combination to patients with localised unfavourable-intermediate risk/high risk/very high risk prostate cancer who are eligible for curative radical prostatectomy.

Saruparib is a novel PARPi that has the unique properties to potently and selectively inhibit and trap PARP1. In biochemical assays, saruparib has an IC_{50} against the PARP1 recombinant enzyme of 3.6 nM, with a > 2-log-fold selectivity for PARP1 against PARP2 and any of the other members of the PARP family (Illuzzi et al 2021, Johannes et al 2021, Leo and Johannes, 2021). All currently approved PARPi are almost equipotent in targeting PARP1 and PARP2 (2 members of the PARP family). Recent literature reports suggest that inhibition of only PARP1 is required for the anti-proliferative effect (Murai et al 2012), and that PARP2 has been shown in animal models to play a key role in the survival of haematopoietic stem progenitor cells (Farrés et al 2013, Farrés et al 2015). These observations suggest that inhibition and trapping of PARP2, a feature shared by all of the currently approved PARPi, is not needed for anticancer effects, and is hypothesized to be a potential contributor to haematological toxicity observed in patients. For these reasons, saruparib may offer a more efficacious and less toxic cancer treatment compared with currently approved PARPi. Saruparib is currently being developed as an oral therapy, both as a monotherapy and in combination with chemotherapy and antibody drug conjugates.

2.1 Study Rationale

This window of opportunity clinical trial, ASCERTAIN, was designed to elucidate the mechanism of action of saruparib or darolutamide alone, or when given in combination in prostate cancer.

Despite recent emerging data suggesting that combining a PARPi and an NHA can further improve survival benefit for patients with metastatic prostate cancer, the mechanisms behind this combination benefit are not fully understood. For example, the addition of olaparib to abiraterone acetate + ADT has demonstrated a significant improvement in rPFS compared with abiraterone acetate + ADT for both men with mCRPC who had previously received docetaxel (Clarke et al 2018), and those who had not received a prior line of systemic therapy in the setting of mCRPC, irrespective of HRRm status (Clarke et al 2022).

It is hypothesized that by sparing PARP2, saruparib may offer a more efficacious and less toxic cancer treatment in the combination settings compared with currently approved PARPi.

Collectively, these data provide the rationale to explore the underlying combination mechanism of action of PARP1 selective inhibitor saruparib and the NHA of darolutamide in patients who are diagnosed with localised prostate cancer and are eligible for radical prostatectomy. ASCERTAIN was designed to generate a comprehensive biopsy and biomarker-driven investigation in order to elucidate the mechanism of action of saruparib

alone and in combination with darolutamide, to inform further clinical development in prostate cancer.

2.2 Background

Prostate cancer is the second most common cancer in men. With an estimated 375,304 deaths in 2020 worldwide, prostate cancer is the fifth leading cause of death from cancer in men and represents 6.8% of total cancer death in males (Sung et al 2021). Localised prostate cancer management has evolved significantly in the last few decades. For patients requiring treatment, 3 modalities are usually considered: surgical removal of the organ and adjacent structures (radical prostatectomy); in situ radiotherapy (brachytherapy); or external radiotherapy, which can be combined with systemic androgen deprivation. For patients eligible for prostatectomy, there is no evidence that systemic treatment before surgery would provide additional benefit; therefore, surgery is the solely defined standard of care for this population. After surgery, patients could be considered for another surgical intervention or other modalities of local/systemic treatment depending on the histopathological findings of the surgical specimen. On the other hand, for metastatic prostate cancer, treatment is based on ADT such as luteinising hormone-releasing hormone analogues or orchiectomy, which is usually initially effective at controlling metastatic disease. However, patients inevitably progress from an androgen sensitive to a castration-resistant phenotype which is associated with 90% of overall mortality (Scher et al 2015).

The recent approval of several NHAs has significantly altered the treatment landscape for patients with metastatic prostate cancer and NHAs are now considered standard of care in both the mCRPC and mCSPC settings (Mohler et al 2019, Parker et al 2020). Abiraterone acetate, enzalutamide, and darolutamide in combination with ADT have demonstrated robust improvements in progression-free survival and OS and have shown a significantly prolonged time to initiation of cytotoxic chemotherapy (in patients with CRPC) (Beer et al 2014, Ryan et al 2013, Fizazi et al 2019). Additionally, recent data have demonstrated the benefit of NHAs in patients with mCSPC. Abiraterone acetate + prednisone with ADT demonstrated significant survival benefits compared with ADT alone, by further prolonging OS and delaying initiation of chemotherapy and subsequent therapy (Fizazi et al 2019). Enzalutamide + ADT significantly reduced the risk of radiographic progression or death versus placebo + ADT as well as reduced risk of PSA progression, initiation of new antineoplastic therapy, first symptomatic skeletal event, castration resistance, and pain progression (Armstrong et al 2019). A Phase III trial is ongoing to evaluate darolutamide in combination with standard ADT in patients with mCSPC (ARANOTE Trial).

However, patients eventually progress under available treatment options and there is an unmet medical need for new treatment options. Recent emerging data suggest that combining a PARPi and an NHA has an enhanced antitumour effect and can further improve survival benefit for patients with metastatic prostate cancer (Section 2.1) (Clarke et al 2018,

Clarke et al 2022). Additionally, there are multiple ongoing Phase III studies evaluating the benefit of adding a PARPi to an NHA in both the mCRPC and mCSPC spaces. In mCRPC (all evaluated as first-line therapy for mCRPC and with or without HRRm) these trials include the study of talazoparib + enzalutamide in patients with mCRPC, which has recently shown a statistically significant and clinically meaningful improvement in rPFS compared with placebo + enzalutamide (Agarwal et al 2023). Niraparib in combination with abiraterone acetate and prednisone versus abiraterone acetate and prednisone for the treatment of patients with mCRPC (MAGNITUDE Trial), and a clinical study evaluating the benefit of adding rucaparib to enzalutamide for men with metastatic prostate cancer that has become resistant to testosterone-deprivation therapy (CASPAR Trial) (Table 3). In mCSPC, the ongoing Phase III trials include talazoparib in combination with enzalutamide versus placebo with enzalutamide in men with DDR gene-mutated mCSPC (TALAPRO-3, NCT04821622) and niraparib in combination with abiraterone acetate and prednisone versus abiraterone acetate and prednisone for the treatment of patients with deleterious germline or somatic HRR gene-mutated mCSPC (AMPLITUDE Trial) (Table 4).

Additional rationale for the current study is based on the results of a recent AstraZeneca sponsored study, Study D081DC00008 (Study 8; NCT01972217). Study 8 was designed to explore the hypothesis that PARP inhibition acts synergistically with inhibition of the androgen pathway in post-chemotherapy patients who were biomarker unselected. Preliminary efficacy data from 142 enrolled patients showed median rPFS was 13.8 months (95% CI 10.8 to 20.4) with olaparib + abiraterone acetate and 8.2 months (5.5 to 9.7) with placebo + abiraterone acetate (HR 0.65, 95% CI 0.44 to 0.97, p=0.034). Median OS was 22.7 months (95% CI 17.4 to 29.4) in the olaparib + abiraterone acetate group compared with 20.9 months (95% CI 17.6 to 26.3) in the placebo + abiraterone acetate group. Importantly, retrospective subgroup analyses suggested that the benefit for the combination of olaparib and abiraterone acetate was irrespective of HRRm status (Clarke et al 2018). Modestly increased toxicity was seen in the olaparib group compared with the placebo group which was expected, with many, but not all, observed AEs being consistent with the current safety profile for olaparib.

Table 3 PARPi in Combination with New Hormonal Agents Ongoing Clinical Trials in mCRPC

Trial		TALAPRO-2	MAGNITUDE	CASPAR
Phase		3	3	3
Trial arm		Talazoparib + enzalutamide vs. placebo + enzalutamide	Niraparib + abiraterone acetate vs. placebo + abiraterone acetate	Rucaparib + enzalutamide vs. Placebo + enzalutamide
Planned sample size (N)		1150	765	1002
Baseline characteristics	mCRPC	Yes	Yes	Yes
	Biomarker selection	Unselected	Unselected	Unselected
	1L in mCRPC	Yes	Yes	Yes
	Prior NHA	Excluded	Excluded	Not excluded except enzalutamide
Primary endpoint		rPFS	rPFS	rPFS

1L = first line of therapy; mCRPC = metastatic castrate resistant prostate cancer; NHA = new hormonal agents; rPFS = radiographic progression free survival.

Table 4 PARPi in Combination with New Hormonal Agents Ongoing Clinical Trials in mCSPC

Trial		TALAPRO-3	AMPLITUDE
Phase		3	3
Trial arm		Talazoparib + enzalutamide vs. placebo + enzalutamide	Niraparib + abiraterone acetate vs. placebo + abiraterone acetate
Planned sample size (N)		550	788
Baseline characteristics	mCSPC	Yes	Yes
	Biomarker selection	HRRm	HRRm
	Prior NHA	≤ 3 months	≤ 1 month
	Prior ADT	≤ 6 months	≤ 6 months
Primary endpoint		rPFS	rPFS

ADT = androgen deprivation therapy; HRRm = homologous recombination repair gene mutation; mCSPC = metastatic castration-sensitive prostate cancer; NHA = new hormonal agents; rPFS = radiographic progression free survival.

2.2.1 Investigational Product Background

The study treatments in this study are saruparib and darolutamide.

2.2.1.1 Saruparib

Saruparib is a novel PARPi that has the unique properties to potently and selectively inhibit and trap PARP1. Poly (adenosine diphosphate–ribose) polymerase inhibitors with clinical activity as monotherapy selectively inhibit and trap PARP at sites of ssDNA damage, preventing ssDNA repair and causing replication dependent DNA double strand breaks (Pommier et al 2016). Normal cells have the ability to repair the damage accurately and efficiently via the HRR pathway; in HRD cancer cells, such as those with deleterious BRCA1/2 mutations, treatment with PARPi leads to an increase in genomic instability, which ultimately leads to cancer cell death, while sparing normal cells. Therefore, PARPi monotherapy works through "synthetic lethality", where both PARPi and HRD are needed to lead to a targeted anticancer effect.

A description of the chemistry, pharmacology, efficacy, and safety of saruparib is provided in the IB.

The primary pharmacology of saruparib is described in the IB (see Section 4.1 of the IB) and further described in (Illuzzi et al 2022), with key data described below.

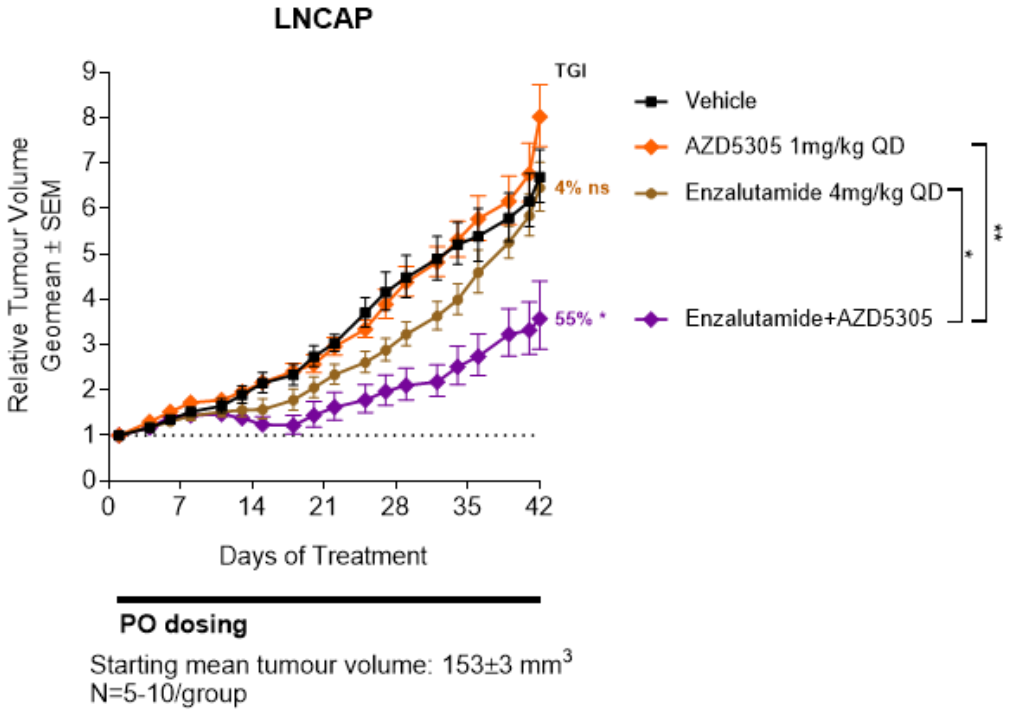
- In biochemical assays, saruparib has an IC_{50} against the PARP1 recombinant enzyme of 3.6 nM, with a > 2-log-fold selectivity for PARP1 against PARP2 and any of the other members of the PARP family (Illuzzi et al 2022, Johannes et al 2021; Leo and Johannes, 2021) Table 1 in the IB.
- In A459 cells, saruparib has an IC_{50} for PARylation inhibition of 1.5 nM against PARP1 (in cells lacking PARP2 expression) (Figure 1 in Illuzzi et al 2022). In contrast, in isogenic cells lacking PARP1 expression saruparib has an IC_{50} for PARP2 PARylation inhibition of 653 nM (Figure 1 in Illuzzi et al 2022). This results in a selectivity window of approximately 500-fold for PARP1 inhibition over PARP2 in cells. For comparison, olaparib had a mean potency of approximately 4 nM for both PARP1 and PARP2 being equally sensitive and no selectivity window (Supplementary Figure S1 Illuzzi et al 2022).
- In A549 cells, saruparib exhibits potent and selective PARP1 trapping with significant trapping occurring at 2 to 3 nM and increasing to a maximum between 100 to 1000 nM (Figure 1 in Illuzzi et al 2022; Figure 5 in IB Section 4.1.1.1). Olaparib traps both PARP1 and PARP2 with significant trapping occurring at concentrations from 100-1000nM (Supplementary Figure S1 Illuzzi et al 2022).
- In cell line models of HRD with loss of BRCA2, PALB2 or RAD51C, saruparib displays potent anti-proliferative activity at single digit nM potency, and a wide selectivity window of > 10,000-fold in isogenic wild type cells (IC_{50} >10,000 nM). Olaparib displays double digit IC_{50} in these HRD models, with a selectivity window compared to the wild type cells of >1000-fold. (ref for both saruparib and olaparib – Figure 2 and Supplementary Figure S2 in Illuzzi et al 2022; Figures 6 and 7 in IB).

- In vivo, in tumour xenograft models, saruparib exhibits potent anti-tumour activity in multiple models of HRD (MDA MB436, HBCx-17, DLD1 BRCA2 KO) with doses ranging from 0.1-10 mg/kg causing tumour regressions (Figure 3 Illuzzi et al 2022; IB Section 4.1.1.2 Figures 8 to 12; Type C Briefing Document dated 15 Dec 2022, Section 8.1). Similar or superior activity to olaparib at 100 mg/kg was observed in these models, with longer duration of responses.
- Saruparib caused potent inhibition of PARylation in tumour models in vivo with complete and sustained inhibition of PARylation for > 24 h observed at doses from 0.03 mg/kg to 10 mg/kg (Supplementary Figure S4 Illuzzi et al. 2022)

In vitro and in vivo, saruparib shows equal or superior potency and activity to olaparib in many non-clinical models.

An in vivo model of prostate cancer (LNCaP) was evaluated for response to saruparib and enzalutamide in monotherapy and in combination (Figure 2). This model is not deficient in HRR, and as such is not sensitive to saruparib monotherapy. This model is partially sensitive to enzalutamide, although it did not lead to significant tumour growth inhibition in this study. However, combination of 1 mg/kg saruparib with 4 mg/kg enzalutamide achieved significant tumour growth inhibition and was more effective than either single agent.

Figure 2 Combination of Saruparib + Enzalutamide is Superior to Single Agents in LNCaP Prostate Cancer Xenograft Model



PO = oral; QD = once daily; SEM = standard error of the mean.

Non-clinical data support the hypothesis that selective inhibition of PARP1 may result in an improved safety profile compared to current clinical PARPi. The wider therapeutic index of saruparib monotherapy seen non-clinically is supportive of literature reports that inhibition of only PARP1 is required for the anti-proliferative effect of PARPi (Murai et al 2012), and that PARP2 may be the major contributor to the haematological toxicity observed in patients (Farrés et al 2013).

As of the DCO of 02 September 2023, safety data are available from 2 ongoing studies:

1 Study D9720C00001, a Phase I/IIa study, which is a modular, open-label, multi-centre study of saruparib administered orally, either as monotherapy or in combination with anticancer agents to study safety, tolerability, PK, pharmacodynamics, and preliminary efficacy in patients with advanced solid malignancies (PETRA; NCT04644068) and
2 Study D9720C00003, a Phase I/IIa, open-label, multi-centre study of saruparib administered orally, in combination with NHAs to study safety, tolerability, PK, pharmacodynamics, and preliminary efficacy in patients with metastatic prostate cancer (PETRANHA; NCT05367440).

Refer to Section 4.3 for details of safety data from the ongoing PETRA and PETRANHA studies.

2.2.1.2 Darolutamide

Darolutamide is an AR antagonist specifically inhibiting AR nuclear translocation. Uniquely, darolutamide and the active metabolite (ORM-15341) each inhibited wild-type AR as well as clinically relevant AR mutations AR (F876L), which trigger enzalutamide and apalutamide antagonist to agonist switch, as well as AR (W742L) and AR (T877A) which cause bicalutamide agonist switch (Moilanen et al 2015). Darolutamide has a low potential for drug-drug interaction (Shore et al 2019) and provides promising reductions in brain penetrance, as well as effectively inhibiting all known AR mutations (Fizazi et al 2015). Darolutamide was approved by the FDA on 30 July 2019 for use in non-metastatic CRPC, based on performance in the ARAMIS trial (NCT02200614) (Fizazi et al 2019) which showed metastasis free survival was 40.4 months in darolutamide treated patients compared to 18.5 months in placebo treated patients. Darolutamide was also approved for patients with mCSPC when used in combination with docetaxel (NUBEQA Prescribing Information 2019).

2.2.2 Scientific Rationale for Combination Therapy

PARP1 is a DNA damage response protein that facilitates the repair of both DNA single strand and double strand breaks (Ray Chaudhuri and Nussenzweig 2017). Saruparib, as a monotherapy, is a potent oral PARP1 selective inhibitor that also stabilizes PARP proteins on DNA, which induces DNA damage. The AR, in addition to its role in binding androgen and stimulating prostate cancer cell growth (Westaby et al 2022), also contributes towards the

general repair of DNA damage, including damage not normally repaired by homologous recombination repair (Goodwin et al 2013, Polkinghorn et al 2013).

Multiple clinical studies evaluating combinations of PARPi and NHAs have been conducted or are ongoing, and as discussed above have shown benefit in some cases even in a non-HRD background. A number of hypotheses have been proposed to explain this combination benefit in patients with and without HRR deficiencies.

PARP enzymes are implicated in AR signalling in addition to their role in DNA repair; PARP1 has been identified as a positive co-regulator of the AR-driven gene expression of AR targets. PARP1 was shown to regulate AR association with chromatin and inhibition of PARP enzymes prevented them from positively modulating the transcription of AR targets, leading to reduced gene expression of AR targets and enhanced anti-tumour activity in prostate cell lines (Schiewer et al 2012, Schiewer and Knudsen 2014).

An alternative hypothesis was also proposed, whereby NHAs were shown to induce an HRR-deficient phenotype through inhibition of AR signalling (Asim et al 2017, Li et al 2017). Homologous recombination repair gene transcripts and protein levels were found to be upregulated in response to enhanced AR signalling in prostate cancer, and increased radioresistance was observed in the presence of functional AR signalling while decreased HRR gene expression was seen in NHA-treated cells and tumour biopsies. As a result, the induction of an HRR-deficient phenotype by NHA leads to increased sensitivity to olaparib.

The role of AR in DNA repair is well documented and has been linked to radiation treatment resistance (Bartek et al 2013, Goodwin et al 2013, Polkinghorn et al 2013, Tarish et al 2015), hence the combination of NHAs with radiation as standard of care treatment. Primary pharmacology data (report on file) demonstrate that AR's ability to associate with chromatin bound DNA in response to DNA damage is dependent primarily on PARP1 and treatment with olaparib or saruparib inhibits this AR-association with DNA. Thus, in addition to the well-established role of PARP inhibitors in single strand break repair and inducing PARP1 trapping, PARP1 can also regulate AR-dependent DNA repair. The DNA repair role of AR is not, however, limited to HRR-dependent repair in the S and G2 phases of the cell cycle and in fact previously published data has linked AR-associated repair with DNA-PK and non-homologous end joining that is the primary DNA double strand break repair pathway in the G1 phase of the cell cycle (Schiewer et al 2012, Goodwin et al 2013, Polkinghorn et al 2013, Schiewer and Knudsen 2014). The NHA combination with a PARP1 trapper such as saruparib will therefore be predicted to induce greater levels of DNA double strand breaks than either agent alone, and while the greatest sensitivity to this DNA damage might be expected to be observed in BRCA2 mutant mCSPC, the effects should also extend beyond to broader tumour backgrounds.

Moreover, while translational analysis of the NHA + PARPi combination from ongoing studies could elucidate the mechanisms of the combination, the results should be seen in the light of biases (eg, heterogeneous population, distinct treatment exposure period, and statistical power). The ASCERTAIN trial design aims to answer the mechanistic question as a primary endpoint and reduce the biases by recruiting treatment naïve patients, restricting to prostate cancer with similar risk categories, standardising the period of drug exposure and focussing on high quality translational evaluation of surgical specimens.

2.3 Benefit/Risk Assessment

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, and applicable regulatory requirements.

The current study is intended to assess the changes in biomarkers in the prostate tumour, safety, PK, pharmacodynamics, and mechanism of the combination of saruparib with darolutamide. Detailed information about the known and potential risks of saruparib can be found in the IB. As of the DCO of 02 September 2023, a total of 308 patients have received saruparib monotherapy in PETRA and overall, the saruparib doses ranging from 10 to 90 mg were well tolerated. Importantly, no clinically significant overlapping toxicities are predicted for the combination therapies based on known mechanism of actions of these drug molecules, available safety data for saruparib, class effects and safety data available from other PARPi/NHAs combination trials. In the combinations with NHAs (abiraterone, enzalutamide and darolutamide) in the PETRANHA trial, no clinically significant overlapping toxicities were observed, and overall the combinations have been well tolerated with saruparib dosed at 60 mg QD overall.

There remains an unmet need for improved treatment options for patients with metastatic and localised prostate cancer and the benefit/risk assessment for this Phase I study is favourable based on the available safety data of saruparib, well-established risk profile for darolutamide and predicted superior efficacy of the combination therapy. Although possible, it is unclear if the duration of treatment in this study may induce some benefit for some of the patients but it may support future clinical studies to offer new treatment options to prostate cancer patients.

2.3.1 Risk Assessment

Table 5 summarises the risks/potential risks of clinical significance and the mitigation strategies for saruparib in combination with darolutamide based on safety data from non-clinical toxicology studies and clinical data available to date, as well as per the darolutamide prescribing information. More detailed information about the known and expected benefits and potential risks of saruparib may be found in the IB. Please also refer to local and national prescribing guidelines for additional details about darolutamide.

Table 5 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention: Saruparib		
• Based on clinical and non-clinical data early and late onset toxicities of saruparib or combination-related • Delay in surgery	1 Participants could experience a delay in the day of surgery given toxicities related to the treatment. 2 Late onset toxicities are unlikely to occur but possible.	Restrictive inclusion and exclusion criteria (Sections 5.1 and 5.2), population treatment naïve, short study treatment duration (21 days with a maximum of 28 days), TMG and adaptation of toxicity management leaving to PIs discretion to pause the treatment earlier (Section 6.6.1).
Based on the available non-clinical and clinical data, risks identified for saruparib include: Identified Risks: • Anaemia, neutropenia, thrombocytopenia • Fatigue/asthenia • Nausea and vomiting Important Potential Risks: • MDS/AML • New primary malignancies (other than MDS/AML) • Embryofoetal toxicity, effects on male reproduction Potential Risk: • Pneumonitis	Based on available non-clinical and clinical data with saruparib, cumulative review of the literature and available clinical data with current approved PARPi.	Strict inclusion/exclusion criteria (Sections 5.1 and 5.2), contraception requirement, intensive safety monitoring including haematology, vital signs and ECG collection (Section 8.3) and TMGs (Section 6.6.1) have been included in this clinical study protocol to mitigate these risks.
Study intervention: Darolutamide		
• Ischaemic heart disease • Seizure	Ischaemic heart disease occurred in 3.2% of patients receiving darolutamide and 2.5% receiving placebo. Additionally, ischaemic heart disease occurred in 2.9% of patients receiving darolutamide with docetaxel and 2% receiving placebo with docetaxel. Grade 1-2 seizure occurred in 0.2% of patients receiving	Strict inclusion/exclusion criteria (Sections 5.1 and 5.2) and monitoring/ management guidelines (Section 6.6) are currently in place to mitigate the risks of ischaemic heart disease associated with darolutamide; eg, participants with a history of clinically significant heart disease are excluded. Participants will be closely monitored with ECGs and BP measurements.

Table 5 Risk Assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	darolutamide and 0.2% receiving placebo. Additionally, seizure occurred in 0.6% of patients receiving darolutamide with docetaxel and 0.2% receiving placebo with docetaxel.	

AML = acute myeloid leukaemia; BP =blood pressure; ECG = electrocardiogram; MDS = myelodysplastic syndrome
PI = Principal Investigator; TdP = Torsades de Pointes; TMG = toxicity management guidelines.

2.3.2 Benefit Assessment

Early reduction of PSA levels can be expected when anti-androgen treatment is administered to patients with localised prostate cancer before surgery (Devos et al 2022, Lee et al 2022, Montgomery et al 2017). In the metastatic setting, saruparib induced PSA reduction in patients with mCRPC (AACR 2022). Although possible, it is unclear if the duration of treatment in this study may induce some benefit for all patients. The results of this study will contribute to the overall body of scientific knowledge and future study designs of clinical trials for prostate cancer. The NHA used in this study (darolutamide) has been approved for the treatment of patients with non-metastatic CRPC and mCSPC and has an acceptable safety profile.

2.3.3 Overall Benefit/Risk Conclusion

The current study will evaluate the mechanisms of action underlying the combination benefits between a PARPi (saruparib) and an NHA (darolutamide) in patients with localised prostate cancer.

All participants in the study are planned to receive a standard of care radical prostatectomy; the short treatment with saruparib, darolutamide or the combination of both prior to the surgery are expected to be well tolerated based on available non-clinical and clinical data for these study drugs. At the time of the CSP amendment #4, an SDMC meeting was held in May 2024 where none of the first 10 participants enrolled across the 3 treatment arms had a surgical delay due to AEs nor were there any AEs leading to study dose interruption, reduction or discontinuation. The safety of the intervention will be continually monitored during the study.

Considering the measures taken to minimise risk to participants in this study and the potential benefits that may be afforded to participants, the overall benefit/risk assessment supports the proposed study design.

3 OBJECTIVES and ENDPOINTS

Table 6 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the effects of study treatment on γH2AX change in participants with localised prostate cancer	• Fold change in % γH2AX positive cells from baseline value in tumour samples
Secondary	
• To assess the safety and tolerability of study treatment in participants with localised prostate cancer	• Incidence and severity of AEs/SAEs per CTCAE v5.0 • Changes from baseline in laboratory findings, vital signs, and ECGs
• To assess the impact of study treatment on surgical feasibility in participants with localised prostate cancer	• Number of participants undergoing planned surgery • Reasons and number of participants requiring treatment-related and non-treatment related delays of surgery and delays > 7 days from scheduled day
• To assess the effects of study treatment on Ki-67 change in participants with localised prostate cancer	• Change in Ki-67 % positive cells from baseline in tumour samples
Exploratory	
• To characterise the PK in plasma of saruparib and darolutamide as monotherapy and in combination	• Plasma concentrations of saruparib and darolutamide (parent and metabolite(s) if applicable) and plasma PK parameters as data allow
• To evaluate the genomic landscape of the study population, including BRCA mutations	• Assessment of BRCA and other HRR mutations in tumour tissue • Analysis may also include evaluation of germline mutations from blood samples
• To evaluate the effect of treatment on HRR status	• Assessment may include but is not limited to gene expression of HRR genes, HRD gene expression signature and RAD51 foci assessment
• To evaluate the effect of treatment on AR signalling	• Assessment of AR-driven gene expression
• To investigate pharmacodynamic biomarker changes mediated by saruparib, darolutamide, or combination on prostate tumour	• Assessment of modulation in pharmacodynamic biomarkers from PBMC, and/or tumour samples • Analysis of PARP1 inhibition including, but not limited to PARylation inhibition
• To investigate biomarkers of disease biology and response to treatment with saruparib, darolutamide, or combination	• Assessment of biomarkers which may include but not limited to mRNA (including single cell RNAseq, spatial transcriptomics), proteins, genetic / epigenetic biomarkers, tumour and microenvironment assessment and immune profiling.

Table 6 Objectives and Endpoints

Objectives	Endpoints
• To evaluate the effects of study treatment on ctDNA	• Assessment of changes from baseline in ctDNA
• To evaluate the surrogates of antitumour activity of study treatment in participants with localised prostate cancer	• PSA change from baseline • Histo-pathological assessment of surgical specimen • Tumour grading per mpMRI (optional)
• Future exploratory research into factors that may influence development of cancer and/or response to treatment may be performed on the collected and stored archival tumour samples, blood samples (and their derivatives)	• Future research analysis that may include but is not limited to analysis of DNA, RNA, proteins, metabolites, tumour and microenvironment analysis and immune profiling

γH2AX = gamma-histone 2AX (Ser139); AE =adverse event; AR = androgen receptor; CTCAE = Common Terminology Criteria for Adverse Events; ctDNA = circulating tumour deoxyribonucleic acid; DNA = deoxyribonucleic acid; ECG = electrocardiogram; HRD = homologous recombination deficient; HRR = homologous recombination repair; mpMRI = multiparametric magnetic resonance imaging; mRNA = messenger RNA; PARP = poly (adenosine diphosphate ribose) polymerase; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetics; PSA = prostate-specific antigen; RNA = ribonucleic acid; RNAseq = RNA sequencing; SAE = serious adverse event.

4 STUDY DESIGN

4.1 Overall Design

This is an open-label, randomised, Phase I, multi-centre study in newly diagnosed patients with localised prostate cancer who have unfavourable-intermediate risk/high risk/very high risk disease and are eligible for curative radical prostatectomy.

The study will be conducted at approximately 15 centres in approximately 6 countries.

Patients diagnosed with primary prostate cancer who are scheduled for curative radical prostatectomy will be recruited. Recruitment procedures are conducted according to local country or site-specific regulations. Participants will be allocated to either treatment (up to 100 biomarker evaluable patients) or to no-treatment (up to 20 biomarker evaluable patients) arms prior to receiving surgery.

Allocation to treatment or no-treatment arms would be decided by the participant and Investigator during screening.

Following the screening visit, eligible participants who consented to treatment will be randomised to receive one of the following 3 study treatments:

1 Saruparib (up to 40 biomarker evaluable patients),
2 Darolutamide (up to 20 biomarker evaluable patients) or,
3 Saruparib + darolutamide (up to 40 biomarker evaluable patients).

Darolutamide dose will be 600 mg BID. Saruparib dose will be 60 mg QD.

Participants who do not meet eligibility criteria except for inclusion criteria 1 to 8 (Section 5.1) can be allocated to the no-treatment arm at the discretion of the participant and the Investigator.

For treatment arms, Day 1 is the start of treatment and treatment should be started as soon as possible and no later than 3 days after randomisation. Participants randomised to treatment arms will receive continuous study treatment for 21 days unless unacceptable toxicity occurs, or the participant withdraws consent. Following the 21 days of study treatment, participants should undergo radical prostatectomy on Day 22 (if no surgical delays). If there are radical prostatectomy delays due to reasons not related to the study procedures/toxicities, participants can receive up to a maximum of 28 days of study treatment and participants should undergo radical prostatectomy the next day if feasible but no later than 7 days after the last dose of the study treatment. In case of unforeseen circumstances, treatment pauses to accommodate the new surgery date can be agreed with the medical monitor and it is preferable that participants receive a minimum of 7 days of study treatment prior to receiving radical prostatectomy.

For the no-treatment arm, Day 1 is defined as participant allocation date with no study treatment to be taken by the participants in this arm. Radical prostatectomy should be performed as per local practice.

Participants will be randomised to saruparib: darolutamide: saruparib + darolutamide at a 2:1:2 ratio until the total number of planned biomarker evaluable patients per treatment arm has been achieved.

The SDMC will undertake review of safety and biomarker data (Section 6.6.7).

Recruitment may continue after the 120 biomarker evaluable patients enrolled with a protocol amendment based on any findings suggesting imbalance across arms including but not limited to prevalence of *BRCAm*.

Assessments in the treatment period will be performed in the first 21 days (up to 28 days), on Day 1, Day 15, and the Day before RP, and the post-surgery follow-up visit is expected to happen 7 to 90 days after surgery.

4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this protocol and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and

considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct or participate the study. The Investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with GCP, and minimise risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining reconsent for the mitigation procedures (note, in the case of verbal reconsent, the ICF should be signed at the participant's next contact with the study site).
- Home or remote visit: Performed by a site qualified HCP or HCP provided by a TPV.
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix F.

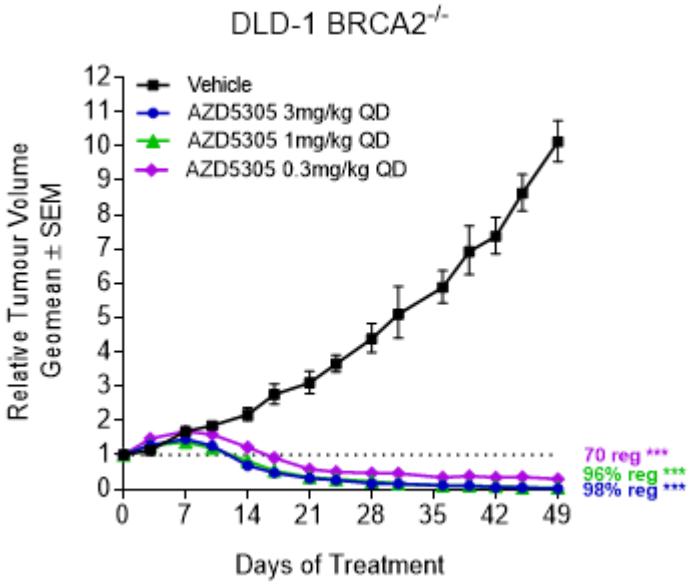
4.2 Scientific Rationale for Study Design

ASCERTAIN, is an open-label, randomised, Phase I, multi-centre study to evaluate the mechanism of action of saruparib or darolutamide alone, or when given in combination to patients with localised unfavourable-intermediate risk/high risk/very high risk prostate cancer who are eligible for curative radical prostatectomy.

This study includes 4 arms (3 study treatment arms and one no-treatment arm). To understand the mechanism of action of saruparib in combination with darolutamide, the Sponsor will perform several translational analyses.

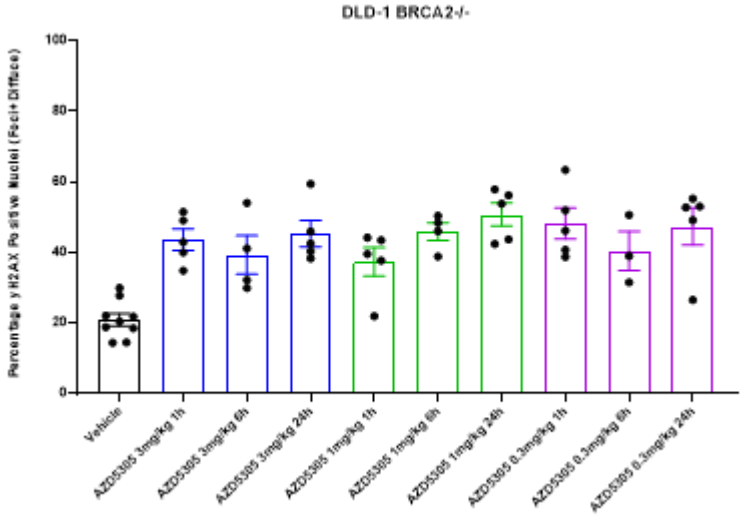
The primary hypothesis to be assessed is whether the combination of saruparib with darolutamide increases DNA damage in the tumour. Phosphorylated histone H2AX (γH2AX) is a widely used surrogate of DNA damage that is a well-recognised biomarker of DNA damage and genome instability (Ciccia and Elledge 2010, Redon et al 2010). Changes in γH2AX will be evaluated after treatment with single agents or combination to determine whether the combination increases DNA damage. In non-clinical in vivo studies with the DLD1 BRCA2 -/- xenograft model, doses of saruparib that caused tumour regressions induced approximately 2-fold increase in γH2AX positive nuclei (Figure 3 and Figure 4), indicating that this fold change can be sufficient for significant anti-tumour efficacy.

Figure 3 Saruparib Causes Tumour Regressions in the DLD1 BRCA2 -/- Model



QD = once daily; SEM = standard error of the mean.

Figure 4 Saruparib Induces ~2-fold Increase in γH2AX at Doses Leading to Tumour Regressions



Mice were dosed with 0.3, 1 or 3 mg/kg saruparib (AZD5305) and tumours harvested for analysis after 5 days of treatment. γH2AX = phospho-histone 2AX (Ser139).

One limitation of previous studies that have investigated mechanisms of combination benefit of PARP inhibitors and NHAs is the use of non-clinical prostate cancer models that may not accurately reflect human disease biology. There are a very limited number of prostate cancer cell lines, many of which have lost AR sensitivity, and do not contain HRD mutations that are found in human prostate cancer. The majority of prostate cancer PDX models have also lost

androgen dependence and so are not suitable for these investigations, and in vivo models do not accurately capture any component of the tumour microenvironment that could contribute to clinical benefit.

This trial is designed to investigate reported combination hypotheses in clinical material, in order to further gain insight into the mechanisms of these interactions.

A comprehensive range of exploratory analyses will be performed to assess the contribution of other potential mechanisms of action to the combination of saruparib and darolutamide.

Previous studies have shown that saruparib alone (PETRA) or in combination with darolutamide (PETRANHA) is well tolerated as monotherapy and at saruparib 60 mg in combination with darolutamide. Further details are included in Section 2.2.1.1 and Section 4.3.

The statistical design for this study is provided in Section 9.

4.3 Justification for Dose

The dose of saruparib 60 mg QD, either as monotherapy or in combination with darolutamide, was selected by unanimous members agreement at the May 2023 SDMC. Clinical data from the ongoing PETRA study (saruparib monotherapy) and PETRANHA study (saruparib in combination with abiraterone acetate or darolutamide) support saruparib 60 mg to be well-tolerated and efficacious.

The PETRA (NCT04644068) study has explored a wide range of dose levels of saruparib monotherapy. As of the DCO of 02 September 2023, a total of 308 patients have received saruparib monotherapy (with doses ranging from 10 mg to 140 mg QD) and there have been 2 DLTs reported; 1 patient in the 60 mg QD Cohort (Grade 2 ECG QT prolonged) and 1 patient in the 140 mg QD Cohort (Grade 2 thrombocytopaenia leading to AZD5305 dose interruption for > 2 weeks). In the monotherapy population, 94.2% (290/308 patients) had at least 1 AE (all grades). The most frequently reported AEs (all grades; *denotes grouped terms) were anaemia* (38.3%), nausea (35.7%), fatigue and asthenia (28.2%), neutropenia* (25.6%), thrombocytopaenia* (25.3%), diarrhoea (14.0%), vomiting (13.6%), and headache (13.3%). A total of 139 patients (45.1%) reported at least 1 AE (regardless of causality) that was Grade ≥ 3 in severity, with anaemia* (20.8%) being the most frequently reported AE in this category. SAEs were reported in 19.8% (61/308) patients. AEs that resulted in discontinuation were reported for 14 patients (4.5%). No clinically significant changes in HR, BP and QT intervals were observed. Based on these data, the safety profile of saruparib is characterised by typical PARPi related toxicities including haematological toxicity (particularly anaemia), gastrointestinal toxicity (particularly nausea) and fatigue/asthenia. Dose levels up to and including 90 mg have been well tolerated and the frequency of AEs leading to dose reductions and treatment discontinuations was low, with most AEs being reported as CTCAE Grade ≤ 2.

Based on safety, efficacy, PK, and PD data of PETRA study of dose levels at 20, 60, and 90 mg QD from latest interim analysis of 02 June 2023, saruparib 60 mg QD was selected as RP2D dose for monotherapy and in combination with hormonal agents.

The PETRANHA (NCT05367440) study is currently evaluating a saruparib dose of 60 mg QD in combination with NHAs, based on the 60 mg dose having been declared tolerable in the PETRA study. As of the DCO of 10 July 2023, a total of 55 patients with mCRPC or mCSPC had received saruparib in combination with an NHA. In the 48 patients who have had the opportunity for 3 months follow-up across Arm 1 (saruparib 60 mg QD + enzalutamide 160 mg QD; n = 11), Arm 2 (saruparib 60 mg QD + abiraterone acetate 1000 mg QD; n = 19), and Arm 3 (saruparib 60 mg QD + darolutamide 600 mg BID; n = 18), the treatment-emergent AEs were mainly CTCAE Grade ≤ 2 and were manageable by dose interruption and/or reduction of saruparib. The most commonly reported AEs were anaemia, fatigue and asthenia, neutropenia, and nausea. These AEs occurred predominantly at a low grade and were overall consistent with the safety profile known of saruparib and NHA monotherapies. The proportion of patients with Grade ≥ 3 events was between 18.2% and 33.3% across the NHA arms. The frequency of dose reductions of saruparib was 10% to 20% across the treatment arms. AEs leading to discontinuation of saruparib were low at < 10%. Additionally, AEs leading to discontinuation of NHA were infrequent across the treatment arms. The 3 treatment arms had an acceptable rate of SAEs (Arm 1: 9.1% of patients; Arm 2: 15.8% of patients; Arm 3: 27.8% of patients), which appeared to be primarily disease-related. Overall, the data from the PETRANHA study demonstrate an acceptable safety profile and good tolerability of saruparib in combination with NHAs including darolutamide.

The dose of darolutamide for the treatment of patients with non-metastatic CRPC and mCSPC, and in this study, is 600 mg orally BID (NUBEQA Prescribing Information 2019). No significant DDI is expected with combination of saruparib and darolutamide.

4.4 End-of-study Definition

For the purpose of Clinical Trial Transparency the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements define 2 completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and

AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if they have completed all phases of the study including the post-surgery follow-up visit. The study will end after up to 120 biomarker evaluable patients are recruited and have completed the post-surgery follow-up visit. The study could be completed early or the number of patients required could be adjusted based on the futility interim at approximately 50 biomarker evaluable patients.

4.4.1 Study Stopping Criteria

AstraZeneca reserves the right to temporarily suspend or permanently terminate this study or components of the study at any time. The reasons for temporarily suspending or permanently terminating the study may include, but are not limited to the following:

- Fatal event deemed related to study therapy (probable or certain causality after full etiological work-up). This will also result in a comprehensive review of safety.
- Unexpected and life-threatening events deemed related to study therapy.
- Sponsor decision that the study participants are placed at undue safety risk.
- Participant enrolment is unsatisfactory.
- Noncompliance that might significantly jeopardise the validity or integrity of the study.
- Sponsor decision to terminate development of the study intervention.

If AstraZeneca determines that temporary suspension or permanent termination of the study or components of the study are required, AstraZeneca will discuss the reasons for taking such action with all participating Investigators. When feasible, AstraZeneca will provide advance notice to all participating Investigators of the impending action.

If the study or components of the study are suspended or terminated for safety reasons, AstraZeneca will promptly inform all Investigators and/or institutions conducting the study. AstraZeneca will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the Investigator must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination. If the study or components of the study are suspended for safety reasons and it is deemed appropriate by AstraZeneca to resume the study or components of the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known

as protocol waivers or exemptions, is not permitted.

Investigators should keep a record, ie, participant screening log of participants who entered screening.

To be eligible for randomisation, each participant must meet all of the inclusion criteria and none of the exclusion criteria for this study at the time of starting study treatment. Participants who do not meet eligibility criteria except for inclusion criteria 1 to 8 can be allocated to the no-treatment arm.

5.1 Inclusion Criteria

Participants must fulfil all of the following criteria to be eligible to be included in the study:

For Study Treatment and No-treatment Arms

Type of Participant and Disease Characteristics

1 Male participants ≥ 18 years of age at the time of screening.

2 Participants deemed suitable for radical prostatectomy as judged by the Investigators based on the local practice.

3 Participants must have localised prostate cancer with unfavourable-intermediate risk/high risk/very high risk (defined below in Table 7) who are eligible for radical prostatectomy.

Table 7 Definitions of Unfavourable-intermediate Risk/High Risk/Very High Risk According to NCCN Guidelines Version 4.2023 Prostate Cancer

Intermediate risk	Unfavourable-intermediate risk	High risk	Very high risk
Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more IRF: cT2b–cT2c Grade Group 2 or 3 PSA 10–20 ng/mL	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive (eg, ≥ 6 of 12 cores)	Has no very-high-risk features and has exactly one high-risk feature: • cT3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL	Has at least one of the following: • cT3b–cT4 • Primary Gleason pattern 5 • 2 or 3 high risk features • > 4 cores with Grade Group 4 or Grade Group 5

IRF = intermediate risk factors; PSA = prostate-specific antigen.
Source: NCCN Clinical Practice Guidelines 2023.

4 Adequate organ and marrow function (in the absence of transfusions or growth factor support within 14 days prior to enrolment) as defined below in Table 8.

Table 8 Criteria for Adequate Organ and Marrow Function

Category	Parameter	Value
Haematological	Haemoglobin	≥ 10.0 g/dL (6.21 mmol/L)
	Absolute neutrophil count	≥ 1.5 × 10^9/L (1,500 per mm^3)
	Platelet count	≥ 100 × 10^9/L (100,000 per mm^3)
Hepatic	Total bilirubin	≤ 1.5 × ULN in the absence of Gilbert's syndrome
		≤ 3 × ULN if the participant has Gilbert's syndrome
	ALT and AST	≤ 2.5 × ULN
	INR	≤ 1.5
Renal	Calculated creatinine clearance by modified Cockcroft-Gault	≥ 45 mL/minute

ALT = alanine aminotransferase/transaminase; AST = aspartate transaminase; INR = international normalised ratio; ULN = upper limit normal.

5 Criterion no longer applicable as removed in a protocol amendment.

Informed Consent

6 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

7 For participants participating in the Optional Genetic Research Only: Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports the Genomic Initiative (see Appendix D 2).

Other Inclusion Criteria

8 Available FFPE diagnostic tumour biopsy samples. Participants who do not have sufficient diagnostic tumour samples (FFPE) can also be eligible for the study provided they undergo pre-treatment fresh biopsy during the screening procedures, prior to planned Day 1 to meet the sample requirement.

For Study Treatment Arms Only

Sex and Contraceptive/Barrier Requirements

9 Male participants:

a) Must use a condom (with spermicide [in accordance with local guidelines]) from screening to ***6 months*** after the last dose of study treatment with all sexual partners.

Female partners of male participants who are of childbearing potential should use a highly effective method of contraception throughout this period.

b) Must refrain from fathering a child or donating sperm from screening to ***6 months*** after the last dose of study treatment.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Note: for the no-treatment arm, if any participant meets exclusion criteria 4, 9 or 11 they should not be included in the study, as these factors can influence the primary endpoint.

Medical Conditions

1 As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases, including, active bleeding diatheses, or active infection including HepB, hepatitis C and HIV. Screening for chronic conditions is not required.

   a) Active HBV is defined by a known positive HBsAg result. Participants with a past or resolved HBV infection (defined as the presence of HepB antibody and absence of HBsAg) are eligible.

   b) Participants positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

2 Participants with any known predisposition to bleeding (eg, active peptic ulceration, recent [within 6 months] haemorrhagic stroke, proliferative diabetic retinopathy).

3 Participants with history of MDS/AML or with features suggestive of MDS/AML (as determined by prior diagnostic investigation.). In case there is no clinical MDS/AML suspicion, no specific screening for MDS/AML (by bone marrow/bone biopsy) is required.

4 Prior malignancy within 3 years of screening whose natural history, in the Investigator's opinion, has the potential to interfere with safety and efficacy assessments of the investigational regimen.

5 Concomitant use of drugs that are known to prolong or shorten QT and have a known risk of TdP.

6 Any of the following cardiac criteria:

   a) Mean resting corrected QT interval (QTcF) > 450 milliseconds or
   QTcF < 340 milliseconds obtained from triplicate ECGs and averaged, recorded within 5 minutes.

   b) Any factors that increase the risk of QT prolongation, shortening or risk of arrhythmic events such as hypokalaemia, congenital long or short QT syndrome, family history of long QT syndrome, familial short QT syndrome or unexplained sudden death under

40 years of age or any concomitant medication known to prolong or shorten the QT interval (Appendix G).

c) Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG eg, complete left bundle branch block, second or third degree atrioventricular block and clinically significant sinus node dysfunction not treated with pacemaker.

7 Other CVS diseases as defined by any of the following:

Symptomatic heart failure (as defined by NYHA class ≥ 2).

uncontrolled hypertension.

hypertensive heart disease with significant left ventricular hypertrophy.

History of acute coronary syndrome/acute myocardial infarction, unstable angina pectoris, coronary intervention procedure with percutaneous coronary intervention or coronary artery bypass grafting within 6 months prior to screening.

cardiomyopathy of any aetiology.

presence of clinically significant valvular heart disease.

history of atrial or ventricular arrhythmia requiring acute treatment; participants with atrial fibrillation and optimally controlled ventricular rate (heart rate < 100 bpm) are permitted.

transient ischaemic attack, or stroke within 6 months prior to screening.

participants with symptomatic hypotension at screening.

8 Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of saruparib.

9 History of prior malignancy, treated with chemotherapy, biological therapy, radiation therapy, androgens, thalidomide, immunotherapy, or other anticancer agent within 3 years of screening. Previously localised surgically treated malignancy is acceptable, if no evidence of recurrence.

10 Known allergy or hypersensitivity to investigational product(s) or any of the excipients of the investigational product(s).

Prior/Concomitant Therapy

11 Prior treatment with any systemic or localised anti-cancer treatment for the localised prostate cancer.

12 During the 4 weeks prior to the first dose, receiving immune modulatory agents including but not limited to, continuous corticosteroids at a dose of > 10 mg prednisone/day or equivalent.

13 Concomitant use of medications or herbal supplements known to be:

- Strong CYP3A4 inducers/inhibitors (applies for saruparib arm and saruparib + darolutamide arm)
- Strong or moderate CYP3A4 and P-glycoprotein inducers (applies to darolutamide arm and saruparib + darolutamide arm)

This is including, but not limited to, the prohibited medications listed in Appendix G, or inability to stop the use thereof, at least 21 days or at least 5 half-lives (whichever is longer) before the first dose of study treatment until 30 days after the last dose of study treatment.

14 Treatment with any investigational agents or study interventions from a previous clinical study within 5 half-lives or 3 weeks (whichever is longer) of the first dose of study treatment.

Other Exclusions

15 Participants with contraindication to darolutamide for treatment arms.

16 Unable to comply with the visits and assessments.

17 In the opinion of the Investigators should not be included in this study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study (eg, no more than a small glass of grapefruit juice [120 mL], half a grapefruit, or 1 to 2 teaspoons [15 g] of Seville orange marmalade daily). Please also see the prohibited concomitant medications (exclusion criteria #13 and Appendix G).

5.3.2 Contraception

Non-sterilised male participants who are sexually active with a female partner of childbearing potential must use a condom with spermicide from screening to 6 months after the last dose of saruparib (Note: Male condoms are not reliable as a sole contraception method. In countries where spermicide is not approved, use of male condoms without spermicide is permitted). IT IS STRONGLY RECOMMENDED THAT female partners of male participants also use at least one highly effective method of contraception throughout this period. In addition, male participants must refrain from fathering a child or donating sperm during the study and for 6 months after the last dose of study treatment. For darolutamide monotherapy, males who have female partners who may become pregnant should use effective birth control (contraception) during treatment and for 1 week after the last dose of darolutamide. Refer to Appendix I for definitions of females of childbearing potential (partners of male participants)

and highly effective methods of contraception.

5.4 Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

Minimal information including demography, screen failure details, eligibility criteria, and any AEs/SAEs will be recorded from participants who failed screening. Participants who met core inclusion criteria (inclusion criteria 1 to 8) can be allocated to the no-treatment arm.

Participants who do not meet the criteria for participation in this study (screen failure) must not be rescreened.

5.5 Criteria for Temporarily Delaying Enrolment/Randomisation/Administration of Study Intervention

Not applicable.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention or study treatment is defined as any investigational intervention/treatment (including marketed product, comparator and placebo) intended to be administered to a participant according to the study protocol. Refer to the individual arm for the dose details of study treatments used in this study. Of note: study intervention, investigational product, and study treatment are used synonymously in the protocol to denote saruparib or darolutamide as monotherapy, or in combination treatment.

6.1 Study Intervention(s) Administered

The preparation, handling, storage, and administration instructions for darolutamide should follow the approved labelling and local guidelines where available. Table 9 includes more information on the study medications.

Table 9 Study Intervention

Arm name	Saruparib	Darolutamide
Intervention name	Saruparib	NUBEQA
Type	Study intervention	Study intervention
Dose formulation	Film-coated tablets	Film-coated tablets
Unit dose strength(s)	20 mg	300 mg

Table 9 Study Intervention

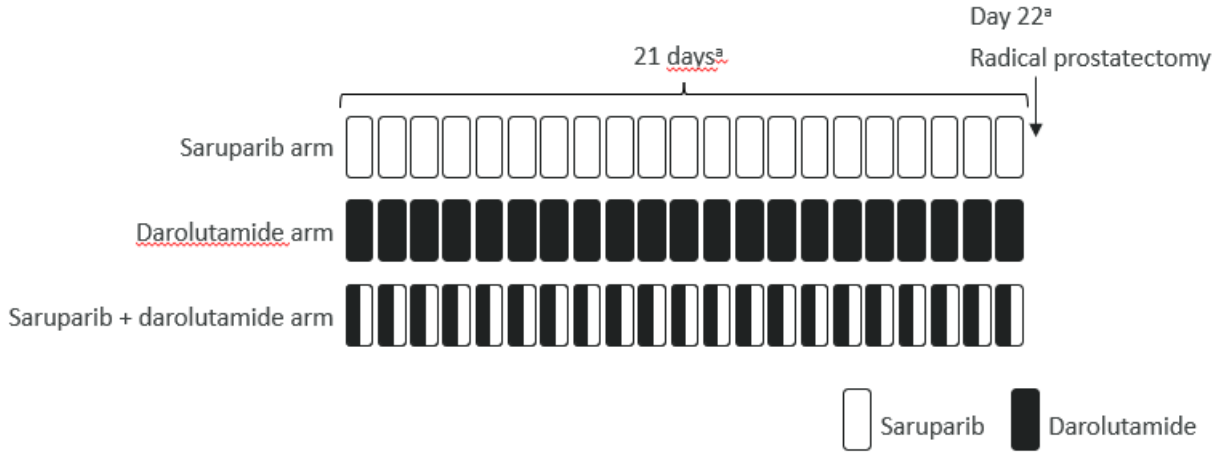
Arm name	Saruparib	Darolutamide
Dosage level(s)	As per SDMC decision: 60 mg	600 mg, modified as per label
Dose frequency	QD	BID
Route of administration	Oral	Oral
Food effect	Fasted/fed	Fed
Dosing instructions	No food restrictions	Must be taken with food
Timing of dosing with saruparib	N/A	Can be taken together with saruparib and with food
Use	Experimental	Experimental
IMP or NIMP	IMP	IMP
Sourcing	AstraZeneca	AstraZeneca [a]
Packaging and labelling	Tablets will be packaged into packs and will be labelled in accordance with Good Manufacturing Processes.	For the new hormonal agents, if Clinical Unit sourced, they would be labelled as per local requirements.

[a] May be sourced by the Clinical Unit in the event that AstraZeneca is unable to source.
BID = twice daily; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; QD = once daily; SDMC = Safety and Data Monitoring Committee.

6.1.1 Administration of Study Interventions

The schedules of study treatment arms are presented in Figure 5.

Figure 5 Schedules of Study Treatment Arms



a Participants should receive 21 days of study treatment and undergo radical prostatectomy on Day 22 (if no surgical delays). Participants can continue the study treatment for a maximum of 28 days in total if there are radical prostatectomy delays due to reasons not related to the study procedures/toxicities. In such a case, participants should undergo radical prostatectomy the next day if feasible but no later than 7 days after the last dose of the study treatment.

6.1.1.1 Saruparib

Saruparib is available as film-coated tablets containing 20 mg saruparib.

Participants will self-administer saruparib orally; All participants should swallow 60 mg or 3 tablets of saruparib QD, commencing on Day 1. Tablets should be taken with water, with or without food.

Saruparib tablets should be taken approximately 24 hours apart (± 2 hours).

If a dose is missed, it is acceptable to take the scheduled dose up to 2 hours after the scheduled dose time. If greater than 2 hours, the missed dose should not be taken, and the participant should continue with the next dose at the allotted time. If vomiting occurs shortly after saruparib is swallowed, the dose should not be replaced. Resume dosing at the following scheduled dose.

6.1.1.2 Darolutamide

Darolutamide is available as tablets containing 300 mg of darolutamide.

Participants will self-administer darolutamide orally at a total dose of 1200 mg per day; all participants should swallow 600 mg or 2 tablets of darolutamide BID, commencing on Day 1. Tablets should be taken with water and food.

In the event of a missed dose, the dose should be taken as soon as the participant remembers up to 2 hours after the scheduled time. The participant should not take 2 doses together to make up for a missed dose.

Participants should take darolutamide doses at a similar time each day (12 hours ± 2 hours). Tablets should be taken whole with food.

6.1.2 Duration of Treatment

Participants in the saruparib treatment arm will receive saruparib 60 mg QD orally for 21 days (+ up to 7 days).

Participants in the saruparib + darolutamide treatment arm will receive saruparib 60 mg QD orally and darolutamide 600 mg BID orally for 21 days (+ up to 7 days).

Participants in the darolutamide treatment arm will receive darolutamide 600 mg BID orally for 21 days (+ up to 7 days).

6.2 Preparation, Handling, Storage, and Accountability

- The Investigator or designee (eg, unblinded pharmacist) must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention

received at the site and throughout the entire study until authorisation is provided for on-site destruction or removal of the IMP, reflecting completion of the study. In the event of a temperature excursion detected at any time during the study, sites will follow the reporting procedures for notifying AstraZeneca (or designated party); release of IMP for clinical use can only occur once the event has been reviewed and approval is provided by AstraZeneca (or designated party).

- Only participants enrolled in the study may receive study intervention, and only authorised site staff may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.
- The Investigator, institution, the head of the medical institution (where applicable), or authorised site staff are responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

The study treatments provided for this study will be used only as directed in this protocol. The study site staff will account for all study treatments dispensed to and returned from the participant. The study site staff will account for all study treatments received at the site, unused study treatments and for appropriate destruction of all unused study treatments. Certificates of delivery and destruction should be signed and filed in the study documentation.

6.3 Assignment to Study Intervention

Participants will be randomised to study intervention using an IRT for those who consented to the treatment arms. Before the study is initiated, the telephone number and call-in directions for the IRT and/or the log in information and directions for the RTSM will be provided to each site. Study intervention will be dispensed at the study visits summarised in the SoA. Returned study intervention should not be re-dispensed to the participants.

Participants will be randomised as they become eligible. To reduce potential bias, eligible participants will be randomised to saruparib: darolutamide: saruparib + darolutamide at a ratio 2:1:2 until the total number of participants planned per treatment arm has been achieved. Treatment should start as soon as possible after randomisation.

Alternatively, participants will be assigned to the no-treatment arm at the Investigators/ participants decision during screening.

If a participant withdraws from study, then the enrolment/randomisation code cannot be reused.

6.4 Blinding

This is an open-label study.

6.5 Study Intervention Compliance

The administration of all study treatments should be recorded in the appropriate sections of the electronic eCRF. Any changes from the dosing schedule, dose interruptions, and dose discontinuations should be recorded in the eCRF. The reason should also be documented.

All study medications are oral and to be self-administered.

The study treatment Storage Manager is responsible for managing the study treatments from receipt by the study site until the destruction or return of all unused study treatments. The Investigator is responsible for ensuring that the participant has returned all unused study treatment.

Use of doses in excess of that specified in the protocol is considered to be an overdose. Refer to Section 6.7 for procedures in case of overdose.

6.6 Dose Modification

Toxicity management guidelines will be under continuous review and will be updated as new safety data become available. The guidelines provided here should be considered alongside local and national guidelines. The USPI or equivalent national pharmaceutical source list of combination agents should be referred to for specific guidance.

If a participant experiences a clinically significant and/or unacceptable toxicity, not attributable to the disease or disease-related processes under investigation, dosing will be interrupted and supportive therapy administered as required.

The decision whether to continue with trial medication should be based on the individual circumstance and the responsible clinician’s judgement that continuation is in the participant’s best interest. Any uncertainties about continuation of study treatment and any deviations from the TMGs should be discussed with the AZ study physician.

All AEs experienced will be graded for severity according to the NCI CTCAE Version 5.0 toxicity criteria.

Toxicity management guidelines below offer a specific guidance for each AE category. However, the Investigator can decide to discontinue the study treatment based on the emerging safety data of the participant with the agreement with the medical monitor, to ensure that radical prostatectomy can occur safely and on time as a priority.

6.6.1 Dose Modification Guidelines for Saruparib

See 4.4.1 for stopping criteria. Clinically significant abnormal laboratory values must be repeated at regular intervals until resolved to the participant's baseline or until improvement (CTCAE Grade ≤ 2).

If the toxicity resolves or reverts to ≤ CTCAE Grade 1 within 6 days of study treatment, saruparib may be restarted using the rules shown in Table 10 for dose modifications.

If the toxicity does not resolve to ≤ CTCAE Grade 1 after 6 days, then the participant should be withdrawn from the study and observed until resolution of the toxicity.

Table 10 Dose Modifications for Saruparib

Toxicity grade	Dose modifications
Any grade leading to a total treatment interruption period of ≥ 7 days	Participant should be permanently discontinued from study drugs and the clinical trial. Participant should receive optimal supportive care until resolution of event and undergo to surgical procedure at earliest convenience.
Grade 1 to 2 toxicity	Investigator judgement to continue treatment or interrupt dose. Initiate optimal supportive care and investigate causality. If the toxicity does not resolve to < CTCAE Grade 1 after 6 days (for Grade 2 toxicity), the participant should be withdrawn from the study and undergo surgical procedure at earliest convenience. Resuming treatment with the same dose level with prophylactic treatment should be based on Investigator judgement and can be discussed with the medical monitor.
Grade 3 to 4 toxicity (1st event)	Interrupt study treatment, initiate optimal supportive care according to site guidelines, and investigate causality. Participants should permanently discontinue study treatment and undergo surgical procedure at earliest convenience.

CTCAE = Common Terminology Criteria for Adverse Events.

6.6.2 Management of Prolonged Haematological Toxicities

If a participant develops prolonged haematological toxicity such as:

- ≥ 2 weeks of CTCAE Grade 3 or worse anaemia and/or development of blood transfusion dependence.
- ≥ 2 weeks of CTCAE Grade 3 or worse neutropenia (ANC < 1×10^9/L).
- ≥ 2 weeks of CTCAE Grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (Platelets < 50×10^9/L).

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters (including vitamin B12 and folate) remain clinically abnormal after

4 weeks from onset of the Grade 3 event, the participant should be referred to a haematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard haematological practice.

Development of a confirmed MDS or other clonal blood disorder should be reported as an SAE and full reports must be provided by the Investigator to AstraZeneca Patient Safety.

6.6.3 Management of CVS Toxicity

If any of the following CVS criteria are met at any time during the study, dosing should be interrupted and the AstraZeneca Study Physician should be informed. If any of the following are observed on Day 1, Day 15 or the Day before RP at the discretion of the Principal Investigator, the participant should be kept under observation for 24 hours (trigger points listed below concern daytime values after 5 minutes rest in sitting or supine position):

- Heart rate > 125 bpm
- Symptomatic tachycardia
- Clinically relevant increase of blood-pressure from baseline

6.6.4 Dose Modification Guidelines for Darolutamide

Refer to below for darolutamide dose modification for AST or ALT increased. For dose modification due to other toxicities, please follow the darolutamide label.

Darolutamide Dose Modifications for AST or ALT increased:
Cases of idiosyncratic DILI with increases in ALT and/or AST to ≥ 5 and ≥ 20 × ULN, including with concomitant bilirubin elevation > 2 × ULN, have been reported with darolutamide. Liver function test abnormalities were reversible upon darolutamide discontinuation. Participants who experience hepatic transaminase elevations suggestive of idiosyncratic DILI considered to be causally related to study drug (darolutamide), should discontinue darolutamide. Should there be any cases of suspected or potential DILI please notify the Sponsor promptly regarding the suspected case.

If ALT or AST rise to > 3 × ULN, participants should be discontinued from the study treatment and monitored until ALT and/or AST return to baseline or normal values.

6.6.5 Dose and Safety Management

Dosing will begin at Day 1 and participants will start at a fixed dose of saruparib (that was agreed by SDMC prior to dosing the first participant and will be 60 mg QD) and darolutamide (600 mg BID) either in monotherapy or combination according to the arm allocated by randomisation. Dose reduction for saruparib is not allowed given the nature of the study but if deemed appropriate, the Investigator could consider pausing the treatment for up to 6 days of the treatment, offer supportive medication/therapy and rechallenge with the same dose if

clinically appropriate, as summarised in TMG guidelines. Participants should be discontinued from saruparib treatment in the first occurrence of any Grade 3/4 event. Dose modification for darolutamide should follow the label. Participants that have not taken ≥ 75% of planned doses will not be included in the biomarker analysis set but will be included in the safety analysis set.

Justification for the dose is outlined in Section 4.3.

Participants will be randomised as they become eligible as outlined in Section 6.3.

6.6.6 Definition of Biomarker Evaluable Patient

A total of up to 120 participants may be randomised or allocated across 4 arms (randomisation N = 100: saruparib, darolutamide, saruparib + darolutamide, or allocation N = 20: no-treatment arm). Patients will be considered biomarker evaluable if they have:

- completed at least 75% of the assigned study treatment in each treatment arm (eg, minimum 16 days of treatment out of 21 days),
- or who have been assigned to the no-treatment arm, and;
- whose tumour samples are biomarker evaluable for γH2AX analysis, as defined in the Pathology Manual.

Non-biomarker evaluable patients may be replaced.

6.6.7 Safety and Data Monitoring Committee

The SDMC will decide on the starting dose of saruparib prior to recruitment of the first participant based on emerging data from ongoing saruparib studies. During the study conduct, the SDMC will undertake review of safety data when approximately 10 participants across the treatment arms have completed Day before RP visit and radical prostatectomy. Additionally, the SDMC will review the safety data when data are available for 25 and 50 participants, respectively, in the study treatment arms together with available safety data from the no-treatment arm. Available biomarker data at the time of the SDMC meetings may also be presented. Based on the SDMC outcome, the study design may change, including revision on tumour sample requirement or randomisation ratio, with a protocol amendment.

Ad-hoc SDMC may be planned based on emerging safety data. A separate SDMC charter will specify further details such as timings and data to be reviewed in addition to SDMC remit and membership.

Recruitment will continue during the SDMC reviews.

6.7 Treatment of Overdose

Overdose, defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. An “excessive and medically important” overdose includes any overdose in which either an SAE, a non-serious AE, or no AE occurs and is considered by the Investigator as clinically relevant, ie, poses an actual or potential risk to the participant.

Overdose is always serious. By definition, an overdose is medically important, which meets the seriousness criterion of important medical event. An overdose can occur with or without an AE. Adverse events can either be serious or non-serious. Details of the overdose including dosage of study treatments, clinical course, associated AEs, and outcome must be captured in the narrative form of the CRF within EDC. Use of saruparib or darolutamide (according to labels) in doses that are in excess of those specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of the study treatments used in the study, and possible symptoms of overdose are not established. Refer to the local prescribing information for treatment in cases of an overdose related to standard of care combination partners. The Investigator will use clinical judgement to treat any overdose. Investigators should be advised that any participant who receives a higher dose than that intended should be monitored closely, managed with appropriate supportive care, and followed up expectantly.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the overdose CRF module.
- An overdose without associated symptoms is only reported on the overdose CRF module and not the AE module.

If an overdose of a study treatment, with or without associated AEs/SAEs, occurs during the course of the study, then the Investigator or other site personnel must inform the appropriate AstraZeneca representative immediately, or no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply, see Section 8.4.13. For other overdoses, reporting must occur within 30 days.

6.8 Prior and Concomitant Therapy

6.8.1 Concomitant Therapy

Any medication or vaccine, including over-the-counter or prescription medicines, vitamins,

and/or herbal supplements that the participant is receiving at the time of enrolment or receives during the study must be recorded, together with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Note: Medications used as a standard of care during trial related procedures not required to be reported (eg, anaesthetics, post-operative medication).

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

Table 11 gives the details on the prohibited concomitant medications. Please also refer to local and national prescribing guidelines for additional details about darolutamide.

Table 11 Prohibited Concomitant Medications

Prohibited medication/class of drug	Usage
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy (bisphosphonates are exceptions) for cancer treatment other than those under investigation in this study.	Should not be given concomitantly while the participant is on study intervention. Concurrent use of hormones for non-cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable.
Any substances with a potential to significantly alter the prostate cancer and/or the androgen receptor pathway.	Patient with ongoing treatment with 5-alfa reductase inhibitors (eg, finasteride and dutasteride) could be allowed if currently at a stable dose and taken for at least 24 weeks prior to enrolment
Drugs that are known to prolong or shorten QT and have a known risk of Torsades de Pointes should not be combined with saruparib	See Appendix G for details.
Saruparib arm and saruparib + darolutamide arm only: Strong inducers and inhibitors of CYP3A4 (Appendix G)	Strong inhibitors and inducers of CYP3A4 should not be combined with saruparib. Strong inhibitors or inducers of CYP3A4 should be stopped at least 21 days or at least 5-times half-lives (whichever is longer) before the first dose of study treatment until 30 days after the last dose of medication.
Darolutamide arm and saruparib + darolutamide arm only: Strong or moderate CYP3A4 and P-gp inducers (Appendix G)	Strong and moderate CYP3A4 inducers and/or P-gp inducers should not be combined with darolutamide. Strong and moderate CYP3A4 inducers and/or P-gp inducers should be stopped at least 21 days or at least 5 times half-lives (whichever is longer) before the

Table 11 Prohibited Concomitant Medications

Prohibited medication/class of drug	Usage
	first dose of study treatment until 30 days after the last dose of medication.
Live virus and bacterial vaccines	Prohibited whilst on study and during 28-day follow-up period.
Herbal and natural remedies	Should be avoided on study where possible
Blood transfusions	Blood transfusions are allowed at any time during the study as a treatment but should not be administered prophylactically.
Warfarin (coumarin derivatives)	It is recommended that participants switch from warfarin to subcutaneous heparin, low molecular weight heparin, or NOACs. Participants unable to switch may participate in the study; however, it is recommended that INR is monitored frequently. If NOACs are used, it is preferable to avoid CYP3A substrates (eg, apixaban and rivaroxaban) if possible.
Darolutamide only: BCRP, OATP1B1, and OATP1B3 substrates (darolutamide arm and saruparib + darolutamide arm only; Appendix G)	Avoid concomitant use with drugs that are BCRP, OATP1B1 and OATP1B3 substrates where possible. If used together, monitor participants more frequently for adverse reactions and consider dose reduction of the BCRP substrate drug.

BCRP = breast cancer resistance protein; CYP# = cytochrome P450 subunit number; INR = international normalised ratio; NOAC = Non-vitamin K antagonist oral anticoagulants; OATP = Organic anion transporting polypeptides; P-gp = P-glycoprotein; QT = QT interval.

Table 12 gives the details on the permitted concomitant medications.

Table 12 Permitted Concomitant Medications

Supportive medication/class of drug	Usage
Bone-modifying agents	eg, denosumab, pamidronic acid and zoledronic acid are permitted as long as they are started 4 weeks or more before enrolment.
COVID-19 Vaccination	Although AstraZeneca recommends avoiding administering COVID-19 vaccination for 72 hours prior to administration of the first dose of investigational product (to avoid biases in the interpretation of safety data, due to the potential overlap of vaccine-related AEs with investigational product's AEs), discretion is granted to the Investigator as individual benefit/risk analysis may vary.
Anti-emetics	eg. Cyclizine and metoclopramide are permitted as a PRN or prophylactic medication for nausea. Other anti-emetics could be used if not in the prohibited medications list and have no risk of QT prolongation.

COVID-19 = Corona Virus Disease 2019; PRN = as needed.

Participants are allowed to receive any intervention or therapy clinically indicated for improvement of AEs related or unrelated to study treatment/ interventions, if not listed in the prohibited medications/interventions list. In case a new intervention/therapy is given/taken by the participant, it should be registered in the eCRF and linked to the corresponding AE. The sponsor recommends the Investigator uses the latest IB version of saruparib that will be provided to the sites.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

7.1 Discontinuation of Study Intervention

Note that discontinuation from study intervention is *not* the same thing as a discontinuation or withdrawal from the study (see Section 7.2).

If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study. Refer to each arm's SoA (Table 1 and Table 2) for data to be collected at the time of follow-up and for any further evaluations that need to be completed.

The participant should continue attending subsequent study visits and data collection should continue according to the study protocol. If the participant does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the participant when clinically indicated/feasible, or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A participant who agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Participants may be discontinued from study treatment in the following situations:

- Participant decision: The participant is, at any time, free to discontinue treatment, without prejudice to further treatment. A participant who discontinues study treatment is normally expected to continue to participate in the study (eg, for safety follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments.
- Occurrence of any AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing.
- Occurrence of any AE that meets the criteria for permanent discontinuation as defined in TMGs for saruparib (Section 6.6.1) or as defined in the local prescribing information for any combination treatment.

- Participants incorrectly initiated on study treatment (see Section 7.1.1).
- Severe non-compliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from study treatment (eg, refusal to adhere to scheduled visits).
- Life-threatening or other unacceptable toxicity.
- The discovery of an unexpected, significant, or unacceptable risk to the participants enrolled in the study.
- Decision to modify the development plan of the study intervention.
- Initiation of alternative anticancer therapy including another investigational agent.
- Death.

7.1.1 Procedures for Handling Participants who are Incorrectly Initiated on Study Treatment

Participants who do not meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study intervention. There can be no exceptions to this rule.

Where participants that do not meet the inclusion/exclusion criteria are enrolled in error or incorrectly started on treatment, or where participants subsequently fail to meet the study criteria post initiation, the Investigator should inform the Study Physician immediately. When the reason does not impact safety, the risk/benefit to the participant of stopping treatment will be considered.

Any participant who is found to have failed to comply with all of the selection criteria, but has not started treatment, will be removed from the study following completion of safety follow-up activities.

Every effort should be made to keep all participants, whether eligible or ineligible, in the study until completion of safety follow-up activities.

The Study Physician and Medical Monitor are to ensure all such contacts are appropriately documented.

7.1.2 QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QT interval corrected using QTcF) after enrolment, the Investigator or qualified designee will determine if the participant can continue on the study intervention and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an

AE.

7.2 Participant Discontinuation/Withdrawal From the Study

Discontinuation of the participant from the study by the Investigator:

- A participant may be discontinued from the study at any time at the discretion of the Investigator for safety, behavioural, compliance, or administrative reasons.
- At the time of discontinuing from the study, if the participant has not been discontinued from the study intervention, see Section 7.1.

Voluntary withdrawal from the study by the participant:

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant who wishes to withdraw from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- If the participant withdraws consent for disclosure of future information, AstraZeneca may retain and continue to use any data collected before such a withdrawal of consent.
- If the participant withdraws from the study, AstraZeneca may retain and continue to use any samples collected before such a withdrawal of consent for the purposes the participant originally consented unless the participant withdraws consent for use of samples already collected. If the participant specifically withdraws consent for any use of samples, it must be documented in the site study records by the Investigator and the Investigator must inform the Local and Global Study Team. Destruction of any samples taken and not yet tested should be carried out in line with documented sample withdrawal wishes in conjunction with what was stated in the informed consent and local regulation. See also Appendix C 2.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The participant should be counselled on the importance of maintaining the

assigned visit schedule. At this time ascertain whether the participant should or wishes to or continue in the study.

- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, texts, emails, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Efforts to reach the participant should continue until the end of the study (Section 4.4). Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants enrolled, including those who did not get study treatment. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. AstraZeneca personnel will not be involved in any attempts to collect vital status information.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in Section 1.3 SoA. Protocol waivers or exemptions are not allowed.
- Urgent safety concerns should be discussed with AstraZeneca immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Instructions for the collection and handling of HBS will be provided in the study-specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on handling of HBS see Appendix C.

- In the no-treatment arm, a total of approximately 72 mL of blood will be required for all screening tests, which will be conducted during the 28-day screening period. No more than approximately 96 mL (inclusive of screening) will be collected in any 28-day period. In the study treatment arms, a total of approximately 80 mL of blood will be required for all screening tests. No more than approximately 225 mL will be collected during the 21-day (+ up to 7 days) study treatment period. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General/Baseline Procedures

Other administrative and general/baseline procedures include obtaining informed consent, and recording demographic and medical history, height, weight and concomitant medications.

8.2 Disease Evaluation

8.2.1 Multiparametric MRI

Multiparametric MRI (mpMRI) will be performed as optional at timepoints indicated in the SoA (Table 1). Diagnostic mpMRI images (collected outside the screening window) are acceptable for the screening timepoint. If the diagnostic images are available, the mpMRI procedure at the screening timepoint does not need to be repeated. Images will be collected at and sent to an AstraZeneca-appointed vendor and/or AstraZeneca for storage. Central reading of scans may be conducted, if deemed appropriate by AstraZeneca. Digital copies of all original scans should be stored at the Investigator site as source documents. Electronic image transfer from the sites to the vendor is strongly encouraged. Guidelines for image acquisition, deidentification, storage of digital copies at the investigative site (as source documents), and transfer to the vendor will be provided in a separate document.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in Section 1.3 SoA (Table 1 and Table 2).

The assessments should occur in the following order: ECG followed by vital signs and then PK blood draws.

8.3.1 Physical Examinations

Physical examination will be performed at timepoints as specified in Section 1.3 SoA (Table 1 and Table 2). Physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, CVS, gastrointestinal, urogenital, musculoskeletal, neurological, dermatological, haematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Situations in which physical examination results should be reported as AEs are described in Section 8.4.4. Targeted physical examinations will be performed throughout the

treatment period, at the discretion of the Investigator eg, for new or worsening symptoms and/or signs.

8.3.2 ECOG Performance Status

Performance status will be assessed at timepoints as specified in Section 1.3 SoA (Table 1 and Table 2) according to ECOG criteria. Any significant change from baseline or screening must be reported as an AE.

The ECOG scale and Karnofsky conversion is described in Appendix H.

8.3.3 Vital Signs

Vital signs (to be taken pre-dose before blood collection for laboratory tests on Day 1 and Day 15, then if clinically indicated) will be performed at timelines as specified in Section 1.3 SoA (Table 1 and Table 2).

Participant BP and heart rate will be measured during routine study visits to monitor any changes to heart rate or BP during the study. During routine study visits, BP and heart rate will be measured preferably using a validated semi-automatic BP recording device with an appropriate cuff size after 5 minutes rest in sitting or supine position.

Situations in which vital signs results should be reported as AEs are described in Section 8.4.4.

8.3.4 Electrocardiograms

Refer to each arm's SoA (Table 1 and Table 2) for details of ECG measurements. In addition, ECGs will also be performed when clinically indicated. ECGs will be performed pre-dose before blood collection for laboratory tests on Day 1 and Day 15.

At Screening and on Day 1 (for treatment arms patients only), ECGs will be performed in triplicate (all 3 within a 5-minute time period, at least 1 minute apart). At all other time points, a single ECG will be obtained pre-dose. A single ECG will also be obtained at screening for the no-treatment arm patients.

All ECG recordings will be made with the participant in a supine position having rested in this position for at least 5 minutes before the start of the ECG.

Electronic software will be used to assess the following parameters: pulse rate, RR, QRS, QT, and QTc time intervals. All ECGs must be reviewed by the Principal Investigator or a medically qualified designee before the start of treatment administration, when required, according to the SoA. In case of a clinically significant ECG abnormality (eg, occurrence of de- or re-polarization disorders, arrhythmic disorders), including QTc interval prolongation by Fridericia's formula of > 500 milliseconds, a minimum of 2 additional 12-lead ECGs should

be obtained over a brief interval (eg, 30 minutes) to confirm the abnormality based on manual over-read by a medically qualified person. Such abnormalities and any obvious changes in ECG parameters from baseline will be assessed by the Principal Investigator for clinical significance. If clinically significant, the ECG abnormality should be recorded as an AE in the eCRF. Clinical interpretation and any associated management of participants related to ECG abnormalities will be done locally and will be based on interpretation by a medically qualified person at the site.

Situations in which ECG results should be reported as AEs are described in Section 8.4.4.

8.3.5 Clinical Safety Laboratory Tests

Blood samples for determination of serum chemistry (Table 13), haematology (Table 14), coagulation (Table 15), and other assessments (Table 16) will be collected at the times indicated in the SoA (Table 1 and Table 2) of each arm and as clinically indicated.

Clinical laboratory safety tests will be performed in a local licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The following clinical laboratory tests will be performed (for the frequency of these assessments, including "other assessments" please see the SoA):

Table 13 Serum Chemistry

Calcium	Gamma-glutamyl transpeptidase
Magnesium	AST
Creatinine	ALT
Sodium	ALP
Blood urea nitrogen or urea	LDH
Potassium	Total protein
TBL	Albumin
Indirect bilirubin [a]	
Phosphate	

[a] To be measured if TBL results are abnormal.
Note for serum chemistry: Tests for AST, ALT, ALP, and TBL must be conducted concurrently and assessed concurrently. If TBL is ≥ 2 × ULN, indirect bilirubin should be assessed unless previously documented Gilbert's disease.
ALP = alkaline phosphatase; ALT = alanine aminotransferase/transaminase; AST = aspartate transaminase; LDH = lactate de-hydrogenase; TBL = total bilirubin; ULN = upper limit of normal.

In case a participant shows an AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN please refer to Appendix E, for further instructions.

Table 14 Haematology

Haemoglobin	Platelet count
Total leukocyte count [a]	Mean cell volume
Leukocyte differential count (absolute count)	Reticulocyte count

[a] Absolute differentials are required.

Table 15 Coagulation

International normalised ratio	Activated partial thromboplastin time

Table 16 Other Assessments

Testosterone	

8.4 AEs, SAEs, and Other Safety Reporting

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Participants (or, when appropriate, a caregiver, surrogate, or the participant's legally authorised representative) will notify the Investigator or designees of symptoms. These must then be assessed by the Investigator and if considered an AE it will be reported by the Investigator.

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

AE Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity or changes in intensity
- Changes in CTCAE Grade (report only the maximum CTCAE grade for a calendar day)
- Whether the AE is serious or not

- Investigator causality rating against the IMP(s) (yes or no)
- Action taken with regard to IMP(s)
- AE caused participant's withdrawal from the study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- AE description
- AE is serious due to seriousness criteria
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse Events will be collected from the time of signature of the ICF throughout the treatment period and until the follow-up period is completed 7 to 90 days after surgery.

Serious Adverse Events will be recorded from the time of signing of the ICF.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical study in a treated participant, the Investigator shall, without undue delay, report the SAE to AstraZeneca.

8.4.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment in the post-surgery follow-up in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.4.3 Causality Collection

The Investigator should assess causal relationship between IMP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B.

8.4.4 AEs Based on Examinations and Tests

Deterioration as compared with baseline in protocol-mandated laboratory values, vital signs, physical examination, and ECGs should only be reported as AEs if they meet any of the following:

- fulfil any of the SAE criteria
- are the reason for discontinuation of the IMP
- are clinically relevant as judged by the Investigator (which may include but is not limited to consideration as to whether intervention or non-planned visits were required or other action was taken with the IMP, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting Investigator uses the clinical, rather than the laboratory term (eg, anaemia vs low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the DUS.

The results from the protocol mandated laboratory tests, vital signs, and ECGs will be summarised in the CSR.

8.4.5 AEs Based on Signs and Symptoms

All signs or symptoms spontaneously reported by the participant or reported in response to the

open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?' or revealed by observation will be collected and recorded in the eCRF.

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.4.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.4.7 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the IMP is being studied. It may be an increase in the severity of the DUS and/or increases in the symptoms of the disease. The development of metastasis or clinically significant increase of the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as AEs during the study.

8.4.8 Reporting of SAEs

All SAEs must be reported, whether or not considered causally related to the IMP. All SAEs will be recorded in the eCRF.

If any SAE occurs during the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports the SAE via secure method to the appropriate AstraZeneca representative by fax.

When the EDC is temporarily not accessible, the AstraZeneca Study Representative should confirm that the Investigator/site staff enters the SAE in the AstraZeneca EDC when access resumes.

For further guidance on the definition of an SAE, see Appendix B.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca IMP and for the active comparator product (including any AstraZeneca comparator.).

8.4.9 Pregnancy

All pregnancies of the participant's partners and outcomes of pregnancy should be reported to AstraZeneca.

8.4.9.1 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 6 months following the last dose.

Pregnancy of the participant's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly), occurring from the date of the first dose until 6 months after the last dose should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the pregnant partner must be obtained before the Pregnancy Report Form is completed.

8.4.10 New Cancers

The development of a new cancer, including haematological malignancy, should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the study intervention, and have been identified after the participant's inclusion in this study. They do not include metastases of the original cancer.

8.4.11 Deaths

All deaths that occur during the study intervention period, or within the protocol-defined follow-up period after the administration of the last dose of study intervention, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the DUS, the AE causing the death must be reported as an SAE within 24 hours. It should also be documented in the eCRF. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Death with an unknown cause should always be reported as an SAE. It should also be documented in the eCRF. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual time frames.

8.4.12 Medication Error, Drug Abuse, and Drug Misuse

8.4.12.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.4.8) and **within 30 days** for all other events.

8.4.12.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication error can be found in Appendix B 4.

8.4.12.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

8.4.12.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or

AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

8.4.13 Reporting of Overdose

Refer to Section 6.7 for definition and treatment of overdose.

- An overdose with associated AEs is recorded as the AE diagnoses/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an IMP or AstraZeneca NIMP occurs in the course of the study, the Investigator or other site personnel must inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see Section 8.4.8) and **within 30 days** for all other overdoses.

8.5 Pharmacokinetics

- Plasma samples will be collected for measurement of plasma concentrations of saruparib and darolutamide (parent and metabolite[s] if applicable) as specified in Section 1.3 SoA (Table 1 and Table 2) and Table 17.
- Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and AstraZeneca, eg, for urgent safety reasons, and this may be reflected as a protocol deviation.
- The timing of sampling may be altered during the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.
- Plasma samples will be used to analyse the PK of saruparib and darolutamide. Samples collected for analyses of saruparib and darolutamide concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. Any residual sample remaining after PK analysis has been performed may be used to identify, characterise, and establish the concentration of saruparib metabolites and drug-related products in plasma and/or to conduct exploratory biomarker research.

- Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.
- For storage, re-use, and destruction of samples for PK see Appendix C.
- Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.
- Additional analyses may be conducted on the anonymised, pooled, or individual PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.5.1 Collection of Samples for Pharmacokinetics

Refer to the SoA for each arm (Table 1 and Table 2) and Table 17 for details of the collection schedule and procedures for PK sample collection.

Table 17 PK/Blood for Pharmacodynamic (PAR) Timepoints (Study Treatment Arms)

Day	Timepoints	PK Saruparib[a]	PK Darolutamide [b]	Blood for pharmacodynamics (PAR)
Screening				X
Day 1	Pre-dose	X	X	X
	1 h post-dose (± 10 min)	X	X	X
	1.5 h post-dose (± 10 min)	X		X
	2 h post-dose (± 10 min)	X		X
Day before RP [c]	Pre-surgery	X	X	X
Post-surgery follow-up				X

[a] Saruparib, saruparib + darolutamide arms only.
[b] Darolutamide, saruparib + darolutamide arms only.
[c] Blood for PK/PD will be collected on the Day before the RP visit, which is Day 21 if there are no RP delays or on the Day of the RP visit. If collected on the Day of RP visit, collection to be performed before surgery.
h = hour; min = minutes; PAR = poly (adenosine diphosphate–ribose); PK = pharmacokinetics; RP = radical prostatectomy.

Blood samples will be collected for the determination of concentrations of saruparib and darolutamide (parent and metabolite(s) if applicable) in plasma. The date and time of collection, and the date and time of freezing, of each sample will be recorded. All PK samples need to be collected within ± 10 minutes of the scheduled sampling timepoint to be protocol compliant. Pre-dose samples should be collected within 1 hour prior to dosing. The timing of the PK samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterisation of the plasma concentration-time profiles.

8.5.1.1 Collection of Pharmacokinetic Blood Samples for Saruparib Bioanalysis

Venous blood samples (2.0 mL each) for determination of concentrations of saruparib (parent and metabolite[s] if applicable) in plasma will be collected at the times presented in Table 17. Time points post-dose are relative to the timing of saruparib dose.

8.5.1.2 Collection of Pharmacokinetic Blood samples for Darolutamide Bioanalysis

Venous blood samples (2.0 mL each) for determination of concentrations of darolutamide (parent and metabolite[s] if applicable) in plasma will be collected at the times presented in Table 17. Time points post-dose are relative to the timing of saruparib dose.

8.5.2 Determination of Drug Concentration

Samples for the determination of drug concentrations in plasma will be assayed by selected vendors on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

8.6 Pharmacodynamics

The assessment of pharmacodynamic biomarkers will be used to inform the extent and duration of PARP1 target inhibition, following treatment with saruparib in participants.

Analysis of the effects of saruparib on PARP1 and downstream biomarkers will be assessed and may include, but is not limited to, tumour and PBMC PAR, γH2AX.

8.6.1 Investigation of Pharmacokinetic/Pharmacodynamic Relationship

Where possible, population modelling and simulation methods will be used as part of the evaluation to assess relationships between emerging safety, tolerability, PK and pharmacodynamic and covariates data. AstraZeneca will be responsible for these analyses and, if conducted, will be reported separately from the CSR. Please also see Section 9.4.4.1.

8.6.2 Collection of Samples for Pharmacodynamics

Refer to the SoA for each arm (Table 1 and Table 2) and Table 17 for details of the collection schedule and procedures for pharmacodynamic sample collection.

For Day 1 timepoints for pharmacodynamics (PAR) collection refer to Section 8.5.1.

For storage, re-use, and destruction of samples for pharmacodynamic biomarkers see Appendix C.

8.6.2.1 Tumour Markers

Tumour biomarker samples (PSA) will be collected. Samples should be collected from participants as per the SoA (Table 1 and Table 2). Tumour marker tests will be performed in a licensed clinical laboratory according to local standard procedures.

8.7 Optional Genomics Initiative

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA and is subject to participant agreement in the optional genetic research information ICF.

The blood sample for DNA isolation will be collected from participants who have consented to participate in the genomic component of the study. Participation is optional. Participants who do not wish to participate in genomic research may still participate in the study.

See Appendix D for information regarding the Genomics Initiative samples. Details on processes for the collection and shipment and destruction of these samples can be found either in the appendices of this protocol or in the Laboratory Manual.

8.8 Biomarkers

8.8.1 Mandatory Biomarker Sample Collection

By consenting to participate in the study the participant consents to the mandatory research components of the study. AstraZeneca or designated organisations will investigate tumour/whole blood/plasma and urine samples which will be collected at the times specified in the SoA (Table 1 and Table 2).

The samples for biomarker research will be used to measure changes in γH2AX % positive cells (as primary endpoint) and Ki-67 % positive cells (as secondary endpoint) and for further exploratory work to elucidate the mechanism of action of study treatment.

A peripheral blood sample will be collected at screening to isolate germline DNA to assess HRR mutation status.

The samples and data from this research will be coded and not labelled with any personal details. Each sample will be identified with the study and patient number. In this way biomarker data may be correlated with clinical data, samples destroyed in the event of withdrawal of consent and regulatory audit enabled. However, only the Investigator will be able to link the biomarker sample to the individual participant. The coded samples may be made available to groups or organisations working with AstraZeneca on this research or as part of the development of the study intervention and companion diagnostic. However, the samples and any results will remain the responsibility of AstraZeneca at all times. Biomarker data may be generated in real time during the study or retrospectively and will have unknown

clinical significance. AstraZeneca will not provide biomarker results to participants, their family members, any insurance company, an employer, clinical study Investigator, general physician or any other third party unless required to do so by law. The participant's samples will not be used for any other purpose other than those described in the protocol.

Instructions for the collection and handling of biological samples will be provided in the study specific Laboratory Manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

8.8.2 Collection of Diagnostic Tumour Samples

8.8.2.1 Diagnostic FFPE Tumour Samples (Mandatory)

Collection of a diagnostic FFPE tumour sample is mandatory for all participants but a fresh tumour biopsy sample is acceptable in case the archival diagnostic biopsy tumour sample is not available. Baseline samples should be collected prior to dosing with study treatment but must be taken after the baseline radiological tumour staging. Formalin-fixed paraffin-embedded tumour tissue embedded in paraffin blocks are to be retrieved for all participants (refer to the Pathology Manual for detailed guidelines around sample acceptability). The diagnostic tumour samples are preferably from the time of diagnosis.

Tumour samples will preferably be in the form of an FFPE block (tissue derived from the diagnostic tumour). If it is not possible, a minimum of 10 slides of freshly prepared unstained 5-micron sections and a minimum of 6 slides of freshly prepared unstained 3-micron sections from the diagnostic tumour block may be provided (refer to the Pathology Manual for detailed guidelines around sample acceptability). As uncontrolled oxidation processes affect tumour sections, tumour tissue blocks are preferred. From submitted diagnostic tumour blocks, material may be taken for exploratory biomarker analysis (including 2 cores) for later biomarker analysis. Details of sample collection, processing, shipping and storage will be described in the Pathology and Laboratory Manual.

The diagnostic tumour sample collected may be used for exploratory assessment of the tissue for genomic profiling. In addition, tumour tissue may be used for further exploratory work to elucidate the mechanism of action of study treatment. The tumour samples may also be stored for use to develop future analysis. Please refer to Pathology and Laboratory Manual for further details of diagnostic tissue collection, shipping, and storage.

Biomarker analysis for the primary and secondary objectives (γH2AX and Ki-67 positive cells, respectively) will be performed in tumour samples using immunohistochemistry scoring.

For exploratory objectives, the analysis of diagnostic tumour tissue may also include, but is not limited to:

- DNA sequencing for genomic aberrations in DDR genes, assessment of loss of heterozygosity, genomic instability, epigenetic alterations, or tumour mutational burden
  - In patients where a BRCA pathogenic mutation is found, a central confirmation test with a clinically validated assay for germline alterations (eg, Myriad BRACAnalysis CDx®) will be performed. The report of the central test will be available for the site PI responsible for the patient.
- Whole exome or whole genome sequencing
- RNA sequencing, including single-cell or spatial assessments
- Immunohistochemical staining for PARP1, PARP2, or other response-predictive protein biomarkers
- Protein or mRNA expression of immune and other markers

8.8.2.2 Diagnostic Fresh Frozen Tumour Samples (Optional)

The collection of fresh frozen diagnostic tumour tissue samples is optional. Optional biopsies are important for exploratory work performed to understand the mechanism of action of study treatments. Fresh frozen samples from the time of diagnostic tumour collection using core biopsies of the tumour as standard hospital diagnostic procedure at baseline and associated pathology report(s) are optional for all participants enrolled into the study. Participants will not be excluded from the study if optional tissue samples are not collected.

The analysis of fresh frozen diagnostic tumour tissue may include, but is not limited to, scRNA-seq. Using scRNA-seq technology, the heterogeneity among tumour cells and the complexity of the tumour microenvironment may be revealed, providing valuable insights into cancer biology and informing treatment planning.

8.8.3 Collection of Prostatectomy Tumour Samples

Samples will be collected at the times specified in the SoA (Table 1 and Table 2).

Prostatectomy tumour samples for pharmacodynamic assessment, both formalin-fixed paraffin-embedded and fresh frozen samples, for participants recruited to the treatment arms (post-treatment) and no-treatment arm (at radical prostatectomy), are mandatory (see Section 8.8.1 and Section 8.8.2.1).

Cores of tissue will be collected from the prostatectomy specimen following resection. The prostatectomy specimen should be carefully sliced to preserve the resection margins. The tumour nodule needs to be identified with a naked eye and sampled. Visualisation of the tumour in a fresh prostate is often not possible, so patients selected for the study should have clearly defined MRI lesions, otherwise sampling fresh tumour tissue is likely to be frequently unsuccessful. The location of the nodule on the MRI and the diagnostic biopsy report need to

be provided to the pathologist performing the sample collection and processing. Ideally, the tumour region corresponding to the site of the highest-grade tumour in the biopsies should be targeted. At least 2 punch biopsies (≥ 4 mm diameter) should be fixed using formalin and 2 punch biopsies (≥ 4 mm diameter) should be snap frozen.

In addition, at least one punch biopsy (optional; ≥ 4 mm diameter) of non-tumour (benign) prostatic tissue may also be collected from the prostatectomy specimen. Please refer to the Pathology and Laboratory Manual for further information on sample collection, processing, shipping, and storage.

The prostatectomy tumour samples will be analysed as described for the diagnostic FFPE (Section 8.8.2.1) and diagnostic fresh frozen samples (Section 8.8.2.2).

8.8.4 Collection of Peripheral Blood for Pharmacodynamic and Other Biomarkers Analysis

Peripheral blood samples will be collected as detailed in the SoA (Table 1 and Table 2) and Table 17.

PBMCs will be isolated as described in the Laboratory Manual. PBMCs will be assessed for pharmacodynamic changes in biomarkers that may include but are not limited to protein/gene levels and post-translational modifications such as PARylation.

Blood samples will also be collected to monitor the changes in blood biomarkers (eg, immune markers) over time. This may include the analysis of extracellular vesicles (tumour DNA, mRNA, proteins), metabolites or cytokines.

8.8.5 Collection of Plasma Samples for ctDNA

Samples will be collected at the times specified in the SoA (Table 1 and Table 2).

Please refer to the Laboratory manual for details on collection and processing of samples.

A peripheral blood sample will be collected to provide plasma for ctDNA. Testing may include (but is not limited to):

- Whether there is sufficient ctDNA in plasma for mutational testing
- ctDNA characterisation and dynamics on therapy
- Correlation between tumour and plasma mutational status
- Future diagnostic development

8.8.6 Collection of Blood for Germline DNA Analysis

A peripheral blood sample will be collected at screening to isolate germline DNA to assess HRR mutation status. Germline DNA will also be used to assess CHIP to aid interpretation of ctDNA mutation monitoring.

Peripheral blood samples may also be stored for use to develop future diagnostic tests.

8.8.7 Optional Biomarker Sample Collection

Surplus plasma and serum samples, blood, urine, or tissue, including participant specific archival or fresh tumour tissue collected during the course of this study, may be used for potential future exploratory research and assay development for factors that may influence the development of saruparib to treat human disease and/or response to saruparib (where response is defined broadly to include efficacy, tolerability or safety). This may include the analysis of tumour specific and circulating biomarkers, such as extracellular vesicles (tumour DNA, mRNA, proteins), metabolites or cytokines. If additional tumour molecular profiling is required to understand further any response to saruparib, AstraZeneca may request a sample of the most recent fresh tumour biopsy (if available) for additional research.

For storage, re-use, and destruction of biomarker samples see Appendix C.

8.8.8 Other Study-related Biomarker Research

Already collected samples may be analysed on different biomarkers thought to play a role in understanding the mechanism of action across treatment arms including, but not limited to, serum and urine analytes, or tissue biomarkers and/or specific candidate genes/genome-wide analysis for RNA to evaluate their association with the primary and secondary endpoints.

8.9 Health Economics

Health economics/Medical resource utilisation and health economics parameters are not evaluated in this study.

8.10 Study Participant Feedback Questionnaire

This section is not applicable.

9 STATISTICAL CONSIDERATIONS

The SAP will be finalised prior to first-patient-in and it will include a more technical and detailed description of the planned statistical analyses. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

The statistical analyses will be performed by AstraZeneca or a CRO under the direction of

AstraZeneca. A comprehensive SAP will be prepared.

9.1 Statistical Hypotheses

The primary objective is to obtain an estimation of the change in % γH2AX positive cells following treatment with saruparib alone, darolutamide alone, saruparib + darolutamide and without treatment given prior to radical prostatectomy in men with newly diagnosed prostate cancer.

9.2 Sample Size Determination

The study is designed as an exploratory estimation of change in % γH2AX positive cells within different treatment groups.

The sample size is based on the primary endpoint, assessment of fold change in % γH2AX positive cells, and 120 biomarker evaluable patients required to fully evaluate all planned arms. A Fisher's Exact test with a 10% 2-sided level will have 80% power to detect a 30% difference between the 2 group proportions (for saruparib and saruparib + darolutamide) when the sample size in each group is 40.

Four cohorts are planned in this exploratory study: saruparib, darolutamide alone, saruparib + darolutamide or no-treatment. Participants will be randomised to saruparib: darolutamide: saruparib + darolutamide at a 2:1:2 ratio or allocated to the no-treatment arm. Either 40 or 20 biomarker evaluable participants are planned for each of these cohorts with up to 20 biomarker evaluable participants planned for the darolutamide alone and no-treatment arms.

In this study, an estimation of the change in % γH2AX positive cells is a study objective. Furthermore, the proportion of participants achieving a minimum fold change (initial cut off ≥ 2-fold change) has been used to carry out sample size calculations and set targets for evidence of biomarker change. Based on a decision framework (Frewer et al 2016) the target proportion of participants has been set with a TV of 60% and LRV of 40%. A greater than 80% probability that the proportion of participants with a 2-fold change in γH2AX > 40% is considered a good signal.

For example, in saruparib and saruparib + darolutamide arms, a conclusion of lack of evidence of biomarker change may be reached if ≤ 19 participants observe at least a 2-fold change. If the true proportion of participants with at least a 2-fold change is 60% (TV), then the chance of observing no more than 19 participants with at least a 2-fold change in 40 biomarker evaluable participants is ≤ 10%. If the true proportion of participants with at least a 2-fold change is 40% (LRV), then the chance of observing at least 20 participants with at least a 2-fold change in 40 biomarker evaluable participants is 13%.

If lack of sufficient evidence of biomarker change is observed the Sponsor may decide to stop a treatment arm. The totality of evidence available will be considered when making this decision.

Sample size calculations and associated decision criteria are illustrative of the level of evidence that can be obtained from such intra-arm analyses using ≥ 2-fold change in % γH2AX positive cells. Inference on the impact of intervention will also be made using a heuristic overview of all available results from both intra and exploratory inter-arm comparisons.

9.3 Populations for Analyses

For purposes of analysis, the study populations are defined as provided in Table 18. For the safety and PK analyses, participants will be classified according to the treatment they actually received. For the baseline and demography and pharmacodynamics analyses, participants will be classified according to the planned treatment.

Table 18 Study Populations

Population/Analysis set	Description	Endpoint/Output
Safety	All participants who receive at least 1 dose of any study intervention or all participants allocated to no-treatment [Analyse according to treatment received]	Exposure Safety
Full analysis set	All participants who receive at least 1 dose of any study intervention or no-Treatment [analysed according to treatment randomised/allocated to]	Baseline and demography PSA
PK	All participants who receive at least 1 dose of any study intervention with at least 1 reportable concentration	PK concentrations PK parameters
Biomarker evaluable	All participants who have completed at least 75% of the assigned study treatment in each treatment arm (minimum 16 days of treatment out of 21 days), or who have been assigned to the no-treatment arm, and whose tumour samples are biomarker evaluable for γH2AX analysis	Fold change in % γH2AX positive cells/biomarker analysis
Pharmacodynamic analysis set	All participants who have completed at least 75% of the assigned study treatment in each treatment arm (minimum 16 days of treatment out of 21 days), or who have been assigned to the no-treatment arm, and whose tumour samples are biomarker evaluable	Biomarker analysis

γH2AX = gamma-histone 2AX (Ser139); PK = pharmacokinetics; PSA = prostate-specific antigen.

9.4 Statistical Analyses

9.4.1 General Considerations

- Data will be presented by treatment arm.
- Descriptive statistics will be used for all variables. Continuous variables will be summarised by the number of observations, mean, SD, median, minimum, and maximum.
- Categorical variables will be summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated based on the population total, by dose regimen and by timepoint as appropriate.
- SAS® version [9.4] (as a minimum) will be used for analyses presented in the CSR.
- Baseline will be considered the last non-missing value obtained prior to the randomisation/first dose for treatments arms, or allocation for no-treatment arm. Any information taken after the first dose of study treatment for treatment arms, or allocation for no-treatment arm, is regarded as post-baseline information. Detailed rules for deriving baseline values will be described in the SAP.
- Unless otherwise stated, 2 sided CIs will be produced at [95]%.
- Procedures for accounting for missing data, including missing dates, will be described in the SAP.

9.4.2 Pharmacodynamics

9.4.2.1 Primary Endpoint(s)

The primary endpoint is fold change in % γH2AX positive cells from baseline in tumour samples.

γH2AX

Fold change in γH2AX % positive cells in tumour samples will be listed and summarised appropriately by each treatment arm, based on the biomarker evaluable analysis set. Sensitivity analysis approach may be performed to explore the impact of the pre-dose biopsy samples as necessary and will be fully detailed in the SAP.

9.4.2.2 Secondary Endpoint(s)

Ki-67

Change in % Ki-67 positive cells (as secondary endpoint) in tumour samples will be listed and summarised appropriately by each treatment arm using the biomarker evaluable set.

Safety and Tolerability

Safety and tolerability will be assessed in terms of AEs/SAEs. These variables will be

collected for all participants enrolled. All safety analyses will be performed on the safety analysis dataset, defined as participants who received at least one dose of treatment and all participants in the no-treatment arm. For all endpoints, the data will be summarised and/or listed according to the treatment received.

Surgical Feasibility

Surgical feasibility will be assessed in terms of the rate of participants with radical prostatectomy as planned. The rate and reasons of treatment-related and non-treatment related delays of surgery and delays > 7 days from scheduled day will be captured.

9.4.2.3 Analysis of Pharmacodynamic Endpoints

Initial comparisons will be made based on comparing the proportions of participants who exhibit biomarker changes.

If data permit, the change from baseline of biomarker expression score following 21 days (+ up to 7 days) of administration of treatment or no-treatment will be analysed using a mixed effect model of repeated measures. It is expected that the model has fixed effect terms for treatment, biopsy day, treatment by day interaction, and baseline score as a covariate and a random effect for participants within treatment. Estimates of the least squares mean percent change taken from the model will be presented together with 90% CIs.

Normality of the data will be assessed, and if it is judged that the data do not adequately follow a normal distribution, then the use of the natural log transformed data (ratio), or a non-parametric approach could replace the untransformed analysis as the primary approach. It is expected that the distribution of the data for endpoints will not be normally distributed and in this case the data will be naturally log-transformed before being analysed. A non-parametric approach may be performed as necessary and will be fully detailed in the SAP.

Plots of the individual participant biomarker data pre- and post-surgery will be presented by treatment arm.

9.4.3 Analysis of Adverse Events

AEs will be listed individually by participant and treatment arm. For participants who undergo a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose group.

Medical Dictionary for Regulatory Activities will be used to code AEs. Adverse events will be graded according to the NCI CTCAE (Version 5.0). The number of participants in each dose regimen experiencing each AE will be summarised by MedDRA system organ class and preferred term. The number and percentage of participants with AEs in different categories (eg, causally related, CTCAE Grade ≥ 3, etc) will be summarised by dose regimen; events in

each category will be further summarised by MedDRA system organ class and preferred term. Serious adverse events will be summarised separately, if a sufficient number occurs.

Adverse event summary tables will include only TEAEs. Adverse event tables will be provided taking into consideration relationship as assessed by the Investigator. Adverse events will be defined as treatment-emergent if they have an onset or worsen (by Investigator report of a change in intensity) during the study treatment or within 28 days after surgery but prior to subsequent cancer therapy. AEs occurring prior to dosing or starting more than 28 days after surgery may be listed separately but not included in the summaries.

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the CSR. A similar review of laboratory/vital signs (pulse and BP)/ECG data will be performed for identification of OAEs. Examples of these could be marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction, or significant additional treatment.

9.4.3.1 Analysis of Other Safety Data

Duration of exposure will be summarised.

All safety data including clinical chemistry, haematology, coagulation, urinalysis, vital signs, and ECG data will be listed individually by participant and appropriately summarised. For all laboratory variables that are included in the current version of CTCAE, the CTCAE grade will be calculated. Details of any deaths will be listed for all participants. Graphical presentations of safety data will be presented as appropriate.

9.4.4 Other Analyses

9.4.4.1 Pharmacokinetics

Pharmacokinetic analysis will be conducted based on the plasma concentrations of saruparib and darolutamide collected at timepoints specified in the Section 1.3 SoA (Table 1 and Table 2) and Table 17.

Pharmacokinetic concentrations of saruparib and darolutamide will be summarised by treatment arm, and PK concentration data will be listed for each participant in the PK analysis set. Data will be summarised by timepoint using appropriate descriptive statistics. Geometric mean (± geometric SD) concentration-time data will be presented (if applicable).

Saruparib and darolutamide plasma concentration data from this study may be combined with data from other studies to conduct population PK, PK/pharmacodynamic exploratory analysis, metabolite identification, and/or exposure response/safety analyses. These will be described in

dedicated analysis plan(s) and presented separately from the main CSR.

9.4.4.2 Biomarkers

Primary and secondary endpoints of the study are detailed in the associated sections of this protocol detailing the endpoint and plans for analysis which will be further outlined in the SAP.

Biomarker status will be assessed for participants in each treatment arm according to prespecified criteria that may be detailed in the SAP. Additional biomarker exploratory analyses may be described in a separate analysis plan and may be reported outside the CSR in a separate report.

9.5 Interim Analyses

Two interim analyses are planned for the study.

Quality Check Analysis

A quality check will be conducted after approximately 25 participants have been recruited, completed the radical prostatectomy, and analysed to assess the proportion of biomarker evaluable participants. The review will also include participants in the no-treatment arm.

Interim Analysis for Futility

An interim analysis for futility is planned based on biomarker response (proportion of participants with % γH2AX positive cells ≥ 2-fold change) and will be triggered when approximately half (~50 participants) of the participants in the randomised arms are biomarker evaluable. Based on non-clinical data using prostate cancer xenograft models, an increase of ≥ 2-fold γH2AX positive cells is expected upon treatment exposure. The decision criteria will be applied to the saruparib and saruparib + darolutamide arms individually, which are expected to exhibit biomarker activity. It is expected that the darolutamide alone and no-treatment arms will observe < 2-fold changes in responses.

For example, in saruparib and saruparib + darolutamide arms, a conclusion of lack of evidence of biomarker change may be reached within a treatment arm at the interim analysis for futility if ≤ 7 participants observe at least a 2-fold change in 20 evaluable participants. If the true proportion of participants with at least a 2-fold change in γH2AX cells is 60% (TV), then the chance of observing no more than 7 participants with at least a 2-fold change in 20 biomarker evaluable participants is ≤ 10%.

If lack of sufficient evidence of biomarker change is observed the Sponsor may decide to stop a treatment arm. The totality of evidence available will be taken into account when making this decision. Though there is a possibility that enrolment to a treatment arm may be stopped,

meeting a futility criterion is not binding on study conduct.

This is an exploratory study, and in addition to the decision points, the quality of the biopsies will be monitored on an ongoing basis.

The SAP will describe the planned interim analyses in greater detail.

9.6 Data Monitoring Committee

There will be no IDMC for this study. A study-specific SDMC will review the emerging data from the study. See Section 6.6.7.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki as amended at 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, revised protocol, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any revised protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR 312.120, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to AstraZeneca of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All Suspected Unexpected Serious Adverse Reactions (SUSARs) to investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines.

- For all studies except those utilising medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to Investigators as necessary.
  - Adherence to European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the Investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.

  A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.
- If any (potential) serious breach occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.

  AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and Investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The Investigator should have a process in place to ensure that:

  The site staff or service providers delegated by the Investigator/institution are able to identify the occurrence of a (potential) serious breach.

  A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and sub-Investigators will provide AstraZeneca with sufficient, accurate financial information as requested to allow AstraZeneca to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

Investigators are responsible for providing information on financial interests during the study and for one year after completion of the study.

A 3 Informed Consent Process

- The Investigator or their representative will explain the nature of the study to the participant or their legally authorised representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- If new information requires changes to the ICF, consider if participants must be re-consented and if so, this must be to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional HBS. The Investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use, and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by AstraZeneca. Any participant records or datasets that are transferred to AstraZeneca will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related data will be used by AstraZeneca in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by AstraZeneca, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- The participant must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.
- The participant must be informed that in some cases their data may be pseudonymised. The General Data Protection Regulation (GDPR) defines pseudonymisation as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.
- EU personal data will only be shared under a strict 'need to know' basis and in accordance with appropriate controls (such as AstraZeneca's BCR and EU Standard Contract Clauses or equivalent instruments). Data subjects are entitled to receive a copy of the above upon request by contacting AstraZeneca.
- The processing of participant data starts at the study site. Data will be transferred to several data experts to be verified and for results to be calculated. Participant data is also protected by high standard technical security means such as strong access control and encryption.
- Within the sponsor group, coded data are protected by BCR. More information about AstraZeneca's BCRs can be found here: www.astrazenecabindingcorporaterules.com
- In all other cases, coded data are protected by contractual arrangements, Codes of Conduct, or certifications which set the rules for personal information protection to those available in European countries (for example, if all data is stored with a United States hosting company) or other alternatives set forth in the Law.

Personal Data Breaches

- A 'personal data breach' means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored, or otherwise processed.

- In compliance with applicable laws, the Data Controller[1] for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- Whilst AstraZeneca has processes in place to deal with personal data breaches it is important that investigators that work with AstraZeneca have controls in place to protect patient data privacy.

The Investigator should have a process in place to ensure that:

- Allow site staff or service providers delegated by the investigator/institution to identify the occurrence of a (potential) personal data breaches. Any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

AstraZeneca and the site must demonstrate that they:

- Have taken all necessary steps to avoid personal data breaches and
- Have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining, and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
- Where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- Where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

[1] The **data controller** determines the **purposes** for which and the **means** by which personal data is processed, as defined by the European Commission.

Notification of personal Data Breach to participants:

- Notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches occurred within the processing activities of AstraZeneca as the Data Controller, the notification is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the participants. The site and/or Principal Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants.
- If a personal data breach involving an AstraZeneca's representative device (ie Study Monitor laptop), AstraZeneca representative will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the participants. The notification will be done by AstraZeneca solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the participants. If the data breach must be notified to the data subjects, the notification will be done directly by the Study Monitor in collaboration with the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants. The contract between AstraZeneca and the Study Monitor shall expressly specify these conditions.
- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

A 5 Committees Structure

The core SDMC members are detailed in the SDMC Charter.

A 6 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on http://astrazenecagrouptrials.pharmacm.com and www.astrazenecaclinicaltrials.com [http://www.clinicaltrials.gov and https://euclinicaltrials.eu/] as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to AstraZeneca or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the Monitoring Plan(s).
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Medical Oversight Plan.
- AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (eg, CROs).

- Study monitors will perform ongoing source data verification as per the Monitoring Plan(s) to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 25 years after study completion or as required by local regulations, according to the AstraZeneca Global retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

A 8 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).
- A digital copy of all imaging scans should be stored as source documents.

A 9 Study and Site Start and Closure

The study start date is the date on which the first participant consented.

AstraZeneca designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of AstraZeneca. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by AstraZeneca or the Investigator may include

but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, AstraZeneca's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, AstraZeneca shall promptly inform the Investigators, the IRBs/IECs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

A 10 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to AstraZeneca before submission. This allows AstraZeneca to protect proprietary information and to provide comments.
- AstraZeneca will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, AstraZeneca will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B AEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of AEs

An AE is the development of any untoward medical occurrence in a patient or clinical study participant administered a medicinal product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of SAEs

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

Adverse Events for **malignant tumours** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-SAE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new malignant tumour (ie, it is *not* the tumour for which entry into the study is a criterion and that is being treated by the study intervention and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B-cell chronic lymphocytic leukaemia into diffuse large B-cell lymphoma) should not be considered a new malignant tumour.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the medicinal product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a SAE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of important medical events:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment.
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine.
- Intensive treatment in an emergency room or at home for allergic bronchospasm.
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation.
- Development of drug dependency or drug abuse.

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

The grading scales found in the revised NCI CTCAE Version 5.0 will be utilised for all events. This version will be used for the duration of the study. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

B 3 A Guide to Interpreting the Causality Question

When assessing causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the medicinal product.

- Time Course. Exposure to suspect drug. Has the participant received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host, or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgement. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the DUS has deteriorated due to lack of effect should be classified as 'no reasonable possibility'.

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- **Was identified and** intercepted before the participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant

- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which led to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site (DES) using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or

for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at the site.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment, and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca team for the remainder of the sample life cycle.

All appropriately consented samples will be retained for maximum 15 years from last patient last visit.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures the participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant HBSs from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented, and study site is notified.

C 3 International Air Transport Association Guidance Document 62nd Edition

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

The International Air Transport Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B, or Exempt.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.

Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- Are to be packed in accordance with UN 3373 and IATA 650

Exempt Substances are substances which do not contain infectious substances, or substances which are unlikely to cause disease in humans or animals, are not subject to these regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations.
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/contentassets/b08040a138dc4442a4f066e6fb99fe2a/dgr-62-en-pi650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.

Appendix D Optional Genomics Initiative Sample

D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genomic characterisation to explore how genomic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medicinal product.
- This genomic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care, and to the discovery of new diagnostics, treatments, or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA from consenting participants.
- This optional genomic research may consist of the analysis of the structure of the participant's DNA, ie, the entire genome.
- The results of these genetic analyses may be reported in a separate study summary.
- AstraZeneca will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

D 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

All participants will be asked to participate in this genomic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genomic research, participants must fulfil all of the inclusion criteria described in the main body of the protocol and: Provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

Exclusion from this genomic research may be for any of the exclusion criteria specified in the main study or any of the following:

The Genetic exclusion criteria below apply to blood samples.

- Previous allogeneic bone marrow transplant.
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection.

Withdrawal of Consent for Genetic Research

- Participants may withdraw from this genomic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main protocol.

Collection of Samples for Genetic Research

- The blood sample for this genomic research will be obtained from the participants at screening (after eligibility has been confirmed) or Day 1 pre-dose. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at screening or Day 1, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics research during the study.

Coding and Storage of DNA Samples

The processes adopted for the coding and storage of samples for genomic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years from the date of last patient last visit, after which they will be destroyed. DNA are a finite resource that will be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

- An additional second code will be assigned to the samples either before or at the time of sample processing, replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).
- The link between the participant enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

- The principles for ethical and regulatory requirements for the study, including this genomics research component, are outlined in Appendix A.

Informed Consent

- The genomic component of this study are optional and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genomic component of the study the participant must sign and date both the consent form for the main study and the optional genetic research information ICF. Copies of both signed and dated consent forms must be given to the participant and the originals filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely, and that the participant understands that they may freely withdraw from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual sequencing or genotype results to participants, any insurance company, any employer, their family members, or general physician unless required to do so by law. Extra precautions are taken to preserve confidentiality and prevent genomic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a participant's identity and also have access to his or her genomic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genomic files would remain physically separate.

Data Management

- Any genomic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples.
- AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations, or drug- or health-related companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results, but they will not be able to see individual participant data or any personal identifiers.
- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

E 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report potential Hy's Law cases and Hy's Law cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

In case Hy`s law is suspected, the study treatment should be interrupted immediately, optimal supportive care according to site guidelines initiated, and causality investigated. In case the cause is related to any of the study drug, additional to the above recommendations, the drug should be discontinued and participants undergo surgical procedure at the earliest convenience.

During the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential Hy's Law criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of potential Hy's Law and Hy's Law events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, potential Hy's Law criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible potential Hy's Law events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting potential Hy's Law criteria to agree whether Hy's Law criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The Investigator is responsible for recording data pertaining to potential Hy's Law/Hy's Law cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law

Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law

Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For potential Hy's Law and Hy's Law the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

E 3 Identification of Potential Hy's Law Cases

In order to identify cases of potential Hy's Law it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

Local Laboratories Being Used:

The Investigator will without delay review each new laboratory report and, if the identification criteria are met, will:

- Notify the AstraZeneca representative.
- Determine whether the participant meets potential Hy's Law criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

E 4 Follow-up

E 4.1 Potential Hy's Law Criteria Not Met

If the participant does not meet potential Hy's Law criteria the Investigator will:

- Inform the AstraZeneca representative that the participant has not met potential Hy's Law criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the protocol.

E 4.2 Potential Hy's Law Criteria Met

If the participant does meet potential Hy's Law criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within one day of potential Hy's Law criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to the protocol process for SAE reporting.
- For participants who met potential Hy's Law criteria prior to starting IMP, the Investigator is not required to submit a potential Hy's Law SAE unless there is a significant change[#] in the participant's condition.
- The Study Clinical Lead will contact the Investigator, to provide guidance, discuss, and agree an approach for the study participant's follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:

  Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete follow-up SAE Form as required.

  Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Clinical Lead.

  Complete the 3 Liver eCRF Modules as information becomes available.

A 'significant' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Clinical Lead if there is any uncertainty.

E 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this appendix should be followed for all cases where potential Hy's Law criteria are met.

As soon as possible after the biochemistry abnormality is initially detected, the Study Clinical Lead will contact the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting potential Hy's Law criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date potential Hy's Law criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.
- If the alternative explanation is an AE/SAE: Update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term, causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

  The 'Medically Important' serious criterion should be used if no other serious criteria apply.

  As there is no alternative explanation for the Hy's Law case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether the case meets the criteria for Hy's Law, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provide any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to protocol process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether Hy's Law criteria are still met. Update the previously submitted potential Hy's Law SAE report following protocol process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory(Table 19). When local laboratories are used, this list may be modified according to clinical judgement. Any test results need to be recorded.

Table 19 Hy's Law Laboratory Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) [c]
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin
	Transferrin [c] Transferrin saturation

[a] HBV DNA is only recommended when IgG anti-HBc is positive.
[b] HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.
[c] CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly.

E 7 References

Aithal et al, 2011
Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, Hunt CM, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011; 89(6):806-15.

FDA Guidance for Industry, July 2009
FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation' [cited 2024 Aug 27]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

Appendix F Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the Sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

Please note that during civil crisis, natural disaster, or public health crisis, some study assessments and procedures may not be conducted due to international or local policies or guidelines, hospital or clinic restrictions and other measures implemented to ensure the participant's safety. If in doubt, please contact the AstraZeneca Study Physician.

F 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections F 2 to F 4. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

F 2 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified HCP from the study site or TPV service will visit the participants home/or other remote location as per local standard operating procedures, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the protocol.

F 3 Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix, the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by

a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs and concomitant medication, to be reported and documented.

F 4 Data Capture During Telemedicine or Home / Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or TPV service.

Appendix G Guidelines Regarding Potential Interactions of Saruparib and Darolutamide With Concomitant Medications

There are currently no data confirming that there is a PK interaction between any concomitant medication and saruparib. Potential interaction is considered on the basis of non-clinical data only. For a complete overview of the non-clinical DMPK work conducted, including the DDI liability of saruparib, refer to the IB.

G 1 Guidance for Drugs that Prolong QT and Have a Known Risk of Torsades de Pointes

Drugs that are known to prolong or shorten QT and have a known risk of TdP should not be combined with saruparib.

Current knowledge of drugs and their relationship to QT prolongation as well as TdP, has been recorded and documented in the CredibleMeds® list (www.crediblemeds.org).

Relationships are classified as known, conditional, or possible.

Known Risk: These drugs prolong the QT interval AND are clearly associated with a known risk of TdP, even when taken as recommended.

Conditional Risk: These drugs are associated with TdP BUT only under certain conditions of their use (eg, excessive dose, in patients with conditions such as hypokalaemia, or when taken with interacting drugs) OR by creating conditions that facilitate or induce TdP (eg, by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP).

Possible Risk: These drugs can cause QT prolongation BUT currently lack evidence for a risk of TdP when taken as recommended.

Drugs listed as having a possible or conditional risk of QT prolongation and TdP, should be avoided, if possible, but may be administered with caution at the discretion of the PI or delegate.

G 2 Guidance for Drugs That Shorten QT

Drugs that are known to prolong or shorten QT and have a known risk of TdP should not be combined with saruparib.

The short QT syndrome is associated with an increased risk of sudden death and ventricular arrhythmias, particularly ventricular fibrillation. Patients with Familial Short QT syndrome should not be treated with saruparib. Compared with QT-prolonging drugs, there is a substantial gap between the less well-documented potential risks and outcomes associated with

drug-induced QT shortening. The following drugs have been associated with QT shortening based on our present knowledge and they should not be combined with saruparib:

- Anti-convulsants: lamotrigine, rufinamide, cenobamate
- Drugs activating adenosine triphosphate (ATP)-dependent potassium channel: pinacidil, levcromakalim, and nicorandil

G 3 Restrictions Regarding Drugs Affecting CYP3A4 Metabolism

It is probable that saruparib is predominantly eliminated via CYP3A4. Therefore, inhibitors or inducers of CYP3A4 may increase or decrease exposure to saruparib, respectively. Strong inhibitors and inducers of CYP3A4 should not be combined with saruparib. Strong inhibitors or inducers of CYP3A4 should be stopped at least 21 days or at least 5 times half-lives (whichever is longer) before the first dose of study treatment until 30 days after the last dose of medication.

Table 20 and Table 21 below provide examples of CYP3A4 inhibitors and inducers, respectively. These lists are not intended to be exhaustive, and similar restrictions will apply to other drugs that are known to modulate CYP3A4 activity. Appropriate medical judgement is required. Please contact AstraZeneca with any queries you have on this issue. Please refer to full prescribing information for all drugs prior to co-administration with saruparib.

If the Investigator feels that concomitant administration of medications or herbal supplements that strongly modulate CYP3A4 is essential (eg, to treat AEs) saruparib treatment should be discontinued.

Table 20 Drugs Known to be Inhibitors of CYP3A4

Strong CYP3A4 inhibitors (should not be combined with saruparib monotherapy or combination therapy)	**Moderate CYP3A4 inhibitors (may be combined with saruparib monotherapy)**
boceprevir	amprenavir
clarithromycin	aprepitant
conivaptan	atazanavir
elvitegravir/ritonavir	casopitant
fluconazole	cimetidine
grapefruit juice [a,b]	ciprofloxacin
indinavir	crizotinib
itraconazole	cyclosporine
ketoconazole	darunavir
lopinavir/RIT	diltiazem

Table 20 Drugs Known to be Inhibitors of CYP3A4

Strong CYP3A4 inhibitors (should not be combined with saruparib monotherapy or combination therapy)	Moderate CYP3A4 inhibitors (may be combined with saruparib monotherapy)
mibefradil	dronedarone
nefazodone	erythromycin
nelfinavir	grapefruit juice [b]
posaconazole	imatinib
ritonavir	schisandra sphenanthera
saquinavir	tofisopam
telaprevir	verapamil
telithromycin	netupitant
tipranavir/ritonavir	
troleandomycin	
voriconazole	

[a] Double-strength grapefruit juice
[b] Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study (eg, no more than a small glass of grapefruit juice [120 mL] or half a grapefruit or 1 to 2 teaspoons [15 g] of Seville orange marmalade daily)
CYP3A4 = cytochrome P450 3A4.

Table 21 Drugs Known to be Inducers of CYP3A4

Strong CYP3A4 inducers (should not be combined with saruparib monotherapy, darolutamide monotherapy, or combination therapy)	Moderate CYP3A4 inducers (should not be combined with darolutamide monotherapy or combination therapy)
avasimibe	semagacestat [a]
carbamazepine	talviraline [a]
mitotane	bosentan
nevirapine	efavirenz
phenobarbital	etravirine
phenytoin	genistein
rifabutin	lersivirine
rifampin	lopinavir
rifapentine	modafinil
St John’s Wort	nafcillin
	thioridazine
	tipranavir and ritonavir [b]

[a] Not available in the US market.

[b] Ritonavir has dual effects of simultaneous CYP3A4 inhibition and induction; the net PK outcome during chronic ritonavir therapy is inhibition of CYP3A4 activity.
Inducers of CYP3A4 are typically also inducers of P-gp.
CYP3A4 = cytochrome P450 3A4; P-gp = P-glycoprotein; PK = pharmacokinetic(s); US = United States.

G 4 Restrictions Regarding Drugs Affected by Metabolising Enzymes and Transporters

In vitro data suggests that saruparib inhibits drug metabolising enzymes CYP1A2, CYP2B6, CYP2C9 and CYP2C19 and transporters P-gp, OATP1B1, OAT3, MATE1 and MATE-2K. Caution should be used when sensitive substrates (Table 22) of these enzymes or transporters are administered with saruparib. These lists are not intended to be exhaustive, and appropriate medical judgement is required. Please contact AstraZeneca with any queries you have on this issue. Please refer to full prescribing information for all drugs prior to co-administration with saruparib.

Table 22 Examples of Substrates of Drug Metabolising Enzymes and Transporters

Substrate category	Sensitive substrate examples
Drug metabolising enzymes	
CYP1A2	alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, tizanidine
CYP2B6	bupropion
CYP2C9	celecoxib
CYP2C19	S-mephenytoin, omeprazole
Transporters	
P-gp	colchicine, dabigatran, digoxin, loperamide, doxorubicin
OATP1B1/OATP1B3	atorvastatin, bosentan, fluvastatin, lovastatin, pitavastatin, pravastatin, repaglinide, rosuvastatin, simvastatin
OAT3	ganciclovir, methotrexate
MATE1, MATE-2K	dofetilide, metformin

CYP = cytochrome P450; P-gp = P-glycoprotein.

G 5 Restrictions Specific to Darolutamide (Darolutamide Arm and Saruparib + Darolutamide Arm)

In addition to the restrictions already in place due to **saruparib** (Appendix G 1, Appendix G 2, Appendix G 3 and Appendix G 4):

- Avoid strong or moderate CYP3A4 and P-gp inducers (Table 21 and Table 23) during treatment with darolutamide.

- Caution while using strong CYP3A inhibitors (Table 20) during treatment with darolutamide. Monitor patients more frequently for adverse reactions.
- Avoid concomitant use with drugs that are BCRP, OATP1B1 and OATP1B3 substrates where possible. If used together, monitor patients more frequently for adverse reactions and consider dose reduction of the BCRP substrate drug (see Table 24).

Table 23 Examples of CYP3A4 and P-gp Inducers

	Examples of drugs in the category
CYP3A4 and P-gp inducers	Avasimibe, carbamazepine, curcumin, dan-shen (*Salvia miltiorrhiza*), efavirenz, genistein, green tea, phenytoin, quercetin, rifabutin, rifampin, ritonavir, St. John's wort (*Hypericum perforatum*), tivantinib, phenobarbital, tipranavir

P-gp = P-glycoprotein.

Table 24 Examples of BCRP Substrates

	Examples of drugs in the category
BCRP substrates	rosuvastatin, atorvastatin, sulfasalazine

BCRP = breast cancer resistance protein.

Appendix H Performance Status (ECOG/KARNOFSKY SCALE)

Performance status will be assessed based on ECOG as described in Table 25.

Table 25 Performance Status (ECOG/KARNOFSKY SCALE)

Description	ECOG grade	Karnofsky equivalent	
Fully active, able to carry on all pre-disease performance without restriction.	0	100	Normal, no complaints; no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, ie, light housework, office work.	1	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self but unable to carry on normal activity or to do work.
Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2	60	Requires occasional assistance but is able to care for most of personal needs.
		50	Requires considerable assistance and frequent medical care.
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3	40	Disabled; requires special care and assistance.
		30	Severely disabled; hospitalisation is indicated although death not imminent.
Completely disabled. Cannot carry on any self- care. Totally confined to bed or chair.	4	20	Very ill; hospitalisation and active supportive care necessary.
		10	Moribund.
Dead	5	0	Dead

ECOG = Eastern Cooperative Oncology Group.

Appendix I Contraceptive Guidelines

I 1 Definitions

There will be no females enrolled in this study. Contraceptive guidelines below applicable to females are applicable to the female partners of male patients in this study.

- A female of childbearing potential is defined as a female who is not permanently surgically sterilised or post-menopausal.
- Surgical sterilisation includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion (the term occlusion refers to both occluding and ligating techniques that do not physically remove the oviducts).
- Post-menopausal is defined as amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:

  Women under 50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments AND with luteinising hormone and follicle-stimulating hormone levels in the post-menopausal range.

  Women over 50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments.
- A highly effective method of contraception is defined as a method that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly.

I 2 Contraception Methods

The highly effective methods of contraception are described in Table 26.

Table 26 Highly Effective Methods of Contraception

Barrier/Intrauterine methods	Hormonal methods
Intrauterine device	Combined (oestrogen and progestogen containing hormonal contraception)
Intrauterine hormone-releasing system (UIS) [a]	Oral (combined pill)
Bilateral tubal occlusion	Injectable
Vasectomized partner [b]	Transdermal (patch)
Sexual abstinence [c]	Progestogen-only hormonal contraception associated with inhibition of ovulation [d]
	Injectable
	Implantable

[a] This is also considered a hormonal method.
[b] With appropriate post-vasectomy documentation of surgical success (absence of sperm in ejaculate).

[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the participant. However, periodic or occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

[d] Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action (eg, minipill), is not accepted as a highly effective method.

Appendix J Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment (Version 5.0) is located directly before the Table of Contents.

Amendment 3 (31 January 2024)

The Clinical Study Protocol (CSP) version 3.0, 12 September 2023, has been amended to include clarifications and to align with the sponsor's protocol authoring requirements for early development oncology studies.

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Throughout	AZD5305 was updated to saruparib	To ensure consistency across the programme with the updated drug name	Non-substantial
Title page	IND Number added	For completeness of Regulatory Agency Identifiers	Non-substantial
Synopsis	Updated to match main text updates	For consistency	Non-substantial
Abbreviations	BD was updated to BID OD was updated to QD	To align with current industry standards	Non-substantial
Table 1 SoA for Study Treatment Arms	Day before RP ECG assessment was removed	To reduce ECG burden as this is a low risk timepoint	Substantial
Table 1 SoA for Study Treatment Arms	Footnote added for ECG assessments at Screening and Day 1	To clarify triplicate ECGs will be done at Screening and Day 1; single ECG at all other timepoints	Non-substantial
Table 1 SoA for Study Treatment Arms	"Tumour biopsy (Fresh frozen)" was adjusted to "Diagnostic tumour biopsy (fresh frozen)" and the sample at Day of RP was removed	For clarification and to reduce burden on patients as this timepoint is not required	Substantial
Table 1 SoA for Study Treatment Arms	A row for Prostatectomy tumour sample (fresh frozen) was added	For clarification and alignment of SoA with Section 8.8.3	Non-substantial
Table 2 SoA for No-treatment Arm	ECG was specified as single ECG	For clarification	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Table 2 SoA for No-treatment Arm	Footnote d was added to specify which tests do not need to be repeated if done within 72 hours during the screening period	For clarification	Non-substantial
2.2 Background and 11 References	Background information was updated to align with new reference cited	For clarification	Non-substantial
2.2.1.1 Saruparib	Duplicate information on saruparib monotherapy safety data from PETRA was removed and a cross-reference added to Section 4.3	For conciseness	Non-substantial
2.2.1.2 Darolutamide and 11 References	Darolutamide approval for patients with mCSPC when used in combination with docetaxel was added and a new reference cited	For completeness	Non-substantial
2.3 Benefit/Risk Assessment	Total number of patients exposed to saruparib monotherapy in PETRA was updated based on most recent IB DCO of 02 September 2023. Text stating no MTD reached was deleted	To align with the current IB	Substantial
Table 5 Risk Assessment	Saruparib risks were updated and classified into Identified Risks, Important Potential Risks, and Potential Risks	To align with the latest available safety data	Substantial
Table 6 Objectives	Pharmacodynamic biomarker-related objectives were clarified	Clarification to align with the sponsor's protocol authoring requirements for early development oncology studies	Non-substantial
4.1 Overall Design, 4.3 Justification for Dose, and 6.6.5 Dose and Safety Management	Saruparib exposure and safety data were updated based on the recent IB DCO of 02 September 2023. The selected RP2D dose of saruparib 60 mg QD was added, based on interim analysis data from the PETRA study. PETRANHA exposure and safety data were updated. SDMC selection of a saruparib dose of 60 mg QD, either as monotherapy or in combination with darolutamide was added for ASCERTAIN.	To align with the most recent available safety data and include the selected RP2D dose.	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
5.1 Inclusion Criteria	The text stating males are to not plan on fathering any children in the future to be eligible was deleted from inclusion criterion 1.	For clarification and alignment with the treatment arms-specific criterion 9b, requiring males to abstain from fathering a child for 6 months after the last dose of study treatment.	Non-substantial
5.1 Inclusion Criteria; 2 Introduction, 4.1 Overall Design, 4.2 Scientific Rationale for Study Design, 11 References	Inclusion criterion 3 was updated to allow participants with localised prostate cancer with very high risk to be eligible for study participation. The NCCN Clinical Practice Guidelines cited were updated to the most recent version.	To allow a broader population of patients with prostate cancer to participate on the study	Substantial
5.2 Exclusion Criteria	Requirement for eligibility to be discussed with the medical monitor was removed.	To align with EU CT Regulation requirements	Non-substantial
6.1.1.1 Saruparib	Saruparib self-administration dose was updated, and food/water requirements for dosing were clarified.	For clarification	Non-substantial
6.1.1.2 Darolutamide	Darolutamide self-administration dose and food/water requirements for dosing were clarified.	For clarification	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Table 11 Prohibited Concomitant Medications; Appendix G3; 5.1 Inclusion Criterion 5; 5.2 Exclusion Criterion 13	Gonadotropin releasing hormone analogues were deleted (not permitted). Prohibited medications were updated to include substances with a potential to significantly alter the prostate cancer and/or androgen receptor pathway. Updated that for the saruparib arm and saruparib + darolutamide arm, only strong inducers and inhibitors of CYP3A4 are prohibited. Updated that for the Darolutamide arm and saruparib + darolutamide arm, strong or moderate CYP3A4 and P-gp inducers are prohibited. Clarified that warfarin and other coumarin derivatives are prohibited. Clarified that NOACs, subcutaneous heparin, and low molecular weight heparin are permitted.	To align with the latest available safety information and for clarification.	Substantial
8.3.4 Electrocardiograms	ECG section was updated to clarify type of ECG assessment at specified timepoints, procedures, and interpretation.	For clarification	Non-substantial
8.8.2.1 Diagnostic FFPE Tumour Samples (Mandatory)	Details regarding germline alteration confirmation testing with a clinically validated assay (in case of BRCA pathogenic mutations) were added.	For clarification	Substantial
8.8.3 Collection of Prostatectomy Tumour Samples; Table 1 SoA for Study Treatment Arms; Table 2 SoA for No-treatment Arm	Collection of an optional prostatectomy non-tumour sample (fresh frozen) was added.	To assist with tumour biomarkers assessment	Substantial
9.2 Sample Size Determination	The chance of observing at least 20 participants with at least a 2-fold change in 40 biomarker evaluable participants was updated from 87% to 13%.	Correction of typographical error	Non-substantial

Amendment 2 (12 September 2023)

The Clinical Study Protocol (CSP) version 2.0, 25 May 2023, has been amended to include responses to Health Authority Questions.

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1, Section 4.1	Addition of statement to clarify the recruitment process.	To further clarify the recruitment and informed consent procedure.	Non-substantial
Table 1	Updated Section number for prostatectomy tumour sample.	Correction to section number.	Non-substantial
Section 5.1, Section 5.3.2	Inclusion criterion 9, removed 'approximately' from the duration participant must use a condom or refrain from fathering a child.	To provide more clarity on the duration.	Non-substantial
Section 8.8.3	Addition of text to describe the process of taking a prostatectomy tumour biopsy sample.	To further clarify the procedures regarding tumour sample collection and processing.	Non-substantial
Appendix A4	Addition of text to describe transfer of data and measures in case of data security breach.	To align with new EU regulations.	Non-substantial

Amendment 1.0 (Version 2.0, 24 May 2023)

The Clinical Study Protocol (CSP) version 1.0, 02 March 2023 has been amended to correct details about prohibited concomitant medications to ensure compliance with local and national prescribing guidelines for darolutamide. The CSP changes included the correction of prohibited concomitant medications for darolutamide arm and AZD5305 + darolutamide arm to clarify that the use of strong and moderate cytochrome P450 subunit 3A4 (CYP3A4) inducers, P-glycoprotein (P-gp) inducers, breast cancer resistance protein (BCRP), organic anion transporting polypeptide 1 B1 (OATP1B1), and organic anion transporting polypeptide 1 B1 (OATP1B3) substrates is prohibited in both arms. Other CSP changes included the clarification regarding the use of the results of multiparametric Magnetic Resonance Imaging (MRI) performed outside the screening window as acceptable diagnostic results, the removal of details of specific bioanalytical test sites to be used (details to be provided in a separate bioanalytical report) and about quality tolerance limits, the update of sample retention period. Furthermore, some study procedures have been clarified and inconsistencies in the CSP text have been corrected.

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.3 Table 1	In footnote d it was clarified that vital signs, ECG, blood tests and optional Genomic initiative blood sample will be collected pre-dose for all treatment arms.	To ensure correct sampling requirements.	Non-substantial
Section 1.3 Table 1	Footnote added for ctDNA and blood biomarker samples for Day 1, Day 15 and Day before RP visits where blood samples are to be collected pre-dose.	To remove inconsistencies in the protocol.	Non-substantial
Section 1.3 Table 1, Section 1.3 Table 2	References to sections with description of blood biomarker samples corrected in both tables.	To remove inconsistencies in the protocol.	Non-substantial
Section 2.3.1 Table 5	Updated the risks for darolutamide.	To ensure compliance with local and national prescribing guidelines for darolutamide.	Non-substantial
Section 3, Section 9.4.2.2	Corrected definition of the secondary endpoint. “no-treatment related delays of surgery” changed to “non-treatment related delays of surgery.”	To provide clarity in definition and to eliminate any confusion to no-treatment arm.	Non-substantial
Section 4.1, Section 6.6.3	“Day 21 visit” name corrected to “Day before RP visit” as per Section 1.3 Table 1.	To remove inconsistencies in names of visits in the protocol.	Non-substantial
Section 5.2	Added a note for exclusion criteria for the no-treatment arm “If any other exclusion criteria were met, eligibility should be discussed with medical monitor.”	To clarify the exclusion criteria for the no-treatment arm.	Non-substantial
Section 5.2, Section 6.8.1 Table 11, Appendix G 5, Appendix G 5 Table 23	The details about prohibited concomitant medications amended for darolutamide arm and AZD5305 + darolutamide arm. Clarified that the use of strong and moderate CYP3A4 inducers and/or P-gp inducers, BCRP, OATP1B1, and OATP1B3 substrates is prohibited in both arms.	To ensure compliance with local and national prescribing guidelines for darolutamide.	Substantial
Section 6.3	Information about assignment of patients to the no-treatment arm corrected. “After screening” changed to “during screening” as per Section 4.1.	To remove inconsistencies in the protocol.	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 6.6.6	The definition of biomarker evaluable patient was amended.	To include the biomarker evaluable patients of those who extend study treatment beyond Day 21.	Non-substantial
Section 6.8.1	Information about prohibited concomitant medications with reference to local and national prescribing guidelines updated.	To ensure compliance with local and national prescribing guidelines for darolutamide.	Non-substantial
Section 8.2.1	Clarification regarding the use of the results of multiparametric MRI performed outside the screening window as acceptable diagnostic results.	To allow the use of the results of multiparametric MRI even if performed outside the screening window.	Non-substantial
Section 8.5.2	Removed details of specific bioanalytical test sites for the determination of drug concentrations in plasma.	To allow choice of the bioanalytical test site from the list of selected vendors (details to be provided in a separate bioanalytical report)	Non-substantial
Section 8.8.1	Information about sample retention removed.	Amended information about sample retention already provided in the Appendix C.	Non-substantial
Section 8.8.2.1	Information about mandatory diagnostic FFPE tumour samples amended with removal of fine needle aspirates of the tumour.	To clarify how diagnostic FFPE tumour samples will be collected.	Non-substantial
Section 8.8.4	Information about blood samples to be collected over time to monitor the changes in blood biomarkers added.	To clarify how blood samples for blood biomarkers will be collected.	Non-substantial
Section 9.4.1	The definition of baseline corrected.	To clarify the definition of baseline for no-treatment arm.	Non-substantial
Appendix A 7	Information about quality tolerance limits removed.	Identification of systematic issues will be done outside of Quality Tolerance Limit framework	Non-substantial
Appendix C 1 Appendix D 2	Information about sample retention amended from 25 years to 15 years.	To correct error and provide clarity	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Appendix E 6	Reference to the central laboratories removed.	Amended to allow decentralization of the investigations for a quicker decision making	Non-substantial

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