Title: A Modular Phase 2a Multicentre Open-Label Study to Investigate DNA-damage Response Agents (or Combinations) in Patients With Advanced Cancer Whose Tumours Contain Molecular Alterations (PLANETTE)

Sponsor Study Code: D5339C00001

NCT Number: NCT04564027

Date: 04 November 2022

Clinical Study Protocol	
Study Intervention	DNA-damage response agents
Study Code	D5339C00001
Version	Amendment 4
Date	04 November 2022

A Modular Phase 2a Multicentre Open-Label Study to Investigate DNA-damage Response Agents (or Combinations) in Patients With Advanced Cancer Whose Tumours Contain Molecular Alterations (PLANETTE)

Sponsor Name: AstraZeneca AB

Legal Registered Address: 151 85 Södertälje, Sweden

Regulatory Agency Identifier Number(s)

EudraCT number: 2020-002529-27

IND number: 150711

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

Protocol Number: D5339C00001

Amendment Number: 4

Study Intervention: DNA-damage response agents
Study Phase: 2a

Short Title: A Study Investigating DNA-damage Response Agents in Molecularly Altered Advanced Cancer

Acronym: PLANETTE study

Medical Monitor Name and Contact Information will be provided separately

International co-ordinating investigators

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 4	04-Nov-2022
Amendment 3	04-Apr-2022
Amendment 2	27-May-2021
Amendment 1	12-Aug-2020
Original Protocol	17-Jun-2020

The summary of changes for Amendment 4 is provided below. Refer to Appendix M for a summary of the previous amendment.

Amendment 4 (04-Nov-2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

To clarify access to IMP and management of patients ongoing on treatment at final Data Cut off (DCO)

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
CORE			
6.1 Intervention after Final DCO	Addition of text to core protocol to clarify options for continuation of treatment for patients receiving benefit at time of final DCO.	Please see overall rationale	Substantial
MODULE 1 (Section 11): Ceralasertib Monotherapy in ATM Altered Advanced Solid Tumours (aST) and Prostate Cancer			
11.1.1 Synopsis, patient numbers	Correction of typo	Typo	Non-substantial
11.6.7 Intervention after Final DCO	Addition of text to detail management of patients ongoing on treatment post final DCO.	Please see overall rationale	Substantial

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1 PROTOCOL SUMMARY - CORE

1.1 Synopsis

Protocol Title: A Modular Phase 2a Multicentre Open-Label Study to Investigate DNA-damage Response Agents (or Combinations) in Patients With Advanced Cancer Whose Tumours Contain Molecular Alterations (PLANETTE)

Short Title: A Study Investigating DNA-damage Response Agents in Molecularly Altered Advanced Cancer

Rationale: In an era of precision medicine, the use of biomarkers to select patients who can benefit from treatment with a specific anti-cancer agent has the potential to both improve patient outcomes and accelerate drug development. Hence, drugs are increasingly being developed to target subgroups of patients whose tumours contain actionable biomarkers.

This is a phase 2a modular study in which a number of hypotheses may be tested in selected molecularly altered tumours. Examples of relevant molecular alterations may include, but are not limited to, ataxia telangiectasia mutated (ATM) and AT-Rich Interaction Domain 1A (ARID1A), and relevant tumour indications may be confined to a single tumour type, a collection of specific tumour types, or disease agnostic. The patient populations considered are those with advanced/metastatic solid and/or haematological malignancies with molecular alterations.

Objectives and Endpoints (see individual modules for details)

Objectives	Endpoint/Variable
Primary	
• To obtain a preliminary assessment of the efficacy of study intervention as assessed by response rate.	• Please refer to individual modules for details on response criteria.
Secondary	
• To obtain a preliminary assessment of further efficacy endpoints with study intervention.	• Please refer to individual modules for details of efficacy assessments.
• To assess the safety and tolerability profile of study intervention.	• Adverse events (AEs)/Serious AEs • Vital signs, ECG, clinical chemistry, haematology, urinalysis and coagulation parameters.

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

Overall Design

This is a modular, phase 2a, open-label, multicentre study of DNA-damage response agents (or combinations) administered to participants with advanced/metastatic solid tumours and/or haematological malignancies with molecular alterations.

This study is modular in design and the core module provides the overall framework for the study and specific details of the participant population and molecular alterations will be described in each module. A substantial protocol amendment with relevant supportive rationale will be approved before starting a new module.

Number of Participants:

Please refer to individual modules for details.

Intervention Groups and Duration:

This protocol has a modular design, with the potential for future treatment arms to be added via protocol amendment.

This protocol refers to the following modules and study drugs. For specific information on each of the study drugs, please refer to the relevant module.

- Module 1 (Section 11): Ceralasertib monotherapy in ATM altered tumours

Data Monitoring Committee: No

Statistical methods

Please refer to individual modules for details.

1.2 Schema

Please refer to individual modules for details.

1.3 Schedule of Activities

Please refer to individual modules for details.

2 INTRODUCTION - CORE

This is a modular, phase 2a, open-label, multicentre study of DDR agents (or combinations), administered to participants with advanced/metastatic solid and/or haematological malignancies with molecular alterations. This protocol provides the overall framework for the study (core module) and specific details of the participant population and molecular alterations will be described in each module. A substantial protocol amendment with relevant supportive rationale will be approved before starting a new module.

The term “study intervention” throughout the protocol, refers to study treatment/drug.

2.1 Study Rationale

In an era of precision medicine, the use of biomarkers to select patients who can benefit from treatment with a specific anti-cancer agent has the potential to both improve patient outcomes and accelerate drug development. Hence, drugs are increasingly being developed to target subgroups of patients whose tumours contain actionable biomarkers.

This is a phase 2a modular study in which a number of hypotheses may be tested in selected molecularly altered tumours. Examples of relevant molecular alterations may include, but are not limited to, ATM, ARID1A and relevant tumour indications may be confined to a single tumour type, a collection of specific tumour types, or disease agnostic. The participant populations considered are those with advanced/metastatic solid and/or haematological malignancies with molecular alterations.

2.2 Background

Precision medicine trials use rationally incorporated biomarker targets and molecularly selective anti-cancer agents to test the clinical applicability of pairing actionable mutations with targeted therapy (Coyne et al, 2017).

During the last 20 years a deeper understanding of the genomic landscape in the majority of cancer types and the development of sequencing techniques have paved the way towards precision medicine in oncology. This approach has significantly contributed to unravel the complexity of cancer genetic alterations and to provide to cancer patients targeted therapy. The clear objective of precision medicine in oncology is to change clinical practice by treating cancer patients according to their individual molecular profile.

Many potential targets on genetic level, which are essential for proliferation, survival and metastatic spread of cancer cells, were identified. Some of those - so-called driver-mutations – have been elucidated as highly efficient therapeutic targets and nowadays there is a rapid progress in the development of new and more potent molecular targeted therapies to prevent or circumvent primary and secondary resistance mechanisms (Tan et al, 2016).

With this gaining knowledge in cancer genomics, molecular biology and the development of targeted therapies, the classic concept of phase I-III trials has been extended by new clinical trial designs. Basket and umbrella trials entered the field of clinical research (Zimmer et al, 2019). One of the biggest molecular profiling trials, the NCI-MATCH (Molecular Analysis for Therapy Choice) Trial is a landmark precision medicine which is aiming to evaluate > 100 mutations in a basket study design.

Currently, the leading example is the use of BRCA1/2 mutations to select patients whose tumours may be hypersensitive to poly(ADP-ribose) polymerase (PARP) inhibitor treatment (Bryant et al, 2005 and Farmer et al, 2005), which has brought impressive survival rates in ovarian (Moore et al, 2018.), breast (Robson et al, 2017) and pancreatic cancer (Golan et al, 2019).

Furthermore, effective drugs have been approved for tumour agnostic cancers based on studies where patients have been selected according to molecular profiling. For instance, larotrectinib (Vitravki) as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment options (Vitravki SMPC). Pembrozilumab was approved for the treatment of adult and paediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient: solid tumours that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication is approved under accelerated approval based on tumour response rate and durability of response (Keytruda SMPC).

2.3 Benefit/Risk Assessment

The benefit/risk assessments of the specific DDR agents (or combinations) are outlined in the respective modules. More detailed information about the known and expected benefits and risks and reasonably expected AEs are provided in the respective IBs.

3 OBJECTIVES AND ENDPOINTS - CORE

Please see individual modules for detailed objectives and endpoints.

Table 1 Objectives and Endpoints

Objectives	Endpoint/Variable
Primary	
• To obtain a preliminary assessment of the efficacy of study intervention as assessed by response rate.	Please refer to individual modules for details on response criteria.
Secondary	
• To obtain a preliminary assessment of further efficacy endpoints with study intervention.	Please refer to individual modules for details of efficacy assessments.
• To assess the safety and tolerability profile of study intervention.	• AEs/SAEs • Vital signs, ECG, clinical chemistry, haematology, urinalysis and coagulation parameters.
Exploratory	
• CCI [redacted] CCI [redacted]	• CCI [redacted] • CCI [redacted] • CCI [redacted] • CCI [redacted]

4 STUDY DESIGN - CORE

4.1 Overall Design

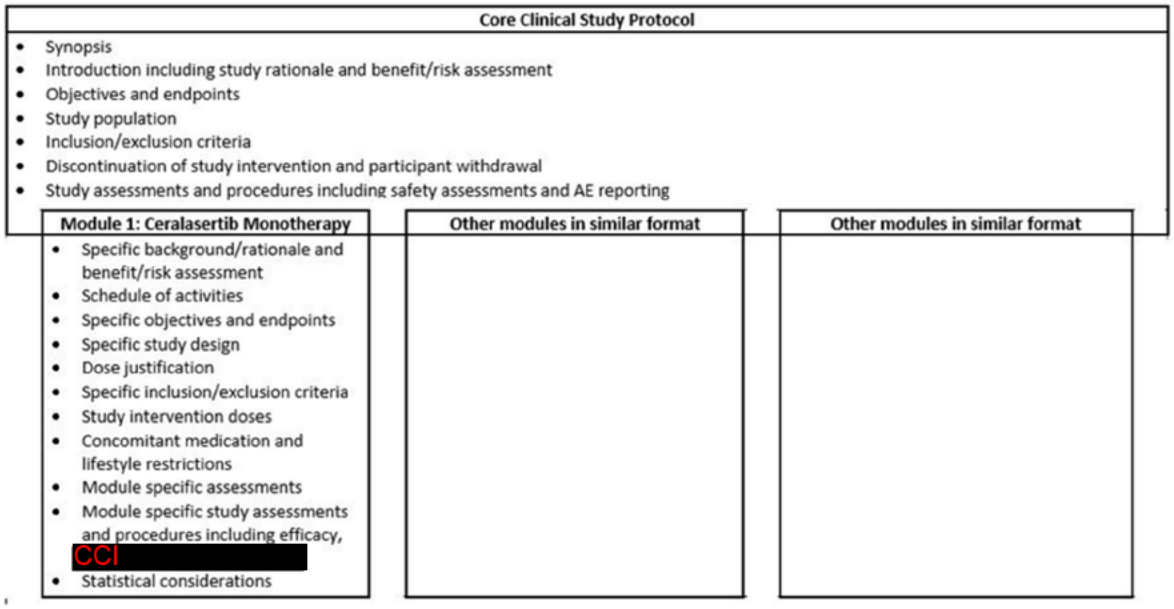
This is a modular, phase 2a, open-label, multicentre study of DDR agents (or combinations), administered to participants with advanced/metastatic solid and/or haematological malignancies with molecular alterations.

The core module provides the overall framework for the study and specific details of the participant population and molecular alterations will be described in each module. A substantial protocol amendment with relevant supportive rationale will be approved before starting a new module.

4.1.1 Modular Protocol Structure

The structure of the study protocol is illustrated in Figure 1, where the core module contains elements common to all modules and then individual modules containing the module specific details relevant to that module.

Figure 1 Modular Protocol Design



Abbreviations: AE=adverse events; CCI [redacted]

4.1.2 Regulatory Amendment for Additional Modules

To support amendment of the protocol for additional modules/cohorts, including any non-comparative randomised expansion cohorts, AstraZeneca will provide a summary of the available data to support the proposed treatment module/cohort, as follows:

Europe and Rest of World

AstraZeneca will provide a substantial amendment for review and approval.

United States of America

AstraZeneca will provide an amendment to the FDA approximately 30 days in advance of planned enrolment into any new cohort. AstraZeneca will begin enrolment of patients into that cohort in the Unites States after IRB approval.

4.1.3 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 CSP 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 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 minimize 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 consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the ICF should be signed at the participant's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated AstraZeneca study physician.
- Home or Remote visit: Performed by a site qualified health care professional or health care professional provided by a third-party vendor.
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home study intervention administration: Performed by a site qualified health care professional, health care professional provided by a third-party vendor or by the participants or the participant's caregiver, if possible. Additional information related to the visit can be obtained via telemedicine.

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

4.2 Scientific Rationale for Study Design

Key aspects of the study, such as the non-comparative design, primary and secondary endpoints, participant population with advanced tumours, cohort size are based upon accepted methodology for efficacy signal detection in phase 2 oncology studies. The study may consist of several treatment modules, each evaluating the efficacy, safety and tolerability of specific study interventions and their combinations. The modular study design will allow the tailoring of study procedures and endpoints to specific treatment regimens and indications.

The sponsor plans to include investigations into variations in CCI CCI CCI. There are many potential benefits of this exploratory research, including the possibility to identify participants most likely to benefit from treatment, explain outliers or non-responders or explain adverse reactions related to drug exposure. This research may result in an understanding of the impact of variation between individuals and how this information can be utilised to bring better drugs to clinic.

Assignment of participants to treatment arms will be made based upon the status of the relevant molecular aberration in a participant's tumour. The strength of clinical hypothesis as well as the prevalence of each aberration will be considered when overlapping or co-occurring qualifying molecular criteria are encountered. Guidelines to inform cohort allocation for participants with overlapping aberrations or more than a single qualifying aberration will be detailed separately where applicable.

4.3 Justification for Dose

Please refer to individual modules for details.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure shown for the individual module that they are included in.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure for the last participant in the study.

5 STUDY POPULATION - CORE

The core study population requirements are described below, please refer to individual modules for further specific details.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

The inclusion criteria that are applicable to all modules in the study are described in this section. Please also refer to the relevant module for specific criteria applicable to each cohort. Where criteria are more stringent in the module rather than the core, the investigator should adhere to the module criteria.

Participants are eligible to be included in the study only if all of the following criteria apply:

Informed Consent

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

2 Provision of written Optional Genetic Research Information informed consent prior to collection of samples for optional genetic research that supports Genomic Initiative.

Age

3 Participant must be at least 18 years of age inclusive, at the time of signing the informed consent.

Sex

4 Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies (see Section 5.3.1).

Other

5 Participant is willing and able to comply with the study protocol for the duration of the study including undergoing treatment and scheduled visits and examinations.

5.2 Exclusion Criteria

The exclusion criteria that are applicable to all modules in the study are described in this section. Please also refer to the relevant module for specific criteria applicable to each cohort. Where criteria are more stringent in the module rather than the core, the investigator should adhere to the module criteria.

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

Medical Conditions

1 Persistent toxicities (> CTCAE Grade 2) caused by previous cancer therapy, excluding alopecia and CTCAE Grade 2 peripheral neuropathy.

2 History of another primary malignancy except for:

- Malignancy treated with curative intent and with no known active disease ≥ 2 years before the first dose of study drug and of low potential risk for recurrence
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated carcinoma in situ without evidence of disease
- Localised non-invasive primary under surveillance

3 Concurrent severe and/or uncontrolled medical condition (e.g., severe COPD, severe Parkinson's disease, active inflammatory bowel disease) or psychiatric condition (screening for chronic disease is not required).

Prior/Concurrent Clinical Study Experience

4 Participants with a known hypersensitivity to study interventions or any of the excipients of the products.

Other Exclusions

5 Major surgery within 2 weeks of starting study intervention: participants must have recovered from any effects of any major surgery.

6 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

7 Judgement by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions and requirements.

8 Previous enrolment in the present study.

9 Participants with gastrointestinal disorders likely to interfere with absorption of the study intervention.

10 Pregnant (confirmed with positive pregnancy test) or breast feeding women.

In addition, the following are considered criteria for exclusion from the optional exploratory host genetic research:

11 Previous allogenic bone marrow transplant.

12 Non-leukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection.

5.3 Lifestyle Considerations

Please refer to the relevant modules. Where restrictions are more stringent in the individual module rather than the core module, the investigator should adhere to the individual module criteria.

5.3.1 Contraception

Male participants: Must use a condom (with spermicide) during the study, and for 1 week after the last dose of study intervention, with all sexual partners. Where a sexual partner of a male participant is a 'woman of childbearing potential' who is not using effective contraception, male participants must use a condom during the study and for 6 months after the last dose of study intervention. Male participants must also not donate sperm for 6 months after the last dose of study intervention.

Female participants: Pregnancy tests on blood (screening) or urine (other time points) samples will be performed for women of childbearing potential prior to the start of study intervention, at the timepoints defined in the individual module SoA.

Women of childbearing potential must use enhanced contraception during the study, and for 1 month after the last dose of study intervention, with all male sexual partners. Contraceptives that are prone to drug-drug interactions may not be effective due to a potential CYP3A4 interaction with study intervention. Contraception used must therefore include a condom and one of:

- Medroxyprogesterone injections (eg, Depo-provera)
- Intrauterine device
- Levonorgestrol Intrauterine System (eg, Mirena)
- Tubal occlusion
- Vasectomised partner

Women who are breast feeding are excluded from the study.

5.4 Screen Failures

Please refer to individual modules for screen failure definitions.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened following consultation with the sponsor. Rescreened participants should be assigned the same participant number as for the initial screening, and re-sign the ICF.

6 STUDY INTERVENTION - CORE

Please refer to the relevant module.

6.1 Intervention after the Final DCO

After the final DCO and as long as the clinical development program is ongoing, AstraZeneca will continue to supply IP treatment to patients who, in the investigator's opinion, continue to benefit from receiving IP treatment.

Depending on what is available at the time, the patients would be followed either:

- Within the current study
- Within a safety expansion study if available
- Within a drug supply program (commercial or compassionate use program) if applicable

In case of treatment continuation after the final DCO within the current study:

- Patients will continue to attend site visits for safety assessments.
- There will be no more data collection except SAE reporting, overdosing and pregnancies. The clinical study database will be closed.
- SAEs, overdoses and pregnancies will be reported following a paper form process. All SAEs, overdose and pregnancies will be reported until 30 days after last dose and recorded in the safety database.
- Drug dispensation and reconciliation will be handled by site at each patient's visit.
- Site will remain open until the last patient treatment discontinuation.

In case of treatment continuation after the final DCO within a safety extension study, if available:

- Safety extension study would have to be approved by Regulatory Authority and Ethics Committee at the patient's site.
- Safety assessments would be performed as per the safety extension study protocol.
- SAEs will be reported following a paper form process. All SAEs, overdose and pregnancies will be reported until 30 days after last dose and recorded in the safety database.
- Patients would be proposed to transition to the safety study and sign a new consent form.

If the study drug is marketed for use in the disease under study indication:

- Patients may discontinue study and switch to marketed product.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL - CORE

7.1 Discontinuation of Study Intervention

Participants may be withdrawn from any aspect of the study at any time, without prejudice to further treatment. Procedures for withdrawal from the exploratory research on collected samples are outlined in Appendix I 2.

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

- Participant or investigator decision. The participant is at any time free to withdraw his/her participation in the study.
- AEs.
- Severe non-compliance to this protocol (participants or investigator) as judged by the investigator and/or AstraZeneca.
- Disease progression.
- Participants incorrectly initiated on study intervention (Section 7.1.2).
  - When the reason does not impact safety consider the risk/benefit to the participant of stopping treatment.
- Life-threatening or other unacceptable toxicity.
- The discovery of an unexpected, significant, or unacceptable risk to the participants enrolled in the study.
- Lack of evaluable and/or complete data.
- Decision to modify the development plan of the drug.
- A decision on the part of the sponsor to suspend or discontinue development of the drug.
- Confirmed pregnancy in women of childbearing potential.

7.1.1 Temporary Discontinuation

Please refer to the relevant module.

7.1.2 Procedures for Handling Participants Incorrectly Initiated on Study Intervention

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.

When participants that do not meet the inclusion/exclusion criteria are enrolled in error or incorrectly started on study intervention, or when participants subsequently fail to meet the study criteria post initiation, the investigator should inform the sponsor Study Physician immediately and these participants will be documented as protocol violations.

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

Any participant started on study intervention in error, and he/she has subsequently been found to have failed to comply with all of the selection criteria, will undergo a risk/benefit

assessment by the investigator/sponsor; if the participant is judged to be receiving clinical benefit, the investigator may choose to continue to dose them with the study intervention.

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

The sponsor Study Physician is to ensure all such contacts are appropriately documented.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she 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 clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should 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 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.
- Should the participant continue to be unreachable, he/she 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. 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. Sponsor personnel will not be involved in any attempts to collect vital status information.

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

8 STUDY ASSESSMENTS AND PROCEDURES - CORE

- Please refer to the relevant individual modules for study procedures and their timings. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor 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 individual module SoAs, 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 individual module SoAs.

8.1 Efficacy Assessments

Please refer to individual modules for details.

8.2 Safety Assessments

Please refer to individual module SoAs for details on the timing/visits for safety assessments.

8.2.1 Physical Examinations

- A complete physical examination with weight will be performed. Height will be recorded at screening only.
- Examination will include general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities) and neurological systems. Investigators should pay special attention to clinical signs related to previous serious illnesses. Situations in which physical examination results should be reported as AEs are described in Section 8.3.5.

8.2.2 Vital Signs

8.2.2.1 Seated blood pressure and pulse rate

Blood pressure and pulse rate will be measured in the sitting position after at least 10 minutes rest.

8.2.2.2 Body temperature

Body temperature will be measured in degrees Celsius.

Any changes in vital signs should be recorded as an AE if applicable.

8.2.3 Electrocardiograms

Resting 12-lead ECG

Twelve-lead ECGs will be obtained after the participant has been resting semi-supine for at least 5 minutes prior to times indicated. All ECGs should be recorded with the participant in the same physical position. A standardised ECG machine should be used that automatically calculates the heart rate and measures PR, QRS, and QT intervals, and the participant should be examined using the same machine throughout the study, where feasible.

For triplicate ECGs, 3 individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes. Results from each replicate of the ECG should be recorded and an assessment of clinical significance recorded for each timepoint. Numerical values (eg, QT, QTcF, PR interval) should be assessed based on an average of the triplicate readings, whilst qualitative findings (eg rhythm and overall evaluation) from all replicates should be taken into account.

After paper ECGs have been recorded, the investigator or designated physician will review each of the ECGs and may refer to a local cardiologist if appropriate. A paper copy should be filed in the participant's medical records. If an abnormal ECG finding at screening is considered to be clinically significant by the investigator, it should be reported as a concurrent condition. For all ECGs details of rhythm, PR, R-R, QRS and QTcF interval and an overall evaluation will be recorded.

8.2.4 Performance Status

- Performance status will be assessed according to US ECOG criteria (Table 2).
- These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis (Oken et al, 1982).

Table 2 Eastern Cooperative Oncology Group Performance Status

Grade	ECOG
0	Fully active, able to carry out all pre-disease activities without restrictions
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature eg, light housework, office work
2	Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours

Grade	ECOG
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled, cannot carry on self-care, totally confined to bed or chair
5	Dead

8.2.5 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken as indicated in the individual specific module SoAs.

Laboratory assessments do not need to be repeated at baseline if the baseline visit is within 3 days of the screening sample. The date of each collection will be recorded in the appropriate eCRF.

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.

Laboratory values that meet the criteria for CTCAE Grade 3 or have changed significantly from baseline and are considered to be of clinical concern will be repeated/confirmed within 7 days and followed up as appropriate.

8.3 Adverse Events and Serious Adverse Events

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 H.

AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

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

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse Events will be collected from the time of the first dose of study intervention throughout the treatment period and including the follow-up period till the last safety follow-up visit or study termination.

SAEs will be recorded from the time of signing of the screening Part 1 ICF throughout the treatment period and including the follow-up period till the last safety follow-up visit.

If an investigator learns of any SAEs, including death, at any time after last safety follow-up visit and he/she considers there is a reasonable possibility that the event is related to study intervention, the investigator should notify AstraZeneca.

If the investigator becomes aware of an SAE with a suspected causal relationship to the investigational medicinal product that occurs after the end of the clinical study in a participant treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment 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.

Adverse event variables

The following variables will be collected for each AE;

- AE (verbatim)
- CTCAEv5 grade
- The date and time when the AE started and stopped
- The date, time and new CTCAEv5 grade if this has changed
- Whether the AE is serious or not
- Investigator causality rating against the study intervention(s) (yes or no)
- Action taken with regard to study intervention(s)
- Outcome.

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

- Date AE met criteria for serious AE
- Date investigator became aware of serious AE
- AE is serious due to
- 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

8.3.3 Causality Collection

The investigator should assess causal relationship between study intervention 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 study intervention?'

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 H to the Clinical Study Protocol.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider 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.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the Clinical Study Protocol-mandated laboratory tests, vital signs, and other safety assessments will be summarised in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, and other safety assessments should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for concomitant therapy, and/or modification or discontinuation of treatment with the study intervention or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study treatment, eg, dose adjustment or drug interruption) unless clearly due to progression of disease under study (see Disease progression Section 8.3.7).

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 versus 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 disease under study.

8.3.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 x ULN together with total bilirubin ≥ 2 x 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.

8.3.7 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the study intervention is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to 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 an AE during the study.**

8.3.7.1 New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New 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.

8.3.7.2 Handling of deaths

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

- Death, which is unequivocally due to disease progression, should be communicated to the study monitor at the next monitoring visit and should be documented in the eCRF module, but should not be reported as a SAE during the study.
- Where death is not clearly due to disease progression of the disease under study the AE causing the death should be reported to the study monitor as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes.
- Deaths with an unknown cause should always be reported as a SAE but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results

(with translation of important parts into English) should be reported in an expedited fashion to an AstraZeneca representative within the usual timeframes.

8.3.8 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the study intervention, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel 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 works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 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 is undertaken immediately. investigators or other site personnel 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 WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site staff how to proceed.

The reference document for definition of expectedness is Section 5 of the individual study intervention IB.

8.3.9 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention

8.3.9.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, study intervention should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs during exposure to study intervention or in the 1 month after discontinuing study intervention, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day ie, 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 1 or 5 calendar days for SAEs (see Section 8.3.9) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.3.9.2 Paternal Exposure

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 abnormality), occurring from the date of the first dose until 16 weeks after dosing after the last dose and as indicated by previous studies (preclinical and clinical) should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

8.3.10 Medication Error

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day ie, 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 completed within 1 (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 medication error (see Section 8.3.8) and within 30 days for all other medication errors.

The definition of a medication error can be found in Appendix H 4.

8.4 Overdose

For this study, any dose of study intervention greater than those specified in the protocol is considered to be an overdose. This may include a higher dose of study intervention or study intervention taken at the correct dose but for longer duration.

- An overdose with associated AEs is recorded as the AE diagnosis/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 AstraZeneca study intervention occurs in the course of the study, the investigator or other site personnel 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 1 or 5 calendar days for overdoses associated with an SAE (see Section 8.3.8) and within 30 days for all other overdoses.

8.5 Human Biological Samples

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 Sample see Appendix I.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- PK 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.
  - PK samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.5.1 Pharmacokinetics

Please refer to individual modules for details.

8.5.2 Pharmacodynamics

Please refer to individual modules for details.

8.6 Human Biological Sample Biomarkers

Please refer to individual modules for details.

8.7 Optional Genomics Initiative Sample

Collection of optional samples for Genomics Initiative research during treatment of progression is also part of this study as specified in the SoA and is subject to agreement in the separate genetic research consent form.

Blood sample for DNA isolation and tissue samples will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

Details on processes for collection and shipment and destruction of these samples can be found either in the appendices or in the Laboratory Manual.

See Appendix J for further information regarding the Genomics Initiative genetic sample.

8.8 Health Economics or Medical Resource Utilisation and Health Economics

Health Economics/Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS - CORE

Please refer to individual modules for details.

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11 MODULE 1: CERALASERTIB MONOTHERAPY IN ATM ALTERED ADVANCED SOLID TUMOURS (AST) AND PROSTATE CANCER

11.1 MODULE SUMMARY - MODULE 1

11.1.1 Synopsis

Rationale

Ataxia telangiectasia mutated (ATM) is a serine/threonine protein kinase that is recruited and activated by DNA double strand breaks and has both checkpoint and repair functions. Ataxia Telangiectasia and Rad3 Related (ATR) is an apical kinase with a critical role in the DNA-damage response. During normal DNA replication, ATR is recruited at stalled replication forks which can progress to double strand breaks if left unrepaired. In normal cells, there is a significant interplay between ATR and ATM as stalled replication forks can be converted into double strand breaks through further DNA-damage and the resection of double strand breaks generates single stranded DNA.

Preclinical models have suggested that ATM-deficient cell lines are sensitised to DNA damaging agents, including platinum chemotherapy and ATR inhibitors. Ceralasertib is an oral inhibitor of the serine/threonine protein kinase ATR, a member of the phosphoinositide-3-kinase related kinase (PIKK) family. There are emerging data which are demonstrating the anti-tumour activity of ATR inhibitors in patients with ATM mutation and/or protein loss.

In line with previous and ongoing studies, it is anticipated that patients with ATM altered aST and mCRPC would benefit from treatment with ceralasertib in this study.

Overall Design

Module 1 is investigating ceralasertib, previously known as AZD6738, monotherapy administered orally, to participants with advanced/metastatic solid malignancies with ATM mutation and/or protein loss.

Number of Participants

Cohort A (aST): A total of ~25 molecularly eligible and centrally confirmed participants will be enrolled into Cohort A.

Cohort B (mCRPC): A total of ~27 molecularly eligible and centrally confirmed participants will be enrolled into Cohort B. Unfavourable CTC count requirement may be introduced for all participants to ensure an adequate (approximately ≥ 50%) number of participants with CTC count ≥ 5/7.5 mL blood.

At the time of protocol amendment 2, 8 participants had been dosed at 240 mg BID in Cohort A, and 1 participant had been dosed at 240 mg BID in Cohort B. Following the reduction of the starting dose from 240 mg BID to 160 mg BID in protocol amendment 2, the intention is to enrol an additional total of ~25 and ~27 participants in Cohort A and B, respectively, at the 160 mg BID.

In case of discordance between local and central testing, additional participants may be enrolled in order to satisfy the intended sample size of molecularly eligible and centrally confirmed participants.

Each Cohort A and Cohort B may be further expanded CCI CCI This would occur in the event an efficacy signal is observed, and subject to a protocol amendment.

Statistical Methods

Data will be presented separately for each cohort of participants within Module 1. No formal statistical analyses will be carried out for this study and the data will be summarised using standard summary statistics.

Cohort A (aST)

Objective response rate is defined as the percentage of participants who have at least one response of CR or PR prior to any evidence of progression (as defined by RECIST 1.1) that is confirmed at least 4 weeks later. Percentage of participants will be accompanied with a 2-sided 80% confidence interval as obtained from a Clopper-Pearson test.

Cohort B (mCRPC)

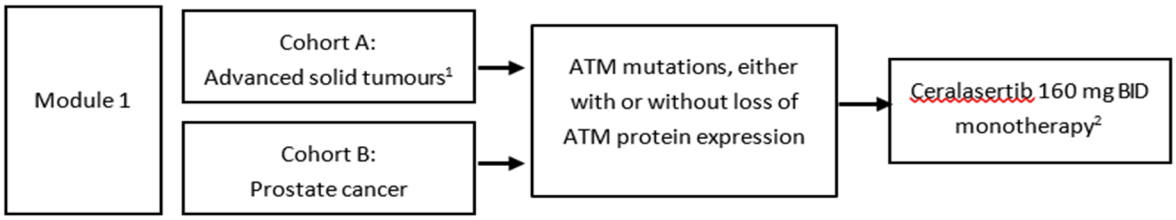
Composite response will be defined on the basis of the following outcomes; if any of these occur in the absence of radiological or PSA progression (according to RECIST 1.1 for soft tissue and visceral lesions, prostate cancer working group 3 (PCWG3) criteria for bone lesions, and PSA) participants will be considered to have responded:

- Investigator assessed radiological objective response by RECIST 1.1 for soft tissue and visceral lesions and PCWG3 criteria for bone lesions. Response must be confirmed at least 4 weeks later. BICR assessment may be introduced if the cohort is expanded, subject to a protocol amendment.
- Conversion of CTC count from ≥ 5/7.5 mL blood (unfavourable) at baseline to < 5/7.5 mL blood (favourable) confirmed by a second consecutive value obtained 3 or more weeks later (as per PCWG3 criteria).
- PSA decline of > 50% confirmed by a second consecutive measurement at least 3 weeks later (based on PCWG1 criteria).

Percentage of participants will be accompanied with a 2-sided 80% confidence interval as obtained from a Clopper-Pearson test.

11.1.2 Schema

Figure 2 Module Design



[1] All aST except NSCLC and prostate cancer.
[2] Ceralasertib administered twice a day between Days 1 to 14 in 28 day cycles.
Abbreviations: aST=advanced solid tumours; ATM=ataxia telangiectasia mutated; BID=twice daily; IHC=immunohistochemistry; NSCLC=non-small-cell lung carcinoma.

11.1.3 Schedule of Activities (SoA)

Table 3 Schedule of Activities

			Cycle										
Visit	**Screening**		**1 (28 days)**			**2**			**3 onwards**	**Study intervention discontinued**	**Safety Follow-up**	**Off-Treatment Follow-up for Progression**	**Details in CSP section**
	Part 1	**Part 2 -28 to -1**	**Day 1**	**Day 8**	**Day 14**	**Day 1**	**Day 8**	**Day 14**	**Day 1**	**Last dose of study intervention**	**30 days after last dose**		
Activity/Visit Window				**±1d**	**-1d**	**-1/+3d**	**±1d**	**-1d**	**-1/+3d**	**+7d**	**±7d**		
ALL COHORTS													
Informed consent	X	X											Section 5.1 and Appendix B 3
Provide copy of local NGS testing report	X[a]												Section 11 .5.1.1
Archival or SoC fresh tumour sample	X[a]												Section 11.4.1, 11.5.1.1, and 11.8.6.1
Optional tumour sample										X[b]		X[b]	Section 11.8.6.1
Inclusion and exclusion criteria	X[c]	X											Section 5.1, 5.2, 11.5.1, and 11.5.2
Demography and Baseline Characteristics	X[d]	X											Section 8.2

			Cycle										
Visit	**Screening**		**1 (28 days)**			**2**			**3 onwards**	**Study intervention discontinued**	**Safety Follow-up**	**Off-Treatment Follow-up for Progression**	**Details in CSP section**
	Part 1	**Part 2 -28 to -1**	**Day 1**	**Day 8**	**Day 14**	**Day 1**	**Day 8**	**Day 14**	**Day 1**	**Last dose of study intervention**	**30 days after last dose**		
Activity/Visit Window				**±1d**	**-1d**	**-1/+3d**	**±1d**	**-1d**	**-1/+3d**	**+7d**	**±7d**		
CCI	X[e]	X[e]	X[e]			X[e]			X[e]	X[e,b]		X[e b]	Section 11.8.6.2
Physical examination including weight		X (including height)	X			X[f]			X[f]	X[f]	X[f]		Section 8.2.1
Medical history		X											Section 8.2
12-lead triplicate ECG		X											Section 11.8.2.3
Vital signs (BP, pulse, and temperature)		X	X	X	X	X	X	X	X	X	X[f]		Section 8.2.2
ECOG performance status		X	X			X			X	X			Section 8.2.1
Complete blood count and other clinical safety laboratory assessments		X	X	X	X	X	X	X	X	X	X[f]		Section 8.2.5 and 11.8.2.6
Coagulation, urinalysis[g]		X											Section 8.2.5
Pregnancy test (WOCBP only)[h]		X	X			X			X		X		Section 8.2.5
PK ceralasertib				X[i]	X[i]		X[i]	X[i]					Section 11.8.5.1

			Cycle										
Visit	**Screening**		**1 (28 days)**			**2**			**3 onwards**	**Study intervention discontinued**	**Safety Follow-up**	**Off-Treatment Follow-up for Progression**	**Details in CSP section**
	Part 1	**Part 2 -28 to -1**	**Day 1**	**Day 8**	**Day 14**	**Day 1**	**Day 8**	**Day 14**	**Day 1**	**Last dose of study intervention**	**30 days after last dose**		
Activity/Visit Window				**±1d**	**-1d**	**-1/+3d**	**±1d**	**-1d**	**-1/+3d**	**+7d**	**±7d**		
CCI [redacted]		X	X	X		X	X		X[j]				Section 11.8.5.2
PGx CCI [redacted] sample (separate ICF)			X[k]										Section 11.8.7 and Appendix J
CCI [redacted]			X						X[j]	X[b]		X[b]	Section 11.8.6.3
Study intervention (dispensed/returned)			X			X			X	X			Section 11.6
Dosing with ceralasertib[l]			X	X	X	X	X	X	X				Section 11.6.1
Adverse Events (AE)	X	X	X	X	X	X	X	X	X	X	X		Section REF _Ref66204534 \r \h 8.3
Concomitant medication		X	X	X	X	X	X	X	X	X	X		Section 11.6.5
Cohort A (aST) only													
Tumour Assessment (CT/MRI including Brain scan at baseline)[m]		X							X[n]			X[n]	Section 11.8.1.1

			Cycle										
Visit	**Screening**		**1 (28 days)**			**2**			**3 onwards**	**Study intervention discontinued**	**Safety Follow-up**	**Off-Treatment Follow-up for Progression**	**Details in CSP section**
	Part 1	**Part 2 -28 to -1**	**Day 1**	**Day 8**	**Day 14**	**Day 1**	**Day 8**	**Day 14**	**Day 1**	**Last dose of study intervention**	**30 days after last dose**		
Activity/Visit Window				**±1d**	**-1d**	**-1/+3d**	**±1d**	**-1d**	**-1/+3d**	**+7d**	**±7d**		
Cohort B (mCRPC) only													
Serum testosterone (not required after bilateral orchiectomy) and PSA (if no radiographic progression, local assessment)		X											Section 11.5.1.4
Tumour Assessment (CT/MRI and Bone scan per PCWG3)		X							X[n]			X[n]	Section 11.8.1.2
CTC clinical blood sample		X	X			X			X[o]	X		X[o]	Section 11.8.1.2
PSA (central assessment)			X			X			X[o]			X[o]	Section 11.8.1.2

[a] Screening Part 1 applies to all study participants. For participants who have already undergone local ATM NGS testing, submission of the local test report is mandatory. If prospective central ATM NGS testing is introduced, participants who do not have a local ATM NGS result available at the site must submit a sample for prospective NGS central testing. All participants must submit a tumour sample for central confirmation (NGS and IHC).
[b] Sample taken once radiographic objective disease progression is established (+2 weeks window). Only 1 sample is required.
[c] Confirmation of tumour type (aST or mCRPC) and age.
[d] Baseline demography and disease stage to be collected.
[e] CCI .
[f] As clinically indicated.
[g] Coagulation and urinalysis will be performed at screening and as clinically indicated during subsequent visits.
[h] Women of childbearing potential only. Serum pregnancy test at screening, urine test at other time points.
[i] PK sample will be collected in all participants at pre-dose and 1 hour (+/- 30 min) post-dose
[j] Only for Cycle 3.
[k] Optional pharmacogenetics blood sample may be collected on Cycle 1 Day 1 or any time later.

[l] Study intervention administered twice a day between Day 1 and Day 14 in 28 day cycles. All safety assessments and laboratory results must be reviewed by the Investigator or physician designee prior to start of each study treatment dosing cycle.

[m] Baseline contrast enhanced CT brain scan assessment (MRI where CT is contraindicated) applies to advanced solid tumour participants only (Cohort A [aST]). A CT brain scan will be performed if participant is not known to have brain metastases. If the participant has known brain metastases, a baseline MRI will be performed.

[n] CT scans of the chest, abdomen, and pelvis (or MRI where CT is contraindicated) and bone scans (Cohort B [mCRPC] only) should be conducted every 8 weeks (±1 week) after the start of treatment (Cycle 1 Day 1) up to 1 year, then every 12 weeks (±1 week) until objective disease progression as per RECIST 1.1 or PCWG3 criteria. In the event of treatment interruptions or delays, tumour assessments should proceed to schedule relative to Cycle 1 Day 1. Bone progression observed by bone scan (Cohort B [mCRPC]) requires confirmation by bone scan at least 6 weeks later and preferably no later than the next scheduled scan (see Section 11.8.1.2). Soft tissue or visceral progression observed by CT or MRI, according to RECIST 1.1, does not require a confirmatory scan.

[o] Clinical CTC counts and PSA levels (Cohort B [mCRPC] only) will be assessed every cycle up to Cycle 5 Day 1, then every 8 weeks (±1 week) up to 1 year, then every 12 weeks (±1 week), aligned with tumour assessments (except those aligned with C1D1, C2D1, and C4D1), until radiographic objective disease progression as per RECIST 1.1 or PCWG3 criteria or off-study. CTC count conversion, PSA response by PCWG1 criteria, and PSA progression by PCWG3 criteria will need to be confirmed 4 weeks (±1 week) later unless a radiographic objective disease progression is registered within 12 weeks of PSA progression in which case concurrent PSA progression will be regarded as confirmed. In the absence of radiographic progression, if confirmatory PSA sample is not taken in 4 weeks (±1 week), it should be taken as soon as possible before the next scheduled assessment.

Abbreviations: AE=adverse events; aST=advanced solid tumour; ATM=ataxia telangiectasia mutated; BP=blood pressure; CR=complete response; CSP=clinical study protocol; CT=computed tomography; CTC=circulating tumour cells; CCI [redacted]; ECG=electrocardiogram; d=day; DNA=deoxyribonucleic acid; ECOG=Eastern Cooperative Oncology Group; G3=grade 3; ICF=informed consent form; IHC=immunohistochemistry; mCRPC=metastatic castration-resistant prostate cancer; MRI=magnetic resonance imaging; NGS=next generation sequencing; PCWG3=the prostate cancer working group 3; PGx=pharmacogenetic; PK=pharmacokinetic; PR=partial response; PSA=prostate specific antigen; RECIST=response evaluation criteria in solid tumours; SAE=serious adverse event; SD=stable disease; SoC=standard of care; WOCBP=women of childbearing potential.

11.2 INTRODUCTION - MODULE 1

Module 1 is testing ceralasertib, previously known as AZD6738, in 2 participant populations (Cohort A and Cohort B) whose tumours contain deleterious or suspected deleterious genetic alterations in the ATM gene. Cohort A is recruiting participants with ATM altered aST, except participants with non-small-cell lung carcinoma and prostate cancer. Cohort B is recruiting participants with ATM altered mCRPC. Molecularly eligible participants in Module 1 will have tumours containing alterations in ATM. A molecularly eligible participant is defined as a participant with deleterious or suspected deleterious ATM mutation in tumour or blood (germline or ctDNA), tested in a locally accredited laboratory using a validated test in line with local regulations (eg, CAP/CLIA laboratory, where available). Definitions of qualifying ATM mutations include deleterious/suspected deleterious, pathogenic/likely pathogenic, disease, or cancer-associated variants. Variants of unknown significance or benign variants are not eligible for enrolment. Cohort A and Cohort B will each enrol participants with ATM IHC > 5% and ≤ 5%. Prospective selection of patients with ATM IHC ≤ 5% may be introduced in each cohort based on emerging ATM protein deficiency prevalence and ceralasertib clinical activity data.

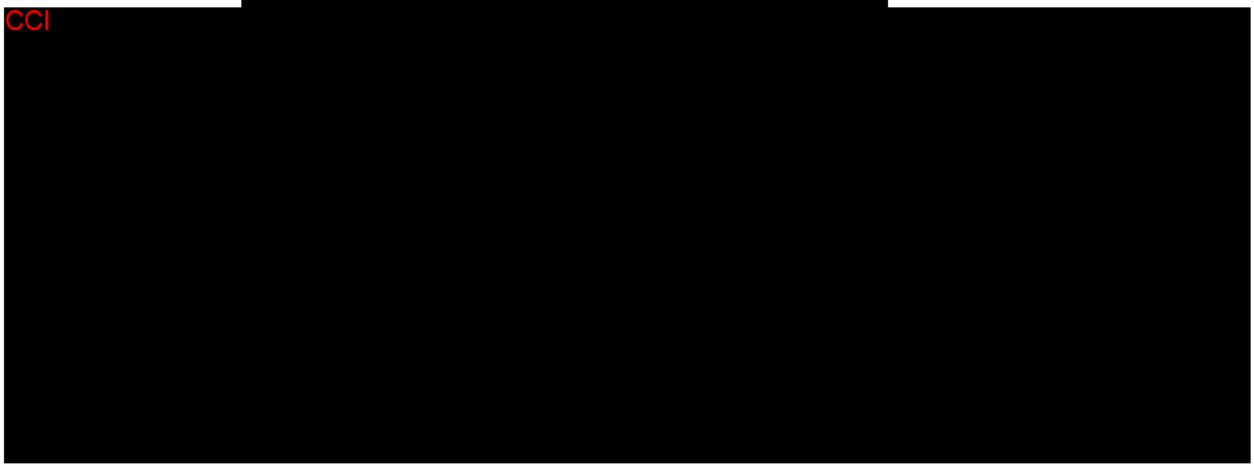
11.2.1 Module Rationale

ATM is a serine/threonine protein kinase that is recruited and activated by DNA double strand breaks and has both checkpoint and repair functions. Ataxia telangiectasia and rad3 related protein (ATR) is an apical kinase with a critical role in the DNA-damage response. During normal DNA replication, ATR is recruited at stalled replication forks which can progress to double strand breaks if left unrepaired. In normal cells, there is a significant interplay between ATR and ATM as stalled replication forks can be converted into double strand breaks through further DNA-damage and the resection of double strand breaks generates single stranded DNA (Thuss et al, 2011, and Toledo et al, 2011).

Preclinical models have suggested that ATM-deficient cell lines are sensitised to DNA damaging agents, including platinum chemotherapy and ATR inhibitors (Reaper et al, 2011). Ataxia telangiectasia mutated protein loss of function has been described in various tumour groups: up to 22% of metastatic tumours from patients with gastric cancer might have low or undetectable ATM expression, (Kim et al, 2013), 8% in colorectal cancer. Synthetic lethality between ATR inhibition and ATM deficiency was recently demonstrated in gastric cancer warranting further clinical studies for ceralasertib in ATM deficiency tumours (Min et al, 2017).

AstraZeneca internal data for the prevalence of ATM mutations and prevalence of ATM protein loss CCI [redacted] is presented in Table 4.

Table 4 CCI



In the first-in-human study of the oral ATR inhibitor BAY 1895344 in participants with aST (NCT03188965), 22 patients with advanced metastatic solid tumours resistant or refractory to standard treatment, with and without DDR defects, were included across 6 dose escalation cohorts. Twenty patients who received at least 1 dose of BAY 1895344 and had post-baseline tumour scans were included in the evaluation of antitumor activity/response. Among 11 patients with known ATM mutations and/or ATM protein loss in tumour, there were 4 patients (36.4%) with partial response, 3 patients (27.3%) with stable disease, 1 patient who achieved stable disease as RECIST best response but who had investigator-assessed clinical disease progression at the same time point, 2 patients with radiologic progressive disease, and 1 patient with no data from post-baseline assessment. Hence it could be concluded that the ATR inhibitor BAY 1895344 was tolerated at biologically active doses with anti-tumour activity against cancers with DDR defects, including ATM protein loss (Yap TA et al, 2021).

Ceralasertib is an oral inhibitor of the serine/threonine protein kinase ATR, a member of the PIKK family. There are emerging data which are demonstrating the anti-tumour activity of ATR inhibitors in patients with ATM mutation and/or protein loss.

11.2.1.1 Advanced Solid Tumours

In a phase I study of olaparib and the ATR inhibitor ceralasertib in relapsed, refractory cancer participants with HRR mutations (NCT02576444), 24 previously pre-treated participants were enrolled. One of 5 participants with ATM mutations had a complete response, 2 participants had clinical benefit ongoing at more than 12 months. The combination of olaparib and ceralasertib demonstrated preliminary activity in participants with tumours harbouring ATM mutations. Activity in ATM mutant tumours (not tested for ATM IHC) with an ATR inhibitor is consistent with the expected synthetic lethality of these interwoven DNA repair pathways (Eder et al, 2019).

Preclinically, ceralasertib has demonstrated anti-tumour activity in gastric cancer cells. In SNU-601 cells with dysfunctional ATM, ceralasertib treatment led to an accumulation of DNA-damage due to dysfunctional RAD51 foci formation, S phase arrest, and caspase 3 whereas, SNU-484 cells with functional ATM were not sensitive to ceralasertib. In addition, in an in vivo tumour xenograft mouse model, ceralasertib significantly suppressed tumour growth and increased apoptosis. These findings suggest synthetic lethality between ATR inhibition and ATM deficiency in gastric cancer cells (Min et al, 2017).

Signs of preliminary efficacy (unpublished internal data) were observed in an ongoing study of ceralasertib combined with durvalumab in patients with NSCLC and ATM mutation or protein expression loss previously treated with immune checkpoint inhibitors (NCT03334617).

11.2.1.2 Prostate Cancer

The concept of synthetic lethality of DDR inhibitors in DDR-deficient backgrounds has been explored clinically in mCRPC: PARPi have been used in BRCA1/2 mutations and HRR mutations, including ATM mutations. The ongoing TRITON2 study of rucaparib in participants with DNA-Damage Repair-deficient mCRPC associated with HRR gene alterations demonstrated confirmed radiographic responses in 44.0% of participants with a deleterious BRCA1/2 alteration. In addition, male patients who had progressed on an androgen receptor directed therapy and chemotherapy demonstrated confirmed PSA responses in 51.1% of participants with a deleterious BRCA1/2 alteration. Based on this data, the US FDA granted breakthrough therapy designation for rucaparib as a monotherapy for patients with BRCA1/2-mutated mCRPC who have received ≥ 1 prior androgen receptor directed therapy and a taxane based chemotherapy (Wassim Abida et al, 2018).

Interim results from the TALAPRO-1 study of talazoparib monotherapy demonstrated anti-tumour activity in mCRPC patients with DDR alterations who had previously received taxane therapy and NHT with confirmed overall ORR of 25.6%.

Efficacy was most notable in patients whose tumours harboured BRCA1/2 alterations with a confirmed ORR of 50%. The composite response in patients with deleterious or suspected deleterious ATM mutations was reported to be 6.7% (1/15) and the PSA decline > 50% was reported in one patient out of 15 (De Bono et al, 2020).

The GALAHAD study of niraparib in patients with mCRPC and DRD demonstrated CTC0 and CTC conversion of 49% (45.5% in patients with measurable disease and 55.6% in patients with non-measurable disease) (Smith et al, 2020). The CTC conversion in patients with measurable disease was similar to ORR per RECIST 1.1, concluding that in patients with measurable and non-measurable disease, CTC is correlated with longer time on treatment and prolongation of survival. Hence CTC conversion should be considered as a validated endpoint regardless of measurable or non-measurable diseases.

Prostate cancer is recognised to have interpatient molecular heterogeneity and genomic aberrations that interfere with DNA repair which accounts for approximately 25 to 30% of all sporadic, castration-resistant prostate cancers (Grasso et al, 2012). For mCRPC, PCWG3 strongly recommends incorporating molecular profiling of tumours into clinical study strategies for a better understanding of the disease biology to identify predictors of sensitivity to a specific therapy. In line with the afore mentioned, we could anticipate that patients with ATM altered aST and mCRPC would benefit from treatment with ceralasertib in this study.

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

11.2.2 Background

11.2.2.1 Role of ATR

During normal DNA replication, ATR is recruited at stalled replication forks which can progress to double strand breaks if left unrepaired. ATR is also recruited to single strand DNA coated with RPA following single strand DNA-damage or the resection of double strand breaks. Recruitment and activation of ATR leads to cell cycle arrest in the S phase while the DNA is repaired, and the stalled replication fork resolved, or nuclear fragmentation and entry into programmed cell death/apoptosis (Cimprich and Cortez 2008).

Loss of ATR function leads to the inability to resolve stalled replication forks, the accumulation of DNA-damage and rapid cell death exemplified by nuclear fragmentation. ATR deletion is embryonic lethal in mice, however severe ATR hypomorphism is tolerated in humans leading to Seckel Syndrome. Normal cells from patients with Seckel Syndrome have reduced ATR function and show extensive DNA breaks when subjected to replication stress (Ajani et al, 2007, and Alderton et al, 2004).

11.2.2.2 Disease Linkage

Humans with loss of ATM function, typically through homozygous mutation of ATM, suffer from ataxia telangiectasia and have a 37-fold increased risk of cancer. Ataxia telangiectasia patients have approximately a 10% risk of developing lymphoma or leukaemia (NCI 2006). There is also a substantial risk of breast cancer, especially in women less than 50 years of age (relative risk=4.94), and an excess risk of colorectal cancer (relative risk=2.54) and stomach cancer (relative risk=3.39) (Thompson et al, 2005). Patients with ataxia telangiectasia show hypersensitivity to radiation.

Sporadic ATM deficiency is reported in many tumour types, and ATM deficiency is expected to sensitise tumour cells to ATR inhibition through their complementary roles in DNA-damage repair. Patients with ATM-deficient malignancies can be clinically identified and, in most cases, are known to have a poor prognosis with current therapies.

During tumourigenesis, ATM can be inactivated or lost providing a selection advantage for the tumour cell through the increased potential for genome alteration, and an increased dependence on ATR function. Similarly, oncogene activation such as c-Myc leads to increased replication stress, an accumulation of stalled replication forks and dependence on ATR function (Murai et al, 2012 and Murga et al, 2011).

A full description of non-clinical and clinical studies are presented in the IB.

11.2.3 Benefit/Risk Assessment

11.2.3.1 Risk Assessment

Data from non-clinical studies and emerging data from the clinical development programme has not identified any risks that would preclude investigation of ceralasertib in advanced cancer setting and shows that ceralasertib has a manageable safety profile in an advanced cancer population.

Effects on bone marrow, particularly anaemia and thrombocytopenia, are anticipated in the clinic and may occur in the second or third week of dosing. These events are deemed schedule limiting, rather than dose limiting toxicities as the main issue is a delayed recovery of the platelets. Myelosuppression has been successfully managed with dose interruptions, dose reductions (dose and schedule) and supportive measures such as blood transfusions in the ongoing studies. Routine monitoring of haematology and biochemistry blood counts is planned.

A number of other potential risks based on toxicology data for ceralasertib and clinical findings when it is used with various combinations are being monitored in ongoing clinical trials. For updates on the emerging safety data and a detailed description of all potential risks for ceralasertib please refer to the latest ceralasertib IB.

11.2.3.2 Benefit Assessment

Ceralasertib is considered to have a positive benefit-risk profile for patients with advanced cancer. Preclinical data suggest that, where tumour cells are dependent upon ATR for DNA repair through defects in HR or other DNA repair pathways eg ATM or BRCA mutations, ceralasertib selectively increases tumour sensitivity to therapy in advance cancer patients.

Early proof of concept data from multiple studies has shown evidence of efficacy from ATR inhibition patients whose tumours contain ATM mutations and ATM protein loss (see Section 0). Participants in this study will benefit from the monitoring of all AEs arising during the clinical study, related or not related to the study intervention. In addition, they will be contributing to the development of new therapies for advanced cancer.

11.2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimise risk to participants enrolling in this study, the potential risks identified in association with ceralasertib are justified by the anticipated benefits that may be afforded to participants with advanced/metastatic solid malignancies.

Further details can be found in the most recent version of the ceralasertib IB.

11.3 OBJECTIVES AND ENDPOINTS - MODULE 1

11.3.1 Cohort A: aST

Table 5 Objectives and Endpoints – Cohort A

Objectives	Endpoint/Variable
Primary	
• To obtain a preliminary assessment of the efficacy of ceralasertib in participants with ATM altered aST refractory to standard treatments options, as assessed by ORR.	Investigator assessed ORR, as defined by RECIST version 1.1.
Secondary	
• To further assess the efficacy of ceralasertib.	Investigator assessment, as defined by RECIST version 1.1: • DoR • Percentage change in tumour size • PFS
• To assess the safety and tolerability profile of ceralasertib.	• AEs/SAEs • Vital signs, haematology, and clinical chemistry parameters.
Exploratory	
• CCI [redacted] CCI [redacted]	• CCI [redacted] • CCI [redacted] • CCI [redacted] CCI [redacted] • CCI [redacted] CCI [redacted]

11.3.2 Cohort B: mCRPC

Table 6 Objectives and Endpoints – Cohort B

Objectives	Endpoint/Variable
Primary	
• To obtain a preliminary assessment of the efficacy of ceralasertib in participants with ATM altered metastatic castration-resistant prostate cancer as assessed by composite response rate.	• Composite response rate (investigator assessed radiological response as defined by RECIST 1.1 for soft tissue and visceral lesions and by PCWG3 for bone lesions, PSA decline, and/or CTC conversion).
Secondary	
• To further assess the efficacy of ceralasertib.	• ORR by RECIST 1.1 for soft tissue and visceral lesions and by PCWG3 criteria for bone lesions. • Proportion of participants with confirmed CTC count conversion from unfavourable to favourable. • Proportion of participants with confirmed PSA decline > 50%. • Best percentage change in tumour size. • Duration of radiological response. • Radiological PFS using RECIST 1.1 for soft tissues and visceral lesions and PCWG3 for bone lesions.
• To assess the safety and tolerability profile of ceralasertib.	• AEs/SAEs. • Vital signs, haematology, and clinical chemistry parameters.

11.4 MODULE DESIGN - MODULE 1

11.4.1 Overall Design

This is a phase 2a, open-label, multicentre study of ceralasertib monotherapy, administered orally, in participants in Cohort A and Cohort B.

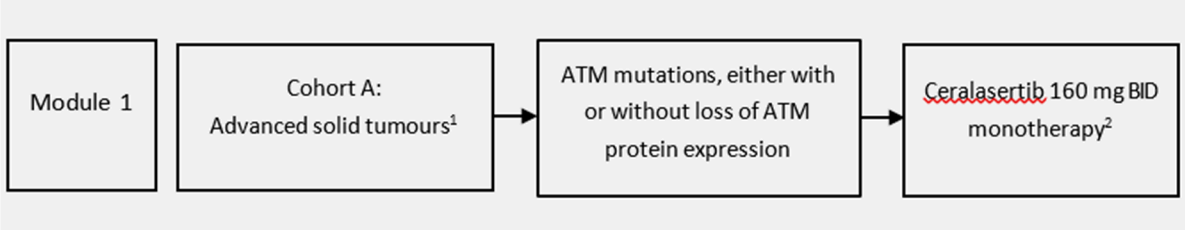
11.4.1.1 Cohort A

Cohort A is recruiting participants with ATM altered aST, except participants with NSCLC and prostate cancer (Figure 3). Restrictions may be introduced on tumour types with low ATM mutation prevalence and to ensure a balanced number of tumour types. A total of ~25 molecularly eligible and centrally confirmed participants dosed at ceralasertib 160 mg BID will be enrolled into Cohort A.

Cohort A may be further expanded, CCI [redacted]. This would occur in the event an efficacy signal is observed, and subject to a protocol amendment.

For timing of assessments refer to the SoA in Section 11.1.3.

Figure 3 Study Design – Cohort A



[1]All aST, excluding participants with NSCLC and prostate cancer.
[2]Ceralasertib administered twice a day between Days 1 to 14 in 28 day cycles.
Abbreviations: ATM=ataxia telangiectasia mutated; BID=twice daily; IHC=immunohistochemistry; NSCLC=non-small-cell lung carcinoma.

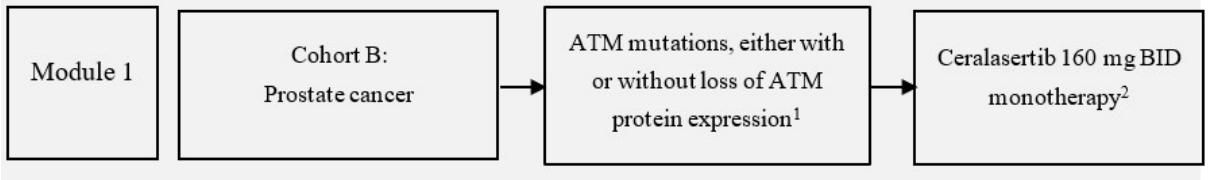
11.4.1.2 Cohort B

Cohort B is recruiting participants with ATM altered metastatic mCRPC (Figure 4). A total of ~27 molecularly eligible and centrally confirmed participants dosed at ceralasertib 160mg BID will be enrolled into Cohort B. Unfavourable CTC count requirement may be introduced for all participants to ensure adequate (approximately ≥ 50%) number of participants with CTC count ≥ 5/7.5 mL blood.

Cohort B may be further expanded, CCI [redacted]. This would occur in the event an efficacy signal is observed, and subject to a protocol amendment.

For timing of assessments refer to the SoA in Section 11.1.3.

Figure 4 Study Design – Cohort B



[1] Unfavourable CTC count requirement may be introduced for all participants to ensure adequate (approximately ≥ 50%) number of participants with CTC count ≥ 5/7.5 mL blood. ATM 'deficient' is defined as ATM IHC ≤ 5% ATM-positive tumour nuclei using the Ventana assay (VENTANA ATM (Y170) RPA Assay).
[2] Ceralasertib administered twice a day between Days 1 to 14 in 28 day cycles.
Abbreviations: ATM=ataxia telangiectasia mutated; BID=twice daily; IHC=immunohistochemistry.

11.4.1.3 Confirmation of ATM Protein Expression and ATM Mutation Status

Participants with deleterious or suspected deleterious ATM tumour mutations (mono or biallelic) will be identified by approved local pre-existing test results of mutations in tumour or blood (germline or ctDNA). Definitions of qualifying ATM alterations include deleterious/suspected deleterious, pathogenic/likely pathogenic, disease- or cancer-associated mutations/variants or equivalent wording. Variants of unknown significance or benign/likely benign variants are not eligible. To assist the sites, rules for determining qualifying ATM mutations are attached in Appendix K. Central prospective NGS testing to determine ATM mutation status for participant eligibility into the study may be introduced. Sites will be required to submit a blood sample and tumour tissue to confirm centrally ATM mutations from local pre-existing tests in blood/tumour and to assess tumour ATM IHC status. To ensure sufficient participants are recruited with ATM IHC deficiency, prospective testing for ATM status by IHC may be introduced.

For a pre-existing NGS ATM mutation test to be acceptable for assessment of eligibility, it should meet the following criteria:

1 Test is validated and conducted in a CLIA-certified (for the US sites) or with local accreditation laboratory (for sites outside of the US).
2 Meets the acceptance criteria specified by the study sponsor (details of proposed pre-existing NGS test should be provided in the NGS testing laboratory questionnaire for sponsor approval).
3 Information from local test result is provided, including location where it was performed, methodology, specimen type and minimal data on the analytical performance.
4 Site agrees to provide the minimum required tumour tissue samples for central confirmation of ATM status by central NGS and IHC testing as defined in the Central Laboratory Manual.

Provision of an FFPE tumour tissue sample or slides is mandatory. The definition of ATM-deficient is staining of ATM protein of 0-5% of tumour nuclei by IHC using the VENTANA ATM (Y170) RPA Assay.

For participants with a local ATM mutation test when ATM IHC testing is retrospective, participants may proceed to Screening Part 2 following submission of the mutation test result. If the central test result is subsequently different to the local test result, the participant may continue treatment if it is considered in their best interests.

Two-step consent procedure will be implemented for all participants. Part 1 consent (Screening Part 1) may be taken whilst the participant is receiving a prior line of treatment. However, if an ATM alteration is identified, this does not guarantee a reserved participant place in Part 2 (Screening Part 2). Test results (from Screening Part 1) will be disclosed after

participants have been confirmed ineligible at Screening Part 2 or have concluded their participation in the study. If a participant does not have an archival sample and if a new tissue sample is available (for example if it is routine at a site to undertake biopsy of metastatic lesions) then the new biopsy specimen can be used if taken as part of standard of care management.

T A switch to using prospective participant selection using ATM protein status and two-step consent procedure for all sites, may be introduced. The decision to trigger prospective participant selection may be based on preliminary data from subgroup analysis. Prospective ATM IHC status will be confirmed at an accredited central laboratory. Once prospective testing is introduced, the participant should only undergo Screening Part 2 procedures once the ATM IHC status is confirmed.

11.4.2 Scientific Rationale for Study Design

The study design allows the evaluation of the anti-tumour activity, safety, tolerability, and pharmacokinetics of ceralasertib, in participants with advanced malignancies.

As part of the clinical drug development programme for ceralasertib, investigations into variations in CCI [redacted] CCI [redacted]
There are many potential benefits of this exploratory research, including the possibility to identify patients most likely to benefit from treatment and inform diagnostic development, explain outliers or non-responders or explain adverse reactions related to drug exposure. This research may result in an understanding of the impact of variation between individuals and how this information can be utilised to bring better drugs to the clinic.

The collection of samples is included to allow characterisation of the PK of ceralasertib for the safety.

11.4.3 Justification for Dose

The starting dose of ceralasertib is 160 mg BID Day 1 to Day 14, in a 28-day cycle.

Initially, a CCI [redacted] starting dose of ceralasertib was selected for this study, at CCI [redacted] mg BID, Day 1 to Day 14, of every 28-day cycle. This dose had been used as CCI [redacted] and in CCI [redacted] mg Day 1, of every 28-day cycle. Preliminary safety data from the CCI [redacted] indicated that CCI [redacted] mg BID Day CCI [redacted] to Day CCI [redacted] of every 28-day cycle was well tolerated. The studies which had used CCI [redacted] at CCI [redacted] mg BID included:

- CCI [redacted] CCI [redacted]

- CCI
  CCI
  CCI CCI
  CCI
  CCI

At Protocol Amendment 2, the sponsor elected to reduce the starting dose from 240 mg BID to 160 mg BID based on emerging safety data of Grade ≥ 3 haematological toxicity in 5 molecularly selected patients (out of the first 7 patients) in the current study.

Ceralasertib has been investigated as monotherapy at the dose of 160 mg BID Day 1 to Day 14 in a 28-day cycle in several ESR studies across diverse tumour indications, and has been well tolerated with emerging evidence of clinical activity. According to the published data ceralasertib was investigated as monotherapy in the PATRIOT study (NTC02223923) in patients with advanced solid tumours (Dillon et al, 2019). Among 20 patients enrolled in the dose expansion of the PATRIOT study using ceralasertib 160 mg BID Day 1 to Day 14, 20% Grade ≥ 3 treatment related AEs were observed and only 1 patient discontinued the treatment due to toxicity. Although the study population was heterogeneous with respect to tumour indication and there was no molecular selection, preliminary evidence of efficacy was observed with 5/20 (25%) patients with stable disease ≥ 16 weeks, 4/44 partial responses across the entire study. Other ongoing ESR studies in molecularly selected populations using ceralasertib at 160 mg BID Day 1 to Day 14 in a 28-day cycle include the Aggarwal study (NCT03682289) and ATARI (NCT04065269), treating an additional 39 patients.

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11.4.4 End of Study Definition

Please refer to core protocol (Section 4.4).

11.5 MODULE POPULATION - MODULE 1

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

11.5.1 Inclusion Criteria (Cohort A [aST] and Cohort B [mCRPC])

The screening will have 2 parts, Part 1 and Part 2, which apply for both Cohort A and Cohort B. Participant consent for Part 1 will allow the submission of a pre-specified local test report or tumour sample to confirm molecular eligibility. All participants must submit blood and FFPE tumour samples for central confirmation of ATM mutation and ATM IHC testing. Participants will then be asked to also consent for Part 2 allowing further assessments to confirm study eligibility.

11.5.1.1 Screening Part 1 (Molecular eligibility)

Screening Part 1 is for all participants in Module 1. For participants who have already undergone local ATM NGS testing, submission of the local test report is mandatory. If prospective IHC ATM testing is triggered, local ATM NGS test report must be provided prior to Screening Part 2. . All participants must submit a FFPE tumour sample for central confirmation (NGS and IHC).

Mandatory ATM IHC protein loss according to central testing may be introduced.

Screening Part 1 may be conducted whilst the participant is receiving a prior line of treatment. If an ATM alteration is identified, this does not guarantee a reserved participant place in Screening Part 2.

1 Participants must have a histologically confirmed diagnosis of aST (excluding NSCLC) or mCRPC tumour.
2 Participants must have a deleterious or suspected deleterious ATM mutation in tumour or blood (germline or ctDNA). Definitions of qualifying ATM mutations may include deleterious/suspected deleterious, pathogenic/likely pathogenic, disease- or cancer-associated variants, or equivalent wording. Variants of unknown significance, benign or likely benign alterations are not qualifying. To assist the sites rules for qualifying ATM mutations are attached in the Appendix K. Testing must be performed in a locally accredited laboratory using a validated test in line with local regulations (eg, CAP/CLIA laboratory where available). Submission of a copy of local test result is mandatory for eligibility.
3 All participants must submit a FFPE sample for central confirmation of ATM IHC and NGS status. If retrospective testing is used, Screening Part 1 and Part 2 can be done simultaneously with local NGS result. If prospective testing is enabled, then all participants must submit a FFPE tumour sample for central confirmation of ATM IHC and NGS status at Screening Part 1 and wait for the result before proceeding to Screening Part 2. For the specific tumour sample requirements please refer to the respective Screening Part 2 inclusion criteria.

11.5.1.2 Screening Part 2 (Study eligibility)

Participants must meet the eligibility criteria described in the core module for all participants (Section 5.1) and those listed below.

Type of Participant and Disease Characteristics

1 Participants who have no standard treatment options available or in whom the standard treatment options are contraindicated.

2 Eastern Cooperative Oncology Group performance status of 0 to 2.

3 Life expectancy ≥ 16 weeks.

4 Normal organ and bone marrow function measured within 28 days prior to the first dose of study intervention as defined below:

(a) Haemoglobin ≥ 9.0 g/dL with no blood transfusions (packed red blood cells) in the past 28 days. Participants already receiving erythropoietin at the time of screening for the study may continue it providing they have been receiving it for more than one month at the time study intervention is started.

(b) Absolute neutrophil count ≥ 1.5×10^9/L.

(c) Platelet count ≥ 100×10^9/L with no platelet transfusions in the past 28 days.

(d) Total bilirubin ≤ 1.5 × institutional ULN unless the participant has documented Gilbert's Syndrome in which case it must be ≤ 3 × institutional ULN.

(e) Aspartate aminotransferase/alanine aminotransferase ≤ 2.5 × institutional ULN unless liver metastases are present in which case they must be ≤ 5 × ULN.

(f) Participants must have creatinine clearance of ≥ 45 mL/min estimated or measured using standard methodology at the investigating site (ie, Cockcroft-Gault, Modification of Diet in Renal Disease, chronic kidney disease Epidemiology Collaboration, ethylenediaminetetraacetic acid or 24 hour urine):

$$\text{Estimated CrCl} = \frac{(140 - \text{age [years]}) \times \text{weight (kg)} (\times 0.85)}{\text{serum creatinine (mg/dL)} \times 72}$$

Other

5 Participant must be able to swallow tablets whole.

In addition, participants are eligible to be included in Cohort A and Cohort B only if all of the following criteria apply, respectively.

11.5.1.3 Cohort A – aST

1 Participants must fulfil all the core and Module 1 eligibility criteria.

2 Availability of archival or fresh tumour FFPE specimens for central testing of ATM protein loss using IHC and for confirmation of ATM mutation using NGS. Submission of the sample is mandatory for enrolment. If archival samples are submitted, they must have

been obtained within 3 years. If an archival specimen is not available fresh standard of care tumour sample may be provided. The site needs to refer to the pathology manual for acceptable sample types for testing. Fine needle aspirates are not acceptable.

3 Participants with histologically confirmed aST (excluding participants with NSCLC and prostate cancer).

4 Measurable disease by RECIST 1.1 criteria.

5 Radiological evidence of disease progression on previous treatment prior to study entry.

11.5.1.4 Cohort B – mCRPC

1 Participants must fulfil all the core and Module 1 eligibility criteria.

2 Availability of archival or fresh tumour FFPE specimens for central testing of ATM protein loss using IHC and for confirmation of ATM mutation using NGS. Submission of the sample is mandatory for enrolment. If archival samples are submitted, they must have been obtained within 5 years. If an archival specimen is not available fresh standard of care tumour sample may be provided. The site needs to refer to the pathology manual for acceptable sample types for testing. Fine needle aspirates are not acceptable.

3 Previously received and progressed on at least one NHA (eg, abiraterone acetate, apalutamide, and/or enzalutamide) and at least one taxane regimen for the treatment of prostate cancer (unless the participant has contraindications to taxanes).

4 Participants with histologically confirmed metastatic castrate resistant prostate cancer. Participants whose disease spread is limited to regional pelvic lymph nodes or local recurrence (eg, bladder, rectum) are not eligible.

5 Documented prostate cancer progression at study entry while on androgen deprivation or after bilateral orchiectomy as assessed by the investigator with one or both of the following:

- Radiographic progression based on PCWG3 criteria.
- PSA progression defined by a minimum of 3 rising PSA levels with an interval of ≥ 1 week between each determination. The PSA value at the Screening Part 2 visit should be ≥ 2 ng/mL; participants receiving systemic glucocorticoids for control of symptoms must have documented progression while on systemic glucocorticoids prior to commencing Cycle 1 Day 1 of study intervention.

6 One or both of the following:

- Measurable disease according to RECIST 1.1 (except bone lesions).
- Unfavourable CTC count (≥ 5/7.5 mL blood) according to local or central test. Submission of a copy of the test result is mandatory for eligibility. [Unfavourable CTC count requirement for all participants by local or central testing may be introduced to ensure adequate (approximately ≥ 50%) number of participants with

CTC count ≥ 5/7.5 mL blood.]. If participant has no measurable disease, then prospective testing may be done in order for participant to enrol.

7 Serum testosterone levels ≤ 50 ng/dL (≤ 1.75 nmol/L) within (≤) 28 days before enrolment (not required for participants after bilateral orchiectomy).

8 Participants without prior surgical castration must be currently taking for at least 4 weeks and willing to continue LHRH analog (agonist or antagonist) therapy throughout the duration of study intervention period.

11.5.2 Exclusion Criteria (Cohort A [aST] and Cohort B [mCRPC])

Participants must meet the eligibility criteria described in the core module for all participants (Section 5.2) and those listed below.

Medical Conditions

1 Any of the following cardiac diseases currently or within the last 6 months:

- Unstable angina pectoris.
- Congestive heart failure > Class 2 as defined by the New York Heart Association (see Appendix C).
- Acute myocardial infarction.
- Significant ventricular or supraventricular arrhythmias (participants with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible).
- Mean resting corrected QT interval (QTc) > 470 msec obtained from 3 electrocardiograms (ECGs) in 24 hours using the Fredericia formula.
- Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, immediate family history of long QT syndrome or unexplained sudden death under 40 years of age.
- For Cohort B (mCRPC), surgery or local prostatic intervention (excluding a prostatic biopsy) within 28 days of Cycle 1 Day 1.

2 Participants with known active infections (ie, hepatitis B or C, tuberculosis, or COVID-19).

3 Participants considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection.

- Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on high resolution CT scan or any psychiatric disorder that prohibits obtaining informed consent, and any other medical condition that, in the opinion of the investigator, places the participant at unacceptable risk of toxicity.

4 Participants with symptomatic and/or uncontrolled brain metastases.

- A contrast enhanced CT brain scan (MRI where CT is contraindicated), to confirm the absence of brain metastases is part of baseline disease assessment for participants with aST. If new asymptomatic brain metastases are discovered, an interval scan (minimum 4 weeks) should be conducted to confirm the new brain lesions are not progressing and do not require local CNS-directed therapy. If local treatment is necessary, this should occur before study entry.
- Participants with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically SD for 28 days.
- Participants who have experienced a seizure or seizures within 6 months of study intervention or who are currently being treated with cytochrome P450 enzyme inducing anti-epileptic drugs for seizures (use of anti-epileptic drugs to control pain is allowed in participants not suffering from seizures unless drug is excluded due to CYP3A4 induction - phenytoin, carbamazepine, phenobarbital).
- Participants with a history of treated CNS metastases are eligible, provided they meet all of the following criteria: Disease outside the CNS is present. No clinical evidence of progression since completion of CNS-directed therapy. Minimum of 3 weeks between completion of radiotherapy and Cycle 1 Day 1 and recovery (Grade ≤ 1) from significant acute toxicity with no ongoing requirement for > 10 mg of prednisone per day or an equivalent dose of other corticosteroid. If on corticosteroids, the participant should be receiving a stable dose of corticosteroids, started at least 4 weeks prior to study intervention.

4a Participants with INR ≥ 1.5 (except those who receive vitamin K antagonists and direct factor Xa inhibitors) or with other evidence of impaired hepatic synthesis function.

Prior/Concomitant Therapy (see Appendix D)

5 Previous therapy with an ATR inhibitor.

6 Any systemic anti-cancer therapy within 14 days or 5 half-lives (whichever is longer) of Cycle 1 Day 1. For biological therapeutics, including monoclonal antibodies and vaccines (eg, Sipuleucel-T), the minimum washout period shall be 28 days. The participant can receive a stable dose of bisphosphonates or denosumab for bone metastases, before and during the study as long as these were started at least 5 days prior to study intervention.

- Agents such as 5α-reductase inhibitors (finasteride, dutasteride), oestrogen compounds (including estramustine) and megesterol are considered as anti-cancer agent in prostate cancer and prohibited within 14 days or 5 half-lives (whichever is longer) prior to study intervention. Ongoing treatment with LHRH analogs for prostate cancer are required in absence of prior bilateral orchiectomy.

7 Exposure to a small molecule IP within 14 days or 5 half-lives (whichever is longer) prior to Cycle 1 Day 1.

8 Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study intervention, with the exception of participants receiving radiation to more than 30% of the bone marrow or with a wide field of radiation who should not start study intervention within 21 days after radiation.

9 Concomitant use of known strong CYP 3A inhibitors (eg itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) (Table 14). The required washout period prior to starting study intervention is 2 weeks.

10 Concomitant use of known strong CYP 3A inducers (eg phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) (Table 14). The required washout period prior to starting study intervention is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents.

11.5.3 Lifestyle Considerations

11.5.3.1 Meals and Dietary Restrictions

Participants must fast (water to drink only) from at least 2 hours prior to taking a dose to at least 1 hour post-dose for all doses.

Participants should avoid concomitant drugs, herbal supplements and/or ingestion of foods known to modulate CYP3A4 activity (See Section 11.6.5 and Appendix D).

11.5.3.2 Skin

Study intervention may increase the skin's sensitivity to sunlight, which may result in sunburn. Participants should therefore take appropriate precautions when out in the sun (eg limit exposure, wear appropriate clothing [hat and sunglasses] and use sunscreen).

11.5.3.3 Contraception

Please refer to the core protocol (Section 5.3.1).

11.5.4 Screen Failures

Screen failures are defined as participants who consent to participate in Screening Part 1 (molecular eligibility) and who are not subsequently entered in Screening Part 2 (study eligibility) or participants who consent to participate in Screening Part 2 (study eligibility) but are not subsequently entered in the study.

Participants will only receive their central molecular test results (from Screening Part 1) after they have been confirmed ineligible at Screening Part 2 or have concluded their participation in the study.

Please refer to the core protocol for further details (Section 5.4).

11.6 STUDY INTERVENTION - MODULE 1

Study intervention is defined as any investigational intervention(s) or marketed product(s) intended to be administered to a study participant according to the study protocol.

11.6.1 Study Intervention Administered

Eligible participants will receive study intervention as described in Table 7. For both Cohorts A and B, study intervention will be administered by oral tablet twice a day between Day 1 and Day 14 in 28 day cycles. Study intervention will be dispensed and returned as shown in the SoA (Section 11.1.3).

Table 7 Investigational Products

ARM Name	AZD6738
Intervention Name	Ceralasertib
Type	Drug
Dose Formulation	Tablet
Unit Dose Strength(s)	AZD6738 tablets 20 mg or 80 mg
Dosage Level(s)	160 mg twice daily*
Route of Administration	Oral
Use	Experimental
Sourcing	AstraZeneca R&D
Packaging and Labelling	Study intervention will be provided in high density polyethylene (HDPE) bottles. Each bottle will be labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirements.

*AstraZeneca elected to reduce the starting dose of ceralasertib from 240 mg BID to 160 mg BID with protocol amendment 2. Participants who are receiving treatment and have completed Cycle 1 and Cycle 2 without severe haematological toxicity or SAEs and are deemed to be benefitting from treatment, may continue on the current dose of 240 mg BD 2 weeks on / 2 weeks off at the investigator's discretion.
Abbreviations: BID=twice daily; SAE=serious adverse events.

11.6.2 Preparation/Handling/Storage/Accountability of Interventions

1 Study intervention will be supplied by AstraZeneca R&D supply chain as individual bottles of tablets. Additional information about study intervention may be found in the Investigator Brochure.

2 Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines by AstraZeneca R&D supply chain. The labels will fulfil Good

Manufacturing Practice Annex 13 requirements for labelling. Label text will be translated into local language.

3 The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

4 Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention (after instruction of medical team participants should not take their study intervention until authorised by study team). 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.

5 The investigator, institution, or the head of the medical institution (where applicable) is 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.

11.6.3 Measures to Minimise Bias: Randomisation and Blinding

This is a modular, open-label study. Module 1 is a non-randomised, monotherapy, 2 cohort design.

11.6.4 Study Intervention Compliance

When participants self-administer study intervention at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and counting of returned tablets during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of study intervention tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

Overdose is described in Section 8.4.

11.6.5 Concomitant Therapy

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

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 along with:

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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

If medically feasible participants taking regular medication, with the exception of potent inhibitors or inducers of CYP3A, should be maintained on it throughout the study period.

Pre-medication

- **Anti-emetic treatment:** No primary prophylactic treatment with anti-emetics is advised. However, anti-emetic treatment may be administered as secondary prophylaxis or treatment according to the guidelines of the participating sites. Please note: aprepitant (Emend®) is a substrate, moderate inhibitor and inducer of CYP3A4 and also an inducer of CYP2C9.

  Therefore, the use of aprepitant is NOT allowed in this study for the treatment of nausea and vomiting induced by the study intervention. In general, drugs that interfere with CYP3A4 are not allowed in this study, and aprepitant is NOT an exception. For further information about CYP3A4, CYP2C9 or prohibited/allowed medication in this study, see Appendix D.

Supportive care

Participants will be permitted to receive appropriate supportive care measures as deemed necessary by the treating physician including but not limited to the items outlined below:

- **Diarrhoea:** Diarrhoea should be treated promptly with appropriate supportive care, including administration of an anti-diarrheal agent according to standard practice guidelines. Anti-diarrheal agents should not be taken prophylactically. Participants should be instructed to begin taking anti-diarrheal medication at the first sign of: 1) poorly formed or loose stool, 2) occurrence of more bowel movements than usual in one day or 3) unusually high volume of stool. Anti-diarrheal agents should be deferred if blood or mucus is present in the stool or if diarrhoea is accompanied by fever. In this setting, appropriate diagnostic microbiologic specimens should be obtained to exclude an infectious aetiology. Participants should also be advised to drink liberal quantities of clear fluids to help prevent dehydration.
- **Nausea/vomiting:** Nausea and vomiting should be treated adequately, and strong consideration should be given to the administration of secondary prophylactic anti-emetic

therapy according to standard institutional practice. Participants should be strongly encouraged to maintain liberal oral fluid intake. **Supportive care with aprepitant (a CYP3A4 inhibitor / inducer / substrate) according to institutional guidelines in the context of standard of care chemotherapy is NOT allowed. See Appendix D.**

- **Anaemia:** Transfusions and/or erythropoietin may be utilised as clinically indicated for the treatment of anaemia but should be clearly noted as concurrent medications. No blood transfusions in the 28 days prior to first dose is allowed.
- **Neutropaenia:** Colony-stimulating factors including G-CSF, pegylated G-CSF or GM-CSF according to Institutional Standards, following discussion with the Principal Investigator and AstraZeneca.

Blood transfusions are allowed at any time during the study.

- Avoid concomitant medications, herbal supplements and/or ingestion of foods that significantly modulate CYP3A4 or Pgp activity (see Appendix D). Note these include common azole antifungals, macrolide antibiotics, etc. For participants receiving study intervention in the absence of discontinuation criteria, if the investigator feels that concomitant administration of medications, herbal supplements or foods that significantly modulate CYP3A4 activity is necessary based upon medical judgement, such products may be administered with caution following discussion between the investigator and the sponsor Study Physician.

Concomitant medication may be given as medically indicated with the following exceptions.

11.6.5.1 Therapy that may NOT be administered

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy [LHRH analogues in prostate cancer and hormone replacement therapy are acceptable], biological therapy or other novel agent) for the disease under study is to be permitted while the participant is receiving study intervention.

Live attenuated virus and bacterial vaccines should not be administered, eg yellow fever, measles, influenza, rubella, mumps, typhoid, mycobacterium tuberculosis (BCG), Yersinia pestis (EV). An increased risk of infection by the administration of these vaccines has been observed with conventional chemotherapy and the effects with ceralasertib are unknown. The administration of killed vaccines is allowed. Examples of killed vaccines are cholera, bubonic plague, polio vaccine, hepatitis A and rabies.

11.6.5.2 Drug-Drug Interaction Between Ceralasertib and Other Drugs

Ceralasertib is an investigational drug for which no data on in vivo interactions are currently available. Potential interaction and guidelines below are considered on the basis of preclinical in vitro data only.

The lists of CYP and transporter inhibitors/inducers, and CYP and transporter substrates are available in Appendix D. They are not exhaustive and the absence of a drug from these lists does not imply that its combination with ceralasertib is safe. If ceralasertib is being administered in combination, potential interactions of the combination partner should also be considered.

- **Restrictions regarding drugs affecting CYP metabolism**

  The principal enzyme for metabolising ceralasertib is CYP3A4. Participants should avoid concomitant drugs, herbal supplements, and/or ingestion of foods known to modulate CYP3A4 activity from the time they enter the screening period until 28 days after the last dose of study intervention.

  – Prior to study intervention, use of potent inducers or inhibitors of CYP3A are not permitted. For participants taking any of these drugs (examples provided in Appendix D) the required washout periods before starting ceralasertib is five half-lives; except for St. John's wort, which is 3 weeks.

  – On study intervention, if there is no suitable alternative concomitant medication other than a potent inhibitor of CYP3A, the investigator must interrupt ceralasertib for the duration of the potent CYP3A inhibitor and wait for the required washout period (five half-lives) before dosing ceralasertib again. If potent CYP3A inducers are considered necessary for the participant's safety and welfare, this may diminish the clinical efficacy of ceralasertib and the participant should be monitored carefully for any change in the efficacy of study intervention. Refer to Appendix D for additional guidance.

  – The use of any herbal supplements or 'folk remedies' (and medications and foods that significantly modulate CYP3A activity) should be discouraged. If deemed necessary, such products may be administered with caution and the reason for use documented in the eCRF.

  In vitro data also suggest that ceralasertib may be metabolised by CYP2C8 but a lesser extent, therefore caution should be applied with co-administration of potent inhibitors or inducers of CYP2C8 (examples provided in Appendix D).

- **Drugs known to be inhibitors or inducers of Pgp and/or BCRP, undertake appropriate monitoring if co-administration is necessary**

  - Ceralasertib is also a P-gp substrate. Co-administration of P-gp inhibitors or inducers may affect exposure to ceralasertib and therefore should not be co-administered with ceralasertib. If the use of any inhibitors or inducers of P-gp are considered necessary for the participant's safety and welfare, the investigator must contact the study office and a decision to allow the participant to continue in the study will be made on a case-by-case basis.

- Ceralasertib is a substrate of BCRP. Co-administration of BCRP inhibitors or inducers may affect exposure to ceralasertib; therefore, it is recommended that the investigators must interrupt ceralasertib for the duration of the BCRP inhibitor or inducer and wait for the required washout period of the BCRP modulator (five half-lives) before dosing ceralasertib again.

- **Drugs known to be substrates of CYP3A4 and/or CYP2B6, undertake appropriate monitoring if co-administration is necessary**

  Ceralasertib is a potential inducer of CYP3A4 and CYP2B6. Caution should be applied with co-administration of drugs that are either completely metabolised by CYP3A4 and/or CYP2B6, or that are CYP3A4 and/or CYP2B6 substrates and also have a narrow therapeutic index. Investigators should be aware that the exposure of other drugs metabolised by CYP3A4 and/or CYP2B6 may be reduced.

- **Drugs known to be substrates of OATP1B1 and BCRP, undertake appropriate monitoring if co-administration is necessary**

  Ceralasertib is an inhibitor of OATP1B1 and BCRP. Co-administration of substrates of OATP1B1 and/or BCRP may affect exposure to ceralasertib; therefore, it is recommended that caution should be applied when such drugs are to be administered with ceralasertib.

- **Anticoagulation therapy**

  Participants on warfarin may participate in this study but it is recommended that their INR is monitored more frequently.

11.6.6 Dose Modification

11.6.6.1 General Guidance

Any clinically significant and/or unacceptable toxicity observed during the course of the study should be managed by interruption of the dose of study intervention in the first instance, dose reductions if necessary, and administration of supportive therapy.

If the toxicity resolves or reverts to ≤ CTCAEv5 Grade 1 or 2 (depending on the toxicity, see Table 8) treatment with study intervention may be restarted using the rules in Table 8 and Table 9 for dose modifications. Participants who have their dose previously reduced to the lowest possible dose and who have demonstrated an acceptable response to the dose interruption may be permitted to restart at the lowest dose level at the discretion of the investigator.

If the toxicity does not resolve to ≤ CTCAEv5 Grade 1 or 2 (depending on the toxicity) or the participant is not showing clinical benefit, then the participant should be discontinued from study intervention and observed until resolution of the toxicity.

Repeat dose interruptions are allowed as required for a maximum of 28 days on each occasion as recommended in Table 8. If the duration of dose interruption is longer than 28 days, the case should be discussed with the AstraZeneca study physician.

Study intervention dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a participant cannot restart study intervention within 28 days for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the AstraZeneca study physician.

Study intervention should be stopped at least 3 days prior to planned surgery and restarted 10 days post-surgery if the wound has healed. If the wound has not healed well, a further 14 days may be allowed and the participant can recommence ceralasertib if there is no evidence of disease progression based on the clinical judgement. No stoppage of study intervention is required for any biopsy procedure. Study intervention should be discontinued for a minimum of 3 days before a participant undergoes palliative radiation treatment. Study intervention should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

The dose of study intervention must not be adjusted under any other circumstances unless prior agreement is given by the sponsor.

All dose modifications and interruptions (including any missed doses) and the reasons for the modifications/interruptions are to be recorded in the eCRF.

11.6.6.2 Guidance for Dose Modification and Interruption

Refer to Table 8 and Table 9 for dose modification and stopping criteria. Once dose is reduced, escalation is not permitted.

Participants with ≥ G3 anaemia, neutropenia, thrombocytopenia during Cycle 1 and Cycle 2 will be required to attend for additional Day 8 and Day 14 assessments until there is no evidence of ≥ G3 anaemia, neutropenia, thrombocytopenia for at least 2 cycles. Participants who develop a ≥ G3 anaemia, neutropenia, thrombocytopenia later in their treatment, will also need to have additional Day 8 and Day 14 assessments until there is no evidence of ≥ G3 anaemia, neutropenia, thrombocytopenia for at least 2 cycles.

Table 8 Guidance for Dose Modifications, Interruptions and Discontinuations for Ceralasertib

Event	Action
Grade 1 neutropenia and/or thrombocytopenia	Ceralasertib dosing may continue if neutrophil count is ≥ 1500/mm^3 and/or platelet count is ≥ 75,000/mm^3.

Event	Action
Grade 1-2 toxicities (except neutropenia and thrombocytopenia)	Investigator decision whether to interrupt ceralasertib (max 28 days) or continue treatment. Treatment may be resumed at the same dose level or with a dose reduction by 1 level. For prolonged (>2 weeks) or persistent Grade 2 toxicity (>28 days) that does not respond to supportive treatment, ceralasertib should be interrupted and restarted at lower dose.
Grade 2 neutropenia or Grade 3 anaemia	Interrupt ceralasertib (max 28 days) and give appropriate supportive treatment e.g. transfusion, until AE improves to at least neutrophil count $\geq 1500/mm^3$ and haemoglobin ≥ 8.0 g/dL, then restart reducing the dose of ceralasertib by 1 level[1]. If a further dose reduction is required after the level 2 dose reduction, the participant must stop treatment.
Grade 2-3 thrombocytopenia	**First occurrence** Interrupt ceralasertib (max 28 days) and give appropriate supportive treatment until platelets improve to at least ≥ 100,000/mm3. At resolution, it is not mandatory to lower the dose as blood counts may recover during the “off period” on the intermittent schedule. If blood counts do not recover by the start of the next dosing period, ceralasertib should be restarted with a dose reduction by 1 level for ceralasertib. **Subsequent occurrences** Interrupt ceralasertib (max 28 days) and give appropriate supportive treatment. Treatment may be restarted with a reduced dose of ceralasertib when the toxicity is resolved or investigator discretion to stop treatment.
Grade 4 thrombocytopenia	Interrupt ceralasertib (max 28 days) and give appropriate supportive treatment; investigator discretion on whether to restart treatment with a dose reduction by 1 dose level ceralasertib when the platelet count has recovered to $\geq 100,000/mm^3$ or stop treatment. If a second Grade 4 thrombocytopenia occurs and does not recover to baseline or Grade 1 within 28 days treatment must be stopped.

Event	Action
Grade 3-4 toxicity (including Grade 3-4 neutropenia or Grade 4 anaemia) *Excludes Grade 3 anaemia or Grade 3-4 thrombocytopenia (see above)*	**First occurrence** Interrupt ceralasertib (max 28 days) and give appropriate supportive treatment; restart treatment with a dose reduction by 1 level for ceralasertib when the toxicity is resolved (Grade 1 or 2 depending on the toxicity or returns to baseline). **Subsequent occurrences** In case of haematological toxicity or Grade 3 non haematological toxicity, investigator discretion on whether to interrupt ceralasertib (max 28 days) or to stop treatment. Restart treatment with a dose reduction by 1 or 2 levels for ceralasertib. If a second Grade 4 haematological toxicity occurs and does not recover to baseline or Grade 1 within 28 days, treatment must be stopped. If a second Grade 4 non-haematological toxicity occurs treatment must be stopped. If a further dose reduction is required after the level 2 dose reduction, the participant must stop treatment.
Vomiting	If vomiting occurs shortly after study intervention is swallowed, the dose should only be replaced if all of the intact tablets can be counted. Resume with the following scheduled dose.
Missed dose	Allowed 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 participant should continue with next dose at allotted time.

[1] This table is for guidance. Therefore, for example, it may be deemed appropriate by the investigator to reduce the dose by more than one dose level depending on the individual participant circumstances.

Table 9 Dose Reduction Levels for Ceralasertib

Initial dose	160 mg BID days 1-14
Level 1 dose reduction	120 mg BID days 1-14
Level 2 dose reduction	80 mg BID days 1-14
Level 3 dose reduction	Stop treatment

*AstraZeneca elected to reduce the starting dose of ceralasertib from 240 mg BID to 160 mg BID with protocol amendment 2. For any participant continuing at 240 mg BID 2 weeks on / 2 weeks off at the investigator's discretion), the ceralasertib dose should be reduced to 160 mg BID days 1-14 ('initial dose') and thereafter follow the dose reduction levels as tabulated.

Abbreviations: BID=twice daily; SAE=serious adverse events.

11.6.6.3 Individual Stopping Criteria

Cardiovascular

Clinically significant hypotension defined as an asymptomatic decrease of more than 20 mmHg in systolic BP to below 70 mmHg persisting for at least 10 minutes.

Symptomatic orthostatic fall in systolic BP of more than 20 mmHg compared to resting seated systolic BP.

Hepatic

ALT or AST or ALP* > 5 x ULN

ALT or AST or ALP* > 3 x ULN with the appearance of symptoms associated with a clinical diagnosis of hepatitis including right upper quadrant pain or tenderness, fever, rash or eosinophilia (> 5%).

[ALT or AST > 3 x ULN] and [total bilirubin > 2 x ULN or INR^{+} > 1.5 or other evidence of impairment to the synthesis function of the liver].

* In the presence of bone metastases bone specific isoform of raised ALP in the presence of a raised gamma-GT (to ensure the ALP change is specific to the liver).

$^{+}$ Unless participant is receiving warfarin or other vitamin K antagonists, or direct factor Xa inhibitors.

Please refer to Appendix E "Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law."

11.6.7 Intervention after the Final DCO

Patients still receiving IP at the time of final analysis DCO may continue to receive study treatment within the study. Patients will continue to attend study visits as per SoA, section 11.1.3, Table 3, with a reduced number of assessments:

- Physical Examination including weight
- Vital signs
- Complete blood count and other clinical safety laboratory assessments
- Pregnancy test (WOCBP only)
- Dosing with Ceralasertib
- Adverse events (AE)

The Investigator will continue to monitor the patient's safety laboratory results prior to and periodically during treatment in order to manage AEs in accordance with the dose modification and stopping guidelines (see section 11.6.6).

All data from the safety assessments will be recorded in the patient's medical records with the following being reported to AstraZeneca, as applicable:

- SAEs and AESIs
- Pregnancy
- Overdoses

For these patients ongoing at the time of final analysis DCO, tumour assessment and bone scans will be performed as per standard of care frequency, but as with safety assessments, these data will not be reported to AstraZeneca.

11.7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL - MODULE 1

Please refer to the core protocol (Section 6.1).

Patients may receive study intervention until objective disease progression, or as long as they are continuing to show clinical benefit, as judged by the investigator, or treatment discontinuation criteria are met.

Any participant who permanently discontinues study intervention should be followed up till the safety follow-up visit (see follow-up Section 7.3) and until radiographic disease progression is registered and confirmed where necessary according to the protocol requirements.

The SoA (Section 11.1.3) details the data to be collected at the time of study intervention discontinuation, and for any further evaluations that need to be completed.

11.8 MODULE ASSESSMENTS AND PROCEDURES - MODULE 1

Study procedures and their timing are summarised in the SoA (Table 3).

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 300 mL (over a 1-month period). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

11.8.1 Efficacy Assessments

In Cohort A (aST) any tumour lesions will be assessed by RECIST 1.1 criteria.

In Cohort B (prostate cancer) soft tissue and visceral lesions will be assessed by RECIST 1.1 and bone lesions by PCWG3 criteria. Bone lesions will not be included in the RECIST 1.1 soft tissue assessment.

11.8.1.1 Tumour Assessments

RECIST 1.1 guidelines for measurable, non-measurable, TLs and NTLs and the objective tumour response criteria are presented in Appendix F of this Clinical Study Protocol.

Baseline tumour assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual participants. Baseline assessments should be performed no more than 28 days before the start of study intervention, and ideally should be performed as close as possible to the start of study intervention. The methods of assessment used at baseline should be used at each subsequent follow-up assessment. In Cohort A, at the baseline CT scan, assessment of the brain should be included. Follow-up assessments should be performed every 8 weeks (± 1 week) for 1 year and thereafter every 12 weeks (± 1 week) after the start of study intervention until objective disease progression by RECIST 1.1 (in Cohort B RECIST 1.1 for soft tissue and visceral lesions and by PCWG3 criteria for bone lesions) or withdrawal of consent.

If a participant discontinues study intervention (and/or receives a subsequent anti-cancer therapy) prior to objective radiographic disease progression registered according to the protocol requirements, then the participant should still continue to be followed until objective radiographic disease progression.

Any other sites at which new disease is suspected should also be appropriately imaged. If an unscheduled assessment is performed and the participant has not progressed, every attempt should be made to perform subsequent assessments at the scheduled visits whilst the participant remains on study intervention.

Categorisation of objective tumour response assessment will be based on the RECIST 1.1 guidelines for response: CR, PR, SD, and PD.

For participants who only have non-measurable disease at baseline, categorisation of objective tumour response assessment will be based on the RECIST 1.1 guidelines for response for NTLs: CR, PD and Non-CR/Non-PD.

If the investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a new lesion, it is advisable to continue study intervention and reassess the participant’s status at the next scheduled assessment or sooner if clinically indicated.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal disease progression status.

Frequency will be adjusted after 56 weeks of treatment if the tumour is not changing in size (SD, PR or CR) and will occur every 12 weeks (±1 week).

It is important to follow the assessment schedule as closely as possible. Please refer to the SoAs (Section 11.1.3) and Appendix F.

11.8.1.2 Cohort B

Bone lesions assessment in Cohort B (mCRPC) (Based on PCWG3 Criteria)

Objective tumour response criteria for bone lesions using PCWG3 criteria are presented in Appendix G of this Clinical Study Protocol.

Bone lesions will be assessed by bone scintigraphy commonly performed with Technetium-99 (bone scans). Bone lesions will be assessed by bone scan and will not be part of the RECIST 1.1 malignant soft tissue assessment. The definition for bone progression is based on PCWG3 criteria. Positive hot spots on the bone scan should be considered significant and unequivocal sites of malignant disease to be recorded as metastatic bone lesions.

Progression on a bone scan is defined as:

- At the 8-week scan:
  - If **2 or more** new metastatic bone lesions are observed on the first 8-week scan, the confirmatory scan performed (at least 6 weeks later), must show **2 or more additional new** metastatic bone lesions (for a total of **4 or more new** metastatic bone lesions since the baseline assessment).
  - Note - The first bone scan completed after baseline will be considered the '8-week scan' regardless if taken at Week 8 or at an unscheduled assessment.
- After the 8-week scan:
  - For participants **without progression** at the 8-week scan, this scan now serves as new baseline for all subsequent scans, i.e., all bone scans after Week 8 are compared to the Week 8 scan. If **2 or more** new metastatic bone lesions are observed on scans obtained after the first 8-week assessment (compared to Week 8 scan), a confirmatory scan performed **at least 6 weeks later** and preferably no later than the next scheduled scan must show the persistence of, or an increase in, the number of metastatic bone lesions compared to the prior scan.

The date of progression is the date of the first scan documenting the 2 new lesions. If the investigator is in doubt as to whether progression has occurred, it is advisable to continue study intervention and reassess the bone lesion status at the next scheduled assessment, or sooner if clinically indicated.

The requirements for determination and confirmation of radiographic progression by either bone scan (bone progression) or CT/MRI (soft tissue progression) are summarised in Table 10.

Table 10 Requirements for Documentation of Progression

Visit	Criteria for Bone Progression	Criteria for Soft Tissue Progression
Week 8 scan	2 or more new lesion compared to baseline bone scan. Requires confirmation scan at least 6 weeks later with 2 or more additional new lesions compared to Week 8 scan	Progressive disease on CT or MRI by RECIST 1.1. No confirmation scan required.
Subsequent scans	2 or more new lesion compared to Week 8 bone scan. Requires confirmation scan at least 6 weeks later for persistence or increase in number of lesions	Progressive disease on CT or MRI by RECIST 1.1. No confirmation scan required.

Abbreviations: CT=computed tomography; MRI=magnetic resonance imaging; RECIST=Response Evaluation Criteria in Solid tumours.

It is important to follow the assessment schedule as closely as possible. Please refer to the SoA (Section 11.1.3) and Appendix G.

Prostate Specific Antigen

Blood sample will be taken as detailed in the SoA (Section 11.1.3). For information on sample processing, handling and shipment refer to the Laboratory Manual.

For storage, re-use and destruction of biomarker samples see Section 8.5.

Circulating Tumour Cell Clinical Samples

A whole blood sample will be taken as detailed in the SoA (Section 11.1.3). Circulating Tumour Cell Clinical samples will be shipped under ambient conditions on the day of acquisition so as to be received at an AstraZeneca approved laboratory within 72 hours of blood sampling. Local or central CTC count assessments will be used for screening and

subsequent testing for CTC count will be performed centrally. For information on sample processing, handling and shipment refer to the Laboratory Manual.

For storage, re-use and destruction of biomarker samples see Section 8.5.

11.8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 11.1.3).

For all participants, results of all safety assessments must be available and must be reviewed by the Investigator or their deputy prior to start of each dosing cycle. Samples can be collected the day before dosing cycle start.

Prior to discharge from each in-patient and clinic visit, the Investigator or their deputy will be responsible for reviewing all available safety data, including vital signs and ECGs.

11.8.2.1 Physical Examinations

- A complete physical examination with weight will be performed at the visits as indicated in the SoA and clinically indicated (Section 11.1.3). Height will be recorded at screening only.
  - Please refer to the core protocol (Section 8.2.1).

11.8.2.2 Vital Signs

Seated blood pressure and pulse rate

Blood pressure and pulse rate will be measured in the sitting position after at least 10 minutes rest. Assessments will be performed at the visits as shown in the SoA (Section 11.1.3).

Body temperature

Body temperature will be measured in degrees Celsius at the visits indicated in the SoA (Section 11.1.3).

11.8.2.3 Electrocardiograms

Resting 12-lead ECG

Triplicate 12-lead ECGs will be performed as shown in the SoA (Section 11.1.3).

Please refer to the core protocol (Section 8.2.3).

11.8.2.4 Performance Status

Performance status will be assessed at the visits as indicated in the SoA (Section 11.1.3) according to US ECOG criteria.

Please refer to the core protocol (Section 8.2.4).

11.8.2.5 Brain Scan

At baseline, the imaging modalities used for assessment should be contrast enhanced CT (MRI where CT is contraindicated) scans of the brain (Cohort A only), chest, abdomen and pelvis (including liver and adrenal glands) and should encompass all areas of known predilection for metastases in the disease under evaluation, and should additionally investigate areas that may be involved based on signs and symptoms of individual participants. Follow-up CT or MRI assessments will cover chest, abdomen and pelvis with any other regions imaged at baseline where disease was present. Any other sites at which new disease is suspected should also be appropriately imaged. A CT scan of the brain should be performed in all participants in Cohort A at baseline if the participant is not known to have brain metastases. If the participant is known to have brain metastases then an MRI will be performed.

A contrast enhanced CT brain scan (MRI where CT is contraindicated) forms part of the baseline disease assessment in Cohort A only as indicated in the SoA (Section 11.1.3).

11.8.2.6 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the visits indicated in the SoA (Section 11.1.3).

Please refer to the core protocol (Section 8.2.5).

The clinical chemistry, haematology and urinalysis will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured.

Table 11 Laboratory safety variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
Blood (B)-Haemoglobin	Serum (S)/Plasma (P)-Albumin
B-Leukocyte count	S/P-Alanine transaminase (ALT)
B-Leukocyte differential count (absolute count)[a]	S/P-Aspartate transaminase (AST)
Neutrophils	S/P-Alkaline phosphatase
Lymphocytes	S/P-Bilirubin, total
Monocytes	S/P-Calcium, total
Basophils	S/P-Creatinine
Eosinophils	S/P-Glucose
B-Platelet count	S/P-Magnesium
B-Reticulocytes[b]	S/P-Phosphate
Coagulation[c]	S/P-Potassium

Table 11 Laboratory safety variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-INR	S/P-Sodium
APTT	S/P-Urea nitrogen or Urea
Urinalysis (dipstick)[c]	S/P-C - reactive protein
U-Protein	S/P-Thyroid stimulating hormone (TSH)[d]
U-Glucose	
U-Blood	
Other screening tests	
Serum (screening) and urine (other time points) human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)	

[a] If absolute differentials not available please provide % differentials
[b] If absolute particle counts not available please provide relative particle count
[c] Coagulation and urinalysis are only scheduled for baseline and as clinically indicated post-baseline
[d] Free triiodothyronine (T3) or free thyroxine (T4) will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

NB. In case a participant shows an AST **or** ALT ≥ 3 x ULN together with total bilirubin ≥ 2 x ULN please refer to Appendix E. Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.

Additionally, a serum (screening) or urine (other time points) sample will be collected from all women of childbearing potential at the visits indicated in the SoA (Section 11.1.3).

11.8.3 Adverse Events and Serious Adverse Events

Please refer to the core protocol (Section 8.3).

11.8.4 Overdose

Please refer to the core protocol (Section 8.4).

11.8.5 Human Biological Samples

11.8.5.1 Pharmacokinetics

- Venous blood samples for determination of concentrations of study intervention in plasma will be taken at the times specified in the SoA (Section 11.1.3). The date and time of collection of each sample will be recorded.
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor eg for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data to ensure appropriate monitoring. The total volume of blood taken from each participant will not exceed that presented in Section 11.8.1.

- Plasma blood samples will be used to analyse the PK of the study intervention. Samples collected for analyses of study intervention concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Determination of Drug Concentration

Samples for determination of study intervention in plasma will be assayed by bioanalytical test sites operated by or 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.

11.8.5.2 Pharmacodynamics

CCI will be used to inform the extent and duration of ATR target inhibition following treatment with study intervention. CCI will also be used to obtain assessment of the ceralasertib CCI relationship in participants and determine any retrospective correlations with ATM status and response to study intervention.

CCI

The collection of blood based CCI samples will provide assessment of downstream effects of ceralasertib administration in participants. Additional CCI CCI may be assessed. CCI will be collected and processed as detailed in the SoA (Section 11.1.3). This sample may also be used to assess CCI.

Additional details of blood, archival and fresh frozen tissue collection, shipping and storage of samples for biomarker assays can be found in the Laboratory Manual.

For storage, re-use and destruction of CCI see Section 8.5 and Appendix I.

11.8.6 Human Biological Sample Biomarkers

11.8.6.1 Collection of Archival Tumour Samples

Formalin fixed tumour tissue embedded in paraffin blocks are to be requested for all participants. Archival samples from either primary or metastatic tumour will be accepted but tissue from the primary tumour is preferred. However, tissue from the most recent biopsy would be preferred where a participant has archival tissue samples from multiple time points.

Approximately 30 freshly cut (within 30 days) unstained sections from the archival tumour block are accepted if tumour blocks cannot be submitted, however tumour tissue blocks are preferred. Specimens with insufficient tumour content or fine needle aspirates are inadequate to establish participant eligibility. Where available, provision of a copy of the pathology report associated with the tumour sample is also required.

Details of sample collection, processing, shipping and storage will be described in the Laboratory Manual and/or the Pathology and Genomic Testing manual.

11.8.6.2 Collection of Plasma Samples for CCI

A peripheral blood sample will be collected to provide plasma for CCI
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Details of sample collection, processing, shipping and storage will be described in the Laboratory Manual.

11.8.6.3 Collection of CCI

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For storage, re-use and destruction of CCI see Section 8.5.

11.8.7 Optional Genomics Initiative Sample

Please refer to core module for details.

11.9 STATISTICAL CONSIDERATIONS - MODULE 1

11.9.1 Statistical Hypotheses

No formal statistical hypotheses are being conducted for this study.

11.9.2 Sample Size Determination

Cohort A (aST): A total of ~25 molecularly eligible and centrally confirmed participants dosed at ceralasertib 160mg BID will be enrolled into Cohort A.

Cohort B (prostate cancer): A total of ~27 molecularly eligible and centrally confirmed participants dosed at ceralasertib 160mg BID will be enrolled into Cohort B. Unfavourable CTC count requirement may be introduced for all participants to ensure adequate (approximately ≥ 50%) number of participants with CTC count ≥ 5/7.5 mL blood.

At the time of protocol amendment 2, 1 participant had been dosed at 240 mg BID in Cohort A, and 8 participants had been dosed at 240 mg BID in Cohort B. Following the reduction of the starting dose from 240 mg BID to 160 mg BID in protocol amendment 2, the intention is to enrol an additional total of ~25 and ~27 participants in Cohort A and B, respectively, at the 160 mg BID.

The primary objective of this study is to determine investigator assessed objective response rate (Cohort A) and composite response rate (Cohort B) of study intervention. The number of participants has been based on the desire to obtain adequate response, tolerability, safety, pharmacokinetic and PDc data while exposing as few participants as possible to study intervention and procedures. In Cohort A, the sample size of ~25 participants is expected to give adequate precision in the estimate of the ORR. CCI [redacted] CCI [redacted] CCI [redacted] In Cohort B, the sample size of ~27 participants is expected to give adequate precision in the estimate of composite response. CCI [redacted] CCI [redacted] CCI [redacted]

Please refer to Table 12 for the definition of a molecularly eligible participant. In case of discordance between local and central testing, additional participants may be enrolled in order to satisfy the intended sample size of molecularly eligible and centrally confirmed participants.

Each Cohort A and Cohort B may be further expanded CCI [redacted] CCI [redacted], in case of an efficacy signal, subject to an approved protocol amendment.

11.9.3 Populations for Analyses

The following populations are defined:

Table 12 Populations for Analysis

Population/Analysis set	Description
Enrolled Analysis Set	All study participants who signed the ICF (including screening failures).
Evaluable for Response Set	Cohort A: All study participants with measurable baseline disease who received at least 1 dose of study intervention.

Population/Analysis set	Description
	Cohort B: All study participants with measurable disease and/or unfavourable CTC count at baseline who received at least 1 dose of study intervention.
'Molecularly Eligible Centrally Confirmed[a] Evaluable for Response Set	Cohort A: All molecularly eligible and centrally confirmed study participants with measurable baseline disease who received at least 1 dose of study intervention. Cohort B: All molecularly eligible and centrally confirmed study participants with measurable disease and/or unfavourable CTC count at baseline who receive at least 1 dose of study intervention. Please refer to protocol Section 11.2 for the definition of a molecularly eligible participant.
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]
Safety Set	All participants who received at least 1 dose of study intervention.
Molecularly Eligible Centrally Confirmed Set	All molecularly eligible and centrally confirmed participants who received at least 1 dose of study intervention.

[a] Participants with any or both of the following conditions will be considered molecularly eligible centrally confirmed:
1) Centrally confirmed deleterious or suspected deleterious ATM mutation by NGS.
2) Centrally confirmed ATM IHC ≤ 5%.

11.9.4 Statistical Analyses

The SAP will be finalised prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. Any deviations from the planned analysis will be described in an SAP addendum and justified in the final integrated CSR.

Data that will be analysed at each timepoint is presented Table 13.

Table 13 Summary of Analyses and Data Cut-off Triggers

Analysis	Trigger	Data Type Included
Interim Cohort A	Approximately 4 months after 18 molecularly eligible centrally confirmed evaluable for response participants are enrolled.	At a minimum, key efficacy and safety data for Cohort A, Details to be provided in the SAP

Analysis	Trigger	Data Type Included
Interim Cohort B	Approximately 6 months after 12 molecularly eligible centrally confirmed evaluable for response participants are enrolled.	At a minimum, key efficacy and safety data for Cohort B, Details to be provided in the SAP
Primary analysis Cohort A	Approximately 6 months after 25 molecularly eligible centrally confirmed evaluable for response participants are enrolled.	All data for Cohort A
Primary analysis Cohort B	Approximately 6 months after 27 molecularly eligible centrally confirmed evaluable for response participants are enrolled.	All data for Cohort B

Abbreviations: ATM=ataxia telangiectasia mutated; RECIST=response evaluation criteria in solid tumours.

11.9.4.1 General Considerations

All statistical analysis will be performed by Parexel International Biostatistics or other designated third party providers, under the direction of the Biostatistics Group, AstraZeneca. Further detail will be provided in the SAP. All statistical analysis will be performed using the latest available version of SAS® (SAS Institute Inc., Cary, North Carolina, US), version 9.4 or higher. Exploratory analyses may be reported outside of the CSR.

Safety data will be presented separately by starting dose (and total) for each cohort of participants within Module 1. Summaries of efficacy data will only be presented for participants receiving 160 mg BID starting dose, however, listings will include all participants (240 mg BID and 160 mg BID starting dose).

- Cohort A: aST except NSCLC and prostate cancer
- Cohort B: Metastatic castration-resistant prostate cancer

No formal statistical analyses will be carried out for this study and the data will be summarised using standard summary statistics.

Deviations from the protocol will be assessed as “important” or “not-important”. Deviations will be defined before database lock to determine the impact on any planned analyses. Important deviations will be defined in a separate protocol deviation document.

All important protocol deviations will be listed by participant for all enrolled participants. Further details will be described in the SAP.

Demographic data

Characteristics of the participants, including medical history and disease characteristics at baseline will be listed for each participant and summarised by cohort.

Reasons for discontinuation of study intervention will be listed including the study day of treatment discontinuation and will be summarised by cohort.

Exposure

Exposure to study intervention will be listed for all participants by cohort.

11.9.4.2 Safety

Safety and tolerability will be assessed in terms of AEs, laboratory data, vital signs, and physical examination. These will be collected for all participants. Appropriate summaries of these data will be presented.

During the evaluation of AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation of study intervention. Based on the expert's judgement, AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered other significant adverse events and reported as such in the CSR. A similar review of laboratory values, vital signs, ECGs and other safety assessments will be performed for identification of other significant AEs.

Examples of these are 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.

11.9.4.3 Pharmacokinetic Variables

A statistical summary of ceralasertib concentration per the nominal time point and a listing of individual concentrations of ceralasertib will be generated.

11.9.4.4 Pharmacodynamic Variables

CCI [redacted], CCI [redacted] CCI [redacted]

11.9.4.5 Efficacy

Cohort A

Primary Endpoint(s)

Determination of objective response rate is the primary objective. The primary analysis will occur approximately 6 months after all participants have been enrolled into the cohort.

Blinded independent central review assessment may be introduced if the cohort is expanded, subject to an approved protocol amendment.

Objective Response Rate

Objective response rate is defined as the percentage of participants who have at least one response of CR or PR prior to any evidence of progression (as defined by RECIST 1.1) that is confirmed at least 4 weeks later. The primary analysis of objective response rate will be based upon the 'molecularly eligible centrally confirmed evaluable for response' population. Additionally, objective response rate will also be provided for the 'evaluable for response' population. Percentage of participants will be accompanied with a 2-sided 80% confidence interval as obtained from a Clopper-Pearson test.

Secondary Endpoint(s)

Duration of Response

Duration of response will be defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression, the end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR.

If a participant does not progress following a response, then their duration of response will use the PFS censoring time.

Descriptive data will be provided for the duration of response in responding participants, including the associated Kaplan-Meier estimate of median duration of response, where there are sufficient number of responders.

Percentage Change in Tumour Size

The percentage change in TL tumour size from baseline will be summarised using descriptive statistics by visit. Waterfall plots showing the best percentage change from baseline in sum of the diameters of TLs will be produced. Spider plots showing the percentage change from baseline in tumour size for each subject over time will be produced.

Progression Free Survival

Progression free survival is defined as the time from start of study intervention until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the participant withdraws from therapy or receives another anti-cancer therapy prior to progression. Participants who have not progressed or died at the time of

analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the participant progresses or dies after 2 or more missed visits, the participant will be censored at the time of the latest evaluable RECIST assessment. If the participant has no evaluable visits or does not have baseline data, they will be censored at 0 days unless they die within 2 visits of baseline.

The PFS time will always be derived based on scan/assessment dates not visit dates.

For further details see Appendix F of this Clinical Study Protocol.

Analyses of PFS will be based upon the 'molecularly eligible centrally confirmed' population. Kaplan-Meier plots of PFS will be presented. Summaries will include the median PFS with respective CIs calculated using the Kaplan-Meier technique. Summaries will also provide the number and percentage of participants experiencing a PFS event, and the type of event (progression or death).

Cohort B

Primary Endpoint(s)

Determination of composite response rate is the primary objective. The primary analysis will occur approximately 6 months after all participants have been enrolled into the cohort.

Composite Response Rate

Composite response will be defined on the basis of the following outcomes; if any of these occur in the absence of radiological or PSA progression (according to RECIST 1.1 for soft tissue and visceral lesions, prostate cancer working group 3 (PCWG3) criteria for bone lesions, and PSA) participants will be considered to have responded:

- Investigator assessed radiological objective response by RECIST 1.1 for soft tissue and visceral lesions and PCWG3 criteria for bone lesions. Response must be confirmed at least 4 weeks later. BICR assessment may be introduced if the cohort is expanded, subject to a protocol amendment.
- Conversion of CTC count from ≥ 5/7.5 mL blood (unfavourable) at baseline to < 5/7.5 mL blood (favourable) confirmed by a second consecutive value obtained 3 or more weeks later (as per PCWG3 criteria).
- PSA decline of > 50% confirmed by a second consecutive measurement at least 3 weeks later (based on PCWG1 criteria).

Overall radiological visit assessment in prostate cancer is provided in Appendix G.

The primary analysis of composite response rate will be based upon the ‘molecularly eligible centrally confirmed evaluable for response’ population. Additionally, composite response rate will also be provided for the 'evaluable for response' population. Percentage of participants

will be accompanied with a 2-sided 80% confidence interval as obtained from a Clopper-Pearson test.

Secondary Endpoint(s)

Radiological Objective Response Rate

Radiological ORR is defined as the percentage of participants with a confirmed response of CR or PR in their soft tissue and visceral lesions assessed by RECIST 1.1 in the absence of bone progression assessed by PCWG3. The denominator is the number of participants in the evaluable for response set. The soft tissue ORR and overall radiological ORR will be summarised descriptively.

Duration of Radiological Response

Similar to Cohort A, duration of radiological objective response is defined as the time from the date of first documented response until date of objective radiologic disease progression or death. Descriptive data will be provided for the duration of response in responding participants, including the associated Kaplan-Meier estimate of median duration of response, where there are sufficient number of responders.

Percentage change in tumour size

Percentage change in tumour size will be summarised descriptively, as described for Cohort A.

CTC Count conversion

Conversion of CTC count are defined as a conversion from unfavourable at baseline (≥ 5/7.5 mL blood) to favourable post-baseline (< 5/7.5 mL blood). Post-baseline result should be confirmed with a second consecutive value obtained 3 or more weeks later. The percentage of participants with CTC count conversion based on those with unfavourable CTC at baseline, will be presented for this study.

Confirmed PSA Decline

Proportion of participants with a PSA decline of > 50% confirmed by a second consecutive measurement at least 3 weeks later.

Radiological PFS (rPFS)

rPFS is defined as the time from the start of treatment until the date of objective radiographic disease progression or death.

Participants who have not progressed (ie, who have a CR, PR or SD by RECIST 1.1, and non-progressive disease by PCWG-3) at the time of analysis will be censored at the time of the latest date of their last evaluable RECIST 1.1 assessment or bone scan assessment that showed fewer than 2 new lesions. However, if the 2 or more consecutive scheduled radiographic assessments immediately prior to progression or death were not evaluable, the participant will be censored at the time of the latest evaluable RECIST 1.1 and bone scan assessment prior to the 2 or more missed assessments. If the participant has no evaluable visits or does not have baseline data, he will be censored at Day 1 unless he dies within 2 visits of baseline (in which case the participant's date of death will be used). The rPFS time will always be derived based on scan/assessment dates, not visit dates. When the investigator is in doubt as to whether progressive disease has occurred and therefore reassesses the patient at a later date, the date of the initial scan should be declared as the date of progression if the repeat scans confirm progression.

Analyses of rPFS will be based upon the 'molecularly eligible centrally confirmed' population. Kaplan-Meier plots of rPFS will be presented. Summaries will include the median rPFS with respective CIs calculated using the Kaplan-Meier technique. Summaries will also provide the number and percentage of participants experiencing a rPFS event, and the type of event (progression or death).

11.9.4.6 Biomarker Variables

The analyses of biomarker variables include, but are not limited to, CCI [redacted]. Change from baseline and percent change from baseline for biomarker variables will be calculated for all participants.

11.9.5 Interim Analyses

11.9.5.1 Cohort A

An administrative interim analysis will be conducted approximately 4 months after approximately 18 molecularly eligible centrally confirmed evaluable for response participants dosed at ceralasertib 160mg BID have been enrolled. The assessment of key efficacy and safety will be performed. The purpose for administrative interim is to inform internal decision making only with no planned adaptions to the study.

11.9.5.2 Cohort B

A futility interim analysis will also be conducted approximately 6 months after at least 12 molecularly eligible centrally confirmed evaluable for response participants have been enrolled dosed at ceralasertib 160mg BID. The futility stopping rule for the prostate cohort will be based on the primary endpoint, composite response. AstraZeneca may decide to cease recruitment for the prostrate cohort at the interim analysis if there are ≤ 2 responders out of 12 molecularly eligible and centrally confirmed participants. This stopping rule is for guidance

only, and any decision to cease recruitment will be based on sponsor review of all safety and efficacy clinical data available. Further details will be provided in the SAP.

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12 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A 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 patient's safety. If in doubt, please contact the AstraZeneca Study Physician.

A 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 Section 11.1.3 and Sections 11.8.1 to 11.8.7. 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.

A 2 Rescreening of Participants To Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The investigator should confirm this with the designated AstraZeneca study physician.

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrolment into the study or commencing of dosing with IP. If this delay is outside the screening window specified in Section 11.1.3 the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to rescreen a participant in addition to that detailed in Section 11.5.4. The procedures detailed in Section 11.5.1.1 must be undertaken to confirm eligibility using the same randomization number as for the participant.

A 3 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified healthcare professional from the study site or third party vendor service will visit the participants home/or other remote location as per local standard of procedures, as applicable. Supplies will be provided for a safe and efficient visit. The qualified healthcare professional will be expected to collect information per the CSP.

A 4 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 adverse events, concomitant medication to be reported and documented.

A 5 At-home or Remote Location IP Administration Instructions

If a site visit is not possible, at-home or remote location administration of IP may be performed by a qualified healthcare professional, provided this is acceptable within local regulation/guidance, or by the participant or his/her caregiver. The option of at-home or remote location IP administration ensures participants safety in cases of a pandemic where participants may be at increased risk by traveling to the site/clinic. This will also minimize interruption of IP administration during other study disruptions, eg, site closures due to natural disaster.

A 5.1 At-home or Remote Location IP Administration by the Participant or His/Her Caregiver

Prior to at-home or remote location IP administration the investigator must assess the participant or his/her caregiver to determine whether they are appropriate for at-home or remote location administration of IP. Once the participant or his/her caregiver is deemed appropriate for at-home or remote location administration, he/she must receive appropriate training. All necessary supplies and instructions for administration and documentation of IP administration will be provided. More information related to the visit can be obtained via a telemedicine or home / remote visit.

A 6 Data Capture During Telemedicine or Home / Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified healthcare professional from the study site or third party vendor service, or by the participant themselves.

Appendix B Regulatory, Ethical, and Study Oversight Considerations

B 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 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the 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.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a 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.
- The sponsor 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. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- 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.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.

B 2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor 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 course of the study and for 1 year after completion of the study.

B 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her 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 or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) 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.
- Participants must be re-consented 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 or the participant's legally authorised representative.
- Please refer to individual modules for specific details.
- For Module 1, the screening will have 2 parts, Part 1 and Part 2. Part 1 will confirm molecular eligibility and Part 2 will confirm study eligibility.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. 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.

B 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor 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 his/her personal study-related data will be used by the sponsor 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 his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

B 5 Committees Structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the CSP and letters to investigators.

B 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov 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.

B 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or 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 (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 provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organisations).
- Study monitors will perform ongoing source data verification 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 20 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be

destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

B 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 reported on the eCRF or 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.
- Source data may include, but is not limited to: medical history and physical examination notes, hospital discharge summary, autopsy report when available, results of relevant diagnostic tests completed.

B 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant enrolled and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. 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 the sponsor or 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, the sponsor'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, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organisation(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.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

B 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 the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a co-ordinating 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 C New York Heart Association

C 1 New York Heart Association Functional Classification

NYHA	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Abbreviation: NYHA=New York Heart Association.

C 2 References

Criteria Committee of the New York Heart Association, 1994
The Criteria Committee of the New York Heart Association. (1994). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels (9th ed.). Boston: Little, Brown & Co. pp. 253–256.

Appendix D Guidelines Regarding Potential Interactions of Ceralasertib with Concomitant Medications

Restrictions regarding drugs affection CYP3A metabolism

There are currently no data confirming that there is a pharmacokinetic (PK) interaction between these agents and ceralasertib; a potential interaction is considered on the basis of preclinical and in vitro data only. Ceralasertib is predominantly eliminated via CYP3A metabolism, therefore CYP3A inhibitors or inducers may increase or decrease exposure to ceralasertib, respectively. Potent inhibitors or inducers of CYP3A should not be combined with ceralasertib. In vitro data also suggest that ceralasertib may be metabolised by CYP2C8 but a lesser extent, therefore caution should be applied with co-administration of potent inhibitors or inducers of CYP2C8.

These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate CYP3A or CYP2C8 activity. 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 ceralasertib.

Table 14 Drugs Known to be Inhibitors of CYP3A4

Potent CYP3A inhibitors	Potent CYP3A inducers
Boceprevir	Apalutamide
Ceritinib	Avasimibe
Clarithromycin	Carbamazepine
Cobicistat (GS-9350)	Enzalutamide
Conivaptan	Ivosidenib
Danoprevir / RIT	Lumacaftor
Elvitegravir / RIT	Mitotane
Grapefruit juice[a]	Phenobarbital
Idelalisib	Phenytoin
Indinavir	Rifampin
Indinavir /RIT	Rifapentine
Itraconazole	St John's Wort extract
Ketoconazole	
LCL161	
Lopinavir / RIT	
Mibefradil	
Mifepristone	
Nefazodone	
Nelfinavir	
Posaconazole	
Ribociclib	
Ritonavir	
Saquinavir	
Saquinavir / RIT	
Telaprevir	
Telithromycin	
Tipranavir/RIT	
Troleandomycin	
VIEKIRA PAK2[b]	
Voriconazole	

[a] Double-strength grapefruit juice. Participants should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits e.g., grapefruit juice or marmalade) during the study (e.g., no more than a small glass of grapefruit juice [120 mL] or half a grapefruit or 1-2 teaspoons [15 g] of Seville orange marmalade daily).

[b] VIEKIRA PAK = 150/100 mg paritaprevir/ritonavir + 25 mg ombitasvir + 800 mg dasabuvir for 28 days.

List created using the University of Washington Drug-Drug Interaction Database July 2019.
RIT=Ritonivir. Ritonavir has dual effects of simultaneous CYP3A inhibition and induction, and the net pharmacokinetic outcome during chronic ritonavir therapy is inhibition of CYP3A activity

Table 15 Drugs Known to be Inhibitors and Inducers of CYP2C8

Potent CYP2C8 inhibitors	Potent CYP2C8 inducers
Gemfibrozil Clopidogrel	None identified

List created using the University of Washington Drug-Drug Interaction Database Jan 2020.

Drugs known to be inhibitors or inducers of Pgp and/or BCRP, undertake appropriate monitoring if co-administration is necessary

Ceralasertib is a substrate of Pgp and BCRP. Co-administration of Pgp inhibitors/inducers or BCRP inhibitors/inducers may affect exposure to AZD6738 therefore it is recommended that these are not co-administered with ceralasertib.

These lists are not intended to be exhaustive, and similar restrictions will apply to other agents that are known to modulate Pgp activity or BCRP activity. 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 ceralasertib.

Table 16 Drugs Known to be Inhibitors or Inducers of P-gp

Drugs Known to be Inhibitors of Pgp	Drugs Known to be Inducers of Pgp
Alogliptin	Apalutamide
Amiodarone	Avasimibe
Asian ginseng (Panax ginseng)	Carbamazepine
Asunaprevir	Danshen (Salvia miltiorrhiza)
AZD5672	Efavirenz
azithromycin	Genistein
Canagliflozin	Green tea
Captopril	Phenytoin
Carvedilol	Quercetin
Clarithromycin	Rifabutin
Clopidogrel	Rifampin
Cobicstat	Ritonavir
Conivaptan	St. John's wort extract
Cremophor EL	Tivantinib
Cremophor RH	
Curcumin	
Daclatasvir	
Daclatasvir/asunaprevir/beclabuvir	
Diltiazem	
Diosmin	
Dronedarone	

Drugs Known to be Inhibitors of Pgp	Drugs Known to be Inducers of Pgp
Elagolix	
Eliglustat	
Erythromycin	
Felodipine	
Five-flavor berry (schisandra chinensis)	
Flibanserin	
Fluvoxamine	
Fostamatinib	
Ginkgo	
Glecaprevir/pibrentasvir	
Indinavir	
Indinavir/ritonavir	
Isavuconazole	
Itraconazole	
Ivacaftor	
Ketoconazole	
Lapatinib	
Lopinavir/ritonavir	
Mibefradil	
Mifepristone	
Milk thistle	
Mirabegron	
Nelfinavir	
Neratinib	
Nifedipine	
Nitrendipine	
Osimertinib	
Paritaprevir/ritonavir/ombitasvir	
Paroxetine	
Piperine	
Propafenone	
Quercetin	
Quinidine	
Quinine	
Ranolazine	
Rifampin	
Ritonavir	
Rolapitant	
Rucaparib	
Saquinavir/ritonavir	
Sarecycline	

Drugs Known to be Inhibitors of Pgp	Drugs Known to be Inducers of Pgp
Simeprevir	
Sofosbuvir/velpatasvir/voxilaprevir	
St. John's wort extract	
Surfactant TPGS	
Suvorexant	
Talinolol	
Telithromycin	
Telaprevir	
Telmisartan	
Tezacaftor/ivacaftor	
Ticagrelor	
Tipranavir/ritonavir	
Tolvaptan	
Valbenazine	
Valspodar (PSC 833)	
Vandetanib	
Velpatasvir	
Vemurafenib	
Verapamil	
Voclosporin	
Vorapaxar	

Table 17 Drugs Known to be Inhibitors or Inducers of BCRP

Drugs Known to be Inhibitors of BCRP	Drugs Known to be inducers of BCRP
Afatinib	Please check individual drugs on a case-by-case basis
Aripiprazole	
Curcumin	
Cyclosporine	
Elacridar	
Erlotinib	
Fluvastatin	
Fumitremorgin	
Gefitinib	
Ivermectin	
Lapatinib	
Nilotinib	
Novobiocin	
Pantoprazole	
Pitavastatin	

Drugs Known to be Inhibitors of BCRP	Drugs Known to be inducers of BCRP
Ponatinib	
Quercetin	
Quizartinib	
Rabeprazole	
Regorafenib	
Rilpivirine	
Sulfasalazine	
Sunitinib	
Tacrolimus	
Teriflunomide	
Trametinib	
Trifluoperazine	
Vismodegib	
eltrombopag	
Atazanavir	
Lopinavir	
Ritonavir	
Tipranavir	
Omeprazole	
Estrone	
17b-estradiol	
Imatinib mesylate	

List created using http://dmd.aspetjournals.org/content/dmd/43/4/490 full.pdf
Note: Although BCRP is involved in a number of clinically relevant drug-drug interaction, none of the cited inhibitors above is truly specific for this transporter

Drugs known to be substrates of CYP3A4 and/or CYP2B6, undertake appropriate monitoring if co-administration is necessary

Ceralasertib is a potential inducer of CYP3A4 and CYP2B6. Therefore, caution should be applied with co-administration of drugs that are either completely metabolised by CYP3A4 and/or CYP2B6, or that are substrates of CYP3A4 and/or CYP2B6 and also have a narrow therapeutic index. Investigators should be aware that the exposure of other drugs metabolised by CYP3A4 and/or CYP2B6 may be reduced.

Table 18 Drugs Known to be Metabolised by CYP3A4 and/or CYP2B6 and Have a Narrow Therapeutic Index

Metabolised by **CYP3A4** and with a narrow therapeutic index	Metabolised by **CYP2B6** and with a narrow therapeutic index
Alfentanil	Bupropion

Metabolised by **CYP3A4** and with a narrow therapeutic index	Metabolised by **CYP2B6** and with a narrow therapeutic index
Astemizole	Efavirenz
Cisapride	
Cyclosporine	
Diergotamine	
Ergotamine	
Fentanyl	
Pimozide	
Quinidine	
Sirolimus	
Tacrolimus	
Terfenadine	

List created using the University of Washington Drug-Drug Interaction Database October 2019.
Note: This is not an exhaustive list.

Drugs known to be substrates of OATP1B1 and BCRP, undertake appropriate monitoring if co-administration is necessary

Ceralasertib is also an inhibitor of OATP1B1 and BCRP. Caution should be applied with co-administration of substrates of OATP1B1 and/or BCRP as ceralasertib may increase their exposure.

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 ceralasertib.

Table 19 Drugs Known to be Substrates of OATP1B1

Docetaxel
Enalapril
Olmesartan
Phalloidin
Repaglinide
Statins*
Temocaprilat
Valsartan

* all statins
List created using https://www.solvobiotech.com/transporters/OATP1B1, latest access Nov 2019

Table 20 Drugs known to be substrates of BCRP

Anthracyclines

Chlorothiazide
Daunorubicin
Doxorubicin
Imatinib
Irinotecan
Methotrexate
Mitoxantrone
Nucleoside analogs
Pantoprazole
Prazosin
SN-38
Topotecan
Teriflunomide
Rosuvastatin

List created using https://www.solvobiotech.com/transporters/bcrp, latest access Nov 2019

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 (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL 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, PHL 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 Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Serious Adverse Events (SAEs) and Adverse Events (AEs) according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law (PHL)
Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3 x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2 x ULN at any point during the study following the start of study intervention irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)
AST or ALT ≥ 3 x ULN **together with** TBL ≥ 2 x 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 PHL and HL 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 PHL 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 x ULN
- AST ≥ 3 x ULN
- TBL ≥ 2 x ULN

Local laboratories being used:

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

- Determine whether the participant meets PHL criteria (see Section E 2 Definitions within this Appendix 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 PHL criteria the investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

E 4.2 Potential Hy's Law Criteria met

If the participant does meet PHL criteria the investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study intervention (See Section E 6)
- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL 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 CSP process for SAE reporting

- For participants that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change# in the participant's condition

- The Study Physician contacts the investigator, to provide guidance, discuss and agree an approach for the study participants' 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. Completes follow-up SAE Form as required.
  – Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. For studies using a central laboratory add: This includes deciding which the tests available in the Hy's Law lab kit should be used.
  – 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 total bilirubin) 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 Physician if there is any uncertainty.

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

The instructions in this Section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Medical Science Director 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 a 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 HL 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 or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides 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 study intervention and seriousness criteria is medically important, according to CSP 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 HL criteria are still met. Update the previously submitted PHL SAE report following CSP 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 Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to participants with liver metastases who meet PHL criteria on study treatment, having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the investigator will determine if there has been a **significant change** in the participants' condition[#] compared with the last visit where PHL criteria were met[#]

- If there is no significant change no action is required

– If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Section E 4.2

E 7 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a participant meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

> Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection or liver disease or did the participant meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in section 6 of this Appendix?

If **No**: follow the process described in Section E 4.2 for reporting PHL as an SAE

If **Yes**: Determine if there has been a significant change in the participant's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section E 4.2 for reporting PHL as an SAE

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 total bilirubin) 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 Physician if there is any uncertainty.

E 8 References

Aithal et al, 2011
Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

FDA Guidance for Industry, July 2009

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

Appendix F Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 (Response Evaluation Criteria in Solid Tumours)

Introduction

This appendix details the implementation of RECIST (Response Evaluation Criteria in Solid Tumours) 1.1 guidelines (Eisenhauer et al, 2009) for the study with regards to investigator assessment of tumour burden including protocol-specific requirements for this study.

Assessment of Disease using RECIST 1.1

Definition of Measurable, Non-measurable, Target and Non-target Lesions

Participants with at least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by computerised tomography (CT), magnetic resonance imaging (MRI) or plain X-ray should be included in this study.

Measurable lesions

A lesion, not previously irradiated, that can be measured accurately at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have a short axis ≥ 15 mm with CT or MRI and which is suitable for accurate repeated measurements).

Non-measurable lesions

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis at baseline). Nodes with < 10 mm short axis are considered non-pathological and should not be recorded as non-target lesions (NTLs)
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that are not measurable by CT or MRI
- Previously irradiated lesions as localised post-radiation changes, which affect lesion sizes, may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and should be selected as NTLs at baseline and followed up as part of the NTL assessment
- Skin lesions assessed by clinical examination
- Brain metastasis

Special cases

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same participant, these non-cystic lesions should be selected as the target lesions (TLs).

Target lesions

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at baseline.

Non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline.

Methods of Measurement

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up.

The methods to be used for RECIST assessment are summarised in Table 21 and those excluded for tumour assessments in this study are discussed below, with the rationale provided.

Table 21 Summary of Methods of Assessment

Target Lesions	Non-target Lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Plain X-ray (includes chest X-ray)	Plain X-ray (includes chest X-ray)
	Clinical examination	Clinical examination
		Ultrasound
		Bone scan
		FDG-PET

CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TLs selected for response assessment and to assess NTLs and identification of new lesions.

In this study it is recommended that CT examinations will be used to assess tumour burden at baseline (including assessment of brain lesions at baseline in participants with no known brain metastases) and follow-up visits. CT examination with intravenous contrast media administration is the preferred method. MRI should be used where CT is not feasible, or it is medically contraindicated, for pre-existing brain metastases, and when there is a clinical suspicion of brain metastases.

Clinical examination

Clinical examination will not be used for assessment of TLs. Clinically detected lesions can be selected as TLs if they are then assessed by CT or MRI scans. Clinical examination can be used to assess NTLs in participants that also have other lesions assessable by CT, MRI or plain X-ray and to identify the presence of new lesions.

X-rays

Plain X-ray

Plain X-rays may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

Chest X-ray

Chest X-rays will not be used for assessment of TLs as they will be assessed by CT or MRI examination. Chest X-rays can, however, be used to assess NTLs and to identify the presence of new lesions.

Ultrasound

Ultrasound examination will not be used for assessment of TLs and NTLs as it is not a reproducible method, does not provide an accurate assessment of tumour size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed, then new lesions should be confirmed by CT or MRI examination.

Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour measurements.

Tumour markers

Tumour markers will not be used for tumour response assessments per RECIST 1.1.

Cytology and histology

Histology will not be used as part of the tumour response assessment per RECIST 1.1. Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease (SD). In such circumstances, the cytology is necessary to differentiate between response / SD (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or the appearance of a clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTLs or disease progression due to new lesions.

Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or X-ray at baseline should be recorded as NTLs and followed by the same method as per baseline assessment.

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and X-ray is recommended where bone scan findings are equivocal.

FDG-PET scan

FDG-PET (fluorodeoxyglucose positron emission tomography) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake (defined as when an uptake greater than twice that of the surrounding tissue is observed) not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then

follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

Tumour response evaluation

Schedule of evaluation

Baseline tumour assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual participants and should be performed according to the respective schedule of activities until objective radiographic disease progression is registered according to the protocol requirements or withdrawal of consent. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

Target lesions

Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved, should be identified as TLs at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions) but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimetres. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TLs measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is > 5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into 2 or more parts, then record the sum of the diameters of those parts.
- If 2 or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).

- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention eg, radiotherapy, embolisation, surgery etc., during the study, the size of the TL should still be provided where possible.

Evaluation of target lesions

Table 22 provides the definitions of the criteria used to determine objective tumour visit response for TLs.

Table 22 Overall Visit Response for Target Lesions

Complete Response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Not Evaluable (NE)	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response.

Non-Target lesions

Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the investigator. Table 23 provides the definitions of the criteria used to determine and record overall response for NTLs at the investigational site at each visit.

Table 23 Overall Visit Response for Non-Target Lesions

Complete Response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of one or more NTLs.
Progressive Disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST clinically significant for the physician to consider changing or stopping therapy.
Not Evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and in the investigator's opinion they are not able to provide an evaluable overall NTL assessment at this visit. Note: For participants without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in TLs, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

New Lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

If a new lesion is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Tumour response data for participants with 'symptomatic deterioration' which required discontinuation of study treatment and without objective radiographic disease progression according to the protocol requirements will be censored at the date of their last RECIST assessment.

Evaluation of Overall Visit Response and Best Overall Response

The overall visit response will be derived using the algorithm shown in Table 24.

Table 24 Overall Visit Response

Target Lesions	Non-target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
NA	Non-CR/Non-PD	No	SD (Non-CR/Non-PD)
NE	Non-PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR=complete response; IR=incomplete response; NA=not applicable (relevant when no TLs/NTLs at baseline); NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease.

Specifications for Radiological Imaging

These notes are recommendations for use in clinical studies. The use of standardised protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

CT Scan

CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomical regions of interest.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

Anatomic coverage

Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis.

Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual participants. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

Intravenous contrast administration

Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of intravenous contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given participant. It is very important that the same technique be used at baseline and on follow- up examinations for a given participant. For participants who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the participant should be considered not evaluable from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study, then the recommended methods are: CT thoracic examination without contrast and abdominal and pelvic MRI with contrast. If MRI cannot be performed then CT without intravenous contrast is an option for the thorax, abdomen and pelvic examinations.

Slice thickness and reconstruction material

It is recommended that CT scans be performed at 5 mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for the measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TLs should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not "selected" images of the apparent lesion.

MRI Scan

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used, and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

FDG-PET scans

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. If FDG-PET scans are included in a protocol, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of participants with malignancy. Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same

model scanner, for serial scans on the same participant. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all participants and serial scans in the clinical study.

PET/CT scans

At present, low dose or attenuation correction CT portions of a combined PET–CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for tumour measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

F 1 REFERENCES

Eisenhauer et al, 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 2009;45:228-247.

Appendix G Guidelines for Evaluation of Objective Tumour Response Using PCWG3 (Prostate Cancer Working Group Criteria 3) in Bone Lesions

Introduction

This appendix details the implementation of PCWG3 guidelines (Scher et al 2016) for the study with regards to assessment of tumour burden including protocol-specific requirements for this study.

Assessment of Bone Lesions Progression Using PCWG3 Criteria

Bone lesions will be assessed by bone scan and will not be part of the RECIST v1.1 malignant soft tissue assessment.

Method of Assessment

Bone lesions identified on a whole-body isotopic bone scan at baseline should be recorded and followed by the same method as per baseline assessment.

In this study isotopic bone scans will be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive and unequivocal hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion.

Tumour progression evaluation

Schedule of the evaluation

Baseline assessments should be performed no more than 28 days before the start of study intervention. Follow-up assessments will be performed according to the respective schedule of activities until objective radiographic disease progression as defined by RECIST 1.1 (soft tissue) or PCWG3 (bone).

If an unscheduled assessment was performed and the participant has not progressed, every attempt should be made to perform the subsequent assessments at their originally scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some participants being assessed at a different frequency than other participants.

Documentation of lesions

All bone lesions (or sites of disease) should be identified at baseline. Their status should be followed at subsequent visits. At each visit an overall assessment of the bone lesion progression should be recorded by the investigator. This section provides the definitions of the criteria used to determine and record bone progression at the investigational site at each visit.

Progression on a bone scan is identified using PCWG3 as follow:

- At the 8 week scan:
  2 or more new metastatic bone lesions are observed on the first 8-week scan compared to the baseline assessment. The confirmatory scan, performed at least 6 weeks later and preferably no later than the next scheduled visit for a bone scan (ie, Week 16), must show 2 or more additional new metastatic bone lesions (for a total of 4 or more new metastatic bone lesions since the baseline assessment) for progression to be documented.

  Note - The first bone scan completed after baseline will be considered the '8-week scan' regardless if taken at week 8 or at an unscheduled assessment.
- After the 8 week scan:
  2 or more new metastatic bone lesions are observed compared to the 8 week assessment. The confirmatory scan, performed at least 6 weeks later and preferably at the next scheduled visit for a bone scan, must show the persistence of or an increase in the number of metastatic bone lesions compared to the prior scan for progression to be documented.

The date of progression is the date of the scan that first documents the second lesion.

Evaluation of bone progression status

Table 25 provides the definitions for the visit bone progression status for bone lesions.

Table 25 Bone Progression Status

Non-Progressive Disease (Non-PD)	No evidence of progression, or appearance of one new bone lesion, or non-fulfilment of the progression criteria including new lesions without confirmation of progression.
Progressive Disease (PD)	Bone lesions fulfilling the requirements for at least 2 new lesions and confirmation of progression.
Not Evaluable (NE)	Only relevant if a follow-up bone scan is not performed.

Overall radiological visit assessment in prostate cancer.

Table 26 provides the definitions for how the visit responses for soft tissue (according to RECIST 1.1 criteria) and bone progression status (according to PCWG3 criteria) are combined to give an overall radiological objective visit response.

Table 26 Overall Radiological Visit Response

Overall visit soft tissue response (RECIST 1.1)	Bone progression status (PCWG3)	Bone lesions at visit Present/Absent	Overall radiological visit response
CR	Non-PD	Absent	CR
CR	Non-PD	Present	PR
CR	NE	-	PR
PR	Non-PD or NE	Any	PR
SD	Non-PD or NE	Any	SD
NED	Non-PD or NE	Any	Non-PD
NE	Non-PD or NE	Any	NE
PD	Any	Any	PD
Any	PD	Any	PD

Abbreviations: CR=complete response; IR=incomplete response; NE=not evaluable (only relevant if a follow-up bone scan is not performed), NED=No Evidence of Disease (only relevant when there is no TL and NTL from baseline); PD=progressive disease; PR=partial response; SD=stable disease.

Confirmation of response

In this study, imaging for confirmation of response (CR or PR) should be performed at the next scheduled RECIST and PCWG3 assessment (and must not be less than 4 weeks later) following the date the criteria for response were first met.

Table 27 Best Overall Response When confirmation of CR and PR Required

Overall radiological response first time point	Overall radiological response subsequent time point	Best overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD or PD
CR	PD	SD or PD
CR	NE	SD or NE
PR	CR	PR

Overall radiological response first time point	Overall radiological response subsequent time point	Best overall response
PR	PR	PR
PR	SD	SD
PR	PD	SD or PD
PR	NE	SD or NE
NE	NE	NE

Abbreviations: CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease.

[a] if a CR is truly met at first time point, then any disease seen at subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scan suggest small lesions were likely still present and in fact the participant had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

G 1 REFERENCES

Scher et al 2016

Scher HI, Morris MJ, Stadler WM et al. Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol 34 (2016).

Appendix H Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

H 1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a participant 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 considered 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 treatment has been administered.

H 2 Definitions of serious adverse event

A serious adverse event 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-participant 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 (AEs) for **malignant tumours** reported during a study should generally be assessed as **Serious** AEs. 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-Serious** AE. 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 IP under study 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 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 serious AE, 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.

- 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 H 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 a SAE unless it meets the criteria shown in Appendix H 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 a SAE when it satisfies the criteria shown in Appendix H 2.

The grading scales found in the revised National Cancer Institute CTCAE latest version will be utilised for all events with an assigned CTCAE grading. 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).

H 3 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the participant actually 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 disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

H 4 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study intervention 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, for example, 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 fridge when it should be at room temperature

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

- 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
- Errors related to background and rescue medication, or standard of care medication in open-label studies, even if an AstraZeneca product

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

Appendix I Handling of Human Biological Samples

I 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 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.

I 2 Withdrawal of Informed Consent for donated biological samples

If a participant withdraws study consent samples collected from the participant 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.

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 documented and study site notified.

I 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation 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 UN3373 and IATA 650

Exempt - 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/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content

Appendix J Optional Genomics Initiative Sample

J 1 Use/analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic 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 and tissue samples will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant´s DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research continues but no longer than 15 years or other period as per local requirements.

J 2 Genetic research plan and procedures

Selection of genetic research population

- All participants will be asked to participate in this genetic 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 genetic research, participants must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol and: Provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion criteria

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Previous allogeneic bone marrow transplant
  - Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection
  - Healthy Volunteers and paediatric participant samples will not be collected for the Genomics Initiative.

Withdrawal of consent for genetic research:

- Participants may withdraw from this genetic 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 Clinical Study Protocol.

Collection of samples for genetic research

- The blood sample for this genetic research will be obtained from the participants at on Cycle 1 Day 1. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an adverse event (AE). If for any reason the sample is not drawn on Cycle 1 Day 1, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.
- Details of sample collection, processing, shipping and storage are described in the Laboratory Manual.

Coding and storage of DNA samples

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years, from the date of last participant last visit, after which they will be destroyed. DNA is a finite resource that is 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 sample either before or at the time of DNA extraction 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 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 DNA 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 genetics research component, are outlined in Appendix B.

Informed consent

- The genetic component of this study is optional and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the participant must sign and date both

the consent form for the main study and the optional genetic research consent form. Copies of both signed and dated consent forms must be given to the participant and the original 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 withdrawal from the genetic aspect of the study at any time.

Participant data protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic 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 genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

Data management

- Any genetic 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 health insurance 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.
- The results of this pharmacogenetic research will be reported separately and will not form part of the CSR.

Appendix K ATM Alterations Classification Guidance

ATM Classification Algorithm

for Definition of Qualifying Alterations

(based on Lynparza HRR Classification Algorithm v2)

K 1 Introduction

This appendix describes the genomic alterations in the ATM gene that will be classified qualifying for the PLANETTE study ("A Modular Phase 2a Multicenter Open-Label Study to Investigate DNA-damage Response Agents (or Combinations) in Patients With Advanced Cancer Whose Tumours Contain Molecular Alterations"). These rules are based on Lynparza HRR classification algorithm (used in AstraZeneca clinical trials).

The appendix is made available for information purposes only. Use of this guidance outside the PLANETTE study is entirely at the investigator's discretion.

This document contains 3 sections.

- Section K 1.1 describes the generic rules for determining qualifying mutations in ATM (EntrezID 472; RefSeq NM_000051).
- Section K 1.2 describes a look-up list of qualifying mutations that do not meet the generic rules in section K 1.1.
- Section K 1.3 describes the rationale and process for arriving at the qualifying mutations listed in section K 1.2.

K 1.1 Instructions for generic eligibility criteria for ATM

- Classification of variants will be conducted in accordance with the principles published in the American College of Medical Genetics and Genomics (ACMG) standards and guidelines for the interpretation of sequence variants (Richards et al 2015).
- For clarification, only patients with "deleterious" or "suspected deleterious" variants will be considered qualifying within the PLANETTE study. Patients with variants of uncertain significance (VUS) will not be eligible.

The following algorithm implements the criteria specified above. If the variant meets any of the following criteria the patient is considered eligible for the study:

- Mutations that result in truncation of the protein product, including:
  - Any nonsense mutations
  - Any frameshift indels

  - Any mutations in the consensus splice donor and acceptor sequence (5' GT……intron…..AG 3') that disrupts the consensus, including insertions and deletions
- Large-scale genomic deletions (affecting at least one whole exon), insertions or rearrangements
- Any homozygous deletion
- Any missense, splice, nonsense, or short in frame deletions not captured by above but specified as deleterious, pathogenic, clinically important, suspected deleterious or suspected pathogenic in the BIC or ClinVar database, or by a validated Dx device, or known to be founder mutations in a given local region.
- Any mutations not captured above but specified in the lookup table from Section K 1.2.

K 1.2 Special instructions for eligibility criteria for mutations ATM gene

Any variant which does not meet the above generic eligibility criteria in Section K 1.1 should be queried against the variant look-up lists for special variants. If the variant is present in the separate look-up lists, the alteration is considered qualifying.

The current resultant lists are given below as Table 28 and Table 29 with numbering based on NM_000051 (ATM) transcript.

Table 28 Look-up List for Missense and Synonymous Variants

Gene	Variant	Source
ATM	M1T	ClinVar
ATM	K750K	ClinVar
ATM	R2032K	ClinVar
ATM	R2227C	ClinVar
ATM	V2424G	ClinVar
ATM	R2547_S2549del	ClinVar
ATM	G2765S	ClinVar
ATM	R2832C	ClinVar
ATM	S2855_V2856delinsRI	ClinVar
ATM	R3008C	ClinVar
ATM	R3008H	ClinVar

Table 29 Look-up List for Deleterious Intronic Variants

Gene	Chr	Position	Ref	Alt	dbSNP	Source
ATM	chr11	108128198	T	G	rs730881346	ClinVar
ATM	chr11	108214102	AGTGA	A	rs730881295	ClinVar

K 1.3 Procedures used to generate the look-up tables in Section K 1.2

The following procedures were used to generate the static look-up tables with information ClinVar to complement the generic rules from Section K 1.1. The tables were locked down on 11 Jan 2016 (based on a November 2015 extract from ClinVar).

- The ClinVar database for variants in **ATM** was used with the following inclusion criteria:
  - In "Clinical significance", with entries "pathogenic" or "likely pathogenic".
  - And variant specified as missense, or synonymous, or intronic.
  - And in "Review status", with the entry "expert panel", which corresponds to the 3 star rating as discussed with AstraZeneca, or 2 star rating with multiple consistent submission. The 4 star rating is a category called 'Practice guideline' that wasn't available for any missense mutations in these genes.

K 2 References

Richards et al 2015
Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-24.

Appendix L Abbreviations

Abbreviation or special term	Explanation
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé (French National Agency for Medicines and Health Products Safety)
ARID1A	AT-Rich Interaction Domain 1A
aST	Advanced Solid Tumours
AST	Aspartate transaminase
ATM	Ataxia telangiectasia mutated
ATR	Ataxia telangiectasia and rad3 related protein
BCRP	Breast cancer resistance protein
BICR	Blinded independent central review
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
BRCA1	BReast CAncer gene 1
BRCA2	BReast CAncer gene 2
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials

COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CPT	Common Protocol Template
CR	Complete response
CrCl	Creatinine clearance
CRO	Clinical Research Organisation
CSF	Cerebrospinal fluid
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computerised tomography
CTA	Clinical Trial Applications
CTC	Circulating tumour cell
CTCAE	Common Terminology Criteria for Adverse Events
CCI	CCI
CYP	Cytochrome P
DCO	Data Cut Off
DDR	DNA-damage response
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DoR	Duration of response
DRD	DNA-Repair gene Defects
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form

EMA	European Medicines Agency
ESR	Externally Sponsored Research
EU	European Union
FAS	Full Analysis Set
FDA	The Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	Formalin fixed and paraffin embedded
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCV	Hepatitis C virus
HGSOC	High-grade serous ovarian cancer
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HL	Hy's Law
HR	Homologous recombination
HRR	Homologous recombination repair
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
IND	Investigational New Drug

INR	International normalized ratio
IRB	Institutional Review Board
IVRS	Interactive Voice/Web Response System
LHRH	Luteinizing hormone-releasing hormone
mCRPC	Metastatic castration-resistant prostate cancer
MRI	Magnetic resonance imaging
NE	Not evaluable
NGS	Next generation sequencing
NHA	Novel hormonal agent
NTRK	Neurotrophic tyrosine receptor kinase
ULN	Upper limit of normal
NSCLC	Non-small-cell lung carcinoma
NTL	Non-target lesions
OATP1B1	Organic anion transporter protein B1
ORR	Objective response rate
OS	Overall survival
PARP	Poly (ADP-ribose) polymerase
PCWG3	Prostate Cancer Working Group 3
PD	Progressive disease
PDc	Pharmacodynamic
PET	Positron emission tomography
PFS	Progression free survival
PHL	Potential Hy's Law
Pgp	P-glycoprotein
PI	Principal investigator

PIKK	Phosphoinositide-3-kinase related kinase
PK	Pharmacokinetic
PPS	Per Protocol Analysis Set
PR	Partial response
PR interval	The time from the onset of the P wave to the start of the QRS complex
PSA	Prostate specific antigen
QRS	A combination of the Q wave, R wave and S wave, the QRS complex
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
RPA	Replication Protein A
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCHNN	Squamous cell carcinoma of the head and neck
SD	Stable disease
SE	Standard error
SMPC	Summary of product characteristics
SoA	Schedule of activities
SoC	Standard of care
SUSAR	Suspected unexpected serious adverse reactions
TBL	Total bilirubin
TL	Target lesions
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States

UV	Ultraviolet
QT interval	The time from the start of the Q wave to the end of the T wave
QTcF	The corrected QT interval (QTc) according to Fridericia's formula
WBDC	Web Based Data Capture
WHO	World Health Organization
WOCBP	Women of childbearing potential

Appendix M Protocol Amendment History

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

Amendment 3 (04-Apr-2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Preliminary data (Yap et al. Cancer Discov. 2021;11(1):80-91.) showed that patients with either ATM mutation, or ATM protein loss, or both had benefit on an ATR inhibitor. In Module 1 we used an arbitrary 60% threshold for the minimum number of patients with ATM protein loss. However, there is no robust justification for this threshold, and it is impeding recruitment, therefore we propose to remove the 60% threshold for both cohorts A and B. This amendment will not impact the primary analysis, and the subgroup analysis will still be conducted and patients' tumor samples tested retrospectively.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-Substantial
MODULE 1 (Section 11) **Ceralasertib Monotherapy in ATM Altered Advanced Solid Tumours (aST) and Prostate Cancer**			
8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Deletion of the text "a participant has completed the study" and addition of text "last safety follow up visit"	to clarify collection of SAEs discontinues after safety follow up visit.	Non-substantial
11.1.1 M1 Synopsis, Number of Participants Cohort A	Deletion of text "ensuring at least 60% of participants with ATM IHC ≤ 5%"	Please see overall rationale	Substantial
11.1.1 M1 Synopsis, Number of Participants Cohort B	Deletion of text "ensuring at least 60% of participants with ATM IHC ≤ 5%"	Please see overall rationale	Substantial
11.1.2 M1 Study Design	Deletion of footnote 2 "[2] A minimum of 60% participants will be ATM IHC ≤ 5% (ie n=15) in addition to having a deleterious or suspected deleterious (or pathogenic/likely pathogenic) mutation in the ATM gene. ATM 'deficient' is	Please see overall rationale	Substantial

	defined as ATM IHC ≤ 5% ATM-positive tumour nuclei using the Ventana assay (VENTANA ATM (Y170) RPA Assay)"		
11.1.3 Schedule of Activities (SoA) Table 3, Footnote A	Addition of the text "If prospective central ATM NGS testing is introduced" and "must submit a sample"	Clarification that this relates to prospective NGS testing only	Non-substantial
11.1.3 Schedule of Activities (SoA) Table 3, Footnote E	Addition of the text "scheduled"	Clarification that CCI is only taken at scheduled assessments and at progression	Non-substantial
11.1.3 Schedule of Activities (SoA) Table 3, Footnote L	Addition of the text "All safety assessments and laboratory results must be reviewed by the Investigator or physician designee prior to start of each study treatment dosing cycle"	Clarification	Non-substantial
11.2 M1 Introduction	Deletion of the text "ensuring at least 60% of participants with ATM IHC ≤ 5%" and addition of text "Prospective selection of patients with ATM IHC ≤ 5% may be introduced in each cohort based on emerging ATM protein deficiency prevalence and ceralasertib clinical activity"	Please see overall rationale	Substantial
11.2.1.2 Module Rationale, Prostate Cancer	Deletion of text "evaluating rucaparib in patients"	Typo	Non-substantial
11.4.1.1 Study Design Cohort A	Addition of the text "dosed at ceralasertib 160mg BID"	Clarification	Non-substantial
11.4.1.1 Study Design Cohort A	Deletion of the text "with prospective selection, if necessary, to ensure at least 60% of participants with ATM IHC ≤ 5%"	Please see overall rationale	Substantial
11.4.1.1 Study Design Cohort A (Figure 3)	Deletion of foot note 2 "[2]A minimum of 60% participants will be ATM IHC ≤ 5% (ie n=15) in addition to having a	see overall rationale	Substantial

	deleterious or suspected deleterious (or pathogenic/likely pathogenic) mutation in the ATM gene. ATM 'deficient' is defined as ATM IHC ≤ 5% ATM-positive tumour nuclei using the Ventana assay (VENTANA ATM (Y170) RPA Assay)"		
11.4.1.2 M1 Design, Cohort B	Addition of the text "dosed at ceralasertib 160mg BID"	Clarification	Non-substantial
11.4.1.2 Study Design Cohort B	Deletion of the text "ensuring at least 60% of participants with ATM IHC ≤ 5%"	see overall rationale	Substantial
11.4.1.2 Study Design Cohort B (Figure 4)	Deletion of the text "A minimum of 60% participants will be ATM IHC ≤ 5% (ie n=16) in addition to having a deleterious or suspected deleterious (or pathogenic/likely pathogenic) mutation in the ATM gene"	see overall rationale	Substantial
11.4.1.3 Confirmation of ATM Protein Expression and ATM Mutation Status	Deletion of the text "To ensure that a minimum of 60% participants will be ATM IHC ≤ 5% for each disease cohort (ie n=15 aST and n=16 prostate) by the time of the interim and final analyses, an additional enrolment criteria of ATM loss may be implemented. To enable this" Additional text added to clarify that prospective testing may be introduced. The decision to trigger prospective participant selection may be based on preliminary data from subgroup analysis"	see overall rationale	Substantial
11.5.1.1 Inclusion Criteria Screening Part 1 (Molecular Eligibility)	Deletion of the text "if required to ensure a minimum 60% enrolled participants are ATM IHC deficient (defined as ATM protein staining ≤ 5% of tumour nuclei) by the time of interim analysis and final analysis in addition to ATM genetic alteration. Prospective selection by ATM IHC will only be triggered after a maximum number of participants with ATM	see overall rationale	Substantial

	protein staining of > 5% by IHC have been enrolled"		
11.5.1.1 Inclusion Criteria, Screening Part 1 (Molecular Eligibility)	Addition of the text "if prospective ICH ATM testing is triggered, local ATM NGS test report must be provided" Deletion of the text "Prospective ATM NGS central testing may be introduced"	Correction around provision of local ATM NGS tests	Non-substantial
11.5.1.1 Inclusion Criteria, Screening Part 1 (Molecular Eligibility)	Inclusion criterion #2 – Addition of the text to clarify details around ATM mutation	Clarification	Non-substantial
11.5.1.2 Inclusion Criteria, Screening Part 2 (Study Eligibility), Type of Participant and Disease Characteristics	Inclusion criterion #4(a) - Addition of the text "Participants already receiving erythropoietin at the time of screening for the study may continue it providing they have been receiving it for more than one month at the time study intervention is started" This text was moved from Section, 11.6.5, Concomitant Therapy, Supportive Care	Clarification	Non-substantial
11.5.1.3 Inclusion Criteria, Other, Cohort A- aST	Inclusion criterion #2 – Deletion of text "Specimens from bone biopsies"	Details to be added to lab manual allowing bone biopsies post validation	Non-substantial
11.5.1.4 Inclusion Criteria, Other, Cohort B - mCRPC	Inclusion criterion #2 – Deletion of text "Specimens from bone biopsies"	Details to be added to lab manual allowing bone biopsies post validation	Non-substantial
11.5.2 Exclusion Criteria (Cohort A and Cohort B), Medical Conditions	Exclusion criterion #1, 7th bullet point - Addition of text "28 days"	Correction of typo in CSP Amendment 02. Correct wording was in CSP Amendment 01	Non-substantial

11.5.2 Exclusion Criteria (Cohort A and Cohort B), Medical Conditions	Exclusion criterion #4 – Addition of the text "if new asymptomatic brain metastases are discovered, an interval scan (minimum 4 weeks) should be conducted to confirm the new brain lesions are not progressing and do not require local CNS-directed therapy. If local treatment is necessary, this should occur before study entry"	Clarification around identification and management of asymptomantic brain mets	Non-substantial
11.5.2 Exclusion Criteria (Cohort A and Cohort B), Medical Conditions	Exclusion criterion #4a- Addition of the text "and direct factor Xa inhibitors"	Addition of class of drugs that can lead to INR elevation	Non-substantial
11.6.5 Concomitant Therapy	Deletion of text "Paracetamol/Acetaminophen, at doses of ≤ 2 grams/day, is permitted for use anytime during the study. Other concomitant medication may be considered on a case by case basis by the investigator in consultation with the Medical Monitor if required"	Removal of text from protocol template left in error	Non-substantial
11.6.5.1 Concomitant Therapy, Supportive Care	Moving of the text "Participants already receiving erythropoietin at the time of screening for the study may continue it providing they have been receiving it for more than one month at the time study intervention is started" to Section 11.5.1.2 Inclusion Criteria, Screening Part 2 (Study Eligibility), Type of Participant and Disease Characteristics Deletion of the text "Prophylactic erythropoietin should not be started during Cycle 1 of the study, but may be started during Cycle 2 and after, following discussions with the Principal Investigator and AstraZeneca"	Movement of text - clarification Deletion of text - correction	Non-substantial
11.6.6.3 Individual Stopping Criteria, Hepatic	Addition of text "or other vitamin K antagonists, or direct factor Xa inhibitors"	Addition of class of drugs that can lead to INR elevation	Non-substantial

11.7 Discontinuation of study Intervention and Participant Discontinuation/Withdrawal – Module 1	Addition of text "Patients may receive study intervention until objective disease progression, or as long as they are continuing to show clinical benefit, as judged by the investigator, or treatment discontinuation criteria are met"	Clarification of length of study treatment	Non-substantial
11.8.2 Module Assessments and Procedures- Module 1, Safety Assessments	Addition of text "For all participants, results of all safety assessments must be available and must be reviewed by the Investigator or their deputy prior to start of each dosing cycle. Samples can be collected the day before dosing cycle start. Prior to discharge from each in-patient and clinic visit, the Investigator or their deputy will be responsible for reviewing all available safety data, including vital signs and ECGs"	Clarification	Non-substantial
11.8.6.1 Human Biological Sample Biomarkers, Collection of Archival Tumour Samples	Deletion of text "Bone samples are inadequate for central testing"	Details to be added to lab manual allowing bone biopsies post validation	Non-substantial
11.9.2 Sample Size Determination Cohort A	Deletion of text "ensuring at least 60% of participants with ATM IHC ≤ 5%" Addition of text "dosed at ceralasertib 160mg BID"	see overall rationale	Substantial
11.9.2 Sample Size Determination Cohort B	Deletion of text "ensuring at least 60% of participants with ATM IHC ≤ 5%" Addition of text "dosed at ceralasertib 160mg BID"	see overall rationale	Substantial
11.9.2 Sample Size Determination	Deletion of text "It is intended to ensure at least 60% of participants have ATM IHC ≤ 5%, in order to have an adequate number of participants for exploration of efficacy in this subset"	see overall rationale	Substantial
11.9.4 Summary of Analyses and Data Cut-off	Deletion of text "with at least 60% ATM IHC ≤ 5%)"	Please see overall rationale	Substantial

Triggers Cohort A (Table 13)			
11.9.4 Summary of Analyses and Data Cut-off Triggers Cohort B (Table 13)	Deletion of text "with at least 60% ATM IHC ≤ 5%)"	Please see overall rationale	Substantial
11.9.5.1 Interim Analyses Cohort A	Deletion of text "with at least 60% ATM IHC ≤ 5%" Addition of text "dosed at ceralasertib 160mg BID"	Please see overall rationale	Substantial
11.9.5.1 Interim Analyses Cohort B	Deletion of text "with at least 60% ATM IHC ≤ 5%" Addition of text "dosed at ceralasertib 160mg BID"	Please see overall rationale	Substantial
Throughout	Minor administrative changes	To correct errors in format, typography or language	Non-substantial

Amendment 2 (27-May-2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Inclusion of updates made for Amendment FRA-1, a local protocol amendment applicable in France that was prepared in response to queries from the French National Agency for Medicines and Health Products Safety (ANSM), to implement urgent safety measures (adding extra safety visits and reducing dose to 160 mg BID), and for template and other updates to aid sense and flow of the document.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
CORE			
2.2 Background	Deletion of the text "This modular study will investigate the efficiency and tolerability of ceralasertib in patients with various molecular alterations".	Module 1 specific text is not required in the Core section.	Non-substantial
4.1.3 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis	Addition of new section/text relating to study disruption.	To allow greater flexibility for study conduct during current COVID-19 pandemic or other similar situations.	Substantial
5.1 Inclusion Criteria	Inclusion criterion 6 regarding ability to swallow tablets was moved to Module 1, Section 11.5.1.2.	Future modules may not include tablets.	Non-substantial
7.1 Discontinuation of Study Intervention	Text additions clarifying the situations for study intervention discontinuation.	Template text update.	Non-substantial
7.2 Participant Withdrawal from the Study	Text describing procedure for withdrawal of consent for disclosure of future information and use of existing samples has been added.	Template text update.	Non-substantial
	Text describing modified follow-up options was deleted.	This is not applicable to this study.	Non-substantial
	Text describing a study intervention discontinuation visit was deleted.	Visit deleted as there is no such visit in the study.	Non-substantial
8.2.3 Electrocardiograms	Text describing triplicate ECG recordings was added from Module 1 Section 11.8.2.3.	Generic screening ECG details retained in the Core section.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Text was amended to clarify that AEs will be collected throughout treatment period.	Clarification that AEs will be collected from start of study treatment period and not from screening.	Non-substantial
8.3.9.1 Maternal Exposure	The text was changed from "congenital abnormalities" to "congenital anomaly".	Template text update.	Non-substantial
Throughout	Minor administrative changes.	This revision was made to correct errors in format, typography or language.	Non-substantial
MODULE 1 (Section 11): **Ceralasertib Monotherapy in ATM Altered Advanced Solid Tumours (aST) and Prostate Cancer**			
11.1.1 Synopsis	Number of participants was updated to include "Addition of the text "At the time of protocol amendment 2, 1 participant had been dosed at 240 mg BID in Cohort A, and 8 participants had been dosed at 240 mg BID in Cohort B. Following the reduction of the starting dose from 240 mg BID to 160 mg BID in protocol amendment 2, the intention is to enrol an additional total of ~25 and ~27 participants in Cohort A and B, respectively, at the 160 mg BID".	Clarification of sample size following dose reduction to 160 mg BID.	Substantial
11.2 Schema	Figure 2 Module Design was updated to reflect the updated dose of 160 mg BID.	Update following dose reduction to 160 mg BID.	Substantial
11.1.3 Schedule of Activities	In Table 3 (Schedule of Activities), the time window for Cycle 2 Day 1 and from Cycle 3 Day 1 onwards updated to "-1/+3 days".	Update allows for any required assessment results to be received.	Non-substantial
	In Table 3 (Schedule of Activities), the time window for last dose of study intervention was updated from "± 7 days" to "+ 7 days".	There is no possibility of a time window prior to last dose.	Non-substantial
	In Table 3 (Schedule of Activities), "Provide copy of local NGS testing report" was added.	Clarification of this requirement at screening.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	In Table 3 (Schedule of Activities), "Optional tumour sample" was added as a separate row.	Clarification of tumour sampling in SoA. Mandatory at screening and optional at last dose and follow-up. Optional samplings are not archival or standard of care.	Non-substantial
	In Table 3 (Schedule of Activities), "Peripheral blood for [redacted] was moved up in order of appearance in the table.	To group together assessments performed at screening.	Non-substantial
	In Table 3 (Schedule of Activities), addition of "triplicate" in the ECG assessment row for screening. Deletion of assessment timepoints during the study period.	Clarification that triplicate ECGs would be collected at screening only.	Substantial
	In Table 3 (Schedule of Activities), addition of assessment time points for Cycle 1 Day 14 and Cycle 2 Day 14.	To confirm vital signs assessment during the treatment period.	Substantial
	In Table 3 (Schedule of Activities), "Clinical safety laboratory assessments" was changed to "Complete blood count and other clinical safety laboratory assessments".	Clarification.	Non-substantial
	In Table 3 (Schedule of Activities), "Serum testosterone (not required in participants after bilateral orchiectomy) and PSA (if no radiographic progression, local assessment" was added.	Clarification of this requirement as per inclusion criteria for Cohort B.	Non-substantial
	In Table 3 (Schedule of Activities), footnote d for ECG was deleted as no longer required. Subsequent footnote numbering was updated.	Footnote is no longer required.	Non-substantial
	In Table 3 (Schedule of Activities), additional Day 8 visits were added for Cycle 1 and Cycle 2.	Precautionary monitoring of safety assessments related to ≥ G3 thrombocytopenia or ≥ G3 neutropenia.	Substantial
	Footnotes were updated, including re-numbering.	Clarification.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
11.2 Introduction – Module 1	Text was updated from "ATM IHC ≥5%" to "ATM IHC >5%".	Definition should be more than 5% (not equal or more).	Non-substantial
	Text was updated to include "Definitions of qualifying ATM mutations include deleterious/suspected deleterious, pathogenic/likely pathogenic, disease, or cancer-associated variants. Variants or unknown significance or benign variants are not eligible for enrolment".	Clarify definition of ATM mutations.	Non-substantial
11.2.1 Module Rationale	Text was updated from "Ataxia telangiectasia and rad3 related protein…" to "Ataxia telangiectasia mutated protein loss..".	Updated to reflect the description of ataxia telangiectasia.	Non-substantial
	Text was added to describe further details of the first in human ATR inhibitor study.	IRB request.	Non-substantial
11.2.1.2 Prostate Cancer	Text was added "The concept of synthetic lethality of DDR inhibitors in DDR-deficient backgrounds has been explored clinically in mCRPC: PARPi have been used in BRCA1/2 mutations and HRR mutations, including ATM mutations." to replace the original text "Targeted next generation sequencing of advanced prostate cancer has identified an 8% incidence of ATM mutations (Beltran et al, 2013 and Choi et al, 2016)."	Clarity in the description of BRCA mutations.	Non-substantial
11.2.2.2 Disease Linkage	Text was deleted "...a rare, autosomal recessive disorder that leads to progressive neurodegeneration (cerebellar ataxia), orbital telangiectasia, immunodeficiency.."	To aid clarity and flow.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
11.3 Objectives and Endpoints – Module 1	In Table 5 (Objectives and Endpoints – Cohort A), one of the secondary endpoints/variables was reworded to remove the details regarding the urinalysis and coagulation.	These parameters are not collected during the study.	Non-substantial
	In Table 5 (Objectives and Endpoints – Cohort A), one of the secondary endpoints/variables was reworded to remove the details regarding ECG.	ECG is not an endpoint/variable in the study.	Non-substantial
	In Table 5 (Objectives and Endpoints – Cohort A), the exploratory objective for CCI CCI CCI ".	Clarification.	Non-substantial
	In Table 6 (Objectives and Endpoints – Cohort B), the primary objective was reworded to remove the details regarding the previous treatments of participants.	To align objectives with the revised Inclusion Criterion 3 for Cohort B.	Non-substantial
	In Table 6 (Objectives and Endpoints – Cohort B), addition of a secondary endpoint//variable "Duration of radiological response".	Consistency since it is also listed in the statistics section.	Non-substantial
	In Table 6 (Objectives and Endpoints – Cohort B), one of the secondary endpoints/variables was reworded to remove the details regarding the urinalysis and coagulation.	These parameters are not collected during the study.	Non-substantial
	In Table 6 (Objectives and Endpoints – Cohort B), one of the secondary endpoints/variables was reworded to remove the details regarding ECG.	ECG is not an endpoint/variable in the study.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	In Table 6 (Objectives and Endpoints – Cohort B), addition of the exploratory endpoints/variables "CCI [redacted]".	For consistency since it is also listed in the statistics section.	Non-substantial
	In Table 6 (Objectives and Endpoints – Cohort B), the exploratory endpoint/variable for CCI [redacted]	CCI [redacted]	Non-substantial
	In Table 6 (Objectives and Endpoints – Cohort B), the exploratory objective for CCI [redacted] CCI [redacted]	Clarification.	Non-substantial
	In Table 6 (Objectives and Endpoints – Cohort B), the exploratory endpoint/variable for CCI [redacted] was added.	Clarification to be consistent with the objective.	Non-substantial
11.4.1.1 Cohort A	Figure 3 Study Design was updated to reflect the updated dose of 160 mg BID.	Update following dose reduction to 160 mg BID.	Substantial
11.4.1.2 Cohort B	For Figure 4 (Study Design – Cohort B) the footnote was updated with "in addition to having a deleterious or suspected deleterious mutation in the ATM gene".	For consistency with the footnote for Figure 3 (Study Design – Cohort A).	Non-substantial
	Figure 4 Study Design was updated to reflect the updated dose of 160 mg BID.	Update following dose reduction to 160 mg BID.	Substantial
11.4.1.3 Confirmation of ATM Protein Expression and	Section 11.8.3.3 was moved from "Human biological samples" to "Study design" as a new subsection.	To aid clarity since the description of ATM expression and mutation confirmation is part of the study design.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
ATM Mutation Status	The text description was updated to better describe the process for confirming ATM protein expression and ATM mutation status. Text was also updated to define qualifying ATM mutations.	Clarification.	Non-substantial
	The text "This may only be implemented in the study after the 7th participant in the aST cohort or the 4th participant in prostate cancer cohort has been enrolled and is positive for ATM protein staining of > 5% by IHC" was deleted.	To allow flexibility for study conduct.	Non-substantial
11.4.3 Justification for Dose	The whole section was updated to include a description of the change in dose from 240 mg BID to 160 mg BID.	To implement urgent safety measures including reducing dose to 160 mg BID.	Substantial
11.5.1 Inclusion Criteria	Addition of the text "All participants must submit blood and FFPE tumour samples for central confirmation of ATM mutation and ATM IHC testing".	Clarification that submission of a tumour sample is required for central confirmation even if the participant has a local NGS report available.	Non-substantial
11.5.1.1 Screening Part 1 (Molecular eligibility)	Addition of text describing requirements for local ATM NGS testing. Also confirming that all participants must submit a FFPE tumour sample for central NGS and IHC confirmation. Prospective ATM NGS testing may be introduced.	Clarification of the requirements for Screening Part 1.	Non-substantial
	Screening Part 1 Inclusion Criterion 2 was revised to specify that eligible participants have deleterious or suspected deleterious ATM mutation in tumour or blood.	To allow participants with germline mutations to avoid local testing of the tumour.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Screening Part 1 Inclusion Criterion 2 was revised to include "Definitions of qualifying ATM mutations include deleterious/suspected deleterious, pathogenic/likely pathogenic, disease, or cancer-associated variants. Variants or unknown significance or benign variants are not eligible for enrolment".	Clarify definition of ATM mutations.	Non-substantial
	Screening Part 1 Addition of a new inclusion criterion regarding tumour sample for central confirmation of ATM mutation and ATM IHC testing.	For clarity, existing text in the section was moved down/edited and added to the list of criteria.	Substantial
11.5.1.2 Screening Part 1 (Study eligibility)	Screening Part 2 Inclusion Criterion 1 was revised to specify that eligible patients should have no standard treatment available.	Revision was requested by ANSM because early phase clinical trials should enrol participants without therapeutic alternatives.	Substantial
11.5.1.3 Cohort A - aST	Cohort A – aST Inclusion Criterion 2 was revised to include "The site needs to refer to the pathology manual for acceptable tissue types for testing. Specimens from bone biopsies and fine needle aspirates are not acceptable."	For clarity in terms of acceptable tissue types for testing.	Non-substantial
11.5.1.4 Cohort B - mCRPC	Cohort B – mCRPC Inclusion Criterion 2 was revised to include "The site needs to refer to the pathology manual for acceptable tissue types for testing. Specimens from bone biopsies and fine needle aspirates are not acceptable."	For clarity in terms of acceptable tissue types for testing.	Non-substantial
	Cohort B – mCRPC Inclusion Criterion 3 was revised to specify that eligible patients should have received at least one taxane regimen (unless the participant has contraindications to taxanes).	Requested by ANSM.	Substantial
	Cohort B – mCRPC Inclusion Criterion 7 was revised to add "(not required for participants after bilateral orchiectomy)".	For clarity.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
11.5.2 Exclusion Criteria	Exclusion Criterion was added under medical conditions to exclude participants with INR ≥ 1.5 (except those who receive vitamin K antagonists) or with other evidence of impaired hepatic synthesis function.	Requested by ANSM for consistency with Individual Stopping Criteria.	Substantial
11.6.1 Study Intervention Administered	Table 7 Investigational Products was updated to include the change for dose from 240 mg twice daily to 160 mg twice daily. A footnote was also added to clarify the change and additional information.	To implement urgent safety measures including reducing dose to 160 mg BID.	Substantial
11.6.5 Concomitant Therapy	Text was added to detail anti-cancer therapies not allowed during the study.	To specify in more detail the allowed anti-cancer treatments during the study.	Non-substantial
11.6.6.2 Guidance for Dose Modification and Interruption	Additional test was added "Participants with ≥ G3 anaemia, neutropenia, thrombocytopenia during Cycle 1 and Cycle 2 will be required to attend for additional Day 8 and Day 14 assessments until there is no evidence of ≥ G3 anaemia, neutropenia, thrombocytopenia for at least 2 cycles. Participants who develop a ≥ G3 anaemia, neutropenia, thrombocytopenia later in their treatment, will also need to have additional Day 8 and Day 14 assessments until there is no evidence of ≥ G3 anaemia, neutropenia, thrombocytopenia for at least 2 cycles".	Precautionary monitoring of safety assessments related to ≥ G3 anaemia, neutropenia, and thrombocytopenia.	Substantial
	Table 8 was updated to include instructions to specify that treatment must be stopped after 2 occurrences of Grade 4 non-haematological toxicities.	Requested by ANSM.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Table 9 Dose Reduction Levels for Ceralasertib was updated to include the change for dose from 240 mg twice daily to 160 mg twice daily. A footnote was also added to clarify the change and additional information.	To implement urgent safety measures including reducing dose to 160 mg BID.	Substantial
11.6.6.3 Individual Stopping Criteria	This sub-heading was moved up to include the "Cardiovascular" subheading under it.	For clarity of text.	Non-substantial
11.6.7 Intervention after the End of the Study	Possibility to continue treatment after the end of the study was added.	Requested by ANSM.	Substantial
	Additional detail describing the possibility of an extension study was added.	Template text update.	Non-substantial
11.8.1.2 Bone lesions assessment in Cohort B (mCRPC) (Based on PCWG3 Criteria)	In Table 10 (Requirements for Documentation of Progression), the "Week 8 scan" and "Subsequent scans" visit time windows were updated. Minor updates for criteria for bone progression definitions.	Clarification of time windows for assessments.	Non-substantial
	Text describing CCI [redacted] was added from Section 11.8.6 "Human Biological Sample Biomarkers" to Section 11.8.1.2.	For clarity since both are efficacy assessments and to clarify between clinical and CCI [redacted].	Non-substantial
11.8.2.3 Electrocardiograms	Text describing triplicate ECG recordings at Screening Part 2 was moved to Core Section 8.2.3.	To keep the generic screening ECG details in the Core section.	Non-substantial
11.8.2.5 Brain Scan	Text describing the brain scan process was re-ordered.	To aid clarity and flow.	Non-substantial
11.8.2.6 Clinical Safety Laboratory Assessments	In Table 11 (Laboratory safety variables), footnote c was added to confirm that "Coagulation and urinalysis are only scheduled for baseline and as clinically indicated post-baseline".	To clarify collection of coagulation and urinalysis at baseline only.	Non-substantial
11.8.5.2 Pharmacodynamics	Addition of the text "This sample may also be used to assess CCI [redacted]."	Clarification.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
11.8.6.1 Collection of Archival Tumour Samples	Collection of archival tumour samples was moved under Section 11.8.6 Human Biological Sample Biomarkers and updated to remove "decalcified samples" and add "Bone samples are inadequate for central testing".	Bone biopsies are not suitable for IHC.	Non-substantial
11.8.6.3 Collection of Exploratory CCI [redacted]	Text was added to differentiate that these are exploratory CCI samples.	To clarify the clinical CCI samples (efficacy) and these exploratory CCI samples.	Non-substantial
11.9.2 Sample Size Determination	Addition of the text "At the time of protocol amendment 2, 1 participant had been dosed at 240 mg BID in Cohort A, and 8 participants had been dosed at 240 mg BID in Cohort B. Following the reduction of the starting dose from 240 mg BID to 160 mg BID in protocol amendment 2, the intention is to enrol an additional total of ~25 and ~27 participants in Cohort A and B, respectively, at the 160 mg BID".	Clarification of sample size following dose reduction to 160 mg BID.	Substantial
11.9.3 Population for Analyses	In Table 12 (Population for Analysis) updates to description text for CTC count and inclusion of a footnote defining molecularly eligible centrally confirmed.	To clarify the description of population sets regarding CTC count and to clarify what is considered molecularly eligible centrally confirmed.	Non-substantial
11.9.4 Statistical Analyses	In Table 13 (Summary of Analyses and Data Cut-off Triggers) addition of "evaluable for response" when describing molecularly eligible participants.	To clarify the definition of participants as molecularly eligible centrally confirmed evaluable for response participants.	Non-substantial
11.9.4.1 General Considerations	Text was updated to confirm data presentation for safety and efficacy data.	To clarify that only 160 mg BID data will be presented in summary efficacy tables. All other information will be included in the listings.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
11.9.4.2 Safety	Text was updated to removed "ECG changes" from safety analysis.	ECG is not an endpoint/variable in the study.	Non-substantial
11.9.4.3 Pharmacokinetic Variables	Text was updated to delete "Pharmacokinetic analysis of the plasma concentration data for study intervention will be the responsibility of Covance."	To remove specific details of laboratories which will be documented separately.	Non-substantial
11.9.4.5 Efficacy	Addition of text description under secondary endpoints for "Percentage Change in Tumour Size".	For consistency between listed endpoints/variables in Section and the statistical Section 11.3.	Non-substantial
Throughout.	Clarifying the description of the mutation in the ATM gene throughout from "deleterious mutation" to "deleterious or suspected deleterious mutation".	To include participants with suspected deleterious mutations in addition to participants with deleterious mutations.	Non-substantial
	Update of "AST" to "aST" for advanced solid tumours.	To clarify the abbreviations for advanced solid tumour (aST) and aspartate transaminase (AST).	Non-substantial
	Minor administrative changes.	To correct errors in format, typography or language.	Non-substantial
Appendix A Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis	Addition of appendix relating to study disruption.	To describe processes during the current COVID-19 pandemic or other similar situations.	Substantial
Appendix H Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Under Section H2, the text was changed from "congenital abnormalities" to "congenital anomaly".	Template text update.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Appendix G Guidelines for Evaluation of Objective Tumour Response Using PCWG3 (Prostate Cancer Working Group Criteria 3) in Bone Lesions	Minor update of Table 27 title from "Best Overall Response When confirmation of CR and TR Required" to "Best Overall Response When confirmation of CR and PR Required".	Typographical correction.	Non-substantial
Appendix K ATM Alterations Classification Guidance	An appendix was created to provide details on the rules for qualifying ATM mutations.	To provide clarification for ATM mutation definitions.	Substantial
Appendix M Protocol Amendment History	An appendix was created to include summary of changes of previous amendments.	This appendix is required per template when amending the protocol more than once.	Non-substantial

Amendment 1 (12-August-2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Table 8 has been updated to add clarity on the management of neutropenia, anaemia and prolonged or intolerable Grade 2 toxicity.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
11.6.6.2, Guidance for Dose Modification and Interruption, Table 8.	Addition of "discontinuations" to table title.	To clarify that that the table provides guidance for dose modifications, interruption and discontinuations for ceralasertib.	Substantial
	Addition of definition for prolonged Grade 2 toxicity.	To provide greater clarification for the management of Grade 2 toxicity.	Substantial
	Addition of "Grade 2" for thrombocytopenia" under Grade 2 events.	To provide greater clarification for the management of Grade 2 neutropenia and Grade 2 thrombocytopenia.	Substantial
	Addition of "Grade 3-4 neutropenia or Grade 4 anaemia" under Grade 3-4 toxicity	To provide greater clarification for the management of Grade 3 neutropenia and anaemia.	Substantial

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