Clinical Study Protocol	
Study Intervention	Adavosertib (AZD1775)
Study Code	D601HC00002
Version	6.0
Date	20 May 2022

A Phase 2b, Open-label, Single-arm, Multi-centre Study Assessing the Efficacy and Safety of Adavosertib as Treatment for Recurrent or Persistent Uterine Serous Carcinoma (ADAGIO)

Sponsor Name:

Legal Registered Address:

AstraZeneca AB, S-151 85 Södertälje, Sweden.

Regulatory Agency Identifier Number(s):

EudraCT number: 2020-000138-16

IND number: 147430

VERSION HISTORY

Version 1.0, 25 June 2020
Initial creation

Version 2.0, 30 July 2020
The protocol was revised to address the FDA recommendations received on 17 and 28 July 2020: Section 8.3.13.1 was updated to reflect changes in the haematologic toxicity dose modifications management. • **Table 11** was revised to reflect the following: – A second instance of Grade 3 neutropenia with documented infection and/or fever should result in adavosertib discontinuation. However, it is proposed that in exceptional circumstances, the investigator/treating physician may consider continuing dosing at dose level -2 only when the benefits are considered to outweigh the risks and after approval by the Medical Monitor. • **Table 12** was revised to reflect the following: – Further dose reduction to dose level -2 on a third instance of Grade 2 thrombocytopenia. – Action for all events of Grade 2 thrombocytopenia should be taken when the sample was obtained at pre-dose assessment, rather than during the cycle. – Discontinuation of adavosertib on a third instance of Grade 3 thrombocytopenia. However, it is proposed that in exceptional circumstances, for example, when a patient is objectively benefiting from several cycles of treatment and the investigator/treating physician considers that the benefit to the patient of continuing on treatment outweighs the risks, that the dose be resumed at dose level -2 after approval by the Medical Monitor. • **Table 13** was revised to provide further guidance on dose interruption and dose reduction steps if the patient has a recurrent Hb <9 but ≥8 g/dL. Sections 8.3.13.2 and 8.3.13.3 were updated to provide additional clarity on the management of non-haematologic toxicities, with detailed information on dose modifications for the management of gastrointestinal (GI) toxicities. • New tables were added to provide clarity on the management of non-haematologic toxicities (Table 14), with detailed information on dose modifications for the management of diarrhoea (Table 16) and nausea and vomiting (Table 17).

• Information included in Tables 14, 16, and 17 duplicated in the text in Sections 8.3.13.2 and 8.3.13.3 (CSPv1) was deleted. The option of the third dose reduction has been removed and text revised in Sections 1.1, 6.6 (including Table 9) and 8.3.13. Sections 1.1, 4.1, and 9.4.1.1 were updated to clarify that maturity of data will also be taken into account when selecting the date for primary analysis. Section 9.4.1.2 was updated to clarify that a separate analysis will be performed using those confirmed responders that have been followed for a minimum of 6 months after response and using all confirmed responders regardless of follow-up time.
Sections 4.1 and 8.6.1.1 were updated to clarify that all diagnostic tumor tissue samples should be submitted, not only if the diagnostic sample is different from the CCI [redacted]
Section 4.1 Figure 2 was updated to reflect a change in tumor assessment frequency from “every 6 weeks for the first 24 weeks” to every “6 weeks for the first 48 weeks.”
Section 4.1.1 and Appendix J were added to include guidance on how the study could continue in the event of a serious disruption due to cases of civil crisis, natural disaster, or public health crisis with details on mitigation that could be employed to ensure study continuity.
Section 9.5.1 was updated to add additional detail regarding the Safety Review Committee.
Appendix A was updated to remove reference to CT/MRI of the liver and adrenal glands, as this is not applicable for this study.

Version 3.0, 20 April 2021
The protocol was revised to address the recommendations of the Safety Review Committee received on 9th April 2021. Recommendation 1: Additional safety haematology and clinical chemistry assessment along on-site visit on Day 15 (+/- 1 day window) in Cycle 1 and Cycle 2. Safety haematology and clinical chemistry assessment along on-site visit on Day 5 (+/- 1 day window) in Cycle 1 and Cycle 2, in addition to the PK samples already collected. Section 1.3 Table 1, Section 8.2.4 and Section 8.3.13.1 were updated to reflect this recommendation.

Recommendation 2: Review of the Toxicity Management Guidelines for participants with CTCAE Grade 4 infection with Grade 4 neutropenia, to allow participants who recover and have clear clinical benefit that outweighs the risks to continue dosing (at a reduced dose), only after sponsor approval. Section 8.3.13.1 Table 11 was updated to reflect this recommendation. Recommendation 3: Additional guidance in Toxicity Management Guidelines for the G-CSF use in severe neutropenia. Section 8.3.13.1 was updated to reflect this recommendation.
Section 8 was updated in view of the additional laboratory assessments required, to increase the amount of blood collected from each participant accordingly.
Section 8.3.13.1 Tables 11, 12,13,14,15,16 and 17 dose level reductions have been updated for clarity to 'next reduced dose level', to account for the fact that participants may have previously had a dose level reduction due to another toxicity.

Version 4.0, 08 Nov 2021 The protocol was revised in line with the urgent safety measures implemented on 29th October 2021. Based on a preliminary analysis, AstraZeneca identified an association between reduced renal function and the risk of Grade 4 neutropenia. Risk minimization measures implemented regarding renal function.
Section 1.3 Table 1 and Section 8.2.4 updated to include creatinine clearance calculation at each study visit where clinical chemistry is assessed.
Section 2.3.1: Update to risk assessment section to include sepsis as an identified risk. IB (section 5.4) will be updated with DCO Nov-2021.
Section 5.1: Update to threshold for Creatinine Clearance within inclusion criterion 9. Section 5.2: Supplemental exclusion criterion specifically relating to infection.
Section 8.3.13.1 Toxicity management guidelines for Blood neutrophil count decrease updated for first and third occurrence of Grade 3 neutropenia. Recommendation of prophylactic antibiotics and G-CSF in case of severe neutropenia/febrile neutropenia added. Recommendation of secondary prophylaxis by G-CSF in participants who had severe neutropenia in a previous cycle. Section 8.3.13.3 Toxicity management guidelines for moderate/severe renal impairment (low creatinine clearance) added. Section 8.3.13.4 Gastrointestinal toxicity management (title updated) and renal function monitoring reference added.

Version 5.0, 03 Mar 2022 Following the recent safety events of sepsis cases, a comprehensive analysis of the safety and tolerability profile of adavosertib in the overall monotherapy adavosertib program, including the ADAGIO study, was performed leading to implementation of the following additional risk mitigation strategies.
Sections 1.1, 1.2, 1.3, 4.1, Fig 2, 6.1 and 6.6: The starting dose has been changed from 300mg to CCI QD adavosertib for the remaining participants to be recruited to the study; the dosing schedule and regimen has not been changed. Therefore, two cohorts have been defined Cohorts A and B: Cohort A with participants dosed at starting dose of 300mg QD, and Cohort B with participants dosed at a starting dose of CCI QD. No further participants will be enrolled to Cohort A. The enrolment will continue with Cohort B only with participants dosed at a starting dose of CCI QD once this amendment has been approved and implemented.
Sections 1.1, 4.1, 9.4.1.1, 9.5.2: Updated to state that primary analysis will be based on data from Cohort A and final analysis will be based on data from both Cohort A and Cohort B.
Section 1.2, Fig 1: Updated to include updated eligibility criteria and Cohort A and B.
Section 1.3 (Table 1, SoA) and Sections 8.2.4, 8.3.13.1: Additional safety on -site visit, including haematology and clinical chemistry assessments, vital signs , AE and concomitant medication review on Day 12 (+/- 1 day window) in Cycle 1 and Cycle 2. Table 1 also updated for formatting.
Section 2.3: Risk assessment updated to align with IB version 20 (DCO 11-November-2021)
Section 4.3: Section updated to provide rationale for starting dose of CCI QD adavosertib for Cohort B.
Section 4.4: End of study definition updated in view of introduction of Cohort B.
Section 5.1: Inclusion criteria 11 updated to clarify the definition of postmenopausal women ≥ 50 years.
Section 5.2: Exclusion criteria 4 updated for participants with refractory nausea and vomiting.
Section 5.3.3: Updated to include permanent sterilization as a highly effective method of contraception.
Section 6.6, Table 9: Table updated for dose reduction levels for new starting dose of CCI QD.
Section 7.1.2: Updated to clarify onset of 21-day drug interruption period.
Section 8.3.13: Toxicity Management Guidelines updated as below: Section 8.3.13.1 (Table 11): Toxicity management guidelines for Blood neutrophil count decrease updated for febrile neutropenia. Section 8.3.13.2 (Table 14) and 8.3.13.4 (Table 17 and Table 18): Administrative error updates. Section 8.3.13.3 (Table 16): Updated to include investigation of cause of renal impairment and to clarify renal thresholds.

Section 8.3.13.4 (Table 18): Updated guidelines for the management of nausea and vomiting; the updated guideline does not mandate use of dexamethasone as anti-emetic prophylaxis during cycles 1 and 2. Section 8.3.13.5 (Table 19): Introduction of Infection Toxicity Dose modification guideline.
Sections 9.4.1 and 9.4.2: Updated to reflect that efficacy and safety endpoints will be summarised by starting dose.

Version 6.0, 20 May 2022 Throughout the protocol all reference to Cohorts (A and B), and CCI dose have been removed. The CCI dose will not be included in this protocol. Recruitment will close and primary analysis performed based on the 109 patients currently enrolled (91% of planned recruitment).
Additional risk mitigation strategies being implemented in the ADAGIO study following the recent safety events of sepsis cases: **Section 8.3.13:** Toxicity Management Guidelines updated as below: **Section 8.3.13.1 (Table 11):** Toxicity management guidelines for Grade 3 and 4 neutropenia have been updated. **Section 8.3.13.2 (Table 14):** Updated to reflect that an initial occurrence of an Grade 4 non-haematologic toxicity should result in adavosertib discontinuation. **Section 8.3.13.3 (Table 16):** Updated management guidelines for renal impairment during treatment **Section 8.3.13.4 (Table 17):** Updated to reflect that an initial occurrence of an Grade 4 diarrhoea should result in adavosertib discontinuation. **Section 8.3.13.4 (Table 18):** Updated to reflect that an initial occurrence of an Grade 4 nausea and vomiting should result in adavosertib discontinuation. **Section 8.3.13.5 (Table 19):** Update to Infection Toxicity Dose modification guidelines.
Sections 4.1, 4.4, 8.1.1 and 9.4.1.1: The final analysis DCO has been removed.
Sections 9.4.1 and 9.4.2: Updated to reflect the removal of Cohort B.
Section 4.4 (End of Study Definition): Updated to reflect that in the event that a roll-over study is available at the time of the primary DCO and database closure, participant(s) currently receiving treatment with adavosertib may then be transitioned to such a study.

This Clinical Study Protocol has been subjected 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: D601HC00002

Amendment Number: 6.0
Study Intervention: Adavosertib (AZD1775)
Study Phase: Phase 2b

Short Title: Phase 2b Study of Adavosertib as Treatment for Uterine Serous Carcinoma

Medical Monitor Name and Contact Information will be provided separately

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2b, Open-label, Single-arm, Multi-centre Study assessing the Efficacy and Safety of Adavosertib as Treatment for Recurrent or Persistent Uterine Serous Carcinoma (ADAGIO)

Short Title: Phase 2b Study of Adavosertib as Treatment for Uterine Serous Carcinoma

Rationale:

There is an important unmet medical need for treatments in uterine serous carcinoma (USC), an aggressive variant of endometrial carcinoma, with an increased likelihood of recurrence and limited treatment options; the overall 5-year survival for USC is estimated to be only 35 to 50% for women with Stage I-II disease and 0 to 15% for women with Stage III-IV disease. Data from The Cancer Genome Atlas (TCGA) have shown that USC exhibits several genetic alterations that could make this variant more likely to respond to WEE1 kinase inhibition. Specifically, USC exhibits high rates of mutation in *TP53* (up to 90 to 92% of cases) as well as high rates of mutation or amplification in other cell cycle regulators, including *CCNE1*, *FBXW7*, *MYC*, *RB1*, *CCND1*, *TAF1*, and *KRAS/NRAS*.

This Phase 2b study aims to evaluate the efficacy and safety of adavosertib, an inhibitor of the tyrosine kinase WEE1, in participants with recurrent or persistent USC who have previously received at least 1 prior platinum based chemotherapy regimen for the management of USC.

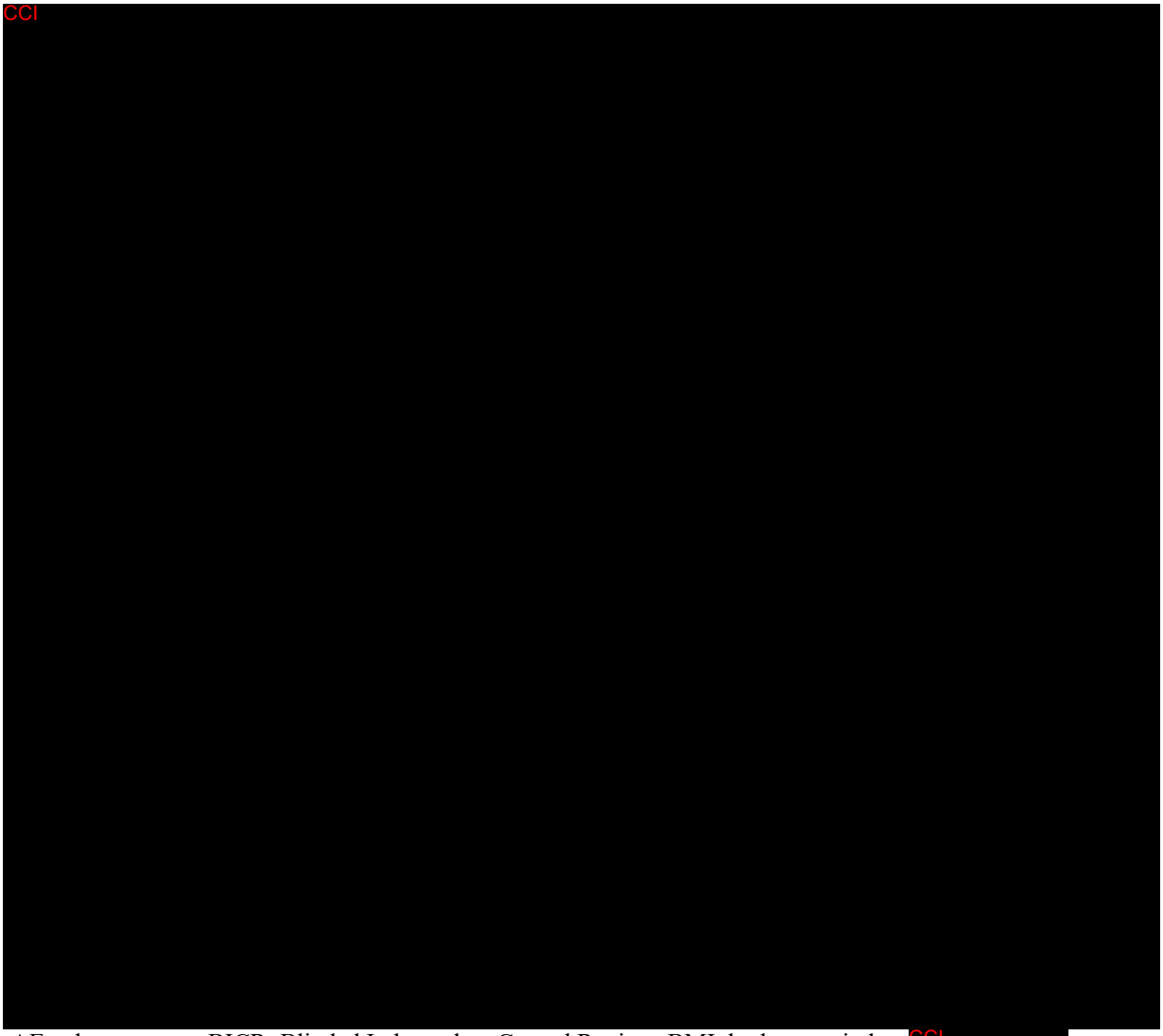
Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of adavosertib by the assessment of objective response rate (ORR).	• ORR is defined as the proportion of participants with measurable disease at baseline who have a confirmed complete response (CR) or partial response (PR), as determined by Blinded Independent Central Review (BICR) per RECIST v1.1.
Secondary	
• To evaluate efficacy of adavosertib by assessment of duration of response (DoR).	• DoR is defined as the time from the date of first documented response until date of documented progression per RECIST v1.1 as assessed by BICR, or death in the absence of disease progression.

• To evaluate efficacy of adavosertib by assessment of depth of response.	• Depth of response is defined as the best percentage change from baseline in Target Lesions.
• To evaluate the efficacy of adavosertib by assessment of progression-free survival (PFS).	• PFS is defined as time from date of first dose until progression per RECIST v1.1 as assessed by BICR, or death due to any cause.
• To evaluate the efficacy of adavosertib by assessment of PFS6.	• PFS6 is defined as the proportion of participants alive and progression free at 6 months, and will be reported as the Kaplan-Meier estimate of PFS per RECIST v1.1 as assessed by BICR at 6 months.
• To evaluate the efficacy of adavosertib by assessment of overall survival (OS).	• OS is defined as time from date of first dose until the date of death due to any cause.
• To evaluate the efficacy of adavosertib by assessment of disease control rate (DCR).	• DCR is defined as the percentage of participants who have a best overall response of CR or PR or who have stable disease for at least 5 weeks after start of treatment (to allow for an early assessment within the assessment window).
• To evaluate the pharmacokinetics of adavosertib.	• Plasma concentration of adavosertib: C_{trough} (pre-dose) and C_{max}.
• To assess the safety and tolerability of adavosertib in participants with USC.	• Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory assessments, ECGs, and AEs leading to dose interruptions, dose reductions, and dose discontinuations. • Vital signs parameters include systolic and diastolic blood pressure, and pulse as well as heart rate, body temperature, body weight, height, and BMI. • Laboratory parameters include clinical chemistry and haematology parameters as well as urinalysis.

CCI

[redacted]



AE, adverse event; BICR, Blinded Independent Central Review; BMI, body mass index; C_{max}, maximum concentration; C_{trough}, lowest concentration; CR, complete response; CTCAE v5.0, Common Terminology Criteria for Adverse Events Version 5.0; DCR, disease control rate; DoR, duration of response; ECG, electrocardiogram; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS6, proportion of participants alive and progression free at 6 months; PK, pharmacokinetic; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; USC, uterine serous carcinoma.

Overall Design

This Phase 2b, single-arm, multi-centre study will assess the efficacy and safety of adavosertib in eligible participants with histologically confirmed recurrent or persistent USC (for the purposes of this study, this includes participants with endometrial carcinoma of mixed histology where the serous component comprises at least 10% of the tumour [McMeekin et al 2007]), evidence of measurable disease as per RECIST v1.1, and who have received at least 1 prior platinum based chemotherapy regimen for the management of USC. Participants with carcinosarcomas are not eligible. There is no restriction on the number of prior lines of systemic therapy a participant may have previously received, and the platinum based chemotherapy may have been given in the adjuvant setting.

Participants are required to provide a formalin-fixed paraffin-embedded (FFPE) tumour sample, collected as part of routine clinical practice, for central confirmation of USC diagnosis and CCI

It is estimated that up to approximately 40 sites from approximately 6 countries will participate in the study.

Disclosure Statement: This is a single group treatment study with an open-label single arm design.

Number of Participants:

Approximately 120 participants will be enrolled and dosed, with an intent to include approximately 40 participants or more who have previously been exposed to programmed cell death-1 receptor (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors. The primary objective is to estimate objective response rate (ORR), and no formal statistical comparisons will be performed. With 120 participants, if the observed ORR is CCI the width of the 2-sided 90% CI will be CCI

Intervention Groups and Duration:

At the time of protocol amendment version 6.0, 109 participants have been dosed with the starting dose of 300 mg QD. No further participants will be enrolled to the study.

Participants will receive oral adavosertib once daily (QD) for 5 days followed by 2 days off in Weeks 1 and 2 out of a 21-day cycle (Days 1 to 5 and Days 8 to 12). Dose reductions or holds are allowed as clinically indicated by the treating physician. For each participant, a maximum of 2 successive dose reductions will be allowed during the study. Dose re-escalations are not allowed.

After start of treatment (Day 1), treatment will be given in 21-day cycles until objective radiological disease progression by investigator assessment using RECIST v1.1, unacceptable

toxicity, withdrawal of consent, or another discontinuation criterion is met.

Participants are permitted to continue to receive adavosertib treatment beyond the end of study if, in the opinion of the investigator, they are continuing to receive clinical benefit. Treatment of participants with adavosertib beyond progression is not allowed.

Independent Data Monitoring Committee: Yes (external)

Statistical methods

The All Patients Set will include all participants who have signed the informed consent form (ICF) (ie, screening failures plus participants dosed) and will be used to describe the patient disposition. The Full Analysis Set (FAS) and the Centrally Confirmed Analysis Set (CCAS) will both be used for all analyses of the efficacy endpoints, and the FAS will be used for the safety endpoints. The FAS will include all participants who received at least one (non-zero) dose of study treatment. The CCAS includes all centrally confirmed USC participants who received at least one (non-zero) dose of study treatment. The Pharmacokinetics Analysis Set will include all dosed participants who had at least one measurable plasma concentration collected post-dose which was obtained without any deviation or event thought to significantly affect the PK analysis.

The primary endpoint of ORR (defined as the percentage of participants with a confirmed complete response [CR] or partial response [PR], based on a subset of all treated participants with measurable disease at baseline per Blinded Independent Central Review [BICR]), and its 90% and 95% confidence interval (CI) (Clopper-Pearson) will be summarized.. Summaries of ORR will be based on imaging BICR; ORR per investigator review will be a sensitivity analysis. The primary analysis will be performed, in both the FAS and centrally confirmed USC populations, 6 months after the last patient first dose or when all participants have progressed or died due to any cause, whichever is earlier. Maturity of duration of response (DoR) data will also be taken into account when selecting the data cut-off (DCO) date for primary analysis No further analyses will be performed beyond the primary analysis.

An interim analysis is planned after approximately 30 participants in the CCAS have had the opportunity to be treated for at least 4 months. Recruitment will not be paused whilst the participants required for the interim are evaluated.

A comprehensive statistical analysis plan (SAP) will be developed and will include a more technical and detailed description of the statistical analyses. A Continuous Monitoring Plan (CMP) will also be produced to describe the approach, decision criteria, statistical analyses and communication plan for continuous monitoring in this study.

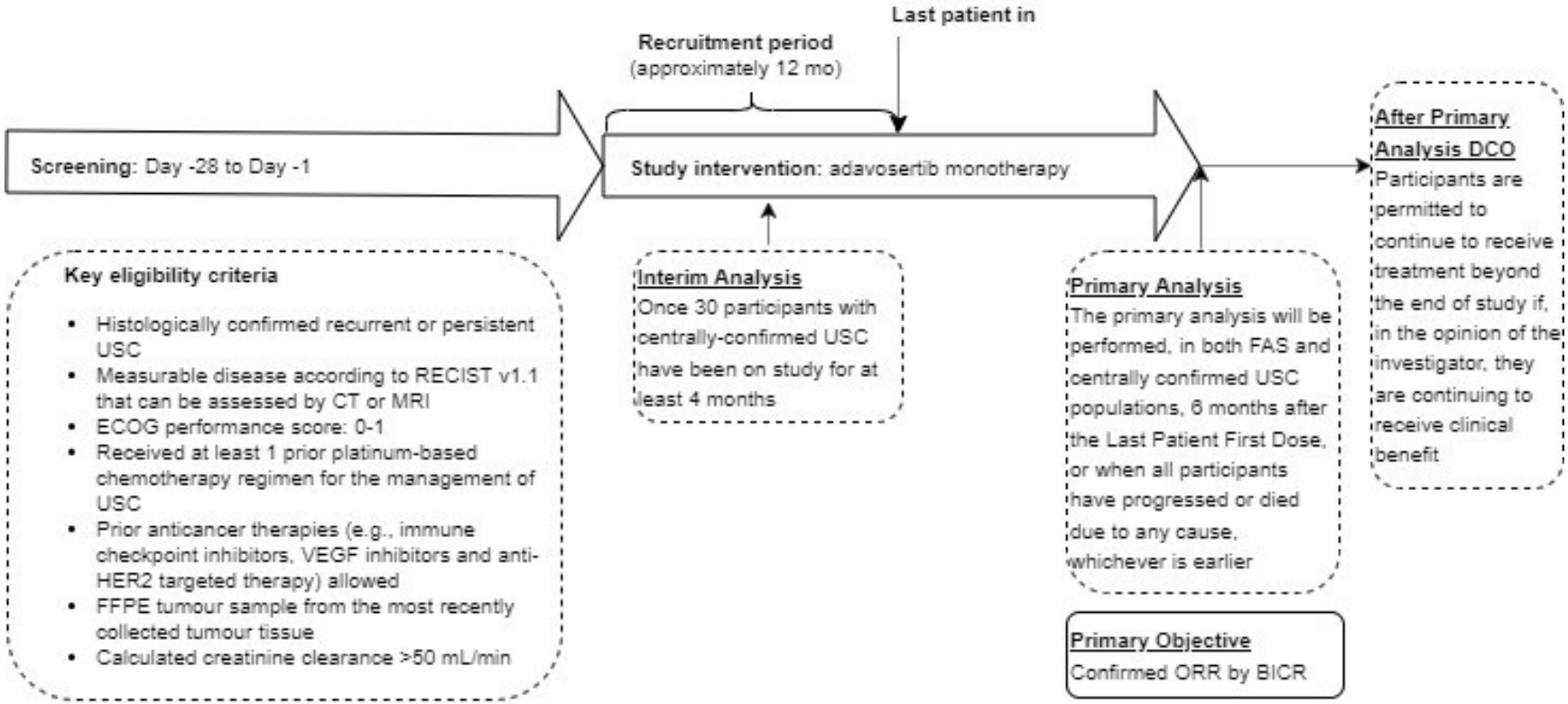
Descriptive statistics will be used for all variables. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum and maximum.

Categorical variables will be summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total.

Additional subgroup analyses of efficacy and safety may be performed and will be specified in the SAP.

1.2 Schema

Figure 1 Study Design



BICR, Blinded Independent Central Review; CT, computed tomography; DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; FFPE, formalin-fixed paraffin-embedded; HER2, Human epidermal growth factor receptor 2; LPFD, last participant first dose; mo, months; MRI, magnetic resonance imaging; ORR, objective response rate; USC, uterine serous carcinoma; VEGF, vascular endothelial growth factor.

1.3 Schedule of Activities

The schedule of study assessments is provided in Table 1.

Table 1 Schedule of Activities

	Screen	Cycle 1 and 2						Cycle 3+		Discontinuation	Progression	Post-treatment follow-up	Survival follow-up	Notes	Details in CSP section or appendix
Timing	**-28 to -1**	**Day 1**	**Day 3**	**Day 5**	**Day 8**	**Day 12**	**Day 15**	**Day 1**	**Day 8**	**If the reason for discontinuation is disease progression, then only the discontinuation visit is required**		**30 days after last dose**	**Every 12 weeks**		
Visit window (days)	**0**	**0**	**±1**	**-1**	**+2**	**±1**	**±1**	**+3**	**+2**	**+7**	**+7**	**±7**	**±14**	**C1/2 D5 safety labs visit window ±1 days**	
Informed consent	X														Section 5.1 & Appendix C
Inclusion/exclusion criteria	X													Recheck inclusion and exclusion criteria prior to first dose	Sections 5.1 & 5.2
CCI [redacted]															
Routine clinical procedures															
Demography	X														Sections 5.1 & 5.2

	Screen	Cycle 1 and 2						Cycle 3+		Discontinuation	Progression	Post-treatment follow-up	Survival follow-up	Notes	Details in CSP section or appendix
Timing	**-28 to -1**	**Day 1**	**Day 3**	**Day 5**	**Day 8**	**Day 12**	**Day 15**	**Day 1**	**Day 8**	**If the reason for discontinuation is disease progression, then only the discontinuation visit is required**		**30 days after last dose**	**Every 12 weeks**		
Visit window (days)	**0**	**0**	**±1**	**-1**	**+2**	**±1**	**±1**	**+3**	**+2**	**+7**	**+7**	**±7**	**±14**	**C1/2 D5 safety labs visit window ±1 days**	
Medical/surgical history	X														Sections 5.1 & 5.2
Previous cancer therapy	X														Section 5.2
Concomitant medication	X	At every study visit													Section 6.5
ECOG performance status	X	X						X		X		X			Appendix B
Physical examination	X	X						X		X		X			Section 8.2.1
Vital signs	X	X		X	X	X	X	X	X	X		X			Section 8.2.2
Height	X														Section 8.2.1
Weight	X	X						X		X		X			Section 8.2.1

	Screen	Cycle 1 and 2						Cycle 3+		Discontinuation	Progression	Post-treatment follow-up	Survival follow-up	Notes	Details in CSP section or appendix
Timing	**-28 to -1**	**Day 1**	**Day 3**	**Day 5**	**Day 8**	**Day 12**	**Day 15**	**Day 1**	**Day 8**	**If the reason for discontinuation is disease progression, then only the discontinuation visit is required**		**30 days after last dose**	**Every 12 weeks**		
Visit window (days)	**0**	**0**	**±1**	**-1**	**+2**	**±1**	**±1**	**+3**	**+2**	**+7**	**+7**	**±7**	**±14**	**C1/2 D5 safety labs visit window ±1 days**	
12-lead ECG	X	As clinically indicated													Section 8.2.3
General assessment through phone call			X											Day 3 phone call for AE assessment	Section 8.3.13.4
Routine safety measurements															
Adverse events	X	At every study visit													Section 8.3 & Appendix E
Pregnancy test (if applicable)	X	X						X				X			Section 8.2.4
Haematology	X	X		X	X	X	X	X	X	X		X		C1/2 D5 safety labs visit window ±1 days	Section 8.2.4

	Screen	Cycle 1 and 2						Cycle 3+		Discontinuation	Progression	Post-treatment follow-up	Survival follow-up	Notes	Details in CSP section or appendix
Timing	**-28 to -1**	**Day 1**	**Day 3**	**Day 5**	**Day 8**	**Day 12**	**Day 15**	**Day 1**	**Day 8**	**If the reason for discontinuation is disease progression, then only the discontinuation visit is required**		**30 days after last dose**	**Every 12 weeks**		
Visit window (days)	**0**	**0**	**±1**	**-1**	**+2**	**±1**	**±1**	**+3**	**+2**	**+7**	**+7**	**±7**	**±14**	**C1/2 D5 safety labs visit window ±1 days**	
Clinical chemistry	X	X		X	X	X	X	X	X	X		X		C1/2 D5 safety labs visit window ±1 days. CrCl to be calculated at each time-point	Section 8.2.4
Coagulation	X	As clinically indicated													Section 8.2.4
Urinalysis	X	As clinically indicated													Section 8.2.4
CCI [redacted]															

	Screen	Cycle 1 and 2						Cycle 3+		Discontinuation	Progression	Post-treatment follow-up	Survival follow-up	Notes	Details in CSP section or appendix
Timing	**-28 to -1**	**Day 1**	**Day 3**	**Day 5**	**Day 8**	**Day 12**	**Day 15**	**Day 1**	**Day 8**	**If the reason for discontinuation is disease progression, then only the discontinuation visit is required**		**30 days after last dose**	**Every 12 weeks**		
Visit window (days)	**0**	**0**	**±1**	**-1**	**+2**	**±1**	**±1**	**+3**	**+2**	**+7**	**+7**	**±7**	**±14**	**C1/2 D5 safety labs visit window ±1 days**	
FFPE tumour sample	X														Section 8.6.1
CCI															

	Screen	Cycle 1 and 2						Cycle 3+		Discontinuation	Progression	Post-treatment follow-up	Survival follow-up	Notes	Details in CSP section or appendix
Timing	**-28 to -1**	**Day 1**	**Day 3**	**Day 5**	**Day 8**	**Day 12**	**Day 15**	**Day 1**	**Day 8**	**If the reason for discontinuation is disease progression, then only the discontinuation visit is required**		**30 days after last dose**	**Every 12 weeks**		
Visit window (days)	**0**	**0**	**±1**	**-1**	**+2**	**±1**	**±1**	**+3**	**+2**	**+7**	**+7**	**±7**	**±14**	**C1/2 D5 safety labs visit window ±1 days**	

CCI [redacted]

	Screen	Cycle 1 and 2						Cycle 3+		Discontinuation	Progression	Post-treatment follow-up	Survival follow-up	Notes	Details in CSP section or appendix
Timing	**-28 to -1**	**Day 1**	**Day 3**	**Day 5**	**Day 8**	**Day 12**	**Day 15**	**Day 1**	**Day 8**	**If the reason for discontinuation is disease progression, then only the discontinuation visit is required**		**30 days after last dose**	**Every 12 weeks**		
Visit window (days)	**0**	**0**	**±1**	**-1**	**+2**	**±1**	**±1**	**+3**	**+2**	**+7**	**+7**	**±7**	**±14**	**C1/2 D5 safety labs visit window ±1 days**	
Pharmacokinetic measurements															
PK plasma samples				Pre-dose and 2h post-dose											Section 8.5.1
Imaging and other assessments															
RECIST v1.1 tumour assessments (CT and/or MRI)	X	Every 6 weeks (±7 days) for the first 48 weeks and then every 9 weeks (±7 days) thereafter, from Day 1 to radiological progression by investigator assessment using RECIST v1.1. Participants who discontinue treatment prior to progression should continue to be scanned until progression.													Section 8.1.1 & Appendix A
Subsequent cancer therapy following discontinuation of study intervention												X	X		Section 8.1.2.1
Survival status													X		Section 8.1.2

	Screen	Cycle 1 and 2						Cycle 3+		Discontinuation	Progression	Post-treatment follow-up	Survival follow-up	Notes	Details in CSP section or appendix
Timing	**-28 to -1**	**Day 1**	**Day 3**	**Day 5**	**Day 8**	**Day 12**	**Day 15**	**Day 1**	**Day 8**	**If the reason for discontinuation is disease progression, then only the discontinuation visit is required**		**30 days after last dose**	**Every 12 weeks**		
Visit window (days)	**0**	**0**	**±1**	**-1**	**+2**	**±1**	**±1**	**+3**	**+2**	**+7**	**+7**	**±7**	**±14**	**C1/2 D5 safety labs visit window ±1 days**	
CCI [redacted]															

	Screen	Cycle 1 and 2						Cycle 3+		Discontinuation	Progression	Post-treatment follow-up	Survival follow-up	Notes	Details in CSP section or appendix
Timing	**-28 to -1**	**Day 1**	**Day 3**	**Day 5**	**Day 8**	**Day 12**	**Day 15**	**Day 1**	**Day 8**	**If the reason for discontinuation is disease progression, then only the discontinuation visit is required**		**30 days after last dose**	**Every 12 weeks**		
Visit window (days)	**0**	**0**	**±1**	**-1**	**+2**	**±1**	**±1**	**+3**	**+2**	**+7**	**+7**	**±7**	**±14**	**C1/2 D5 safety labs visit window ±1 days**	
Adavosertib dispensing and administration															
Adavosertib dispensing		X						X							Section 6.1.1
Adavosertib administration		Dosing on Days 1 to 5 and Days 8 to 12 of 21-day cycle												A minimum of 9 days between the last dosing of a cycle and Day 1 of the next cycle is required.	Section 6.1.1

AE, adverse event; [redacted] CT, computed tomography; [redacted] ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; [redacted] FFPE, formalin-fixed paraffin-embedded; [redacted] MRI, magnetic resonance imaging; [redacted] ORR, objective response rate; OS, overall survival; [redacted] PK, pharmacokinetics; [redacted] RECIST v1.1, Response Evaluation Criteria in Solid Tumors; [redacted]

2 INTRODUCTION

Adavosertib (AZD1775) is an inhibitor of the tyrosine kinase WEE1. AstraZeneca is developing adavosertib for use as monotherapy and in combination with other anticancer agents for a range of therapeutic indications, including recurrent or persistent advanced/metastatic uterine serous carcinoma (USC) and other advanced solid tumours.

2.1 Study Rationale

This Phase 2b study aims to evaluate the efficacy and safety of adavosertib in participants with recurrent or persistent USC who have previously received at least 1 prior platinum based chemotherapy regimen for the management of USC. The rationale for conducting the study is supported by the following:

- Unmet medical need: USC is an aggressive variant of endometrial carcinoma, with an increased likelihood of recurrence and limited treatment options, with the overall 5-year survival for USC estimated to be only 35-50% for women with Stage I-II disease, and 0-15% for women with Stage III-IV disease (Acharya et al 2005)
- Mechanism of action of adavosertib (see Section 2.2.3): data from The Cancer Genome Atlas (TCGA) have shown that USC exhibits several genetic alterations that could make this variant more likely to respond to WEE1 kinase inhibition. Specifically, USC exhibits high rates of mutation in *TP53* (up to 90-92% of cases) in combination with high rates of mutation or amplification in other cell cycle regulators, including *CCNE1, FBXW7, MYC, RB1, CCND1, TAF1*, and *KRAS/NRAS* (Cancer Genome Atlas Research Network 2013, Zhao et al 2013)
- Clinical data from an ongoing Phase 2 clinical study of adavosertib in participants with recurrent or persistent USC: preliminary objective response rate (ORR) of 29.4% (95% CI: 15.1%, 47.5%; n=34) (Liu et al 2020)

The background to the rationale is summarised below in Sections 2.2 and 2.3.

2.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of adavosertib is provided in the Investigator's Brochure.

2.2.1 Endometrial Cancer and Uterine Serous Carcinoma

Endometrial cancer is one of the most common malignancies in the female genital tract with over 380000 new cases worldwide in 2018 (Bray et al 2018), and an estimated 61880 new cases diagnosed in the United States (US) in 2019 (Siegel et al 2019). There is an increasing

prevalence in developed countries and the highest incidences have been observed in the US, Canada, and Northern and Western Europe (Bray et al 2018). From 2006 to 2015, the incidence rate increased by about 1% per year and from 2007 to 2016, the death rate increased by about 2% per year (American Cancer Society 2019).

USC is one of the less common variants of endometrial cancer. However, despite representing only approximately 10% of all endometrial cancer diagnoses, it accounts for up to 39% of endometrial cancer-related deaths (Hamilton et al 2006). Unlike the more common endometrioid variants of uterine cancer, the majority of women with USC have a high risk of relapse, even in the absence of traditional "high-risk" features, such as myometrial invasion or lymphovascular involvement, and USC histology is considered to be high-risk and high-grade by default in the National Comprehensive Cancer Network (NCCN) guidelines (NCCN 2019). The overall 5-year survival for USC is estimated to be only 35-50% for women with Stage I-II disease, and 0-15% for women with Stage III-IV disease (Acharya et al 2005).

2.2.2 Current Standard of Care

Treatment options for these cancers are limited. Currently, the preferred standard of care for participants with recurrent, metastatic, or high risk endometrial cancer is combination chemotherapy with carboplatin and paclitaxel (NCCN 2019). More recently, targeted therapies specifically for USC have been explored, but results thus far have been disappointing. One area of great interest has been targeting of HER2/neu, which has been reported to be highly expressed in between 17 and 50% of women with USC (Talwar and Cohen 2012), and case reports of trastuzumab activity have been reported (Santin et al 2008; Talwar and Cohen 2012). A case report describes the clinical response of a heavily pre-treated patient with a recurrent USC, overexpressing HER2/neu at 3+ level by immunohistochemistry (IHC), to anti-HER2/neu antibody-drug-conjugate trastuzumab-emtansine (TDM-1) with complete resolution of a large metastatic, radiation/chemotherapy resistant tumour (Santin et al 2017). However, a Gynecologic Oncology Group study of single-agent trastuzumab in 33 women with HER2-positive endometrial cancer (of whom 11 had USC) did not demonstrate significant activity, with no women achieving a tumour response (Fleming et al 2010). A recent study (Fader et al 2018) compared carboplatin-paclitaxel with and without trastuzumab in participants with primary advanced or recurrent HER2/neu-positive USC (defined by an IHC score of 3+ or 2+ with gene amplification confirmed by fluorescence in situ hybridization, and with a serous component of ≥10%) reported increased progression-free survival (PFS) for participants treated with the combination compared to those on the carboplatin-paclitaxel control arm; median PFS was 8.0 months (carboplatin-paclitaxel) versus 12.6 months (carboplatin-paclitaxel-trastuzumab; p=0.005; hazard ratio: 0.44; 90% confidence interval [CI]: 0.26, 0.76). Further investigation of these results is needed to determine the impact on overall survival (OS) in this patient population.

Inhibition of programmed cell death-1 receptor (PD-1) signalling by an immune checkpoint inhibitor (pembrolizumab) or co-inhibition of angiogenesis (via vascular endothelial growth factor-mediated suppression; lenvatinib) and PD-1 signalling is emerging as an efficacious anti-tumour strategy for the treatment of endometrial cancer (Makker et al 2019). KEYNOTE-146/Study 111 assessed lenvatinib/pembrolizumab combination in participants with advanced endometrial carcinoma. In the 94 participants with tumours that were not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR), the combination demonstrated an ORR of 38.3% (95% CI: 29%, 49%), with a complete response (CR) rate of 10.6% (n=10) and a partial response (PR) rate of 27.7% (n=26) (FDA 2019, Makker et al 2019). In the US, the FDA has recently approved pembrolizumab for the subset of women with MSI-H, metastatic disease, and the combination of pembrolizumab/lenvatinib for the treatment of participants with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation (FDA 2019).

Deficient mismatch repair has been reported in 33.5% (n=65/194) of endometrioid tumours and 1.6% (n=1/61) of serous tumours (Aghajanian et al 2018), and MSI-H in 40% of endometrioid tumours and 2% of serous tumours (Cancer Genome Atlas Research Network 2013). While USC participants are thus predominantly microsatellite stable (not MSI-H), several ongoing studies are exploring the addition of a PD-1/programmed death-ligand 1 (PD-L1) inhibitor to standard of care combination chemotherapy in the first-line advanced disease setting (clintrials.gov), and new treatments potentially beyond the use of PD-1/PD-L1 are urgently needed. Durvalumab with or without olaparib, as maintenance therapy after first-line treatment of advanced and recurrent endometrial cancer (DUO-E; NCT04269200), is currently being investigated. Therefore, USC still represents an area of unmet medical need.

2.2.3 Adavosertib

Adavosertib is an inhibitor of WEE1, a protein tyrosine kinase. WEE1 phosphorylates and inhibits cyclin-dependent kinase 1 and 2 (CDK1 and CDK2) and is involved in regulation of the intra-S and G2 cell cycle checkpoints. Proper functioning of these checkpoints is essential for DNA metabolism and the DNA damage response (Coleman and Dunphy 1994, Parker and Piwnica-Worms 1992).

Activity of CDK1 (also called cell division cycle 2 protein, or CDC2) drives a cell from the G2 phase of the cell cycle into mitosis. In response to DNA damage, WEE1 inhibits CDK1 to prevent the cell from dividing until the damaged DNA is repaired (G2 checkpoint arrest). CDK2 activity drives a cell into, and through, S-phase of the cell cycle in which the genome is duplicated in preparation for cell division. Inhibition of WEE1 is expected to cause aberrantly high CDK2 activity in S-phase cells that, in turn leads to unstable DNA replication structures and ultimately DNA damage.

Inhibition of WEE1 is expected to release a tumour cell from DNA damage induced arrest at the G2/M boundary, so that unrepaired DNA damage may be taken into mitosis (M-phase). Since cancer cells exhibit higher levels of endogenous damage than normal cells, as well as exhibiting loss of 1 or more DNA damage response capabilities, this is expected to preferentially enhance cancer cell death through mitotic catastrophe compared to normal cells.

In the nonclinical setting, adavosertib has demonstrated significant single-agent anti-tumour activity in cancer cell models associated with high levels of endogenous replication stress resulting from a combination of G1/S checkpoint deficiencies due to p53 mutations or CDKN2A deletions and the over-expression of oncogenic drivers such as MYC, mutant KRAS or the amplification of Cyclin E.

As USC exhibits high rates of mutation in *TP53* (up to 90-92% of cases) in combination with high rates of mutation or amplification in other cell cycle regulators, including *CCNE1*, *FBXW7*, *MYC*, *RB1*, *CCND1*, *TAF1* and *KRAS/NRAS* (Cancer Genome Atlas Research Network 2013, Zhao et al 2013), this tumour type is expected to have high levels of replication stress and endogenous DNA damage, and is therefore expected to be sensitive to WEE1 kinase inhibition.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

As of 11 November 2021, approximately 2083 participants have received adavosertib in its clinical development program, with approximately 349 participants receiving adavosertib monotherapy in AstraZeneca sponsored and Merck sponsored studies.

Based on the safety data from completed adavosertib clinical studies and preliminary data from ongoing studies, identified risks (reported by ≥ 10% of participants) to adavosertib monotherapy include diarrhoea, nausea and/or vomiting, difficulty with digestion, decreased appetite, a decreased number of red blood cells/haemoglobin level, neutrophils and platelets in the blood. Other identified risks include sepsis and febrile neutropenia.

Sepsis has recently been categorised as an identified risk with adavosertib therapy.

Adavosertib has a well characterised safety profile, and the toxicity is considered manageable with effective toxicity management, including dose delays, dose reductions, intermittent dosing and/or the use of supportive care approach in the participants with poor tolerance. More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of adavosertib may be found in Sections 5 and 6 of the current adavosertib IB.

2.3.2 Benefit Assessment

Liu et al (Liu et al 2020) recently assessed the activity of adavosertib as monotherapy in recurrent USC (n=34, evaluable) in an ongoing Phase 2 study (NCT03668340). A preliminary ORR of 29.4% (95% CI: 15.1%, 47.5%), including 9 partial responses (8 confirmed and 1 unconfirmed) and 1 complete response, was observed. The median PFS time was reported to be 6.14 months (95% CI: 4.21 months, 9.92 months), and the proportion of participants progression-free at 6 months (PFS6) was 59.6% (95% CI: 40.6%, 74.3%). The median duration of response (DoR) was 9.03 months (95% CI: 5.29 months, NA).

2.3.3 Overall Benefit: Risk Conclusion

Treatment options for USC are limited (see Section 2.2.2), with poor 5-year estimated OS (35-50%, Stage I-II disease; 0-15% Stage III-IV disease; Acharya et al 2005). Overall, based on the available clinical efficacy and safety data and the limited long-term efficacy provided by the currently available treatment options for USC, the benefit/risk assessment supports the proposed investigation of the therapeutic efficacy of adavosertib in participants with USC in second line plus setting.

3 OBJECTIVES AND ENDPOINTS

3.1 Primary Objectives

The primary objective for the study and associated outcome measures are summarised in Table 2.

Table 2 Primary Objective

Primary Objective	Endpoint
• To evaluate the efficacy of adavosertib by the assessment of objective response rate (ORR).	• ORR is defined as the proportion of participants with measurable disease at baseline who have a confirmed complete response (CR) or partial response (PR), as determined by Blinded Independent Central Review (BICR) per RECIST v1.1.

RECIST v1.1, Response Evaluation Criteria in Solid Tumors

3.2 Secondary Objectives

The secondary objectives for the study and associated outcome measures are summarised in Table 3.

Table 3 Secondary Objectives

Secondary Objectives	Endpoints
• To evaluate efficacy of adavosertib by assessment of DoR.	• DoR is defined as the time from the date of first documented response until date of documented progression per RECIST v1.1 as assessed by Blinded Independent Central Review (BICR), or death in the absence of disease progression.
• To evaluate efficacy of adavosertib by assessment of depth of response.	• Depth of response is defined as the best percentage change from baseline in Target Lesions.
• To evaluate the efficacy of adavosertib by assessment of progression-free survival (PFS).	• PFS is defined as time from date of first dose until progression per RECIST v1.1 as assessed by BICR, or death due to any cause.
• To evaluate the efficacy of adavosertib by assessment of PFS6.	• PFS6 is defined as the proportion of participants alive and progression free at 6 months, and will be reported as the Kaplan-Meier estimate of PFS per RECIST v1.1 as assessed by BICR at 6 months.
• To evaluate the efficacy of adavosertib by assessment of OS.	• OS is defined as time from date of first dose until the date of death due to any cause.
• To evaluate the efficacy of adavosertib by assessment of disease control rate (DCR).	• DCR is defined as the percentage of participants who have a best overall response of CR or PR or who have stable disease for at least 5 weeks after start of treatment (to allow for an early assessment within the assessment window).
• To evaluate the pharmacokinetics of adavosertib.	• Plasma concentration of adavosertib: C_{trough} (pre-dose) and $C_{max.}$
• To assess the safety and tolerability of adavosertib in participants with USC.	• Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory assessments, ECGs, and AEs leading to dose interruptions, dose reductions, and dose discontinuations. • Vital signs parameters include systolic and diastolic blood pressure, and pulse as well as heart rate, body temperature, body weight, height, and BMI. • Laboratory parameters include clinical chemistry and haematology parameters as well as urinalysis.

AE, adverse event; BICR, Blinded Independent Central Review; BMI, body mass index; C_{max}, maximum concentration; C_{trough}, lowest concentration; CR, confirmed response; CTCAE v5.0, Common Terminology Criteria for Adverse Events Version 5.0; ctDNA, circulating tumour DNA; DCR, disease control rate; DNA, deoxyribonucleic acid; DoR, duration of response; ECG, electrocardiogram; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS6, proportion of participants alive and progression free at 6 months; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors; RNA, ribonucleic acid; SAE, serious adverse event; USC, uterine serous carcinoma.

3.3 CCI

CCI

Table 4 CCI

CCI

4 STUDY DESIGN

4.1 Overall Design

This Phase 2b, single-arm, multi-centre study will assess the efficacy and safety of adavosertib in eligible participants with histologically confirmed recurrent or persistent USC (for the purposes of this study, this includes participants with endometrial carcinoma of mixed histology where the serous component comprises at least 10% of the tumour [McMeekin et al 2007]), evidence of measurable disease as per RECIST v1.1, and who have received at least 1 prior platinum based chemotherapy regimen for the management of USC. Participants with carcinosarcomas are not eligible.

Participants are required to provide a formalin-fixed paraffin-embedded (FFPE) tumour sample, collected as part of routine clinical practice, for central testing and central confirmation of USC diagnosis. This should preferably be an FFPE tissue block, or if not possible, freshly-cut, unstained, serial tumour slides from the most recently collected tumour tissue that should be a sufficient quantity to allow for the central confirmation of USC and CCI (Section 8.6.1.1). For the USC central confirmation, haematoxylin and eosin (HE)-stained slide(s) of the sample used by the site for eligibility should also be submitted. Further details on tissue specifications are outlined in the Pathology Manual, Laboratory Manual and the Diagnostic Testing Manual. CCI

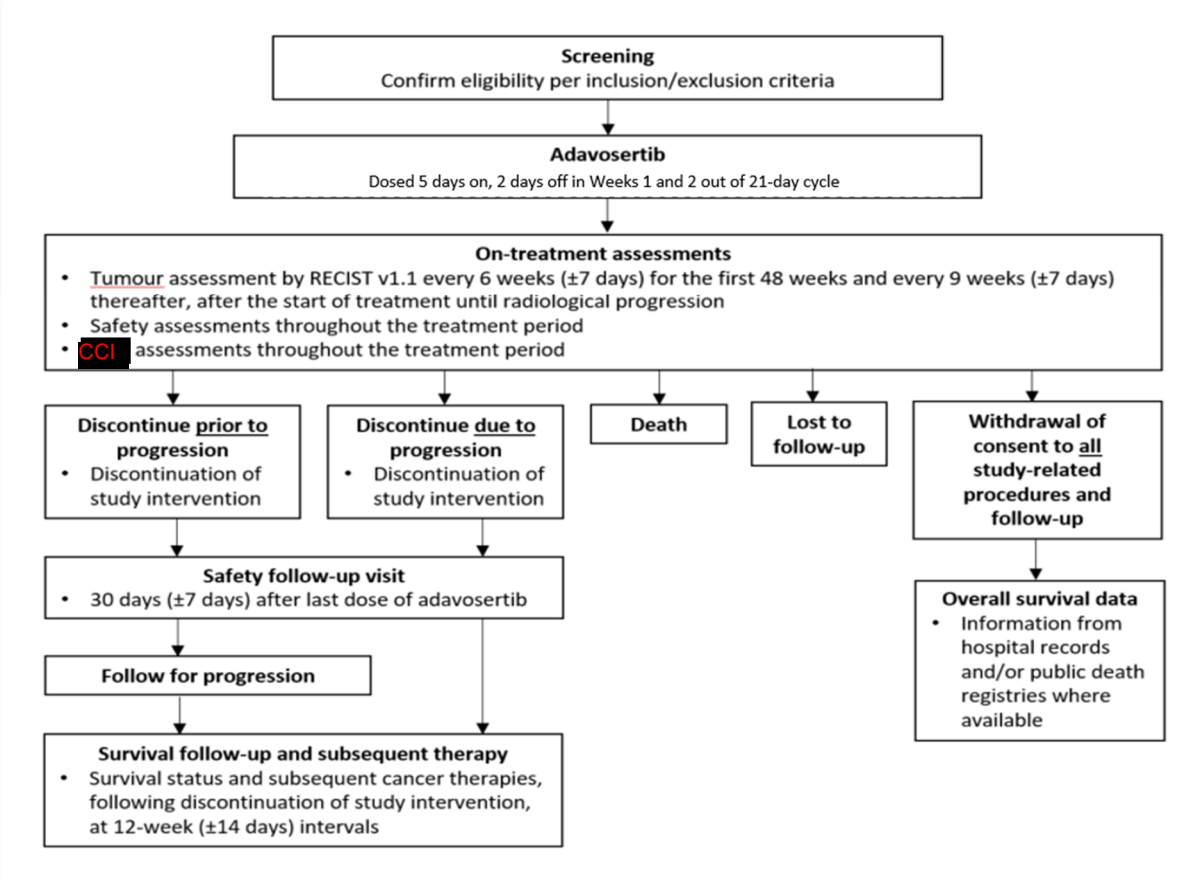
It is estimated that up to approximately 40 sites from approximately 6 countries will participate in the study. Approximately 120 eligible participants will receive oral adavosertib. At the time of protocol amendment version 60, 109 participants have been dosed with the starting dose of 300 mg QD for 5 days followed by 2 days off in Weeks 1 and 2 out of a 21-day cycle until objective radiological disease progression by investigator assessment using RECIST v1.1, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Safety and tolerability will be reviewed periodically by a Safety Review Committee. No further participants will be enrolled to the study.

The primary analysis will be performed in both locally and centrally confirmed USC populations, 6 months after the last patient first dose, or when all participants in have progressed or died due to any cause, whichever is earlier. Maturity of DoR data will also be taken into account when selecting the data cut-off (DCO) date for primary analysis. No further analyses will be performed beyond the primary analysis.. An interim analysis is planned after approximately 30 participants in the Centrally Confirmed Analysis Set (CCAS) have had the opportunity to be treated for at least 4 months. Recruitment will not be paused whilst the participants required for the interim analysis are evaluated.

Section 6.7 describes possible treatment continuation after the end of the study.

The study design is illustrated in a study flow chart (Figure 2) and study schema (Figure 1).

Figure 2 Study Flow Chart



QD, once daily; CCI [redacted] RECIST v1.1, Response Evaluation Criteria in Solid Tumors.

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

The guidance given below supersedes instructions provided elsewhere in this Clinical Study Protocol (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 or participate in 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 Good Clinical Practice (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 informed consent form [ICF] should be signed at the participant's next contact with the study site)
- Rescreening: Additional rescreening for screen failures 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 study physician.
- Home or remote visit: Performed by a site-qualified healthcare professional (HCP) or HCP 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 Investigational Product administration: Performed 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 J.

4.2 Scientific Rationale for Study Design

Adavosertib is under investigation by AstraZeneca for a range of therapeutic indications including recurrent or persistent advanced USC and other advanced solid tumours. Given its mechanism of action (see Section 2.2.3) and benefit/risk assessment (see Section 2.3), there is strong rationale for the evaluation of adavosertib in participants with USC in the second-line and beyond treatment setting where standard of care treatment options are limited.

The single-arm, open-label study design is a standard design for a Phase 2 study where the primary objective of the study is to assess efficacy (ORR, as determined by imaging Blinded Independent Central Review [BICR]) of adavosertib.

The eligibility criteria have been designed to recruit a patient population that is representative of those with recurrent or persistent USC, and who have received at least 1 prior platinum based chemotherapy regimen for the management of USC (the platinum based chemotherapy may have been received in the adjuvant setting).

4.3 Justification for Dose

The study was initiated with a recommended Phase 2 dose (RP2D) of adavosertib 300 mg QD for 5 days followed by 2 days off in Weeks 1 and 2 out of a 21-day schedule .This dose and schedule were established based on the safety, PK and clinical activity observed in PN011 (NCT01748825), REFMAL 398 (NCT02610075) and a Phase 2 study (NCT03668340).

PN011 and REFMAL 398 were Phase 1 studies designed to determine the maximum tolerated dose (MTD)/RP2D for adavosertib monotherapy using different dose levels and schedules as well as QD and twice daily (BID) dosing (Takebe et al 2018, Falchook et al 2019). Steady-state plasma concentration at the 300 mg dose was above that required to provide the necessary IC_{50} for phosphorylated CDK1 activity that had been determined preclinically as well as being within the preclinically-defined targeted cell kill range (500 to 1000 nM) for approximately 16 hours post-dose, supporting adequate target coverage.

The preclinical dose-PK-PD-efficacy modelling, based on two independent animal cancer models and the mathematical modelling looking at the biologically effective dose for adavosertib monotherapy activity, has confirmed the key factors for dose decision in the order of importance are as follows: dose, followed by the number of days of consecutive treatment, followed by the length of the treatment gap. The latter two are important because both in preclinical animal models, and in the early clinical experience, the dose of adavosertib required to provide efficacy could not be sustained as a continuous treatment schedule and therefore an intermittent schedule was needed for RP2D. Multiple intermittent schedules were assessed in preclinical animal models including 5days on/2days off, 7days on/7days off, 5days on/9days off or 3days on/4days off.

These preclinical data identified that:

1 The pharmacokinetics of adavosertib on single or repeat dose in the mouse could be accurately modelled.
2 Preclinical doses of between 60 mg/kg QD and 90 mg/kg QD were effective in inducing tumour regression across multiple models.
3 Time and dose dependence of pCDK1 and RRM2 expression (a surrogate of CDK2 activation) could be modelled with a single IC_{50} value of 0.273 µM total plasma concentration.
4 The changes in pCDK1 and RRM2 could be related to the dose and schedule dependence of efficacy where it was estimated that plasma concentrations above 0.5 µM were required for anti-tumor activity, with maximal tumor cell kill rate achieved at approximately 1 µM.
5 Different doses and schedules provide a consistent relationship between efficacy, dose level and number of days dosed but is greater than linear at the highest dose (90 mg/kg) while a schedule of 5 days on 2 days off represented the optimal intermittent schedule in terms of efficacy and preclinical safety studies.
6 The preclinical efficacious doses of adavosertib of between 60 mg/kg and 90 mg/kg are equivalent to the free drug exposures obtained by the clinical QD doses of 250 mg and 300 mg QD respectively.

Clinical activity of adavosertib as monotherapy was evaluated at RP2D in recurrent USC (n=34, evaluable) in an ongoing Phase 2 study (NCT03668340) (Liu et al 2020). A preliminary ORR of 29.4% (95% CI: 15.1%, 47.5%), including 9 partial responses (8 confirmed and 1 unconfirmed) and 1 complete response, was observed. The median PFS time was reported to be 6.14 months (95% CI: 4.21 months, 9.92 months), and the PFS6 was 59.6% (95% CI: 40.6%, 74.3%). The median DoR was 9.03 months (95% CI: 5.29 months, NA). The most frequently observed AEs included diarrhoea (85%), anaemia (65%), fatigue (65%), and nausea (62%).

As of 11 November 2021, 101 participants have been dosed at 300mg QD adavosertib in the ADAGIO study. The study is ongoing, and hence the data presented below is not fully cleaned and subject to change. Overall, 96 (95.0%) participants have experienced TEAEs. The most common (≥ 30%) TEAEs were diarrhoea (63 [62.4%] participants), nausea (60 [59.4%] participants), anaemia (49 [48.5%] participants), fatigue (39 [38.6%] participants), thrombocytopenia (37 [36.6%], constipation (37 [36.6%] participants), neutropenia (36 [35.6%] participants) and asthenia (36 [35.6%] participants). Overall, 40 (39.6%) participants have experienced SAEs; those experienced by > 1 (1.0%) patient were neutrophil count decreased (4 [4.0%] participants); neutropenia, dyspnoea, pulmonary embolism, and sepsis (3 [3.0%] participants each); and vomiting, fatigue, anaemia, thrombocytopenia, syncope, pleural effusion, embolism, hypotension, and acute kidney injury (2 [2.0%] participants each). Forty participants (39.6%) had an adverse event leading to dose reduction.

At the time of this DCO, five cases of sepsis in the ADAGIO study were reported; three events recovered, and two events were fatal. Four of these five sepsis cases (including the two fatal cases) were associated with Grade 4 neutropenia, which occurred within the first two cycles of treatment and these four cases had either a baseline or on-study decrease in creatinine clearance to <50 ml/min. Both fatalities (Grade 5 biliary sepsis [not related to adavosertib per investigator]; Grade 5 urosepsis [related to adavosertib per investigator]) occurred in patients who had a pre-existing infection (biliary) or a specific predilection for infectious complications (vesico-vaginal fistula).

To understand the relationship of adavosertib exposure and severe haematological events in monotherapy treatment, a pooled exposure-safety analysis was performed and showed that there is a strong correlation between adavosertib plasma exposure, and the predicted probability of Grade ≥3 neutropenia and thrombocytopenia. The predicted probability of neutropenia and thrombocytopenia increases as adavosertib plasma exposure increases. The model predicted probability of developing neutropenia (Grade ≥ 3) at median and 95th percentile of AUCss after 300 mg QD dosing is 12.9% and 45.0 %, respectively, while at 250 mg QD dosing it is 10.6 % and 20.4 %, respectively. This indicates approximately 18% and 55% reduction of predicted probability of neutropenia at 50th and 95th percentile of exposure, respectively, when the dose is reduced to 250 mg QD from 300 mg QD, irrespective of

baseline renal function. This analysis suggests that by reducing the starting dose to 250 mg QD, the risk of severe neutropenia and haematological toxicities will be reduced. Clinical benefit is expected to be maintained at the reduced dose of 250 mg.

A starting dose of adavosertib at 250 mg QD (5 days on, 2 days off in Weeks 1 and 2 out of a 21-day schedule) is recommended for adavosertib monotherapy clinical development. This assessment is based on the preclinical efficacy findings, overall tolerability profile, frequency of dose reductions due to AEs reported at 300 mg QD, exposure-safety analyses, and the reduced predicted occurrence of severe neutropenia and sepsis with lower exposure. For this reason, in future studies with adavosertib monotherapy a starting dose of 250 mg QD will be used (for further details refer to Investigator's Brochure) . In the ADAGIO study no further patients will be enrolled and there are no patients being treated at the 300mg QD dose level.

4.4 End of Study Definition

A participant is considered to have completed the study if she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities (SoA) (Section 1.3).

The end of the study is defined as the date of the last visit of the last participant in the study. The last visit occurs when the last participant of Cohort B has their last scheduled visit, or 6 months after last participant first dose in Cohort B, whichever comes first.

After the primary analysis DCO, the clinical study database will be closed to new data. The final primary analysis DCO will be followed by clinical database lock when all data for all participants have been collected.

The study may be terminated at individual centres if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with adavosertib.

Participants are permitted to continue to receive adavosertib beyond primary DCO in the continued access phase of this study if, in the opinion of the investigator, they are continuing to receive clinical benefit. Participants who continue to receive clinical benefit without meeting any discontinuation criteria at primary DCO may continue to receive adavosertib (to be provided by the Sponsor) if they are deriving clinical benefit in the opinion of the investigator and not fulfilling any discontinuation criteria.

Such participants are to be followed in accordance with the Medical Standard of Care and as deemed appropriate by the investigators. Serious adverse event (SAE) reporting (standard pharmacovigilance process) will continue to ensure safety data collection and monitoring of the participants while receiving the investigational product. It is recommended that

investigators continue to observe ongoing participants at the frequency employed prior to the primary DCO. Protocol dose modification and stopping criteria are to be followed while a participant is receiving adavosertib. Restrictions regarding concomitant medications (Section 6.5) must be followed while the participant is receiving adavosertib. A change in the dose/schedule of adavosertib should only occur for safety reasons, based on the investigator's judgement, and should generally follow the approach for dose reduction and discontinuation as described in this protocol. Combining adavosertib with other anticancer therapy is not allowed.

If in the opinion of the investigator, a participant is no longer receiving clinical benefit from the IP, then the IP will be stopped. The investigator will inform AstraZeneca when a participant discontinues the IP. Participants must return unused medication during routine clinic visits; drug accountability information must continue to be collected in patient source documents until the participant discontinues treatment. Participants will continue to be monitored by their treating physician/investigator for all SAEs and pregnancies while receiving IPs and for 30 days after the last dose of IP.

In the event that a roll-over study is available at the time of the primary DCO and database closure, participants(s) currently receiving treatment will adavosertib may then be transitioned to such a study, and the current study would reach its end. The roll-over or extension study would ensure treatment continuation with visit assessments per its protocol, as applicable. Any participants who would be eligible to move to such a study would be given a new informed consent, as applicable.

5 STUDY POPULATION

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

Each participant should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to receive Cycle 1 of adavosertib.

Under no circumstances can there be exceptions to this rule. Participants who do not meet the entry requirements are screen failures (see Section 5.4).

5.1 Inclusion Criteria

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

Informed Consent

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

2 CCI [redacted]

Age

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

Type of Participant and Disease Characteristics

4 Histologically confirmed recurrent or persistent USC. For the purposes of this study, participants with endometrial carcinoma of mixed histology where the serous component comprises at least 10% of the tumour will be considered eligible. Participants with carcinosarcomas are not eligible.

5 Evidence of measurable disease as per RECIST v1.1 defined as at least one lesion, not previously irradiated, that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with computed tomography (CT) scan or magnetic resonance imaging (MRI) (except lymph nodes which must have short axis ≥ 15 mm) and which is suitable for accurate repeated measurements.

6 At least 1 prior platinum based chemotherapy regimen for the management of USC (there is no restriction on the number of prior lines of systemic therapy that a participant may have previously received, and the platinum based chemotherapy may have been given in the adjuvant setting). Chemotherapy administered only in conjunction with primary radiotherapy as a radiosensitiser should not count as a systemic regimen.

- Prior anticancer therapies (eg, immune checkpoint inhibitors, vascular endothelial growth factor (VEGF) inhibitors and HER2 targeted therapy) are allowed
- Participants who have known MSI-H or dMMR tumours will not be eligible unless they have already received prior therapy with pembrolizumab or another PD-1/PD-L1 immune checkpoint inhibitor, in territories where this treatment is available for this indication, or are deemed not to be a candidate for immune checkpoint therapy

7 Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (see Appendix B) with no deterioration over the previous 2 weeks prior to day of first dosing.

8 Life expectancy ≥ 12 weeks.

9 Participants must have normal organ and marrow function at baseline, as defined below by laboratory values within 7 days prior to study drug(s) administration:

- Absolute neutrophil count (ANC) ≥ 1.5×10^9/L

- Haemoglobin (Hb) ≥ 9 g/dL
- Platelet count ≥ 100×10^9/L
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 x upper limit of normal (ULN) or ≤ 5 x ULN if known hepatic metastases
- Serum bilirubin within normal limits (WNL) or ≤ 1.5 x ULN in participants with liver metastases; or total bilirubin ≤ 3.0 x ULN with direct bilirubin WNL in participants with documented Gilbert's Syndrome
- Calculated creatinine clearance (CrCl) >50 mL/min as determined by the Cockcroft-Gault method (using actual body weight),

  Cockcroft-Gault equation for estimated CrCL:

  $$\text{CrCl (glomerular filtration rate)} = \frac{(140\text{-age}) \times (\text{weight/kg}) \times F}{(72 \times \text{serum creatinine mg/dL})}$$

  NOTE: F= 0.85 for females

10 Consent to submit and provide a mandatory FFPE tumour sample for central testing. The site must confirm that the FFPE sample is available prior to dosing.

Reproduction

11 Female participants who are not of childbearing potential* and women of childbearing potential who agree to use adequate contraceptive measures (see Section 5.3.3) from the time of signing the ICF and until 1 month after study treatment discontinuation, who are not breastfeeding, and who have a negative serum or urine pregnancy test during screening and confirmed on Cycle 1, Day 1 (prior to the start of study treatment).

* Postmenopausal or premenopausal with evidence of non-childbearing potential.

Women will be considered post-menopausal if they have been amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirement apply:

- Women ≥ 50 years of age would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all hormonal replacement therapy, or had radiation-induced menopause with last menses >1 year ago, or had chemotherapy-induced menopause with last menses >1 year ago or
- Women < 50 years of age with any one or more of the conditions below:
  - Amenorrheic for ≥ 1 year in the absence of chemotherapy and/or hormonal treatments,
  - Luteinizing hormone and/or follicle stimulating hormone and/or oestradiol levels in the postmenopausal range,
  - Radiation-induced oophorectomy with last menses > 1 year ago,

- Chemotherapy-induced menopause with > 1-year interval since last menses,
- Surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria applies on Day 1 of the study or as indicated:

Medical Conditions

1 Any underlying medical condition that would impair the ability of the participant to receive study treatment, as judged by the investigator.

2 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection*, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

- *Recurrent, active or suspected infection and/or participants who are predisposed to an increased risk of severe infection. Patients with infections that require antibiotics or antifungal agents may be eligible, provided that infection is resolved and treatment is completed at least 7 days prior to study treatment start.

3 CTCAE v5.0 Grade > 1 toxicity from prior therapy (except alopecia, anorexia or CTCAE grade 2 peripheral neuropathy).

4 Refractory nausea and vomiting, unable to swallow oral medications (**NOTE:** Patient may not have a percutaneous endoscopic gastrostomy tube or be receiving total parenteral nutrition).

5 History of another primary malignancy except for:

- Malignancy treated with curative intent and with no known active disease ≥ 5 years before the first dose of Day 1 of Cycle 1 and of low potential risk for recurrence, as determined by the investigator (participants who have received prior adjuvant chemotherapy for early stage breast cancer may be eligible, provided that it was completed ≥ 3 years prior to registration, and that the patient remains free of recurrent or metastatic disease)
- Exceptions include basal cell carcinoma of the skin and squamous cell carcinoma of the skin that has undergone potentially curative therapy
- Adequately treated carcinoma in situ without evidence of disease

6 Spinal cord compression or metastases unless asymptomatic, stable, and not requiring steroids for at least 4 weeks prior to start of study intervention.

7 Patients with current (or within 28 days prior to Cycle 1, Day 1) signs or symptoms of bowel obstruction, including sub-occlusive disease, related to underlying disease.

8 Any of the following cardiac diseases currently or within the last 6 months:
- Unstable angina pectoris
- Acute myocardial infarction
- Congestive heart failure ≥ Class 2 (as defined by New York Heart Association)
- Conduction abnormality not controlled with pacemaker or medication
- Significant ventricular or supraventricular arrhythmias (participants with chronic rate-controlled atrial fibrillation in the absence of other cardiac abnormalities are eligible)

9 History of Torsades de pointes unless all risk factors that contributed to Torsades have been corrected.

10 a) Resting corrected QTc interval using the Fridericia formula (QTcF) > 480 msec (as calculated per institutional standards) obtained from an electrocardiogram (ECG) (**NOTE:** if one ECG demonstrates a QTcF > 480 msec, then a mean QTcF of ≤ 480 msec obtained from 3 ECGs 2-5 minutes apart, is required at study entry), or b) congenital long QT syndrome

11 Immunocompromised participants, eg, participants who are known to be serologically positive for human immunodeficiency virus (HIV).

12 Patients with known active hepatitis (ie, hepatitis B or C):
- Active hepatitis B virus (HBV) is defined by a known positive HBV surface antigen (HBsAg) result. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody and absence of HBsAg) are eligible
- Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA

Prior/Concomitant Therapy

13 Use of anticancer treatment drug ≤ 21 days (≤ 6 weeks for nitrosoureas or mitomycin C) or use of an investigational product within 5 half-lives prior to the first dose of adavosertib. For PD-1/PD-L1 inhibitors, a minimum of 28 days since last dose is required.

Patients on luteinising-hormone releasing hormone analogue treatment for more than 6 months are allowed entry into the study and may continue at the discretion of the investigator.

14 Palliative radiotherapy with a limited field of radiation within 2 weeks or with wide field of radiation or to more than 30% of bone marrow within 4 weeks prior to the first dose of study intervention.

15 Major surgical procedures ≤ 28 days, or minor surgical procedures ≤ 7 days, prior to beginning study treatment. No waiting period required following port-a-cath or other central venous access placement.

16 Prior receipt of a cell cycle checkpoint inhibitor (eg, CHK1, WEE1, or ATR inhibition)

17 Has had prescription or non-prescription drugs or other products known to be moderate to strong inhibitors/inducers of CYP3A4 (see Appendix D). If the drug could be discontinued, then a wash out of ≥2 weeks prior to Day 1 of dosing is required and the drug will be withheld throughout the study until 2 weeks after the last dose of study drug.

18 Use of herbal medications 7 days prior to first dose of study treatment. Please see Appendix D for further details.

Prior/Concurrent Clinical Study Experience

19 Participants with a known hypersensitivity or contraindication to adavosertib or any of the excipients of the product.

Other Exclusions

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

21 Judgment 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

22 Previous enrolment in the present study.

23 Currently pregnant (confirmed with positive pregnancy test) or breast-feeding.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Grapefruit and Seville oranges are moderate inhibitors of CYP3A4; these fruits or their products (eg, juice, marmalade, etc) should be avoided while taking adavosertib. Please refer to Appendix D for further guidance.

5.3.2 Caffeine, Alcohol, and Tobacco

No interactions with caffeine, alcohol or tobacco have been identified.

5.3.3 Contraception

Women of childbearing potential, defined as women between menarche and menopause who have not been permanently or surgically sterilised, must agree to use a highly effective method of contraception, defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly, from the time of signing of ICF, while taking adavosertib, and for 1 month after stopping adavosertib. Cessation of contraception 1 month after stopping adavosertib should be discussed with a responsible physician.

All highly effective methods of contraception (with the exception of total abstinence) must be used in combination with the use of a condom by a male sexual partner for intercourse.

Highly effective methods of contraception include:

- Total abstinence
- Permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy)
- Tubal ligation (tubes tied)
- Combined oral, transdermal or intra-vaginal hormonal contraceptives (pills, skin patches, or inside the vagina)
- Medroxyprogesterone injections (eg, Depo-provera™)
- Cerzette (desogestrel) pill
- Copper-banded intra-uterine devices
- Hormone impregnated intra-uterine systems (eg, NuvaRing®, Implanon®)
- Vasectomised partner

Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information 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 not be rescreened. However, retesting of eligibility blood samples will be allowed within the 28-day screening window, if the patient has a blood sample abnormality that subsequently improves such that the eligibility criteria are met.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. Details of adavosertib are shown in Table 5.

A schematic presentation of the treatment schedule is presented in Figure 3.

6.1 Study Intervention Administered

6.1.1 Investigational Product

Table 5 Investigational Product

Intervention Name	AZD1775
Type	Drug
Dose Formulation	Dry-filled capsules
Unit Dose Strength(s)	CCI and/or CCI
Dispensing	Day 1 of a 21-day treatment cycle.
Dosage Level(s)	300 mg QD. Participants will be dosed on Days 1 to 5 and Days 8 to 12 of a 21-day treatment cycle. A minimum of 9 days between the last dosing of a cycle and Day 1 of the next cycle is required.
Route of Administration	Oral
Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided centrally by the sponsor
Packaging and Labelling	Study Intervention will be provided in a high-density polyethylene bottle. Each bottle will be labelled as required per country requirement
Current Alias	Adavosertib

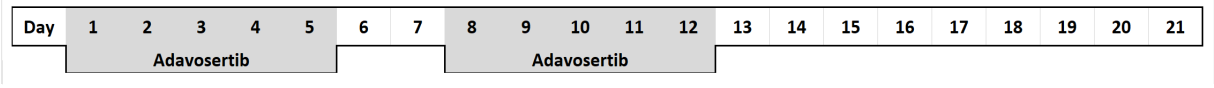
IMP, Investigational Medicinal Product; NIMP, Non-Investigational Medicinal Product; QD, once daily

Adavosertib at the appropriate dose should be taken with 8 ounces (approximately 250 mL) of water and may be taken with or without food. If a participant misses the daily dose according to the schedule, the dose should be taken as soon as possible, but not more than 12 hours after the missed dose was scheduled. If greater than 12 hours, the missed dose should be skipped, and the participant should take the next dose when scheduled.

If vomiting occurs after a participant takes the adavosertib dose, the participant should be instructed not to retake the dose, but to wait until the next scheduled dose of adavosertib. If no dose is scheduled for the following day, the dose will not be 'made up'. If vomiting persists, the participant should contact the investigator. For guidance on management of nausea and vomiting, refer to Section 8.3.13.4.

Adavosertib dose reductions are permitted (see Section 6.6).

Figure 3 Treatment Schedule per 21-day Cycle



6.2 Preparation/Handling/Storage/Accountability of Intervention

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.

Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, 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).

Any study drug remaining at the end of the study must be destroyed or returned according to the sites local standard operating procedures following authorisation by the sponsor.

6.3 Measures to Minimise Bias: Randomization and Blinding

Not applicable – this is a single arm, open-label study.

6.4 Study Intervention Compliance

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed by a patient dosing diary on adavosertib dispensing visits as specified in the SoA (Section 1.3) and documented in the source documents and electronic case report form (eCRF). Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of adavosertib capsules 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.

6.5 Concomitant Therapy

Any medication or vaccine, including over-the-counter or prescription medicines, and/or supplements that the participant is receiving at the time of enrolment or receives during the study (including any prohibited concomitant medications) must be recorded along with:

- Reason for use
- Dates of administration including start and end dates

- Dosage information including dose and frequency

Guidance regarding prohibited concomitant medication and potential interactions of adavosertib with concomitant medications is provided below and in Appendix D.

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

6.5.1 Permitted Concomitant Medications

All concomitant medications received within 14 days before the first dose of study medication and 30 days after the last dose of study medication should be recorded. Concomitant medications must be recorded in the appropriate sections of the eCRF. Permitted concomitant medications are described in Table 6.

Table 6 Permitted Concomitant Medications

Supportive Medication/Class of drug	Usage
Anti-emetics (excluding aprepitant [Emend] and fosaprepitant)	Premedication with anti-emetics is mandatory (excluding aprepitant [Emend] and fosaprepitant) as presented in Section 8.3.13.4
Loperamide (Imodium)	Loperamide (Imodium) is required at the first onset of diarrhoea according to ASCO guidelines (see Section 8.3.13.4).
Medications including but not limited to the following: Bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors (eg, denosumab). Participants requiring therapeutic warfarin or coumadin-derivative anticoagulants will be monitored with INR and Prothrombin Time (PT) as clinically indicated. Low molecular weight heparin, rivaroxaban, or equivalent anticoagulant therapy is permitted where clinically indicated.	Medications may be administered for maintenance of existing conditions prior to study enrolment or for a new condition that develops while on study.

ASCO, American Society of Clinical Oncology; INR, International Normalised Ratio

6.5.2 Prohibited and Restricted Concomitant Medications

The following treatments and the medications listed in Appendix D are prohibited or should be used with caution while on this study. Any further questions regarding concomitant treatments should be referred to the Medical Monitor. Prohibited and restricted concomitant medications are described in Table 7 and Table 8, respectively.

Table 7 Prohibited Concomitant Medications

Prohibited Medication/Class of Drug	Additional Information
Anticancer agents other than the study medications: chemotherapy, immunotherapy, hormonal anticancer therapy, radiotherapy (except for palliative local radiotherapy), biological therapy or other novel agent.	If such agents are required for a participant, then the participant must first be withdrawn from the study.
Concomitant treatment with aprepitant and fosaprepitant is not allowable per protocol until further evaluation.	An exploratory assessment of the effect of aprepitant on adavosertib exposure in oncology participants suggests that there is a drug interaction between adavosertib and aprepitant, as exposure to adavosertib increased by ~60% when aprepitant was co-administered with adavosertib. The observed increase in adavosertib exposure is likely the result of CYP3A4 inhibition by aprepitant. This increase in exposure is statistically significant. At the selected MTDs, this increase may also be of clinical importance.
Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.	Participants should stop using these herbal medications 7 days prior to first dose of adavosertib.
Avoid concomitant use of strong CYP3A inhibitors and moderate CYP3A inhibitors.	See Appendix D
Grapefruit, Seville oranges and their products (eg, juice, marmalade, etc.)	As grapefruit and Seville oranges are moderate inhibitors of CYP3A4, these fruits or their products should be avoided while taking adavosertib.
Receipt of live virus and live bacterial vaccines is not permitted while the participant is receiving study medication and during the 30-day follow-up period. Inactivated flu vaccines are permitted.	See Appendix D

CYP, cytochrome P450; MTD, maximum tolerated dose

Table 8 Restricted Concomitant Medications

Restricted Medication/Class of Drug	Usage
Inhibitors or substrates of P-glycoprotein (P-gp)	In vitro studies have shown that adavosertib may be a substrate and inhibitor for human P-gp. Caution should be exercised when agents that are inhibitors or substrates of P-gp are administered concomitantly with adavosertib (see Appendix D).

Restricted Medication/Class of Drug	Usage
Substrates of Multidrug and Toxin Extruder 1 (MATE1) and MATE2K transporters (eg, cimetidine, acyclovir, fexofenadine)	Caution should be used when administering substrates of MATE1 and MATE2K transporters (eg, cimetidine, acyclovir, fexofenadine) as the clinical relevance of adavosertib inhibition of the MATE pathway is not known in these compounds.
Metformin	Metformin should be used with caution. Adavosertib has been shown to be an inhibitor of MATE1 and MATE2K transporters. A drug interaction with substrates of either transporter cannot be ruled out, the most important substrate known to date being metformin.
BCRP substrates with narrow therapeutic index	Recent in vitro transporter studies have shown adavosertib to be an inhibitor of BCRP (IC_{50} 5.1 µM). This finding is particularly relevant for drugs administered orally where exposure is normally limited by BCRP-mediated efflux, in particular some statins, such as rosuvastatin. Other drugs where the disposition is mediated via BCRP should be administered with caution, dose modification considered or substituted by an alternative drug.

BCRP, breast cancer resistance protein

6.5.3 Palliative Radiotherapy

Participants may receive palliative radiotherapy during the study only for local pain control, and only if in the opinion of the treating investigator the participant does not have disease progression. If palliative radiotherapy is needed for disease progression, the patient should be taken off study treatment.

6.5.4 Other Concomitant Treatment

Medication other than those described above, which is considered necessary for the participant's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

6.6 Dose Modification

Dose reductions or holds are allowed as clinically indicated by the treating physician in line with Table 9. Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity. For each participant, a maximum of 2 successive dose reductions will be allowed during the study. Dose re-escalations are not allowed.

For guidance on treatment interruptions, refer to Section 7.1.2.

For guidance on dose reductions for the management of adavosertib-related AEs, refer to Section 8.3.13.

Table 9 Dose Levels for Adavosertib

Dose Level	Adavosertib Dose	Units	Dosing Schedule
Starting dose	300 mg QD	CCI [redacted]	Days 1 to 5 and Days 8 to 12 of a 21-day treatment cycle
-1	250 mg QD		No change
-2	200 mg QD		No change

QD, once daily

6.7 Intervention after the End of the Study

Participants are permitted to continue to receive treatment beyond the end of study if, in the opinion of the investigator, they are continuing to receive clinical benefit. Adavosertib will continue to be provided by AstraZeneca until the availability of either a local commercial supplier and reimbursement program or an early access program; at which point a change in supply will be requested. Treatment of participants with adavosertib beyond progression is not allowed. For further information on end of study, refer to Section 4.4.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Participants MUST be discontinued from study treatment in the following situations.

- RECIST v1.1-defined radiological progression (refer to Section 8.1.1 and Appendix A)
- Investigator determination that the participant is no longer benefiting from study treatment
- An AE that, in the opinion of the investigator or AstraZeneca, contraindicates further dosing
- Any AE that meets criteria for discontinuation defined in the guidelines for management of treatment-related toxicities (see Section 8.3.13)
- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment. A participant who discontinues treatment is normally expected to continue to participate in the study (eg, for safety and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.2).

- Severe non-compliance with the CSP as judged by the investigator or AstraZeneca
- Pregnancy or intent to become pregnant
- Initiation of subsequent anticancer therapy, including another investigational agent

Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study. See the SoA (Section 1.3) for data to be collected at the time of treatment discontinuation (ie, Discontinuation visit) and follow-up and for any further evaluations that need to be completed. If the reason for discontinuation is disease progression, then only the discontinuation visit is required. The 7-day window (+7 days) applies from the point a decision to discontinue adavosertib is taken either due to progression or another discontinuation criterion.

Participants who have discontinued study treatment prior to objective RECIST v1.1-defined radiological progression will be followed up with tumour assessments as indicated in the SoA (Section 1.3) until RECIST v1.1-defined progressive disease or death, regardless of whether or not the participant started a subsequent anticancer therapy, unless they have withdrawn all consent to study-related assessments.

After discontinuation of study medication at any point in the study, all ongoing AEs or SAEs must be followed until resolution unless, in the investigator's opinion the condition is unlikely to resolve due to the participants underlying disease, or the participant is lost to follow-up (see Section 7.3). All new AEs and SAEs occurring during the follow-up period after the last dose of study medication must be reported (if SAEs, they must be reported to AstraZeneca within 24 hours as described in Section 8.3.10) and followed to resolution as above. For guidance on reporting AEs after the follow-up period see Section 8.3.2.

If the participant does not agree to continue in-person study visits, a modified follow-up should be arranged, whenever possible, to ensure the collection of endpoints and safety information. This could be a telephone contact with the participant, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A participant that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

7.1.1 Procedure for Discontinuation of Study Intervention

The investigator should instruct the participant to contact the site before or at the time if study treatment is stopped. A participant who decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. The date of last intake of study treatment should be documented in the eCRF. All unused adavosertib treatment should be returned by the participant at their next on-site study visit or unscheduled visit. Participants permanently discontinuing adavosertib treatment should be given locally available standard of care therapy at the discretion of the investigator.

7.1.2 Study Intervention Interruption

Treatment interruptions up to a maximum of 21 days are permitted in the event of toxicity (see adavosertib dose modification guidelines [Section 6.6]). The treatment interruption period should be considered from the onset of the toxicity. In the event of a treatment interruption greater than 21 days, then the investigator will require approval from the sponsor to restart the participant on adavosertib treatment.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons.
- A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, a discontinuation visit should be conducted, as shown in the SoA (Section 1.3).
  - The participant will discontinue the study intervention and be withdrawn from the study at that time.
- 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 she still agrees for existing samples to be used in line with the original consent. If 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.

AstraZeneca or its delegate will request investigators to collect information on participants' vital status (dead or alive; date of death when applicable), including participants that withdrew consent or are classified as "lost to follow-up", from publicly available sources, in accordance with local regulations. Knowledge of the vital status at study end in all participants is crucial for the integrity of the study.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if 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, 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. 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 C 9.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA (Section 1.3). 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 the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will be approximately 450 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

8.1.1 RECIST v1.1 Assessments

RECIST v1.1 tumour assessments will be performed using CT or MRI scans of the chest, abdomen and pelvis (with additional anatomy as clinically indicated by extent of disease) at baseline (no more than 28 days before the start of study treatment). A dedicated pelvic MRI protocol is recommended for optimal assessment. After start of treatment (Cycle 1, Day 1), scans will be repeated every 6 weeks (±7 days) for the first 48 weeks and every 9 weeks (±7 days) thereafter, until objective radiological disease progression by investigator assessment using RECIST v1.1. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, every attempt should be made to perform the subsequent image acquisition at the next scheduled imaging visit. For ORR, a visit response of CR or PR must be confirmed by a subsequent scan conducted at least 4 weeks after the initial response is observed. The next RECIST scheduled assessment can be used for the confirmatory scan.

Participants who discontinue treatment prior to RECIST v1.1 progression (eg, discontinuation due to toxicity or clinical progression) should continue to be scanned until RECIST v1.1 progression. If the investigator is in doubt as to whether radiological progression has occurred, particularly with response on non-target lesions or the appearance of new lesions, it is advisable to continue treatment until the next scheduled assessment (or sooner assessment, if clinically indicated) and reassess the participant's status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

The same imaging modality and the same assessment (eg, the same contrast protocol for CT scans of the chest and MRI scans of the pelvis) should be performed at baseline and at all follow-up time-points if possible. Guidelines on the valid methods of assessment and the evaluation of objective tumour response using RECIST v1.1 are provided in Appendix A.

Efficacy assessments of confirmed ORR, DoR, percentage change from baseline in tumour size, PFS, and DCR will also be derived (by AstraZeneca) using RECIST v1.1 assessments based on BICR. All images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed Contract Research Organisation (CRO) to enable BICR up to the primary analysis DCO (when the last participant has their last scheduled visit, or 6 months after last participant first dose, whichever is earlier). After the primary analysis DCO, images will no longer need to be collected centrally. Ongoing collection of site-reviewed tumour assessment is required and must be recorded in the eCRF. Radiological examinations performed in the conduct of this study should be retained at site as source data.

Guidelines for image acquisition, de-identification, and transfer to the imaging CRO will be provided in separate documents. Further details of the BICR will be documented in the Independent Review Charter (also referred to as "Imaging Charter"). Results of the independent reviews will not be communicated to investigators, and results of investigator RECIST v1.1 assessments will not be shared with the central reviewers. The management of participants will be based wholly upon the results of the RECIST v1.1 assessment conducted by the investigator.

For information on ORR, DoR, percentage change from baseline in tumour size, PFS and DCR endpoints, refer to Section 9.4.1.1, Section 9.4.1.2, Section 9.4.1.3, Section 9.4.1.4 and Section 9.4.1.7, respectively.

8.1.2 Survival Follow-up

Assessments for survival will be conducted every 12 weeks from the time of objective disease progression or treatment discontinuation. Survival information may be obtained via telephone contact with the participant, participant's family, by contact with the participant's current physician, or local death registries as described in Section 7.3.

For information on OS, refer to Section 9.4.1.6.

8.1.2.1 Subsequent Cancer Therapy Following Discontinuation of Study Intervention

Details of subsequent cancer therapy following discontinuation of adavosertib will be collected as part of the post-treatment follow-up visit, and at the survival follow-up visit. The choice of subsequent systemic anticancer treatment will be entirely at the discretion of the investigator.

8.1.3 CCI

CCI

8.1.3.1 CCI

CCI

[redacted]

CCI

[redacted]

8.1.3.2 CCI

CCI

[redacted]

CCI

[redacted]

8.1.3.3 CCI

CCI

[redacted]

8.1.3.4 CCI

CCI

8.1.3.5 CCI

CCI

8.1.3.6 CCI

CCI

8.1.3.7 CCI

CCI

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical Examinations

The physical examination will be performed at timelines as specified in the SoA (Section 1.3). A complete physical examination will be performed and will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

Weight and height will be assessed at timelines as specified in the SoA (Section 1.3).

If new or aggravated physical findings imply deterioration compared with baseline, the finding should be reported as an AE (Section 8.3). Performance status will be assessed using the ECOG performance status criteria (see SoA [Section 1.3] and Appendix B).

8.2.2 Vital Signs

Vital signs will be performed at timelines as specified in the SoA (Section 1.3) and prior to dosing with adavosertib. Vital signs to be assessed include: pulse rate, blood pressure, and

temperature.

8.2.3 Electrocardiograms

ECG will be performed at timelines as specified in the SoA (Section 1.3). A 12-lead safety ECG (paper ECG printout of 10 seconds for investigator review) will be taken at screening, and if a prolongation of the QTc interval is detected this must be closely monitored as clinically indicated, and to the best of clinical practice.

The participants will rest for at least 10 minutes before the start of the ECG recording and they must be in the same supine body position (maximum 30 degrees flexion in the hip and feet not in contact with the footboard) at the recording time point.

If one ECG demonstrates a QTcF > 480 msec, then a mean QTcF of ≤ 480 msec obtained from 3 ECGs 2-5 minutes apart, is required for the patient to be eligible for study entry.

The investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided as to whether or not the abnormality is clinically significant or not clinically significant. The paper copy of each ECG reading will be retained with the participant's completed source documents. Any clinically significant abnormalities detected require triplicate ECG results. At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained in succession, within 5 minutes. If there is a clinically significant abnormal unscheduled ECG finding during the treatment period, this should be recorded on the AE eCRF, according to standard AE collection and reporting processes (see Section 8.3).

Attention should be paid to any detected increases in QTc interval. Participants who develop a single resting value of QTc interval of > 480 msec or a shift from baseline of ≥ 60 ms, should pause taking adavosertib. Dosing may be resumed at the same or reduced dose after return of the resting QTc interval to Grade 1 or baseline has been confirmed and correction of possible electrolyte imbalance has been made, if needed, following cardiologists's advice. For more details, see Section 8.3.13.2 and Table 15.

Monitoring of QTc, checking and correction of abnormal electrolyte levels and renal function are advised, especially in case of severe/prolonged diarrhoea. If QTc increases markedly from baseline but stays below the above limit of Grade 1 (per CTCAE v5.0), a cardiologist's advice is recommended.

The concomitant use of ondansetron (known to prolong the QTc interval in rare cases, per labelling) should be taken into account when interpreting QTc changes.

8.2.4 Clinical Safety Laboratory Assessments

Blood and samples for determination of clinical chemistry, haematology, coagulation, and PK

will be taken at the times indicated in the SoA (Section 1.3).

Additional safety samples may be collected if clinically indicated at any time during the cycle at the discretion of the investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry, haematology, urinalysis and pregnancy test 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.

Complete haematology blood counts and clinical chemistry will be obtained for all participants at visits on Day 1, Day 5, Day 8, Day 12 and Day 15 in Cycle 1 and Cycle 2, and at the beginning of each treatment week (on Day 1 and Day 8) in Cycle 3 onwards. Creatinine clearance (CrCl) must be estimated using the Cockcroft-Gault equation at all visits. On dosing days, the results must be reviewed prior to dose administration to ensure that they meet the dosing thresholds. For management of adavosertib-related toxicity management, refer to Section 8.3.13.

Women of childbearing potential must have a negative urine or serum pregnancy test during screening and a confirmatory negative test prior to dosing on Day 1 of each treatment cycle. In the event of suspected pregnancy during the study, the test should be repeated prior to dosing and, if positive, the participant discontinued from study treatment immediately.

The laboratory variables presented in Table 10 will be measured as a minimum (some of these variables may be measured at baseline only).

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.

Table 10 Laboratory Safety Variables

Haematology (2.7 mL whole blood sample)	**Clinical Chemistry (2.7 mL serum or plasma sample)**
B-Haemoglobin	S/P-Albumin
B-Leukocyte	S/P-Alanine aminotransferase (ALT)
B-Haematocrit	S/P-Aspartate aminotransferase (AST)
B-Red blood cell count	S/P-Alkaline phosphatase (ALP)
B-Absolute leukocyte differential count	S/P-Bilirubin, total
B-Neutrophils	S/P-Calcium, total
B-Lymphocytes	S/P-Creatinine
B-Monocytes	S/P-Chloride
B-Basophils	S/P-Potassium
B-Eosinophils	S/P-Sodium
B-Platelet counts	S/P-Urea nitrogen or blood urea nitrogen
B-Absolute neutrophil count	
Coagulation (1.8 mL sample)	**Pregnancy test (blood or urine)**
B-PT or INR with PTT	
Urinalysis (dipstick)	
U-Hb/erythrocytes/blood	
U-Protein/albumin	
U-Glucose	

NB. In case a participant shows an AST **or** ALT ≥ 3 x ULN together with total bilirubin ≥ 2 x ULN please refer to Appendix H: Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; B, blood; Hb, haemoglobin; INR, International Normalised Ratio; P, plasma; PT, prothrombin time; PTT, partial thromboplastin time; S, serum; U, urine.

8.3 Adverse Events and Serious Adverse Events

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

The definitions of an AE and SAE can be found in Appendix E.

AEs 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. For more information on how to follow up AEs see Section 8.3.2.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

AEs will be collected from the time of signature of the ICF throughout the treatment period and including the 30-day follow-up period after the last dose of study drug.

SAEs will be recorded from the time of signing of the ICF.

If the investigator becomes aware of an SAE with a suspected causal relationship to the 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 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)
- The date when the AE started and stopped
- CTCAE v5.0 grade, max CTCAE grade, and changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (yes or no)
- Action taken with regard to Investigational Product(s)
- AE caused participant's withdrawal from study (yes or no)
- 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
- Seriousness criteria
- Date of hospitalisation

- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication
- Description of AE

8.3.3 Causality Collection

The investigator should assess causal relationship between Investigational Product 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 investigational product?'

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 E.

8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff (eg, '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.

They do not include metastases of the original cancer.

8.3.5 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests and vital signs will be summarised in the clinical study report (CSR).

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and ECG abnormalities should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the investigational product or are considered to be clinically relevant as judged by the investigator (which may include but is 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).

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 (see Section 8.3.7).

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 will need to be reported as SAEs if criteria are met for a Potential Hy's Law case. Please refer to Appendix H 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 investigational product 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.

8.3.8 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 treatment and have been identified after the participant's inclusion in this study. They do not include metastases of the original cancer.

8.3.9 Handling of Deaths

All deaths that occur during the study, or within the 30-day follow-up period after the administration of the last dose of study treatment must 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 by entering into the web-based data capture (WBDC) system 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.
- Death 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.

8.3.10 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the investigational product, 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 electronic data capture (EDC) system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports a SAE using paper form to the appropriate AstraZeneca representative by email or fax.

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

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug adavosertib.

8.3.11 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study treatment under investigation may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/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 abnormality) should be followed up and documented even if the participant was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other study centre 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 8.3.10) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report.

8.3.12 Medication Error

For the purposes of this clinical study, a medication error is an unintended failure or mistake in the treatment process for the study drug 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 has:

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were identified 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
- Wrong participant received the medication
- Wrong drug administered to participant

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 see Section 8.4)
- 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.

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 8.3.1) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix E.

8.3.13 Management of Adavosertib-related Toxicities

Please refer to Section 6.6 for guidance on the dose levels to be used for dose modifications.

Treatment with adavosertib should be temporarily interrupted for any intolerable AE regardless of grade or for any AEs grade ≥3 that occurs despite optimal supportive care, are not attributable to

the disease under investigation, where the investigator considers the AE of concern to be specifically associated with adavosertib. Appropriate and optimal supportive treatment of the toxicity is assumed prior to considering dose modifications. The Medical Monitor may be consulted prior to dose reduction or discontinuation of study drug due to toxicities.

8.3.13.1 Haematologic Toxicity Dose Modifications

Complete blood counts (CBC) will be obtained for all participants at Day 1, Day 5, Day 8, Day 12 and Day 15 in the first 2 cycles, and at the beginning of each treatment week (on Day 1 and Day 8) in Cycle 3 onwards. The CBC results must be reviewed prior to dose administration. If haematologic toxicity occurs, treatment should be held, and ANC and platelets should be monitored at least weekly. Participants should be managed as medically indicated in Table 11, Table 12 and Table 13 below.

No more than two dose reductions will be allowed for any participant. Participants requiring further dose reduction due to haematologic toxicity must discontinue study treatment. Dose re-escalation is not allowed. If the participant has concurrent neutropenia and thrombocytopenia, the most conservative guidance in the table below should be followed and discussed with Medical Monitor as needed.

Treatment should not be resumed until the haematological toxicity is resolved (or severity reduced to Grade ≤ 1 for platelet count and to Grade ≤ 2 for neutrophil count).

If haematological parameters do not recover within 21 days, the participant should be removed from study treatment [see Section 7.1.2].

Table 11 Management of Blood Neutrophil Count Decrease

Grade/ neutrophil count	Number of occurrences of haematological toxicity		
	1st Event Action	**2nd Event Action**	**3rd Event Action**
Grade 2 < 1.5-1.0 x 10^9/L	Investigator judgement to continue adavosertib or interrupt until Grade 1 (< LLN to 1.5 × 10^9/L)		
Grade 3[a] < 1.0-0.5 x 10^9/L	Hold Resume at next reduced dose level	Hold Resume at next reduced dose level	Discontinue and follow for disease progression[b]
Grade 3[a] < 1.0-0.5 x 10^9/L with **<Grade 3** documented infection[c]	Hold Resume at next reduced dose level	Discontinue and follow for disease progression	
Grade 3[a] **< 1.0-0.5 x 10^9/L with ≥ Grade 3 documented infection**[c]	Discontinue and follow for disease progression		
Grade 4[a] < 0.5 x 10^9/L	Hold Resume at next reduced dose level	Discontinue and follow for disease progression	
Grade 4[a] **(**< 0.5 x 10^9/L) with documented infection[c]	Discontinue and follow for disease progression		
Febrile neutropenia[a]	Discontinue and follow for disease progression[b]		

[a] Consider empirical prophylactic antibiotics and G-CSF.
[b] In exceptional situations, where it is considered that benefits outweigh the risks, patient can continue dosing at reduced dose level, only after approval by the medical monitor.
[c] Refer to Management of Infection for additional guidance (Table 19).

Neutropenia and/or Febrile neutropenia

Participants experiencing febrile neutropenia with significant symptoms and participants with severe neutropenia at high risk of sepsis should be managed in a hospital setting according to standard procedures, with interruption of study treatment, the urgent initiation of intravenous (IV) antibiotic therapy, and use of granulocyte colony-stimulating factor (G-CSF) according to institutional standards.

Antibiotics and G-CSF are recommended in cases of severe neutropenia, to be administered for 3 days or until the neutrophil count improves to ≤ Grade 2. G-CSF administration should commence 24 – 48 hours after last dose of adavosertib.

Participants with febrile neutropenia without symptoms should be managed according to standard institutional guidelines.

For participants experiencing severe neutropenia in a preceding cycle, secondary prophylaxis with (non-pegylated) G-CSF daily for 3 days commencing 24 – 48 hours after last dose of adavosertib in a treatment cycle is recommended. Secondary prophylaxis is to be administered in addition to any required dose reduction.

Please note that G-CSF is not recommended within 24 hours of the last dose of study treatment. Non-pegylated G-CSF should be stopped at least 48 hours before restarting study drug, and pegylated G-CSF should be stopped 14 days before restarting study drug.

Renal function (measured by creatinine clearance) should be monitored and dose modifications to manage renal impairment followed (Section 8.3.13.3.) as adavosertib exposure and the risk of severe neutropenia might be increased in participants with low creatinine clearance.

Table 12 Management of Blood Platelet Count Decrease

Grade/ platelet count	Number of occurrences of haematological toxicity		
	1st Event Action	2nd Event Action	3rd Event Action
Grade 2 $< 75.0 \times 10^9$/L-50.0×10^9/L	Hold[a] Resume at same dose	Hold[a] Resume at next reduced dose level	Hold[a] Resume at next reduced dose level
Grade 3 $< 50.0 \times 10^9$/L-25.0×10^9/L	Hold Resume at next reduced dose level	Hold Resume at next reduced dose level	Discontinue and follow for disease progression[b]
Grade 4 $< 25.0 \times 10^9$/L without any evidence of bleeding	Hold Resume at next reduced dose level	Hold Resume at next reduced dose level	Discontinue and follow for disease progression
Thrombocytopenic haemorrhage (gross occult bleeding) associated with platelet count $< 50.0 \times 10^9$/L	Discontinue and follow for disease progression		

[a] Pre-dose assessment.
[b] In exceptional situations where it is considered that benefits outweigh the risks, the patient may continue dosing only after approval by the Medical Monitor.

Table 13 Management of Anaemia

Haemoglobin (Hb)	Action to be Taken
Hb <9 but ≥8 g/dL (CTCAE v5.0 Grade 2)	Give appropriate supportive treatment and investigate causality. Investigator judgement to continue adavosertib with supportive treatment or interrupt dose for a maximum of 21 days. If recurrent Hb <9 but ≥8 g/dL, interrupt dose (for a maximum of 21 days) until Hb ≥9 g/dL, and upon recovery, dose reduction may be considered (to next reduced **dose level** as a first step and to next reduced dose level at reoccurrence of the same toxicity).
Hb <8 g/dL	Give appropriate supportive treatment and investigate causality. Interrupt adavosertib for a maximum of 21 days, until improved to Hb ≥9 g/dL. Upon recovery, dose reduce adavosertib. In case of a repeat episode of Hb <8g/dL, interrupt dose for a maximum of 21 days until Hb ≥9 g/dL, and upon recovery, further dose reduce adavosertib. In case of a third episode of Hb <8g/dL, discontinue treatment.

CTCAE v5.0, Common Terminology Criteria for Adverse Events Version 5.0; Hb, haemoglobin

8.3.13.2 Non-haematologic Toxicity Dose Modifications

Participants should be managed as medically indicated in Table 14.

Table 14 Management of Non-haematological Toxicities

Grade	Action
Grade 1/Grade 2	Investigator judgement to initiate supportive treatment and continue adavosertib, or interrupt dose for a maximum of 21 days. For persistent Grade 2 adverse events despite maximum supportive treatment, dosing may be resumed at next reduced dose level, as clinically indicated.
Grade 3[a]	Initiate supportive treatment, interrupt adavosertib for a maximum of 21 days, until improved to ≤ Grade 1, and follow algorithm as below:
Grade 3 toxicity for ≤ 21 days	• Resume at next reduced dose level, maintaining supportive treatment. • At recurrence, dosing may be resumed only with a further dose level reduction, maintaining supportive treatment. Up to a maximum of two dose reductions are permitted.
Grade 3 toxicity for >21 days	• Discontinue treatment, unless approved by the Medical Monitor.[b]
Grade 4[a]	Discontinue treatment permanently.

[a] Despite appropriate supportive care.

[b] In exceptional situations where it is considered that benefits outweigh the risks, the patient may continue dosing only after approval by the Medical Monitor.

ECG should be assessed if electrolyte abnormalities are detected or suspected (eg, in relation to gastrointestinal toxicity). If a prolongation of the QTc interval is detected, this must be closely monitored as clinically indicated. Dose modification guidance for QTc interval prolongation is presented in Table 15.

Table 15 QTc Interval Prolongation (Adavosertib Dose Modifications)

QTc Value (triplicate)[a,b]	Action to be Taken
QTc 481-500 ms (Grade 2)[c]	Hold treatment for up to 21 days. Consider seeking cardiologist's advice. Once QTc interval has returned to Grade 1 and correction of possible electrolyte imbalance has been made, treatment may resume at the same dose level.
QTc ≥ 501 ms or Shift from baseline of ≥ 60 ms (Grade 3)[c]	Hold treatment for up to 21 days. Seek cardiologist's advice and correct any electrolyte imbalance. If QTc interval recovers to ≤ 480 ms (Grade 1) or baseline if there was a shift from baseline of ≥ 60 ms, then treatment may resume at next reduced dose level, if cardiologist agrees. If QTc interval doesn't recover to ≤ 480 ms or baseline if there was a shift from baseline of ≥ 60 ms, then discontinue treatment permanently.
Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia (Grade 4)[c]	Discontinue treatment permanently. Seek cardiologist's advice.

[a] Mean triplicate value

[b] Based on a dedicated QT study conducted to evaluate the effect of single & multiple doses of adavosertib 225 mg on QT prolongation in advanced solid tumour participants, there was no significant relationship found between ΔQTcF and adavosertib concentration. Model prediction of change in QTcF at the geometric mean of C_{max} on Day 1 (712.8 nM) was 2.405 msec (90% CI: 5.939, 1.129). Similarly, model prediction of QTcF at the geometric mean C_{max} on Day 3 (1462 nM) was -0.7568 msec (90% CI: 5.148, 3.634). The upper limit of the predicted 90% CIs for ΔQTcF were well below 10 msec, supporting the conclusion that adavosertib does not have a clinically relevant impact on cardiac repolarization.

[c] Per Common Terminology Criteria for Adverse Events Version 5.0

8.3.13.3 Management of Renal Function Impairment

Creatinine clearance should be monitored intracycle (estimated by the Cockcroft-Gault equation) at the timepoints per the schedule of assessments.

Treatment interruptions up to a maximum of 21 days are permitted in the event of toxicity.

Patients should be managed as per table below:

Table 16 Management of Renal Impairment

Renal Impairment	Adavosertib Dose Adjustment
Moderate (CrCl >30 to <50 ml/min)	Hold dosing, investigate for cause, introduce supportive measures (including hydration) Upon recovery to ≥ 50 ml/min resume at same dose. If CrCl does not recover to ≥ 50 ml/min, resume at next reduced dose level[a].
Severe (CrCl ≤ 30 ml/min)	Hold dosing, investigate for cause, introduce supportive measures (including hydration) Upon recovery to > 50 ml/min, resume at next reduced dose level[a]. If CrCl does not recover to > 50 ml/min within 21 days, permanently discontinue dosing

[a] In the absence of a further clinically relevant decrease in CrCl, the investigator may use their judgment to determine whether a further dose modification or discontinuation of adavosertib is necessary.

8.3.13.4 Gastrointestinal Toxicity Management Guidelines

As per the SoA (Section 1.3), each participant will be contacted for a general assessment on Day 3 (±1 day) of Cycle 1 and 2 to assess for AEs potentially related to adavosertib. In the event of significant diarrhoea, nausea and/or vomiting, or reduced oral intake, it is strongly recommended that the participant is considered for IV fluid rehydration therapy and supportive care measures.

For participants experiencing gastrointestinal toxicities or who are otherwise at risk of dehydration, creatinine clearance should be closely monitored and dose modifications to manage renal impairment followed (see previous section).

Diarrhoea

Due to frequent reports of diarrhoea with adavosertib administration, anti-diarrhoeal treatment with loperamide (Imodium) is required at the **first** onset of diarrhoea according to American Society of Clinical Oncology (ASCO) guidelines. Oral loperamide 4 mg should be administered at the first onset of diarrhoea and then 2 mg every 2 hours until participant is diarrhoea-free for at least 12 hours. The first dose of loperamide could be lowered to 2 mg if the diarrhoea is recurrent and if, in the opinion of the treating physician, the diarrhoea is not severe.

Participants should be managed as medically indicated in Table 17.

Table 17 Management of Diarrhoea

Grade/GI toxicity	Action
	Investigator to provide patient with prescription for loperamide to enable immediate initiation of anti-diarrhoeal treatment.
Grade 1/Grade 2 Diarrhoea	Initiate anti-diarrhoeal treatment immediately with oral loperamide 4 mg and then 2 mg every 2 hours until diarrhoea-free for at least 12 hours (maximum of 16 mg/24 hours). Maintain liberal oral fluid intake. Participants should also be counselled to start a BRAT (bananas, rice, applesauce, toast) diet. Investigator judgement to continue adavosertib with supportive treatment or interrupt dose for a maximum of 21 days For persistent Grade 2 diarrhoea despite maximum supportive treatment, dosing may be resumed at next reduced dose level, as clinically indicated.
Grade 3/ Grade 4 Diarrhoea	Initiate anti-diarrhoeal treatment with oral loperamide 4 mg and then 2 mg every 2 hours until diarrhoea-free for at least 12 hours (maximum of 16 mg/24 hours). Consider admission for IV rehydration and correction of electrolyte imbalances. Interrupt adavosertib for a maximum of 21 days, until improved to ≤ Grade 1.
Grade 3 toxicity for ≤ 21 days Grade 3 toxicity for > 21 days	• Upon recovery, resume at next reduced dose level , maintaining supportive treatment. • For recurrent Grade 3, dosing may be resumed only with a further dose level reduction, maintaining supportive treatment. Up to a maximum of two dose reductions are permitted. • Discontinue treatment, unless approved by the Medical Monitor.[a]
Grade 4 toxicity	Discontinue treatment permanently

GI, gastrointestinal; IV, intravenous

[a] In exceptional situations where it is considered that benefits outweigh the risks, the patient may continue dosing only after approval by the Medical Monitor.

Participants should be instructed to notify the investigator or research staff of the occurrence

of bloody or black stools, symptoms of dehydration, fever, inability to take liquids by mouth, and inability to control diarrhoea within 24 hours of using loperamide or other prescribed anti-diarrhoeal medications.

If diarrhoea is severe (ie, requiring IV rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Participants with severe diarrhoea or any diarrhoea associated with severe nausea or vomiting should be hospitalised for IV hydration and correction of electrolyte imbalances.

Nausea and vomiting

Participants should be managed as medically indicated in Table 18.

Table 18 Management of Nausea and Vomiting

Grade/GI toxicity	Action
Prophylaxis Nausea and vomiting	Mandatory anti-emetic prophylaxis in Cycle 1 and Cycle 2 with the following: • Ondansetron (Zofran) 8 mg QD orally or granisetron (Kytril) 1 mg QD orally prior to each dose of adavosertib • Additional antiemetics can be used as needed, as per local/institutional guidance and/or investigator discretion. • Additional antiemetics can be used as needed, as per local/institutional guidance and/or investigator discretion. Adavosertib can be taken in the evening and/or with a light snack to reduce nausea.Investigator discretion may be applied regarding the mandatory anti-emetic prophylaxis requirements of the participant from Cycle 3 onwards. Promethazine (Phenergan), prochlorperazine (Compazine), and benzodiazepine may still be used as additional adjunctive treatments during adavosertib therapy. **Aprepitant (Emend) and fosaprepitant are not permitted due to known drug-drug interactions (DDIs).** **Dexamethasone can be used as needed per local/institutional guidance and/or investigator's judgment. Dexamethasone can mask the signs and symptoms of infection, including sepsis.**
Grade 1/Grade 2 Nausea and vomiting	Consider additional anti-emetics along with ondansetron/granisetron, as per local/institutional guidance and/or investigator judgment. Maintain liberal oral fluid intake. Investigator judgement to continue adavosertib with supportive treatment or interrupt dose for a maximum of 21 days. For persistent Grade 2 vomiting despite maximum supportive treatment, dosing may be resumed at next reduced dose level, as clinically indicated.

	Dexamethasone can be used as needed per local/institutional guidance and/or investigator's judgment. Dexamethasone can mask the signs and symptoms of infection, including sepsis.
Grade 3 Nausea and vomiting	Consider additional anti-emetics along with ondansetron/granisetron, as per local/institutional guidance and/or investigator judgement. Consider admission for IV rehydration and correction of electrolyte imbalances. Interrupt adavosertib for a maximum of 21 days, until improved ≤ Grade 1. Dexamethasone can be used as needed per local/institutional guidance and/or investigator's judgment. Dexamethasone can mask the signs and symptoms of infection, including sepsis.
Grade 3 toxicity for ≤ 21 days	• Upon recovery, resume at next reduced dose level, maintaining supportive treatment. • For recurrent Grade 3, dosing may be resumed only with a further dose level reduction, maintaining supportive treatment. Up to a maximum of two dose reductions are permitted.
Grade 3 toxicity for > 21 days	• Discontinue treatment.
Grade 4	Discontinue treatment permanently

GI, gastrointestinal; IV, intravenous; PO, oral; QD, once daily
[a]

Suitable alternative medications may be used, with adequate justification, if the use of any of the above medications might interfere with other study procedures or are deemed insufficient.

8.3.13.5 Management of Infection

Participants should be managed as medically indicated in Table 19.

Table 19 Management of Infection

Grade of infection (suspected or confirmed)	Action
Any grade	• Hold adavosertib immediately until infection is resolved and intervention is no longer required. The resolution of infection must be documented. • Start intervention[a] promptly and empirically according to institutional guidelines while awaiting the results of work up. • Monitor participants for signs and symptoms of infection; either new onset or worsening of the existing. • Infection should be evaluated for diagnostic work up including but not limited to, source of infection with susceptibility and appropriate imaging, including diagnostic procedures. • Discontinue adavosertib permanently if infection does not resolve within 21 days.
Grade 1 or 2	• Resume at same dose level after resolution of infection and intervention is no longer required. • At recurrence of the same event, investigator judgment to resume adavosertib at the same dose level or resume at next reduced dose level[b] after resolution of infection and intervention is no longer required. • **If associated with an event of Grade 3 neutropenia, please refer to table 11**
Grade 3[c]	• Resume at next reduced dose level[b] • Consider discontinuing adavosertib permanently, as per investigator judgement based on severity and type of infection. • **If associated with Grade 3 neutropenia, discontinue advosertib permanently.**
Grade 4[c]	• Discontinue adavosertib permanently and follow up for disease progression.

a Consider drug/drug interactions and CYP3A4 effects with adavosertib
b Where it is considered that benefits outweigh the risks, the patient may continue dosing only after approval by the Medical Monitor
c IV therapy is strongly recommended.

8.4 Overdose

A dose of adavosertib in excess of that specified according to the protocol will constitute an overdose. There is currently no known antidote to adavosertib, and the treatment of overdose should be supportive for the underlying symptoms. In addition, adavosertib may be withheld and close monitoring should be implemented as needed.

Such overdoses should be recorded as follows:

- 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 CRF module.

If an overdose of adavosertib occurs in the course of the study, then the investigator or other site personnel will inform AstraZeneca immediately or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided.

For overdoses associated with AEs, the same reporting timelines apply as for reporting of SAEs (see Section 8.3.10). For other overdoses, reporting should be done within 30 days.

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 F.

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.

8.5.1 Pharmacokinetics

Blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of adavosertib as specified in the SoA (Section 1.3) in at least 50% of participants:

- Cycle 1, Day 5 (-1 day): pre-dose and 2 hours post-dose
- Cycle 2, Day 5 (-1 day): pre-dose and 2 hours post-dose

All PK samples need to be collected within 10% of the nominal time (± 6 minutes for a 60-minute sample) to be protocol compliant. Pre-dose samples should be collected within 60 minutes prior to dosing. 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).

Plasma samples will be used to analyse the PK of adavosertib. Samples collected for analysis of adavosertib plasma 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.

8.5.1.1 Determination of Drug Concentration

Samples for determination of adavosertib concentrations in plasma will be analysed by Covance on behalf of AstraZeneca R&D, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

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

8.5.1.2 Storage, Re-use and Destruction of Pharmacokinetic Samples

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalisation or 6 months after issuance of the draft Bioanalytical Report, whichever is earlier, unless requested for future analyses.

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

8.6 CCI

CCI

8.6.1 CCI

CCI

8.6.1.1 CCI

CCI

CCI

[redacted]

8.6.1.2 CCI

CCI

[redacted]

8.6.2 CCI

CCI

[redacted]

CCI

[redacted]

8.6.3 CCI

CCI

[redacted]

8.7 CCI

CCI

[redacted]

CCI [redacted]

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

No formal statistical hypothesis will be tested. For the primary endpoint of ORR, response rate (with 90% and 95% CIs) will be estimated for all dosed participants and for dosed participants with centrally-confirmed USC.

9.2 Sample Size Determination

Approximately 120 participants will be enrolled and dosed, with an intent to include approximately 40 participants or more who have previously been exposed to PD-1/PD-L1 inhibitors. The primary objective is to estimate ORR and no formal statistical comparisons will be performed. With 120 participants, if the observed ORR is CCI [redacted] the width of the 2-sided 90% CI will be CCI [redacted]

9.3 Populations for Analyses

The primary analysis population is the FAS. In addition, the CCAS population is the key subgroup for decision making.

The populations for analyses are defined in Table 20.

Table 20 Populations for Analyses

Population/Analysis set	Description
All Patients	The All Patients Set will include all participants who have signed the informed consent form (ie, screening failures plus participants dosed). The All Patients Set will be used to describe the patient disposition.
Full Analysis Set	The FAS will include all participants who received at least one (non-zero) dose of study treatment. This population will be used for the primary analyses of the efficacy and safety endpoints.
Centrally Confirmed Analysis Set	The CCAS will include all centrally-confirmed uterine serous carcinoma participants who received at least one (non-zero) dose of study treatment. This population will be used for the analyses of efficacy.
Pharmacokinetic Analysis Set	Pharmacokinetics will be summarised as per the PK Analysis Set. The PK analysis set will include all dosed participants who had at least one measurable plasma concentration collected post-dose which was obtained without any deviation or event thought to significantly affect the PK analysis. All plasma concentration data will be summarised and presented according to AstraZeneca standards. This will be described in the statistical analysis plan.

CCAS, Centrally Confirmed Analysis Set; FAS, Full Analysis Set; PK, Pharmacokinetics

9.4 Statistical Analyses

A comprehensive statistical analysis plan (SAP) will be developed 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. A Continuous Monitoring Plan (CMP) will also be produced to describe the approach, decision criteria, statistical analyses and communication plan for continuous monitoring in this study.

Descriptive statistics will be used for all variables. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total.

Additional subgroup analyses of efficacy and safety may be performed and will be specified in the SAP.

9.4.1 Efficacy

All efficacy analyses will be performed separately on the FAS and the CCAS.

9.4.1.1 Primary Endpoint: ORR

ORR is derived using the BICR data to define a confirmed response of CR or PR, with the denominator defined as a subset of all treated participants with measurable disease at baseline per BICR. ORR will also be defined as the percentage of participants with a confirmed investigator-assessed response of CR or PR and will based on a subset of all treated participants with measurable disease at baseline per the site investigator.

A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. Summaries of ORR for the primary analysis will be based on BICR.

ORR and its 90% and 95% CI (Clopper-Pearson) will be summarised. ORR per investigator review will be a sensitivity analysis.

The primary analysis will be performed, in both the FAS and centrally confirmed USC populations, 6 months after the last patient first dose, or when all have progressed or died due to any cause, whichever is earlier. Maturity of DoR data will also be taken into account when selecting the DCO date for primary analysis.No further analyses will be performed beyond the primary analysis.

An interim analysis is planned after approximately 30 participants in the CCAS in Cohort A

have had the opportunity to be treated for at least 4 months. Recruitment will not be paused whilst the participants required for the interim are evaluated. It may be considered futile to continue recruitment into the study if there is CCI probability for the ORR to be greater than CCI This translates into observing C or fewer responders out of 30 participants; an ORR of CCI which has a 2-sided exact binomial 80% CI of CCI to CCI wherein the upper confidence limit is below CCI The analysis will be performed on participants who had the opportunity to be treated for at least 4 months. A sensitivity analysis will be performed on all participants who had the opportunity to be treated for at least 4 months, and those with a best overall response of CR, PR, and progressive disease.

9.4.1.2 Secondary Endpoint: DoR

DoR will be defined as the time from the date of first documented response (which is subsequently confirmed) until date of documented progression or death in the absence of disease progression (ie, date of PFS event or censoring – date of first response + 1). 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 that was CR or PR that was subsequently confirmed.

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

If there are sufficient numbers of responders, and sufficient numbers of responses that have progressed by the point of the analysis, Kaplan-Meier plots of DoR in the responding participants will be produced, and appropriate descriptive summary statistics will be presented by starting dose (n, number of responses that have progressed, median, quartile, minimum and maximum DoR).

Summaries of DoR will be based on BICR; DoR per investigator review will be a sensitivity analysis.

A separate analysis will be performed using those confirmed responders that have been followed for a minimum of 6 months after response and using all confirmed responders regardless of follow-up time.

9.4.1.3 Secondary Endpoint: Depth of Response

Absolute change and percentage change from baseline will be based on RECIST v1.1 Target Lesions (TLs) measurements. Tumour size is the sum of the longest diameters of the TLs. Baseline for RECIST v1.1 is defined as the last evaluable assessment prior to the start of treatment. Percent changes in tumour size from baseline will be determined for participants with measurable disease at baseline and is derived at each visit as the % change in the sum of the diameters of TLs. % change = [(post baseline TL sum – baseline TL sum) / baseline TL sum] *100. Handling of missing data will be described in the SAP. Depth of response will be

summarised using descriptive statistics. 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 participant over time may be produced.

Summaries of percentage change from baseline will be based on BICR.

9.4.1.4 Secondary Endpoint: PFS

PFS is defined as the time from first dose until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the participant withdraws from study drug or receives another anticancer therapy prior to progression (ie, date of PFS event or censoring – date of first dose + 1). 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 v1.1 assessment. However, if the participant progresses or dies after two or more missed visits, the participant will be censored at the time of the latest evaluable RECIST v1.1 assessment prior to the two missed visits.

Summaries of PFS (n, events, medians, quartiles, proportion progression free at 3, 6, 9 and 12 months and corresponding 95% CIs) and Kaplan-Meier plots will be provided by starting dose.

Summaries of PFS will be based on BICR; PFS per investigator review will be a sensitivity analysis.

9.4.1.5 Secondary Endpoint: PFS6

The PFS6 will be defined as the Kaplan-Meier estimate of PFS (per RECIST v1.1) at 6 months.

Summaries of PFS6 will be based on BICR; PFS6 per investigator review will be a sensitivity analysis.

9.4.1.6 Secondary Endpoint: OS

Overall survival is defined as the time from the date of first dose until death due to any cause regardless of whether the participant withdraws from randomised therapy or receives another anticancer therapy (ie, date of death or censoring – date of first dose + 1). Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive (SUR_DAT, recorded within the SURVIVE module of the eCRF).

Note: Survival calls will be made in the week following the date of DCO for the analysis, and if participants are confirmed to be alive or if the death date is post the DCO date these participants will be censored at the date of DCO. The status of ongoing, withdrawn (from the

study) and "lost to follow-up" participants at the time of the final OS analysis should be obtained by the site personnel by checking the participant's notes, hospital records, contacting the participant's general practitioner and checking publicly-available death registries. In the event that the participant has actively withdrawn consent to the processing of their personal data, the vital status of the participant can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

Summaries of OS (n, events, medians, quartiles, proportion alive at 3, 6, 9 and 12 months and corresponding 95% CIs) and a Kaplan-Meier plot will be provided by starting dose.

9.4.1.7 Secondary Endpoint: DCR

Disease control rate is defined as the proportion of participants with best response of confirmed CR, confirmed PR, or who have stable disease at least 5 weeks after first dose (to allow for an early assessment within the assessment window).

DCR and its 95% CI (Clopper-Pearson) will be summarised. Summaries of DCR will be based on BICR; DCR per investigator review will be a sensitivity analysis.

9.4.1.8 Secondary Endpoint: PK

Pharmacokinetic concentration data and summary statistics will be tabulated. Pharmacokinetic parameters will be determined from the raw data. The following PK parameters will be determined after the first and steady-state doses: C_{max} and C_{trough} (as data allows).

CCI

[redacted]

9.4.2 Safety

Safety analyses will be performed using the FAS. Safety data will be presented using descriptive statistics unless otherwise specified.

Baseline

In general, the baseline value for statistical analysis is the last non-missing value prior to administration of the first dose of adavosertib. Details are described in the SAP.

9.4.2.1 Adverse Events

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) that will have been released for execution at AZ/designee.

AEs will be presented by System Organ Class and/or Preferred Term covering number and percentage of participants reporting at least one event and number of events where appropriate.

AEs occurring prior to start of adavosertib and treatment emergent AEs will be presented separately.

An overview of AEs will present the number and percentage of participants with any AE, AEs with outcome of death, serious AEs, and AEs leading to discontinuation of adavosertib, as well as AEs leading to adavosertib dose interruptions, AEs leading to adavosertib dose reduction and AEs leading to withdrawal from study as well as the number of individual occurrences in those categories.

Separate AE tables will be provided taking into consideration relationship as assessed by the investigator, CTC grading, seriousness, death and events leading to discontinuation of adavosertib as well as other action taken related to adavosertib, and timing of events.

An additional table will present number and percentage of participants with most common AEs. Most common (eg, frequency of >x%, ≥x%) will be defined in the SAP.

In accordance with the requirements of the FDA, a separate table will present non-serious AEs occurring in more than 5% of participants.

Key subject information will be presented for participants with AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP.

An AE listing for the safety analysis set will cover details for each individual AE.

Full details of AE analyses will be provided in the SAP.

Treatment emergent

The following events are considered treatment emergent:

- Adverse events with an onset date on or after first dose of adavosertib and within 30 days after last dose of adavosertib
- Worsening of pre-existing events on or after first dose of adavosertib and within 30 days after last dose of adavosertib

9.4.2.2 Vital Signs

Vital sign parameters will be presented. Summary statistics for continuous variables cover n, mean, SD, Min, Q1, median, Q3, and Max. Frequency tables and shift tables cover number and percentage of participants in the respective category.

For each scheduled post-baseline visit, descriptive statistics for all vital sign parameters will be presented for observed values and change from baseline.

Supportive vital sign listings cover observed values and changes from baseline as well as abnormalities.

Details of vital sign analyses will be provided in the SAP.

9.4.2.3 Laboratory Analyses

Laboratory parameters will be presented. Summary statistics for continuous variables cover n, mean, SD, Min, Q1, median, Q3, and Max. Frequency tables and shift tables cover number and percentage of participants in the respective category.

For each scheduled post-baseline visit, descriptive statistics for all clinical chemistry and haematology parameters will be presented for observed values and change from baseline.

Details of laboratory analyses will be provided in the SAP.

9.5 Data Monitoring Committee

9.5.1 Safety Review Committee

A Safety Review Committee will be formed to review safety data during the study conduct. SRC will include approximately 3 key study investigators, and AstraZeneca study personnel. All clinical data, including safety, tolerability, dose modifications, and available PK data will be reviewed periodically at an appropriate time interval (eg 8 weeks). When at least 6 participants have either received ≥2 cycles of study treatment or have discontinued study treatment due to unacceptable toxicity, the Safety Review Committee will convene. SRC will be empowered to make recommendations including the option to modify dosing regimen or stop the study. Full details of SRC procedures and processes are provided in the SRC Charter.

9.5.2 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) will meet for the planned interim analysis when approximately 30 participants in the CCAS have had the opportunity to be treated for at least 4 months, to provide a recommendation based on efficacy observed.

The IDMC will review safety data and will make recommendations to continue, amend, or stop the study based on findings. Serious AEs, AEs, and other safety data will be reviewed, and individual and aggregated safety data will be evaluated by the IDMC.

Full details of the IDMC procedure and processes can be found in the IDMC Charter.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Guidelines for Evaluation of Objective Tumour Response using RECIST v1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

Introduction

This appendix details the implementation of Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1) guidelines (Eisenhauer et al 2009) for this study with regard to investigator assessment of tumour burden including protocol-specific requirements for this study. The differences from the published RECIST v1.1 guidelines are the exclusion of clinical examination and ultrasound as valid modalities to evaluate Target Lesions (TL), Non-Target Lesions (NTL) or new lesions; and a clarification of the use of ^{18}FDG-PET to identify new lesions.

Definitions of measurable, non-measurable, target and non-target lesions

Measurable:

- A tumour lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter for non-nodal lesions or ≥15 mm in short axis diameter[1] for lymph node lesions with computed tomography (CT) or magnetic resonance imaging (MRI) and that is suitable for accurate repeated measurements.

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis diameter at baseline[2]).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion and abdominal masses/abdominal organomegaly identified by physical examination (manual palpation) that is not measurable by CT or MRI.
- Previously irradiated lesions[3]

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[1] The short axis is defined as the longest axis perpendicular to long axis.

[2] Lymph nodes with <10 mm short axis diameter are considered non-pathological and should not be recorded or followed as NTLs.

[3] Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated are typically considered non-measurable and as NTL at baseline and followed up as part of the NTL assessment.

- Skin lesions

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 patient, these should be selected over cystic lesions as TLs.

Target Lesions (TLs):

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. Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ (eg, adrenal glands), a segmented organ (eg, liver), or a multilobed organ (eg, lung) is each considered as a single organ.

Tumour lesions selected for fresh screening biopsy should not be selected as TLs, unless imaging occurred at least ~2 weeks after biopsy, allowing time for healing.

Non-Target Lesions (NTLs):

Additional measurable lesions not recorded as TLs and non-measurable lesions (or sites of disease) should be identified as NTLs at baseline.

Imaging Modalities

A summary of the imaging modalities to be used for RECIST v1.1 assessment of Target Lesions, Non-Target Lesions, and New Lesions is provided in Table 21.

Table 21 Summary of Imaging Modalities for Tumour Assessment

Target lesions	Non-target lesions	New lesions
CT	CT	CT
MRI	MRI	MRI
	Plain X-ray	Plain X-ray
	Chest X-ray	Chest X-ray
		Bone scan (Scintigraphy)
		FDG-PET/CT

CT, Computed tomography; MRI, Magnetic resonance imaging; FDG-PET/CT, ^{18}F-Fluoro-deoxyglucose positron emission tomography/CT

CT and MRI

CT and MRI, each preferably with IV contrast, are generally considered to generate the best currently available and reproducible anatomical images for measurement of TL, assessment of NTL, and identification of any New Lesions.

It is recommended that IV contrast-enhanced CT or MRI examinations of the chest, abdomen and pelvis will be used to assess tumour burden at baseline and follow-up visits. Any other areas of disease involvement (eg, brain) should be additionally imaged based on the signs and symptoms of individual participants. In participants who are sensitive to intravenous CT contrast, a non-contrast CT examination of the chest and an MRI with intravenous MRI contrast of the abdomen is appropriate. In participants with severely compromised renal function a non-contrast CT examination of the chest and abdomen is appropriate. For brain lesion assessment, MRI with IV contrast is the preferred method over IV contrast-enhanced CT. It is strongly recommended to maintain use of the same imaging modality (CT or MRI), acquisition protocol, facility and scanner across all imaging time points per patient.

Clinical examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will not be used for RECIST assessments. Tumours identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

Chest X-ray

Chest X-ray assessment will not be used for assessment of TL. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

Plain X-ray

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

Ultrasound

Ultrasound examination will not be used for RECIST assessment of tumours as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation and may not provide an accurate assessment of true tumour size. Tumours identified by ultrasound will need to be assessed by correlative CT or MRI anatomical scan.

Endoscopy and laparoscopy

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

CCI

Histology and cytology

Histology on tumour biopsy samples will not be used as part of the tumour response assessment as per RECIST v1.1.

Results of cytological examination for the neoplastic origin of any effusion (eg, ascites, pericardial effusion, pleural effusion) that appears or worsens during the study will not be used as part of the tumour response assessment in this study. An effusion that appears or significantly worsens (from trace to large) radiologically by CT/MRI anatomical scans will be considered to be disease progression due to New Lesions or progression of NTLs, respectively.

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 NTL 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 may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan; however, a newly observed equivocal hot-spot on a bone scan which cannot be verified with correlative imaging (CT, MRI, X-ray) of the same anatomical region shall not be the only trigger for a PD assessment at that timepoint.

FDG-PET

^{18}F-Fluoro-deoxyglucose positron emission tomography (FDG-PET) scans may be used as a method for identifying new lesions, according to the following algorithm: New lesions will be

recorded where there is positive ^{18}F-fluoro-deoxyglucose uptake[4] not present on an FDG-PET scan from a previous visit or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no FDG-PET scan available from a previous visit, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or as clinically indicated, in order to confirm new lesions.

Tumour response evaluation

Schedule of evaluation

Baseline 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 within the 28 days prior to Day 1 of Cycle 1 of study treatment and ideally as close as possible to the start of study treatment. Follow-up assessments will be performed at the times specified in the SoA (see Section 1.3).

If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled imaging visits.

Target lesions

Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter 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 TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be

[4] A positive FDG-PET scan lesion should be reported only when an uptake (eg, standardised uptake value) greater than twice that of the surrounding tissue or liver is observed.

calculated and reported as the follow-up sum of diameters.

Special cases

- For TL 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 diameter.
- 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 diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as a New Lesion.
- If a TL splits into two 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, definitive radiotherapy, embolisation, surgery, etc. during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST case report form. If a TL has been completely removed (surgery), the longest diameter should be recorded as 0 mm.

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumour visit response for TL (Table 22).

Table 22 RECIST v1.1 Evaluation of 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 diameter to <10 mm.
Partial response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable disease (SD)	Neither sufficient decrease in sum of diameters to qualify for PR nor sufficient increase to qualify for PD

Progression of disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir) – 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 from nadir
Not evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or not evaluable (eg, missing anatomy) 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
Not applicable (NA)	Only relevant if no TLs present at baseline

TL, target lesion.

Non-target lesions

Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL 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. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit (Table 23).

Table 23 RECIST v1.1 Evaluation of 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 NTL
Progression (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 be 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
Not applicable (NA)	Only relevant if no NTLs present at baseline

NTL, non-target lesion; TL, target lesion.

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 stable disease or

partial response 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. 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 previously new lesion has been assessed as unequivocal and then the progression date should be declared using the date of the initial scan when the new lesion first appeared.

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.

Symptomatic deterioration

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

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective radiologic evidence of disease progression at that time should continue to undergo tumour assessments where clinically feasible.

Evaluation of overall visit response

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

Table 24 RECIST v1.1 Overall Visit Response

Target lesions	Non-target lesions	New lesions	Overall visit 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 or NA	No	PR
SD	Non-PD or NE or NA	No	SD
NA	Non-CR/Non-PD	No	SD (Non-CR/Non-PD)

Target lesions	Non-target lesions	New lesions	Overall visit response
NE	Non-PD or NE or NA	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR, complete response; NA, not applicable (only relevant if there were no target lesions at baseline or no non-target lesions at baseline); NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TL, target lesion.

Study treatment will be discontinued when disease progression per RECIST v1.1 is determined. In the rare instances when the RECIST v1.1-defined radiological findings are considered equivocal by the investigator or there is doubt whether or not there is evidence of objective progression (eg, technical issues including image artefacts), a follow-up scan will be performed preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD. If the repeat scan confirms progression, then study treatment must be discontinued, and the date of the initial scan should be declared as the date of PD. If the subsequent scan does not confirm the immediate prior radiological PD, scanning should continue until the next RECIST v1.1-defined PD.

Study treatment may be administered until radiological PD is confirmed by the subsequent scan, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumour compression, or spinal cord compression) will not be eligible to continue study treatment.

Specifications for anatomical imaging

CT scan

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

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST v1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

a. 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.

b. IV contrast administration: Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV 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 patient. It is very important that the same technique be used at baseline and on follow-up examinations for a given patient. 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 scans if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient 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, the recommended methods are: CT thoracic (chest) examination without contrast and abdominal (and pelvis) MRI with contrast. If MRI cannot be performed, CT without IV contrast is an option for the thorax and abdomen (and pelvis) examination. For brain imaging, MRI with IV contrast is the preferred method.

c. Slice thickness and reconstruction interval: It is recommended that CT scans be performed at 5 mm contiguous slice thickness and this guideline presumes a maximum 5 mm thickness in recommendations for 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 TL 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 (and other anatomies [eg, neck]) with T1 and T2 weighted imaging along with gadolinium-enhanced imaging can be performed. The field of view, matrix, number of excitations, phase encoding steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. CT of the chest is typically recommended over MRI due to significant motion artifacts (heart, major blood vessels, breathing) associated with MRI. 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.

More details on the recommended imaging parameters can be found in the image acquisition guidelines.

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). Eur J Cancer 2009;45(2):228-47.

Appendix B ECOG Performance Status

The Eastern Cooperative Oncology Group (ECOG) performance status scale is presented in Table 25.

Table 25 ECOG Performance Status Scale

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix C Regulatory, Ethical, and Study Oversight Considerations

C 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 International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure (IB), and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (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 Contract Research Organisation (CRO) but the accountability remains with AstraZeneca.

Regulatory Reporting Requirements for Serious Adverse Events (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 utilizing 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 along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

C 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.

C 3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or 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.

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.

C 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 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 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.

C 5 Committees Structure

A Safety Review Committee will be formed to review safety data during the study conduct. All data, including safety, tolerability, and available PK data will be reviewed periodically. The Safety Review Committee will include experts with relevant experience in clinical trial conduct, methodology, and procedures in participants with endometrial carcinoma, and AstraZeneca personnel. Full details of the Safety Review Committee procedures and processes can be found in the Safety Review Committee Charter.

The Independent Data Monitoring Committee (IDMC) will meet for the planned interim analysis when approximately 30 participants in the CCAS have had the opportunity to be treated for at least 4 months, to provide a recommendation based on efficacy observed.

The IDMC will review safety data and will make recommendations to continue, amend, or stop the study based on findings. Serious AEs, AEs, and other safety data will be reviewed, and individual and aggregated safety data will be evaluated by the IDMC. The IDMC will be comprised of fully independent members; full details of the IDMC procedure and processes can be found in the IDMC Charter.

C 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 Study D601HC00002 results when they are available. The clinical study and/or summary of Study D601HC00002 results may also be available on other websites according to the regulations of the countries in which Study D601HC00002 is conducted.

C 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, CROs).
- 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 15 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.

C 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.
- All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as sourced documents. Source data are contained in sourced documents (original records or certified copies).

C 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 date of the first participant enrolment 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 CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants 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.

C 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 coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix D Guidance Regarding Potential Interactions of Adavosertib with Concomitant Medications

The potential for drug-drug interaction described in this protocol are based on findings from in vitro studies and clinical experience.

- A formal clinical drug interaction study (D6014C00006) evaluating the effect of adavosertib on pharmacokinetics of substrates for CYP3A, CYP2C19, CYP1A2 has been conducted in advanced solid tumour participants. The results of this study suggest that adavosertib is a weak inhibitor of these enzymes and is unlikely to result in clinically significant drug interaction.

The following treatments and the medications listed in this Appendix are prohibited or should be used with caution. Any further questions regarding concomitant treatments should be referred to the Medical Monitor.

Prohibited Medications

- Adavosertib is predominantly metabolized by CYP3A4. Strong or moderate inhibitors or inducers of CYP3A4 are prohibited until additional data on drug-drug interactions (DDIs) becomes available. As grapefruit and Seville oranges are known to contain moderate inhibitors of CYP3A4, these fruits or their products (including marmalade, juice, etc.) should be avoided while taking adavosertib.

  An exploratory assessment of the effect of aprepitant on adavosertib exposure in oncology participants suggests that there is a drug interaction between adavosertib and aprepitant, as exposure to adavosertib increased by ~40% when aprepitant was co-administered with adavosertib. The observed increase in adavosertib exposure is likely the result of CYP3A4 inhibition by aprepitant. This increase in exposure is statistically significant. At the selected maximum tolerated doses (MTDs), this increase may also be of clinical importance. Therefore, concomitant treatment with aprepitant and fosaprepitant is not allowable per protocol until further evaluation.
- Herbal preparations/medications are not allowed throughout the study. These herbal medications include but are not limited to those containing: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Participants should stop using these herbal medications 7 days prior to first dose of adavosertib.
- No other anticancer-therapy (chemotherapy, immunotherapy, hormonal anticancer therapy, radiotherapy [except for palliative local radiotherapy]), biological therapy or other novel agent is to be permitted while the participant is receiving study medication.

- Receipt of live virus and live bacterial vaccines is not permitted while the participant is receiving study medication and during the 30-day follow-up period. Inactivated flu vaccines are permitted.

Medications to be used with Caution

- In vitro studies have shown that adavosertib may be a substrate and inhibitor for human P-glycoprotein (P-gp). Caution should be exercised when agents that are inhibitors or substrates of P-gp are administered concomitantly with adavosertib (see relevant section below).
- *in vitro* transporter studies have shown adavosertib to be an inhibitor of BCRP (IC_{50} 5.1 μM). This finding is particularly relevant for drugs administered orally where exposure is normally limited by BCRP-mediated efflux, in particular some statins, such as rosuvastatin. Other drugs where the disposition is mediated via BCRP should be administered with caution, dose modification considered or substituted by an alternative drug.
- Metformin should be used with caution. Adavosertib has been shown to be an inhibitor of MATE1 and MATE2K transporters. A drug interaction with substrates of either transporter cannot be ruled out, the most important substrate known to date being metformin.

In addition, any other drugs should be avoided at the investigator's discretion if, in their opinion, the co-administration with adavosertib may increase the risk of a clinically significant drug interaction.

A list of the main CYP3A4 inhibitors and inducers, P-gp substrates and inhibitors, and BCRP substrates are shown below. This is not an exhaustive list and further details can be found at Expert Opin. Drug Metab. Toxicol 2013;9(6):737-51.

CYP3A4 inhibitors

Strong

- Boceprevir
- Clarithromycin
- Cobicistat (GS-9350)
- Conivaptan
- Danoprevir
- Elvitegravir
- Fosamprenavir
- Grapefruit juice
- Idelalisib
- Indinavir
- Itraconazole
- Ketoconazole
- LCL161
- Lopinavir
- Mibefradil
- Nefazodone
- Nelfinavir
- Posaconazole
- Ritonavir
- Saquinavir
- Telaprevir
- Telithromycin
- Tipranavir
- Troleandomycin
- Voriconazole

Moderate

- ACT-178882
- Amprenavir
- Aprepitant
- Atazanavir
- Casopitant
- Ciprofloxacin
- Crizotinib
- Darunavir
- Dronedarone
- Diltiazem
- Erythromycin
- FK1706
- Fluconazole
- Fosamprenavir
- Imatinib
- Ledipasvir
- Lomitapide
- Netupitant
- Schisandra sphenanthera
- Tofisopam
- Verapamil
- Grapefruit
- Seville oranges

Weak

- Almorexant
- Alprazolam
- AMD070
- Amiodarone
- Amlodipine
- Atorvastatin
- Azithromycin
- Berberine
- Bicalutamide
- Blueberry juice
- Chlorzoxazone
- Cilostazol
- Cimetidine
- Clotrimazole
- Cranberry juice
- Cyclosporine
- Daclatasvir
- Delavirdine
- Everolimus
- Faldaprevir
- Fluvoxamine
- Fosaprepitant (IV)
- Ginkgo
- Goldenseal
- GSK1292263
- GSK2248761
- Isoniazid
- Ivacaftor
- Lacidipine
- Linagliptin
- Lomitapide
- M100240
- Nilotinib
- Oral contraceptives
- Pazopanib
- Peppermint oil
- Propiverine
- Ranitidine
- Ranolazine
- Resveratrol
- Roxithromycin
- Seville orange juice
- Simeprevir
- Sitaxentan
- Suvorexant
- Tabimorelin
- Tacrolimus
- Teriflunomide
- Ticagrelor
- Tipranavir/ritonavir
- Tolvaptan
- Zileuton

CYP3A4 inducers

Strong and Moderate

- Avasimibe
- Bosentan
- Carbamazepine
- Efavirenz
- Enzalutamide
- Etravirine
- Genistein
- Lersivirine
- Lopinavir
- Mitotane
- Modafinil
- Nafcillin
- Phenobarbital
- Phenytoin
- Rifabutin
- Rifampin
- Ritonavir
- Semagacestat
- St John's wort
- Thioridazine
- Tipranavir

Weak

- Amprenavir
- Aprepitant
- Armodafinil
- AZD 7325
- Bexarotene
- Boceprevir
- Brivaracetam
- Clobazam
- Danshen
- Dexamethasone
- Echinacea
- Eslicarbazepine
- Garlic
- Gingko
- Ginseng
- Glycyrrhizin
- LCL161
- Methylprednisolone
- Nevirapine
- Oritavancin
- Oxcarbazepine
- PA-824
- Pleconaril
- Prednisone
- Quercetin
- Raltegravir
- Ritonavir
- Rufinamide
- Sorafenib
- Stribild
- Telaprevir
- Terbinafine
- Ticagrelor
- Ticlopidine
- Topiramate
- Troglitazone
- Vemurafenib
- Vicriviroc and ritonavir
- Vinblastine

P-gp substrates

- Colchicine
- Digoxin
- Fexofenadine
- Indinavir
- Paclitaxel
- Topotecan
- Vincristine

If a participant requires initiation of digoxin during the study, or is already receiving treatment with digoxin, monitoring of digoxin levels is recommended according to local practice (as the levels of digoxin may increase). Monitoring of digoxin levels is also recommended when the participant has completed dosing with study treatment (as the levels of digoxin may then decrease).

P-gp inhibitors (strong)

- Cyclosporine
- Elacridar
- Erythromycin
- Itraconazole
- Ketoconazole
- LY335979
- Quinidine
- Ritonavir
- Valspodar
- Verapamil

BCRP substrates

- Daunorubicin
- Doxorubicin
- Rosuvastatin
- Sulfasalazine
- Topotecan

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

E 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.

E 2 Definitions of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires in-participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality 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 hospitalization, 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:

The grading scales found in the revised National Cancer Institute CTCAE version 5.0 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). The applicable version of CTCAE should be described clearly.

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 E 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 E 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 E 2.

E 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 judgment. 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.

E 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 drug 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
- Wrong participant received the medication
- Wrong drug administered to participant

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 F Handling of Human Biological Samples

F 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.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

F 2 Withdrawal of Informed Consent for donated biological samples

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

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

The investigator:

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

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the

withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented and study site notified.

F 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 G CCI

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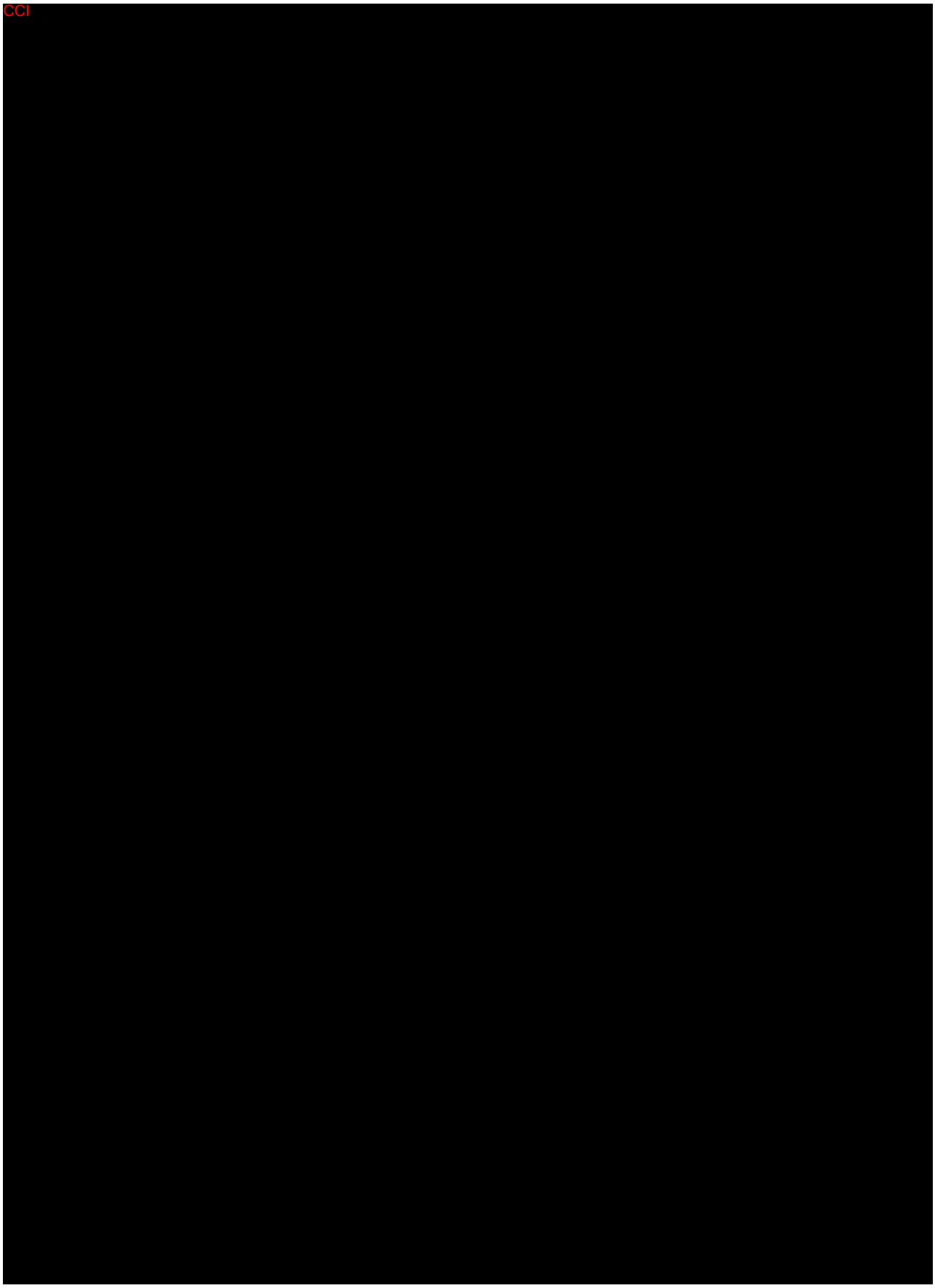

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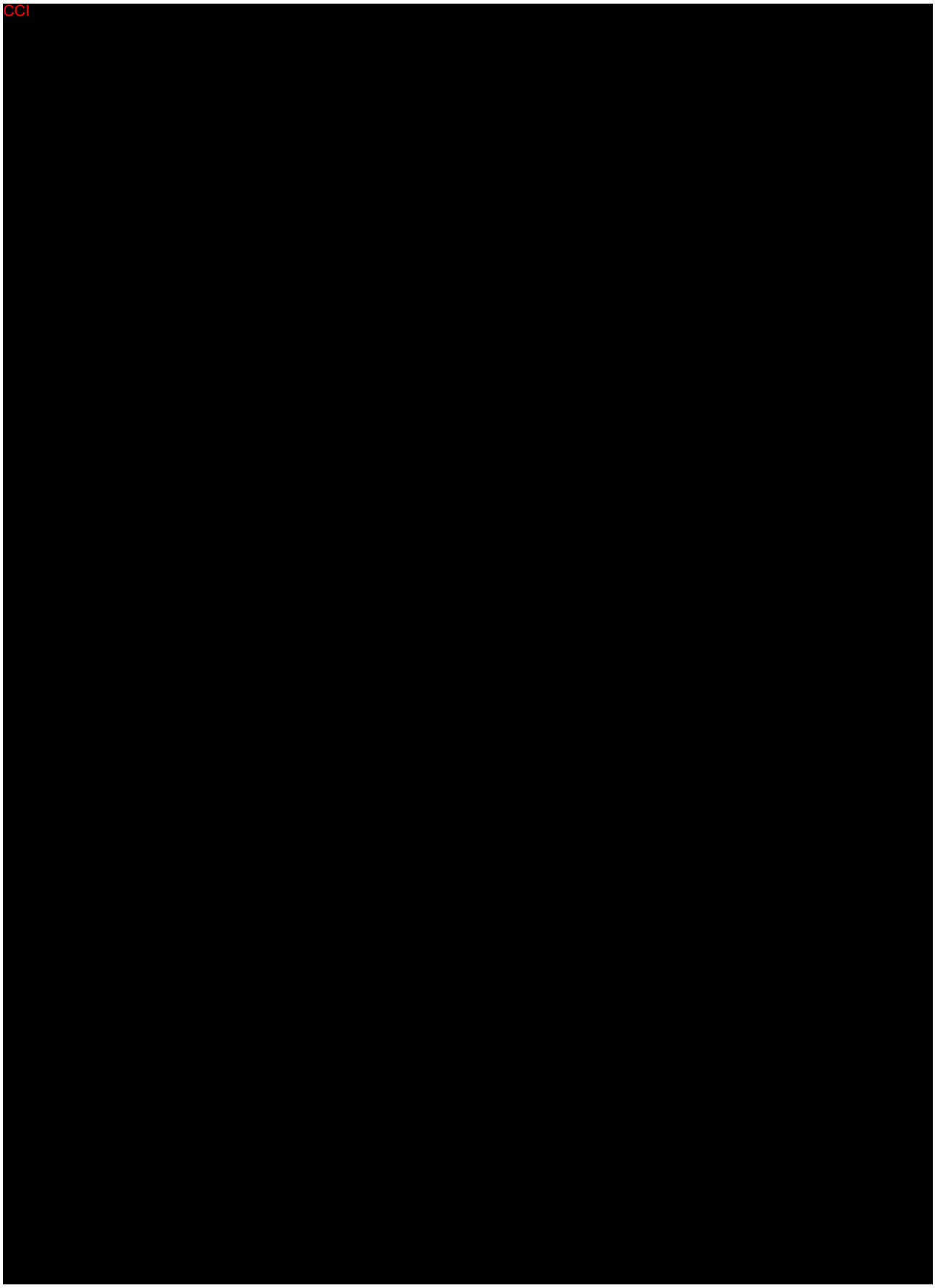

Appendix H Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

H 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.

Specific guidance on managing liver abnormalities can be found in Section 8.3.6 of the Clinical Study Protocol.

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 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 (AE) 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 AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

H 2 Definitions

Potential Hy's Law (PHL)
Aspartate aminotransferase (AST) or Alanine aminotransferase (ALT) ≥ 3x upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)
AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, 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.

H 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 ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

Central laboratories being used:
When a participant meets any of the PHL identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to AstraZeneca representative).

The investigator will also remain vigilant for any local laboratory reports where the PHL identification criteria are met, where this is the case the investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the investigator will without delay:

- Determine whether the participant meets PHL criteria (see Section H 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

H 4 Follow-up

H 4.1 Potential Hy's Law Criteria not met

If the participant does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

H 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 treatment (See Section H 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 PHL; 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. Complete follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which of the tests available in the HL lab kit should be used.
  - Complete the three 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.

H 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, and to ensure timely analysis and reporting to health authorities within 15 calendar days from the date PHL criteria were met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

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

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

H 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 participant's 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 H 4.2

H 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 H 6 of this Appendix?

If **No**: follow the process described in Section H 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 H 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.

H 8 References

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Appendix I

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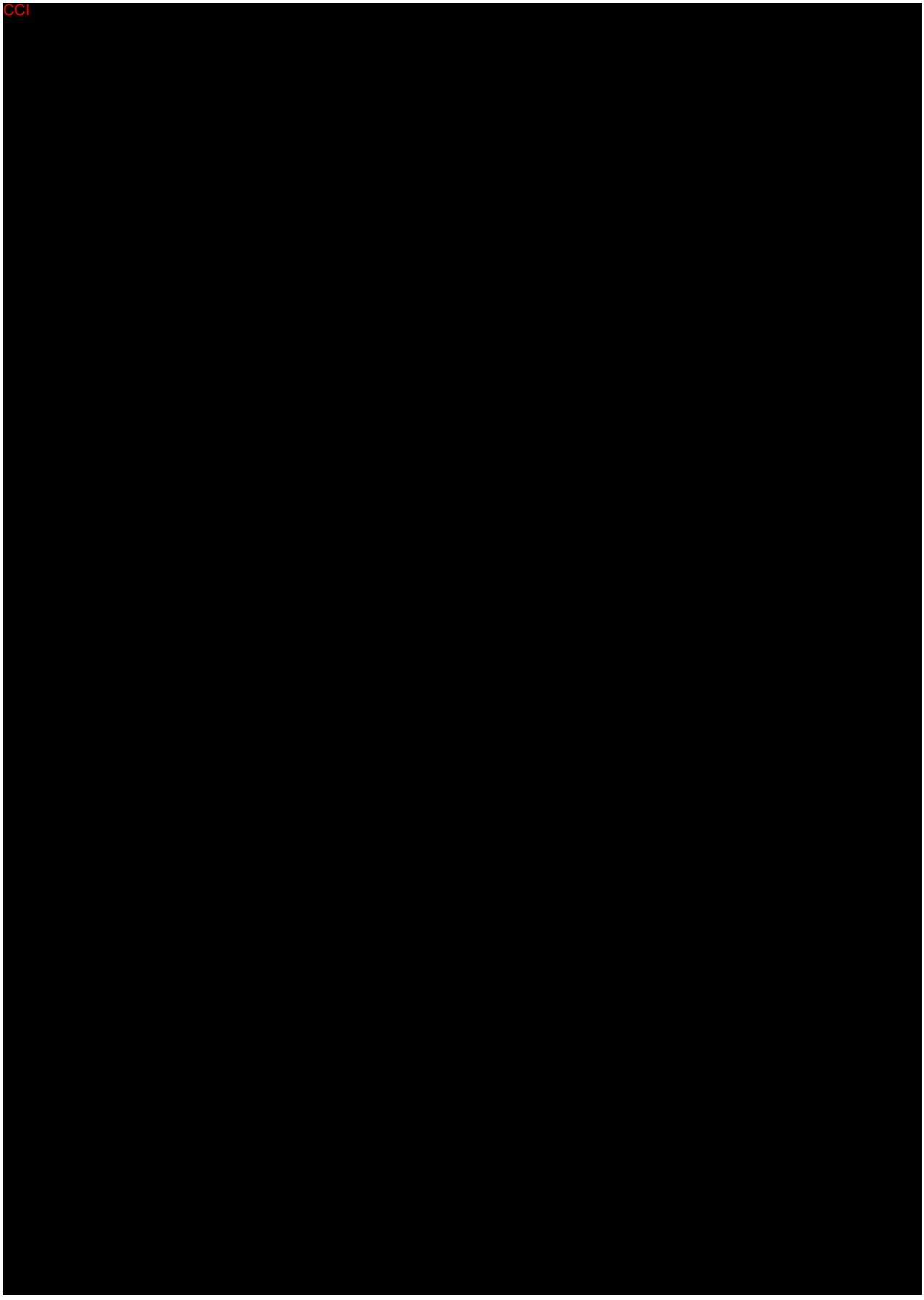

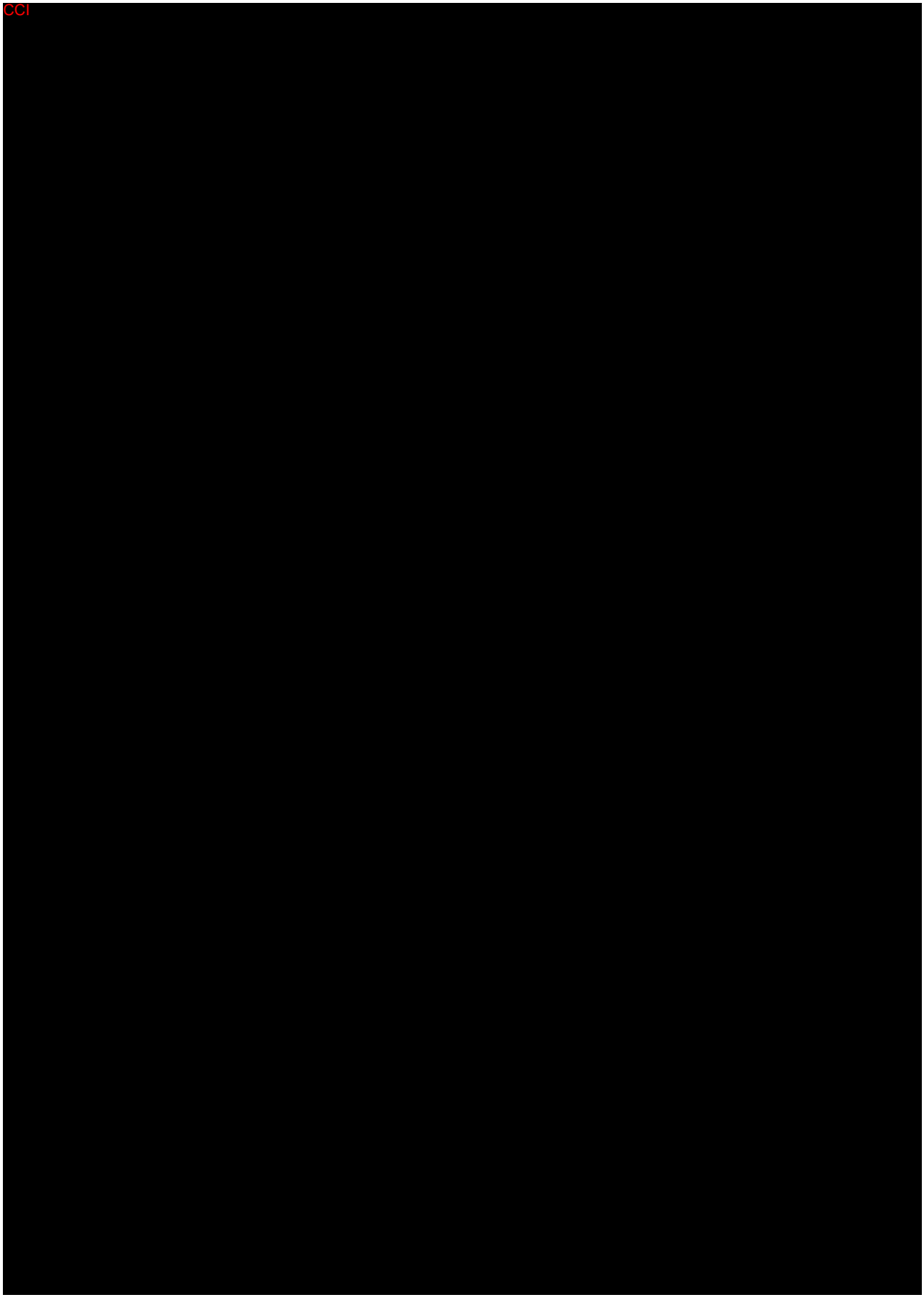
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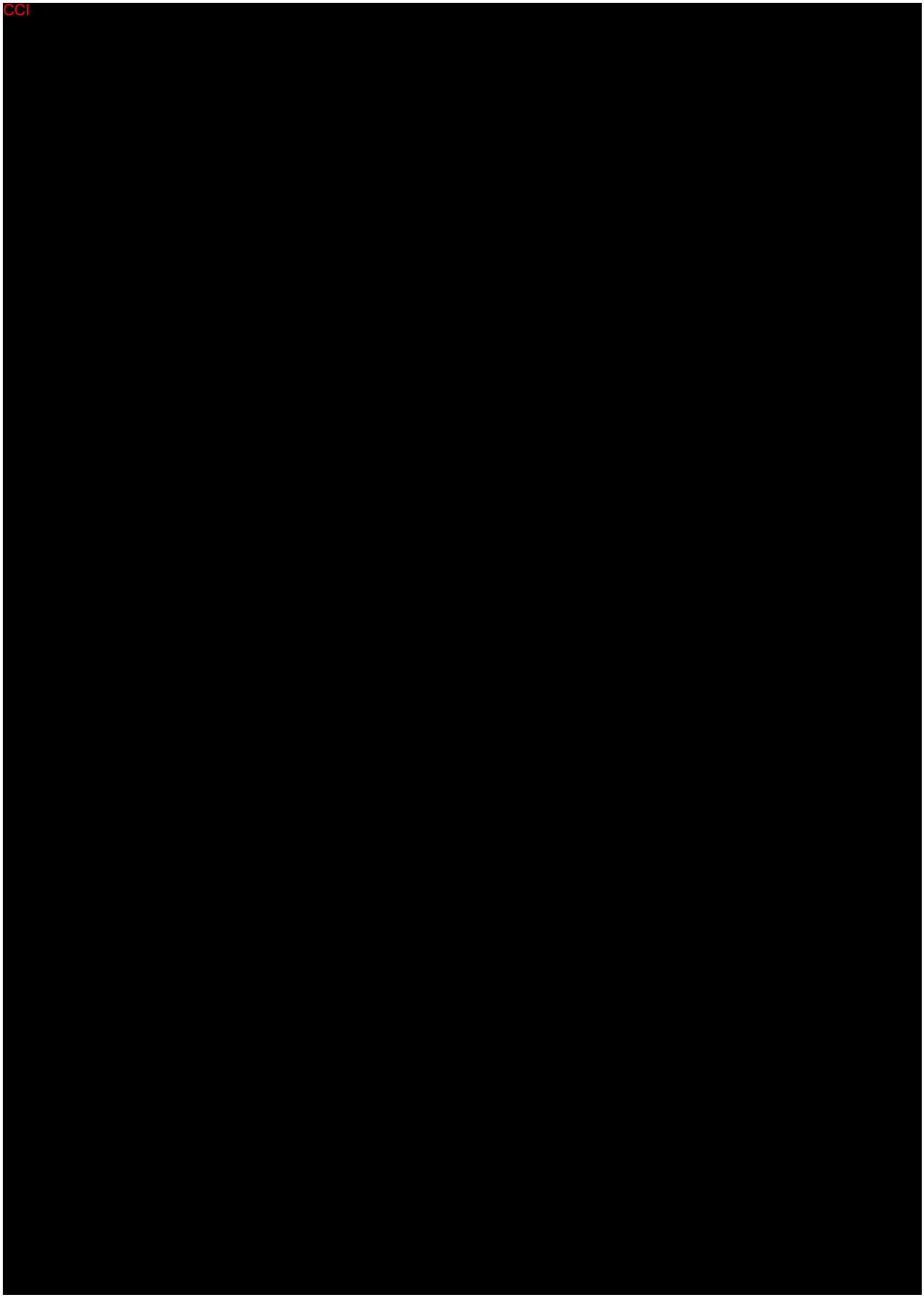

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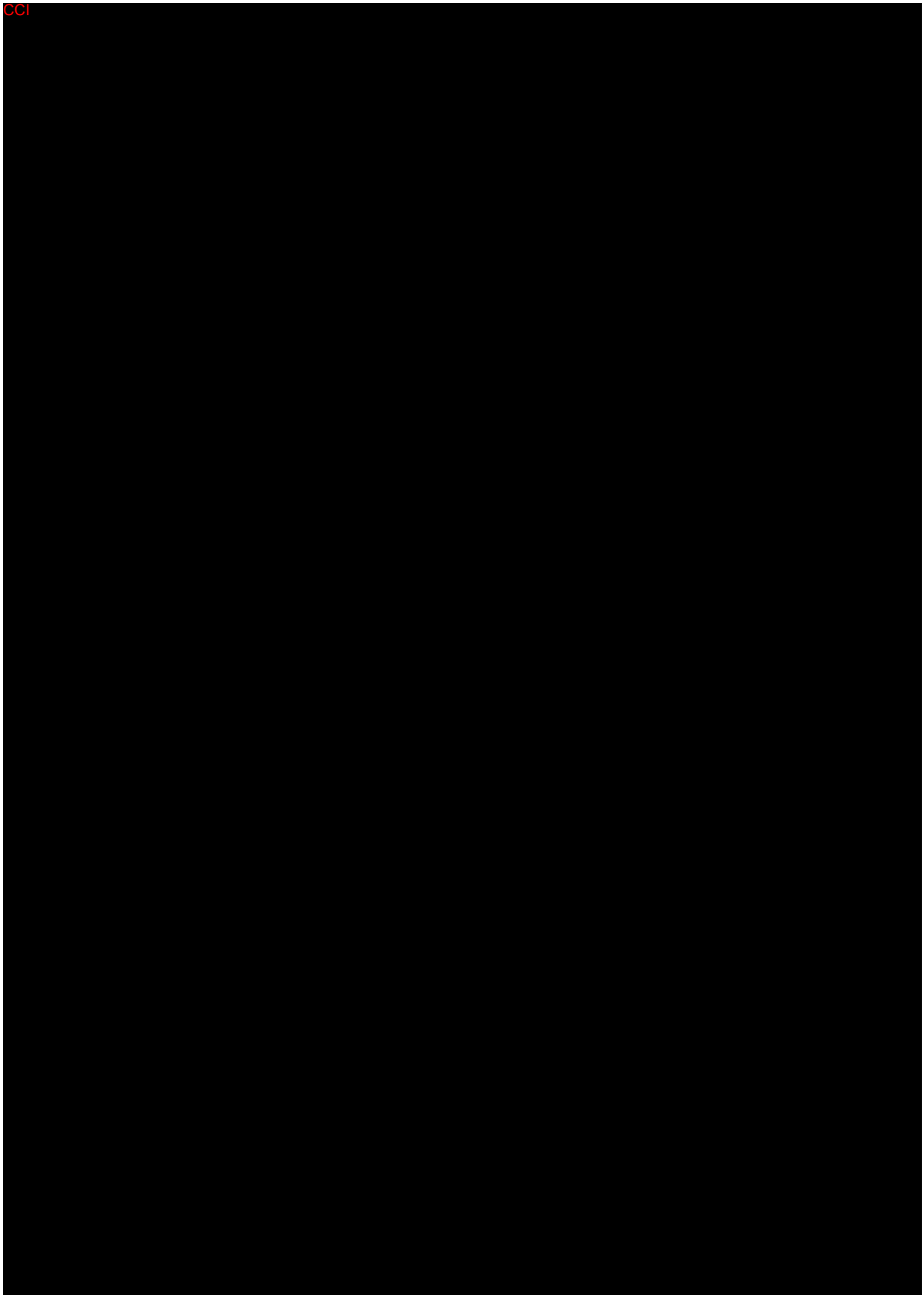

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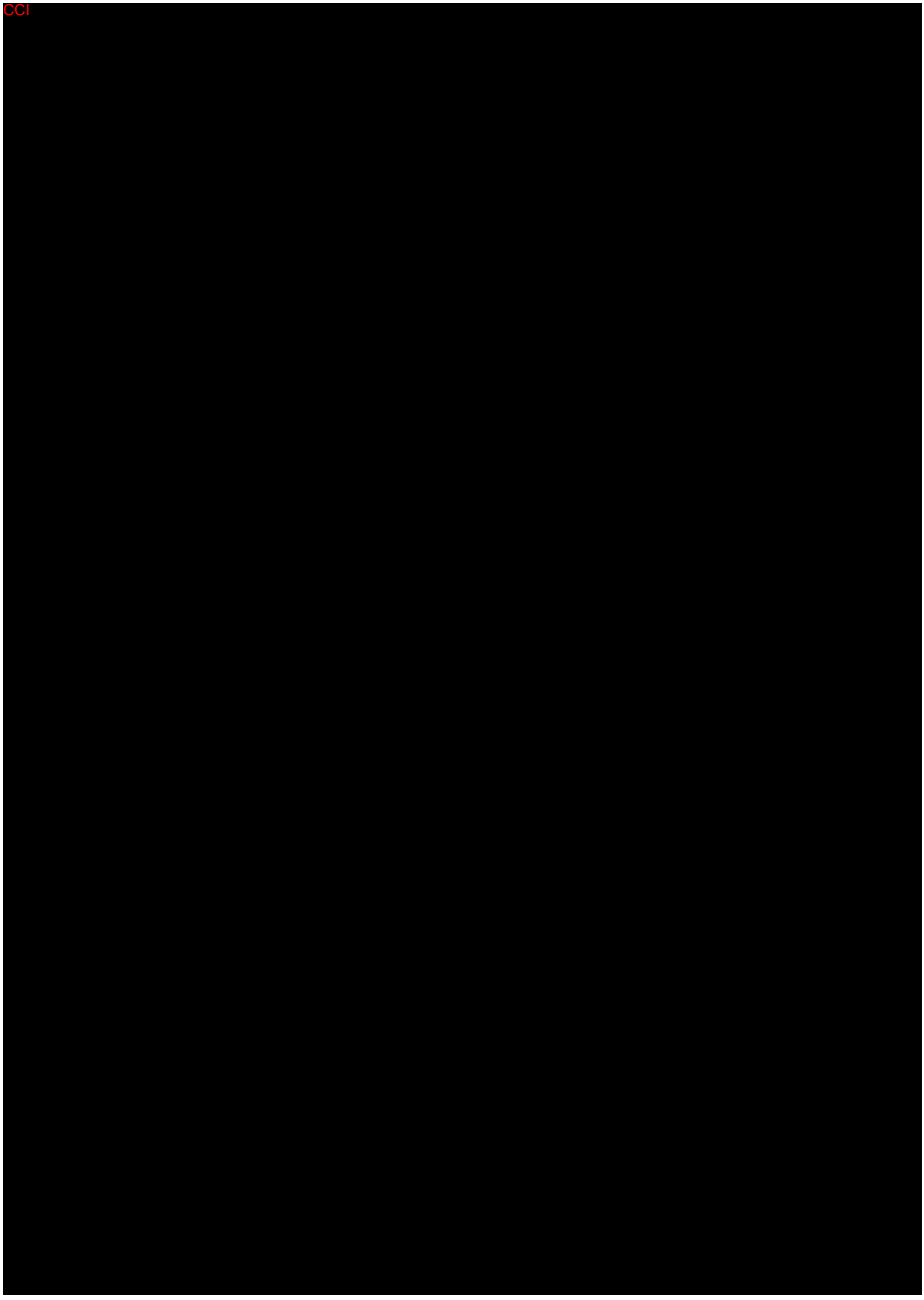

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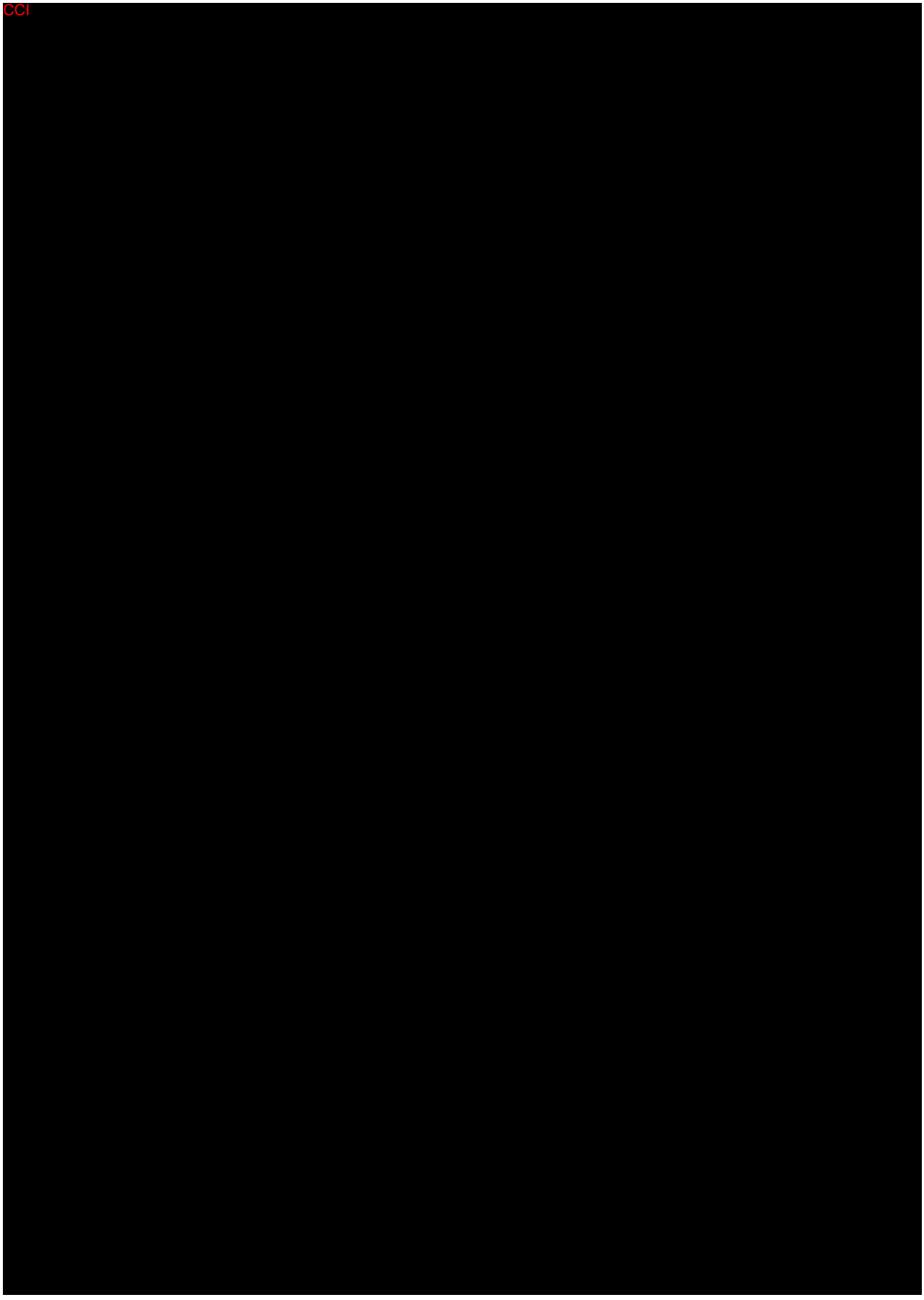

Appendix J Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

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 participant 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 agreement from the sponsor.

J 1 Consent/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. Consent/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 8. Local and regional regulations and/or guidelines regarding consent/reconsent of study participants should be checked and followed. Consent/reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal consent/reconsent, the informed consent form should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining consent/reconsent should be avoided.

J 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 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 investigational product (IP). If this delay is outside the screening window specified in Section 5.4, the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a participant in addition to that detailed in Section 5.4. The procedures detailed in Sections 5.4 must be undertaken to confirm eligibility using the same randomization number as for the participant.

J 3 Home or remote visit to replace on-site visit (where applicable)

A qualified healthcare professional (HCP) from the study site or third-party vendor service

may visit the participant's home or other remote location as per local standard operating procedures, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the Clinical Study Protocol.

J 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 medications, participant report outcome questionnaires, and health economic data to be reported and documented.

J 5 At-home or remote location investigational product administration instructions

If a site visit is not possible, at-home or remote location administration of investigational product may be performed by the participant or his/her caregiver. The option of at-home or remote location investigational product administration ensures participant's 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 investigational product administration during other study disruptions, eg, site closures due to natural disaster.

J 6 At-home or remote location investigational product administration by the participant or his/her caregiver

Prior to at-home or remote location investigational product 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 investigational product. 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 investigational product administration will be provided. More information related to the visit can be obtained via a telemedicine or home/remote visit.

J 7 Data capture during telemedicine or home/remote visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or third-party vendor service in the source documents, or by the participant themselves.

Appendix K Abbreviations

Abbreviation or special term	Explanation
^{18}FDG-PET	^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Plasma concentration time curve (area under the curve)
BCRP	Breast cancer resistance protein
BICR	Blinded Independent Central Review
BID	Twice-daily
BMI	Body mass index
CCI	
CCAS	Centrally-confirmed analysis set
CDK1	Cyclin-dependent kinase 1
CDK2	Cyclin-dependent kinase 2
CI	Confidence interval
C_{max}	Maximum concentration
CMP	Continuous Monitoring Plan
C_{trough}	Lowest concentration
CR	Complete response
CrCl	Creatinine clearance
CRO	Contract research organisation
CSP	Clinical study protocol
CSR	Clinical study report
CT	Clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CCI	
CYP	Cytochrome P450
DCO	Data cut-off
DCR	Disease control rate
DILI	Drug induced liver injury
dMMR	Mismatch repair deficient
CCI	

Abbreviation or special term	Explanation
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECD	Electronic data capture
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
CCI	[redacted]
FAS	Full analysis set
FDA	U.S. Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
G-CSF	Granulocyte colony-stimulating factor
GCP	Good Clinical Practice
Hb	Haemoglobin
HBV	Hepatitis B virus
HBC	Hepatitis C virus
HCP	Healthcare professional
HE	Haematoxylin and eosin
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HL	Hy's Law
CCI	[redacted]
IC_{50}	Half maximal inhibitory concentration
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
CCI	[redacted]
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IV	Intravenous
LPFD	Last participant first dose

Abbreviation or special term	Explanation
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MSI-H	Microsatellite instability-high
MSS	Microsatellite stable
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
CCI	
NIMP	Non-Investigational Medical Product
NTL	Non-Target Lesion
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death-1 receptor
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PFS6	Proportion of participants alive and progression free at 6 months
CCI	
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetics
PR	Partial response
CCI	
PSSR	Project Specific Safety Requirements
QD	Once daily
QoL	Quality of life
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	Corrected QT interval
QTcF	QT corrected by Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumours. This study will use RECIST version 1.1.
CCI	

Abbreviation or special term	Explanation
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
TBL	Total bilirubin
TCGA	The Cancer Genome Atlas
TL	Target Lesion
ULN	Upper limit of normal
US	United States
USC	Uterine serous carcinoma
VEGF	Vascular endothelial growth factor
WNL	Within normal limits

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Study Intervention	Adavosertib (AZD1775)
Study Code	D601HC00002
Version	Errata to Global – v6.0
Date	09 June 2022

A Phase 2b, Open-label, Single-arm, Multi-centre Study Assessing the Efficacy and Safety of Adavosertib as Treatment for Recurrent or Persistent Uterine Serous Carcinoma (ADAGIO)

Sponsor Name:

Legal Registered Address:

AstraZeneca AB, S-151 85 Södertälje, Sweden.

Regulatory Agency Identifier Number(s):

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ERRATA

This addendum accompanies the Global CSP 6.0 and corrects the following passages:

Table 1 Schedule of Activities ~~(Cohort A and B)~~

Clarification: As part of Global CSP 6.0 update, all reference to Cohorts (A and B), and CCI CCI *dose have been removed – this reference to a cohort has incorrectly remained in the protocol.*

4.4 End of Study Definition

"…The end of the study is defined as the date of the last visit of the last participant in the study. The last visit occurs when the last participant ~~of Cohort B~~ has their last scheduled visit, or 6 months after last participant first dose ~~in Cohort B~~, whichever comes first…"
Clarification: As part of Global CSP 6.0 update, all reference to Cohorts (A and B), and CCI CCI *dose have been removed – this reference to a cohort has incorrectly remained in the protocol.*

9.4.1.1 Primary Endpoint: ORR

"…An interim analysis is planned after approximately 30 participants in the CCAS ~~in Cohort A~~ have had the opportunity to be treated for at least 4 months. Recruitment will not be paused whilst the participants required for the interim are evaluated…"

Clarification: As part of Global CSP 6.0 update, all reference to Cohorts (A and B), and CCI CCI *dose have been removed – this reference to a cohort has incorrectly remained in the protocol.*

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