Clinical Study Protocol	
Drug Substance	AZD9833
Study Code	D8530C00002
Version	5.0
Date	15 September 2021

SERENA-2: A Randomised, Open-Label, Parallel-Group, Multicentre Phase 2 Study Comparing the Efficacy and Safety of Oral AZD9833 versus Fulvestrant in Women with Advanced ER-Positive HER2-Negative Breast Cancer

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number(s):

IND: 138 396

EudraCT: 2019-003706-27

VERSION HISTORY

Version 5.0 15 September 2021

Sections 1.2, 4.4, 9.2, 9.4 and 9.4.1.1 have been amended to CCI the maturity at which the primary analysis will be conducted (from CCI to 75% maturity). The primary analysis will now be conducted when at least 108 events for each pairwise comparison are available, ie, at the original follow-up analysis.
Sections 2.3.3, 9.2, 9.4, 9.4.1 and 9.5.1 have been amended to replace the original planned primary analysis by an interim analysis at CCI maturity.
Justification for changes: During the course of the study, results released at the American Society of Clinical Oncology (ASCO) 2021 conference (Lindeman et al 2021) demonstrated shorter progression times for patients who had received prior CDK4/6 inhibitors, compared to historical studies, and in particular for the fulvestrant control arm. D8530C00002 is stratified according to prior CDK4/6 use, such that approximately 50% of patients are to be randomised to each prior CDK4/6 (yes/no) stratum. Given the planned maturity of the original planned primary analysis, CCI events (CCI maturity), that originally planned analysis was likely to be enriched for the prior CDK4/6 yes stratum. In order to ensure that the primary analysis contains sufficient events in both prior CDK 4/6 use strata, as per the design, the primary analysis will be CCI take place at 108 events (75% maturity; the original planned follow-up analysis). This will ensure that both key strata have sufficient maturity, and mitigates against the risk of a prior CDK4/6 inhibitor enriched population at analysis, thus allowing the results and the potential benefit of AZD9833 over fulvestrant to be fully understood.

Section 2.3.2.2: Updated information on CCI in rats and CCI in dogs has been included as recommended by FAMHP (Federal Agency for Medicines and Health Products, Belgium) to align to AZD9833 IB Edition 3.

Sections 1.2, 4.4 and 9.4: Clarification that after the primary data cut off (DCO), efficacy and safety data may continue to be collected. Additional DCOs may be defined for PFS and OS follow-up analyses.

Section 6.5.3 and Appendix B3: New section added presenting preliminary PK data from SERENA-1 suggesting the possibility that AZD9833 may effect clinically relevant CCI inhibition. The appendix has been modified to provide advice regarding the concomitant use of CCI .

Section 8.1.3.1 (Post Primary Analysis): New section added explaining that at the time of final analysis, the clinical study database will close to new data. Patients are, however, permitted to continue to receive study treatment beyond the closure of the database if, in the opinion of the Investigator, they are continuing to receive benefit from study treatment.

Section 10: Reference Lindeman et al 2021 has been added.

Appendix C2: The wording in this section has been modified to change "congenital abnormality or birth defect" to "congenital anomaly or birth defect". Global: Minor administrative and typographical errors were corrected.
Version 4.0 16 December 2020
Sections 1.2, 1.3, 2.3, 4.1, 4.2, 4.4, 6.3, 9, 9.1, 9.2, 9.4 (Table 22), and 9.4.1 have been amended to close further recruitment to the AZD9833 300 mg arm. Careful review of the large SERENA-1 Phase 1 ER-positive advanced breast cancer data set reveals a CCI [redacted] for the increment in dose from 150 mg to 300 mg in terms of CCI [redacted] (Baird, et al., 2020). There is also an increased CCI [redacted] of CCI [redacted] and CCI [redacted] as the AZD9833 CCI [redacted] is increased. CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted]. The 75 and 150 mg AZD9833 arms, and the fulvestrant arm, will continue to recruit as planned to 72 patients per arm. It is important to note that there have been no new concerning safety signals observed with AZD9833. As of December 2020, no new patients will be randomized to the AZD9833 300 mg arm. Patients already randomised to AZD9833 300 mg are able to continue at that dose, with the opportunity for AZD9833 dose reduction, if required, as already described in the protocol. AstraZeneca intends to report all data from the patients who have been randomised to the AZD9833 300 mg arm so far, as per AstraZeneca and local regulatory requirements. The following changes required by the Regulatory Agencies in Germany, France, and Portugal were added: Germany: Inclusion criterion 7 (Section 5.1) has been amended to specify that HER-2 negative status should be determined according to the local laboratory parameters and where those laboratory parameters are in accordance with accepted diagnostic guidelines. Section 8.3.2 has been amended to specify that if the Investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must notify the Sponsor. Section 8.3.7 has been amended to provide guidance on the reporting of deterioration in protocol-mandated laboratory values, ECG and vital signs as compared to baseline; these should be reported as AEs if they are assessed as clinically significant by the investigator, or if they fulfil any of the SAE criteria or are the reason for discontinuation of study treatments. Appendix C 2 has been amended to remove the limitations in the assessment of certain malignant tumours as serious AEs. France: Table 18 AZD9833 dose interruption, reduction and/or discontinuation guidance (Section 6.6.1) has been amended to include guidance for the management of CCI [redacted] and

general guidance for the management of other AEs considered related to AZD9833.

Portugal:
Exclusion criterion 4 (Section 5.1) has been amended to clarify the language related to the HIV, HCV and HBV screening.
Section 1.1 (Schedule of activities), Table 1 (study assessments) was amended to include triplicate ECGs on the 28-day safety follow up visit and clarification text on PRO interviews was added to footnote "f".

Section 4.1 (Overall design), triplicate ECGs and echocardiogram were added to the 28-day safety follow up.

Inclusion criterion 4 (section 5.1), clarification text to the post-menopausal criteria was added

Section 6.1.1, clarification text on AZD9833 dosing instructions in Table 16 (study treatments) was added, and additional instructions regarding missed doses of AZD9833 were added.

Section 6.6.1, clarification text to indicate that Table 18 (AZD9833 dose interruption, reduction and/or discontinuation guidance) refers to AEs assessed as related to AZD9833 was added.

Section 8.1.3 (Survival follow up), clarification text to indicate that new anti-cancer treatments will be documented as part of survival follow up was added.

Section 8.2.1, Table 20 (Laboratory safety variables) clarification that urinalysis is not limited to dipstick was implemented.

Section 8.2.4.2 (Ambulatory ECG), clarification regarding the number of hours ambulatory ECGs can be worn by patients was added.

Section 8.8.5 (Tumour biopsy in selected patients), clarification that paired biopsies from bone tissue are not permitted was added.

Administrative and typographical errors were corrected in sections 6.3, 8.1.4.2, 8.1.4.3 and 8.2.4.1.

Version 3.0 06 April 2020

The protocol has been amended in response to the re-examination of the available pre-clinical data and pharmacokinetic modelling for AZD9833 which identified that a significant inhibition of the metabolism of CCI [redacted] and CCI [redacted] substrates cannot be excluded.
The following have therefore been amended:

Exclusion criteria 1c has been amended to exclude concomitant use of AZD9833 with drugs which are substrates of CCI and/or CCI which have a narrow therapeutic index ie, CCI or inability to stop use within the washout period. Section 6.5.2 CCI substrates and sub-section 6.5.2.2 have been amended to exclude concomitant use of AZD9833 with drugs which are substrates of CCI and/ or CCI, which have a narrow therapeutic index ie, CCI Appendix B 3 Guidance for drugs whose exposure may be affected by AZD9833; has been amended to provide guidance for use of AZD9833 concomitantly with drugs which are substrates of CCI and/ or CCI, which have a narrow therapeutic index CCI, CCI and required washout periods.
Version 2, 20 March 2020
The protocol has been amended in response to emerging non-clinical data from a rat 6-month Good Laboratory Practice (GLP) toxicity study. Section 1.1 Schedule of activities and Section 8.2.4.3 added to include echocardiograms (ECHO) assessments. Section 2.3.2.2 Potential risks updated to include the following as potential risks identified from non-clinical studies: • CCI Section 5.2 Exclusion criteria updated to exclude patients with left ventricular ejection fraction (LVEF) <50% Section 8.2.1 Clinical safety laboratory assessments table 19 updated to include clinical chemistry assessments (serum or plasma) of Troponin and NT-proBNP.
Version 1, 01 October 2019
Initial version

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are

disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1 PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

Table 1 Study assessments

	Screening	Treatment period (28-day cycles)									Post-treatment period			Details in CSP section or Appendix
Visit	**1**	**2**	**3**	**4**	**5**	**7**	**8**	**9**	**11**	**≥12**	**EOT visit**	**28-day safety follow-up**	**Survival follow-up**	
Cycle		**C1**			**C2**	**C3**	**C4**	**C5**	**C6**	**C≥7**				
Cycle day	**-**	**D1**	**D8**	**D15**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**				
Study day	**-28 to -1**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**≥169**	**EOT**	**EOT+28**	**12-weekly**	
Week (Day 1 of)	**-4 to -1**	**1**	**2**	**3**	**5**	**9**	**13**	**17**	**21**	**≥25**	**EOT**	**EOT+4**		
Visit window (days)			**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**+7**	**±14**	
Informed consent	X													5.1
Eligibility criteria	X													5.1, 5.2
Routine clinical procedures														
Demography, medical/surgical history, baseline characteristics	X													5.1
Concomitant medication	X	At every visit and may be conducted by phone												6.5
Survival status, anti-cancer treatments													X	8.1.3
ECOG/WHO performance status	X	X			X	X	X	X	X	every 2 cycles	X	X		8.1.4
Routine safety assessments														
Adverse events	X	At every visit and may be conducted by phone												8.3
Physical examination	X	X			X	X	X	X	X	every 2 cycles	X	X		8.2.2
Weight, height [a]	X	X			X	X	X	X	X	every cycle	X	X		8.2.2
Vital signs (temperature, pulse rate, blood pressure)	X	X	X	X	X	X	X	X	X	every 2 cycles	X	X		8.2.3
Triplicate ECGs	X	pre-dose	X	X	X	X	X	X	X	every 2 cycles	X	X		8.2.4.1
24-hour ECG	X			Once between D15 and D29										8.2.4.2
Echocardiogram[g]	X				X			every 3rd cycle				X		8.2.4.3
Clinical chemistry, haematology, urinalysis	X	X		X	X	X	X	X	X	every 2 cycles	X			8.2.1
Coagulation tests	X	X			X									8.2.1

Table 1 Study assessments

	Screening	Treatment period (28-day cycles)									Post-treatment period			Details in CSP section or Appendix
Visit	**1**	**2**	**3**	**4**	**5**	**7**	**8**	**9**	**11**	**≥12**	**EOT visit**	**28-day safety follow-up**	**Survival follow-up**	
Cycle		**C1**			**C2**	**C3**	**C4**	**C5**	**C6**	**C≥7**				
Cycle day	**-**	**D1**	**D8**	**D15**	**D1**	**D1**	**D1**	**D1**	**D1**	**D1**				
Study day	**-28 to -1**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**≥169**	**EOT**	**EOT+28**	**12-weekly**	
Week (Day 1 of)	**-4 to -1**	**1**	**2**	**3**	**5**	**9**	**13**	**17**	**21**	**≥25**	**EOT**	**EOT+4**		
Visit window (days)			**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**+7**	**±14**	
PK sampling for AZD9833 and, if appropriate, metabolite(s) [b]														
PK sample pre-dose				X	X									8.5
PK samples post-dose (2, 4 hours)				X										8.5
Efficacy assessments														
Tumour imaging (RECIST version 1.1)	X					X [c]		X [c]		8-weekly [c]				8.1.1, Appendix G
Bone scan, skeletal survey	X [d]													8.1.2
Biomarker analyses														
Blood sample for ctDNA	X	pre-dose		X	X	X	X	X		8-weekly [e]	X			8.8.1
Blood sample for CCI	X	pre-dose		X	X	X	X	X		8-weekly [e]	X			8.8.2
Blood sample for CCI	X	pre-dose			X		X				X			8.8.3
Archival tumour tissue	X													8.8.4
Optional tumour biopsy (for selected patients)	X				X					at progression				8.8.5
Patient reported outcomes														
HRQoL questionnaires (EORTC QLQ-C30, EORTC QLQ-BR23, NEI VFQ-25, EQ-5D-5L, CCI)		X			X		X			8-weekly [e]	X	X		8.1.4.2
CCI	X				X		X							8.1.4.3
Optional CCI sampling														
Blood sample		X												8.7

Table 1 Study assessments

	Screening	Treatment period (28-day cycles)									Post-treatment period			Details in CSP section or Appendix
Visit	**1**	**2**	**3**	**4**	**5**	**7**	**8**	**9**	**11**	**≥12**	**EOT visit**	**28-day safety follow-up**	**Survival follow-up**	
Cycle		**C1**			**C2**	**C3**	**C4**	**C5**	**C6**	**C≥7**				
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Study day	**-28 to -1**	**1**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**≥169**	**EOT**	**EOT+28**	**12-weekly**	
Week (Day 1 of)	**-4 to -1**	**1**	**2**	**3**	**5**	**9**	**13**	**17**	**21**	**≥25**	**EOT**	**EOT+4**		
Visit window (days)			**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+7**	**+7**	**±14**	
Study treatment														
Randomisation		X												6.3
Fulvestrant (500 mg IM)		X		X	X	X	X	X	X	every cycle				6.1.1
Dispense/collect AZD9833		X			X	X	X	X	X	every cycle	X			6.4
AZD9833 (PO)		75 mg, 150 mg, or 300 mg once daily												6.1.1

[a] Height will be measured at screening only.

[b] Pharmacokinetic samples will only be collected for patients treated with AZD9833.

[c] The time window for tumour imaging is ±7 days. Assessments will be conducted until disease progression.

[d] The bone scan /skeletal survey should be performed within 12 weeks of treatment start (C1D1).

[e] Sample collection and completion of HRQoL questionnaires will be done 8-weekly (D1 of every 2nd cycle) from Week 25 (C7) to coincide with tumour RECIST assessment.

[f] PRO interviews will only be conducted for patients enrolled in the United States, United Kingdom, and Spain. The interviews will be conducted by phone. The 1st interview will occur at baseline (prior to 1st dose within screening period). Vendor conducting interviews will be notified within a day of identification of an eligible patient and the date of scheduled C1D1. Best efforts will be used to schedule all interviews within the windows allowed. The 2nd interview will occur 4 weeks (±7 days) from C1D1 and the 3rd interview will occur 12 weeks (±21 days) from C1D1.

[g] Echocardiograms time window for visits C2D1, C5D1 and every 3rd cycle thereafter, and 28-day follow-up echocardiograms is ±7 days

CCI [redacted]; CSP=Clinical Study Protocol; CCI [redacted]; Cx=Cycle x; Dx=Day x; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC=European Organisation for Research and Treatment of Cancer; EORTC QLQ-BR23=EORTC quality of life questionnaire - breast cancer module; EORTC QLQ-C30=EORTC quality of life questionnaire - core questionnaire, EOT=end of treatment; EQ-5D-5L=EuroQol 5 Dimension 5 level; HRQoL=health-related quality of life; IM=intramuscular; NEI VFQ-25=National Eye Institute 25-Item Visual Function Questionnaire; CCI [redacted] PK=pharmacokinetics; PO=oral (per os); CCI [redacted]; RECIST=Response Evaluation Criteria in Solid Tumours; WHO=World Health Organisation.

1.2 Synopsis

International co-ordinating Investigator:

PPD, MD
Vall d'Hebron Institute of Oncology
Barcelona, Catalonia, Spain

Protocol title:

SERENA-2: A Randomised, Open-Label, Parallel-Group, Multicentre Phase 2 Study Comparing the Efficacy and Safety of Oral AZD9833 versus Fulvestrant in Women with Advanced ER-Positive HER2-Negative Breast Cancer

Short title:

SERENA-2: A Randomised Comparative Phase 2 Study of AZD9833 versus Fulvestrant in Women with Advanced ER-Positive HER2-Negative Breast Cancer

Rationale:

The oestrogen receptor (ER) alpha (ERα) is a well-established drug target in breast cancer with anti-hormonal endocrine therapies being the mainstay of treatment (Early Breast Cancer Trialists' Collaborative Group 2005). The selective ER degrader (SERD) and antagonist fulvestrant is used as a standard-of-care treatment for ER-positive metastatic breast cancer (Cardoso et al 2018).

Although fulvestrant has demonstrated superior clinical efficacy to other endocrine therapies in this metastatic setting, it is not orally bioavailable and the monthly intramuscular (IM) route of administration may limit its efficacy (Robertson 2007, Robertson et al 2014).

AZD9833 is an orally bioavailable SERD which is being developed for the treatment of women with ER-positive breast cancer.

AZD9833 has the potential to provide superior clinical benefit to existing endocrine therapies through enhanced bioavailability, target engagement and modulation in patients with ER-positive breast cancer.

A first-in-human study (D8530C00001) evaluating AZD9833 in women with advanced ER-positive human epidermal growth factor receptor 2 (HER2)-negative breast cancer completed its monotherapy dose escalation phase. This study evaluated multiple ascending doses of AZD9833 administered once daily to post-menopausal women. Subsequent parts of this study will examine AZD9833 as monotherapy in pre-menopausal women, and also in combination with the cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor palbociclib in a pre- and post-menopausal population. Study D8530C00001 established that AZD9833 doses of 75, 150 and 300 mg administered once daily were safe and well tolerated in that population, and there are sound indications of clinical efficacy at each of these doses.

This open-label Phase 2 study will enrol post-menopausal women with advanced ER-positive HER2-negative breast cancer who are suitable for fulvestrant therapy. The study will evaluate the efficacy and safety of AZD9833 (75, 150 and 300 mg, oral [PO]) administered once daily as a monotherapy in comparison with fulvestrant administered according to its label (ie, slow IM injection into the buttocks [1 to 2 minutes per injection] as two 5-mL injections, 1 in each buttock, on Day 1, Day 15, Day 29 and 4-weekly thereafter).

This study will be key to determining if AZD9833 should be further investigated in Phase 3 clinical trials.

Objectives and endpoints

Primary Objective:	Endpoint/Variable:
To determine the clinical efficacy (as assessed by PFS) of AZD9833 when compared to fulvestrant in women with advanced ER-positive HER2-negative breast cancer	PFS assessed by the Investigator as defined by RECIST version 1.1
Secondary Objectives:	**Endpoints/Variables:**
To determine anti-tumour effect of AZD9833 when compared to fulvestrant in women with advanced ER-positive HER2-negative breast cancer	Based on tumour response assessed by the Investigator, as defined by RECIST version 1.1: • ORR • DoR • Best percentage change in tumour size and percentage change in tumour size at 16 weeks
To determine the effect of AZD9833 on survival and clinical benefit when compared to fulvestrant in women with advanced ER-positive HER2-negative breast cancer	• OS • CBR_{24}
To evaluate the PK of AZD9833 in this patient population at steady state	Plasma concentrations of AZD9833 and, if appropriate, metabolite(s) on Day 15 (pre- and post-dose) and Day 29 (pre-dose)
To evaluate the pharmacodynamics of AZD9833 and fulvestrant in a subgroup of patients with advanced ER-positive HER2-negative breast cancer	• Percent change from baseline in ER and PgR expression assessed by the manual H-score method. • Percent change from baseline in Ki67 labelling index
To evaluate the effect of AZD9833 and fulvestrant on the patients' HRQoL, as assessed by patient-completed HRQoL questionnaires	Changes from baseline in total/subscale scores of the EORTC QLQ-C30, EORTC QLQ-BR23, NEI VFQ-25, and EQ-5D-5L
Safety Objective:	**Endpoints/Variables:**
To evaluate the safety and tolerability of AZD9833 when compared to fulvestrant in women with advanced ER-positive HER2-negative breast cancer	• AEs/SAEs • Vital signs, ECGs, clinical chemistry, haematology, urinalysis parameters

Objectives and endpoints

Exploratory Objectives	Endpoints/Variables:
To investigate predictive markers of response and/or acquired resistance to AZD9833 and fulvestrant	• Change from baseline in amount and mutation status of cancer-associated genes in ctDNA, CCI
To assess the impact of CCI	• Subgroup analysis of CCI during treatment
To evaluate the effect of AZD9833 and fulvestrant on the CCI	• CCI
To examine overall CCI	
Optional CCI : To collect and store CCI according to each country's local and ethical procedures for future exploratory research into CCI that may influence response to treatment	Results from future exploratory research may be reported outside of the CSR.

CBR_{24}=clinical benefit rate at 24 weeks; CCI ; ctDNA=circulating tumour DNA; DoR=duration of response; ECG=electrocardiogram; EORTC=European Organisation for Research and Treatment of Cancer; EORTC QLQ-BR23=EORTC quality of life questionnaire - breast cancer module; EORTC QLQ-C30=EORTC quality of life questionnaire - core questionnaire, EQ-5D-5L=EuroQol 5 dimension 5 level; NEI VFQ-25=National Eye Institute 25-Item Visual Function Questionnaire; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; CCI PgR=progesterone receptor.

Overall design:

This is a randomised, open-label, parallel-group, multicentre Phase 2 study to compare the efficacy and safety of daily PO AZD9833 versus IM fulvestrant in women with advanced ER-positive HER2-negative breast cancer. Post-menopausal women with histologically or cytologically confirmed metastatic or loco-regionally recurrent disease before randomisation and fulfilling all of the inclusion criteria and none of the exclusion criteria will be included. Randomisation will be stratified according to the prior use of CDK4/6 inhibitors and the presence of liver and/or lung metastases.

After the screening visit and confirmation of eligibility, patients will be randomly assigned in a 1:1:1:1 ratio to receive 1 of the following 4 treatments, consisting in 4-week treatment

cycles until disease progression (assessed by the Investigator as defined by Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1):

- AZD9833 (75 mg, PO, once daily)
- AZD9833 (150 mg, PO, once daily)
- AZD9833 (300 mg, PO, once daily)
- Fulvestrant (500 mg IM, Day 1, Day 15, Day 29, and 4-weekly thereafter)

As of December 2020, the Sponsor stopped enrolment to the 300 mg treatment arm. Ongoing patients in the 300 mg treatment arm may continue treatment as planned.

During the treatment period, patients will attend visits on:

- Day 1, Day 8, and Day 15 of Cycle 1
- Day 1 of each subsequent cycle until treatment discontinuation

After the treatment period, patients will attend 2 safety follow-up visits (at the time of treatment discontinuation and 28 days later) and will continue to be followed for survival.

Throughout the study, patients will be asked to report adverse events (AEs) and the use of concomitant medication.

Safety assessments (physical examination, vital signs, electrocardiograms [ECGs], clinical safety laboratory assessments) will be performed at screening, on Day 1 of every cycle (up to Cycle 6) and every 2 cycles (from Cycle 6) and at the end of treatment (EOT) visit. Echocardiograms will be performed at screening, on Day 1 of cycle 2 and 5, every 3 cycles thereafter and at the 28 day follow up visit. Safety assessments will also be performed on Cycle 1 Day 8 (vital signs and triplicate ECGs), Cycle 1 Day 15 (vital signs, ECGs, clinical chemistry, haematology, and urinalysis), at the 28-day safety follow-up (physical exam and vital signs).

Tumour imaging will be performed for the assessment tumour response according to RECIST version 1.1 at screening and every 8 weeks from Week 9 until disease progression.

Patients will complete health-related quality of life (HRQoL) questionnaires on Day 1 of Cycles 1, 2, and 4, then 8-weekly (Day 1 of every 2nd cycle) from Week 25 (Cycle 7) to coincide with tumour imaging, at the EOT and/or disease progression, and at the 28-day safety follow-up.

Blood and plasma samples for circulating tumour (ctDNA) and CCI [redacted] analyses will be collected at screening, on Day 1 and Day 15 of Cycle 1, on Day 1 of Cycles 2

to 5, 8-weekly (Day 1 of every 2nd cycle) from Week 25 (Cycle 7) to coincide with tumour imaging, at the EOT and/or disease progression.

Blood samples for CCI [redacted] will be collected at screening, on Day 1 of Cycles 1, 2, and 4, and at the EOT.

For patients receiving AZD9833, blood samples will be collected for pharmacokinetic (PK) assessments on Cycle 1 Day 15 and Cycle 2 Day 1.

For patients who provide specific consent, the following optional assessments will be performed:

- Up to 12 patients per treatment group will be selected such that they are suitable for providing 1 pre-treatment and 1 on-treatment paired tumour biopsy sample. If provision of paired biopsies becomes clinically unfeasible for a selected patient during the course of her care, the patient may be replaced until up to 12 evaluable biopsy pairs are collected within each treatment group.
- An optional blood sample will be collected at pre-dose on Day 1 of Cycle 1 or later during the study for future genetic research.

Study period:

Estimated date of first patient enrolled: Q4 2019

Estimated date of last patient completed (primary analysis): Q2 2022

Number of patients:

This study will screen approximately 360 patients (assuming a screen failure rate of 20%), in order to randomise 288 patients into 4 treatment groups in a 1:1:1:1 ratio:

- AZD9833 75 mg: 72 patients
- AZD9833 150 mg: 72 patients
- AZD9833 300 mg: 72 patients (closed to recruitment as of December 2020)
- Fulvestrant: 72 patients

As of December 2020, the Sponsor stopped enrolment to the 300 mg treatment arm. Ongoing patients in the 300 mg treatment arm may continue treatment as planned.

Treatments and treatment duration:

Patients will receive study treatment until objective disease progression (according to RECIST version 1.1) or other discontinuation criteria are met.

AZD9833 will be administered once daily:

- 75 mg: 3×25-mg tablets.
- 150 mg: 1×100-mg tablet + 2×25-mg tablets.
- 300 mg: 3×100-mg tablets.

Fulvestrant will be administered on Day 1, Day 15 (±1 day), Day 29 (±3 days), and 4-weekly thereafter:

- 500 mg: 2×5-ml IM injections.

Data Monitoring Committee:

Interim analyses and safety review of the data are planned throughout the study, which may be combined or conducted separately.

The review of safety data will be conducted by the Safety Review Committee (SRC) approximately every 6 months up to the primary analysis for progression-free survival (PFS), and thereafter at the discretion of the SRC.

An independent AstraZeneca data monitoring committee (DMC) will undertake interim analyses for this study.

Statistical methods:

All efficacy analyses will be performed on the full analysis set (FAS). As of December 2020, the Sponsor stopped enrolment to the 300 mg treatment arm. The primary analysis, which is a formal comparison of AZD9833 to fulvestrant, only applies to AZD9833 75 mg and 150 mg treatment arms, and pairwise comparisons only refer to AZD9833 doses 75 mg and 150 mg. Results of all statistical analyses will be presented using 90% confidence intervals (CIs) and 2-sided p-values. The treatment comparisons of interest are each dose level of AZD9833 versus fulvestrant. Data accrued from the AZD9833 300 mg treatment arm will be summarised and reported as appropriate, but will not contribute to the event triggers for the analysis timepoints below.

For the primary analysis, the null hypothesis to be tested is that there is no treatment effect, (ie, there is no difference in PFS between patients treated with any dose of AZD9833 and patients treated with fulvestrant).

- H_0: PFS $HR_{AZD9833/fulvestrant}=1$
- H_1: PFS $HR_{AZD9833/fulvestrant}\neq 1$

Each dose of AZD9833 of interest will be compared with fulvestrant in a pairwise comparison. As this is a Phase 2 study, no adjustments for multiplicity will be made. The primary endpoint will be based on the Investigator assessment of progression, as defined by

RECIST version 1.1. A sensitivity analysis based on the Blinded Independent Central Review (BICR) of scans will be conducted.

The analysis of the primary endpoint of PFS (as assessed by the Investigator) will occur when recruitment to the study has completed and at least 108 events have occurred for the pairwise comparison of 75 mg and 150 mg AZD9833 doses versus fulvestrant (approximately 75% maturity). A further analysis of PFS may also be conducted at a later timepoint based on more mature data, particularly in the subgroups of interest.

A sample size of approximately 288 patients, randomised in equal proportions to the 4 treatment groups will be required to observe a total of at least 108 PFS events for each pairwise comparison against fulvestrant. As of December 2020, and the decision to stop enrolment to the AZD9833 300 mg treatment arm, the resulting total sample size across the 3 enrolling treatment arms is approximately 216, with approximately an additional 20 patients from the AZD9833 300 mg arm (now closed to recruitment). A HR of 0.59 for each pairwise treatment comparison versus fulvestrant is of interest. Under the assumption that a 5-month median PFS will be observed on fulvestrant, this is equivalent to a 3.5-month increase in median PFS over fulvestrant. A minimum of 108 events for the pairwise comparison of each AZD9833 dose of interest versus fulvestrant will provide 86% power at the 2-sided 10% significance level if the assumed true treatment effect is HR = 0.59.

The objective response rate (ORR) will be compared between AZD9833 (each dose level) and fulvestrant using a logistic regression model adjusting for prior use of CDK4/6 inhibitors and presence of lung and/or liver metastases.

The change from baseline in tumour size at 16 weeks and best change from baseline in tumour size will also be summarised and presented by randomised treatment group.

The overall survival (OS) data will be analysed at the time of the primary analysis of PFS and will use the same methodology and model (provided there are enough events available for a meaningful analysis). Further survival analyses may be conducted after CCI and CCI of patients have died, or other maturities as may be appropriate.

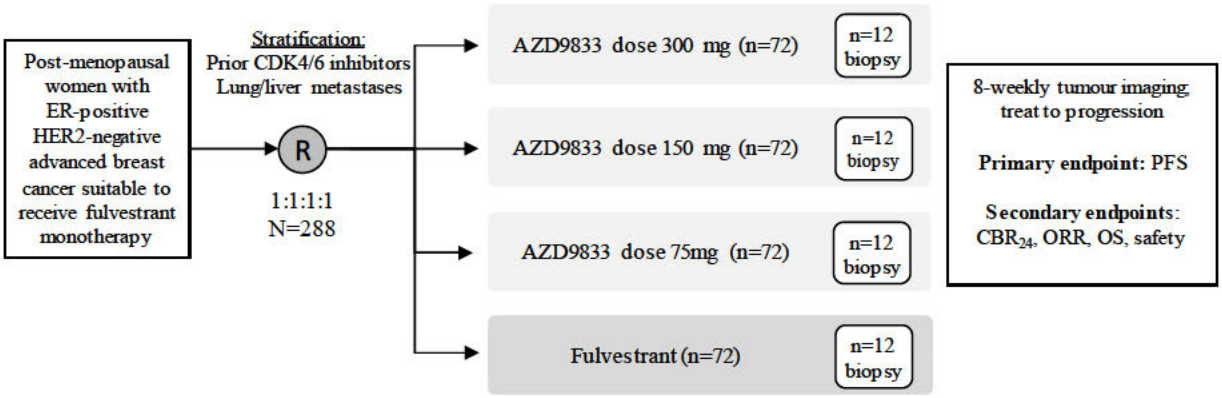
The CBR_{24} will be summarised by treatment group and analysed using a logistic regression model (similarly to the analysis for the ORR).

All safety analyses will be performed on the safety analysis set. Safety data will not be analysed formally.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



R=randomisation.

Note: As of December 2020, the Sponsor stopped enrolment to the 300 mg treatment arm. Ongoing patients in the 300 mg treatment arm may continue treatment as planned.

2 INTRODUCTION

2.1 Study rationale

The ERα is a well-established drug target in breast cancer with anti-hormonal endocrine therapies being the mainstay of treatment (Early Breast Cancer Trialists' Collaborative Group 2005). The SERD and antagonist fulvestrant is used as a standard-of-care treatment for ER-positive metastatic breast cancer (Cardoso et al 2018).

Although fulvestrant has demonstrated superior clinical efficacy to other endocrine therapies in this metastatic setting, it is not orally bioavailable and the monthly IM route of administration may limit its efficacy (Robertson 2007, Robertson et al 2014).

AZD9833 is an orally bioavailable SERD which is being developed for the treatment of women with ER-positive breast cancer.

AZD9833 has the potential to provide superior clinical benefit to existing endocrine therapies through enhanced bioavailability, target engagement and modulation in patients with ER-positive breast cancer.

A first-in-human study (D8530C00001) evaluating AZD9833 in women with advanced ER-positive HER2-negative breast cancer completed its monotherapy dose escalation phase. This study evaluated multiple ascending doses of AZD9833 administered once daily to post-menopausal women. Subsequent parts of this study will examine AZD9833 as monotherapy in pre-menopausal women, and also in combination with the CDK4/6 inhibitor palbociclib in a pre- and post-menopausal population. Study D8530C00001 established that AZD9833 doses of 75, 150 and 300 mg administered once daily were safe and well tolerated in that population, and there are sound indications of clinical efficacy at each of these doses.

This open-label Phase 2 study will enrol post-menopausal women with advanced ER-positive HER2-negative breast cancer who are suitable for fulvestrant therapy. The study will evaluate the efficacy and safety of AZD9833 (75, 150 and 300 mg, PO) administered once daily as a monotherapy in comparison with fulvestrant administered according to its label (ie, slow IM injection into the buttocks [1 to 2 minutes per injection] as two 5-mL injections, 1 in each buttock, on Day 1, Day 15, Day 29 and 4-weekly thereafter).

This study will be key to determining if AZD9833 should be further investigated in Phase 3 clinical trials.

2.2 Background

2.2.1 ER-positive HER2-negative breast cancer

Breast cancer is the second most common cancer in the world and the most frequent cancer in women. An estimated 1.67 million new breast cancer cases were diagnosed in 2012, accounting for 25% of all cancers (Ferlay et al 2013). According to 2017 estimates, over 253000 women in the United States were diagnosed with breast cancer and 41000 died from the disease (Siegel et al 2017). In Europe, it is estimated 367000 women were diagnosed with breast cancer in 2012 and 91000 died from breast cancer (Ferlay et al 2013). Approximately 80% of post-menopausal women with breast cancer have ER-positive disease (Clark et al 1984).

Endocrine therapy has been shown to improve prognosis for patients with ER-positive breast cancer and is a standard-of-care for this patient group (Davies et al 2011). However, disease recurrence occurs steadily through the years subsequent to diagnosis and initial treatment, with the risk of recurrence observed in 10% to 41% of cases within 20 years, depending on tumour stage and grade (Pan et al 2017). Patients with recurrent or advanced disease have a median survival of 2 to 3 years, and a 5-year survival rate of 25% (Cardoso et al 2018).

Current guidelines (Cardoso et al 2018) indicate preferred first-line endocrine therapy for post-menopausal women with advanced disease to be an aromatase inhibitor (AI), tamoxifen, or fulvestrant.

Options for second-line therapy depend on which agents were used in earlier lines of therapy; the optimal sequence of agents is uncertain. Options include AIs, tamoxifen, fulvestrant+palbociclib, AIs+everolimus, tamoxifen+everolimus, fulvestrant, megestrol acetate, and oestradiol.

New, more effective endocrine therapies, for use both alone and in combination, are needed for the treatment of ER-positive breast cancer. AZD9833 has the potential to provide superior clinical benefit to existing endocrine therapies through enhanced oral bioavailability and target engagement and modulation in patients with ER-positive breast cancer.

2.2.2 AZD9833

AZD9833 is a potent, selective non-steroidal ERα antagonist and a potent SERD that can be administered orally. The drug has shown anti-proliferative effects in a wide panel of ER-positive cell lines and significant anti-tumour activity in both tamoxifen-resistant and tamoxifen-sensitive ER-positive wild type models of breast cancer *in vivo* and in a long-term oestrogen deprived model. Additionally, AZD9833 has shown efficacy in a number of oestrogen receptor 1 (ESR1) mutant models of ER-positive breast cancer.

The first-in-human study (D8530C00001) evaluating AZD9833 in women with advanced ER-positive HER2-negative breast cancer has completed its monotherapy dose escalation phase.

AZD9833 doses of 25, 75, 150, 300 and 450 mg once daily have been examined in a multiple-dose escalation Phase 1 design. Patients with metastatic or loco-regionally recurrent disease which was refractory or intolerant to existing therapy(ies) known to provide clinical benefit were enrolled. Prior chemotherapy and/or endocrine therapy for breast cancer was permitted, but no more than 2 lines of chemotherapy for advanced disease were allowed. Progression on at least one line of endocrine therapy in the advanced/metastatic disease setting was required and there was no limit on the number of lines of prior endocrine therapies. Prior treatment with CDK4/6 inhibitors was permitted. Pre-dose and on-treatment paired tumour biopsies were obtained from a subset of patients at each dose level.

The primary objective of the study was to investigate the safety and tolerability of AZD9833, and to define the doses for further clinical evaluation by assessment of dose-limiting toxicities (DLTs), AEs, vital signs, ECGs and clinical chemistry and haematology parameters. Enrolled patients were dosed once daily from study start through to disease progression, or study withdrawal if that occurred in advance of disease progression. The DLT evaluation period was 28 days.

On CCI [redacted], the study SRC determined the AZD9833 dose of 300 mg once daily to most likely be the highest dose that should be taken forward for further clinical development.

Preliminary and un-validated data (data cut-off [DCO] date: CCI [redacted]) from Study D8530C00001 on the safety, tolerability, PK and biological activity of AZD9833 administered once daily at doses up to CCI [redacted] mg is detailed in the current Investigator's Brochure and below.

Of the CCI [redacted] patients exposed to AZD9833 in Study D8530C00001, CCI [redacted] were continuing on study at the DCO date). Durations of exposure at each dose level at the DCO date are shown in Table 2.

Table 2 Duration of exposure

Patient exposure	AZD9833, assigned starting dose					
	25 mg (N=12)	75 mg (N=12)	150 mg (N=13)	300 mg (N=11)	450 mg (N=4)	Total (N=52)
Days						
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minimum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maximum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Months, n (%)						
<3 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3 to 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Study D8530C00001 preliminary data (DCO: [redacted]).

2.2.2.1 Safety and tolerability

Of the [redacted] patients with ER-positive HER2-negative advanced or metastatic breast cancer who received at least 1 dose of AZD9833, [redacted] patients had at least 1 AE during the study. The majority of AEs were Common Terminology Criteria for Adverse Event (CTCAE) Grade 1. There were [redacted] patients with CTCAE Grade ≥3 AEs; including 1 ([redacted]) patient with Grade ≥3 AEs considered treatment-related by the Investigator.

No patients permanently discontinued AZD9833 due to a treatment-related AE. [redacted] patients reported serious adverse events (SAEs); none of which were considered treatment-related by the Investigator. No AEs leading to death were reported.

Table 3 Summary of AEs

Number (%) patients with	AZD9833, assigned starting dose					
	25 mg (N=12)	75 mg (N=12)	150 mg (N=13)	300 mg (N=11)	450 mg (N=4)	Total (N=52)
Any AE	[redacted]					[redacted]
Treatment-related AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade ≥3 AE [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related Grade ≥3 AE [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to dose interruption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related AE leading to dose interruption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 3 Summary of AEs

Number (%) patients with	AZD9833, assigned starting dose					
	25 mg (N=12)	75 mg (N=12)	150 mg (N=13)	300 mg (N=11)	450 mg (N=4)	Total (N=52)
AE leading to dose reduction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related AE leading to dose reduction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related AE leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatal AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related fatal AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] The severity of AEs was graded according to CTCAE version 4.03.
Source: Study D8530C00001 preliminary data (DCO: [redacted]).

The most common AEs (ie, reported in >10% of patients) irrespective of causality were visual impairment, bradycardia, nausea, anaemia, sinus bradycardia, dizziness, arthralgia, vomiting, headache, asthenia and fatigue. AEs considered to be related to AZD9833 by the Investigator are summarised by dose in Table 4.

Table 4 Treatment-related AEs by system organ class and preferred term reported in 2 or more patients

Number (%) of patients	AZD9833, assigned starting dose					
MedDRA SOC Preferred term	25 mg (N=12)	75 mg (N=12)	150 mg (N=13)	300 mg (N=11)	450 mg (N=4)	Total (N=52)
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visual impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Photopsia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vision blurred	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinus bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4 Treatment-related AEs by system organ class and preferred term reported in 2 or more patients

Number (%) of patients	AZD9833, assigned starting dose					
MedDRA SOC **Preferred term**	**25 mg (N=12)**	**75 mg (N=12)**	**150 mg (N=13)**	**300 mg (N=11)**	**450 mg (N=4)**	**Total (N=52)**
Gastrointestinal disorders	CCI					
Nausea	CCI					)
Diarrhoea	CCI					
Dry mouth	CCI					
Vomiting	CCI					
Investigations	CCI					
Electrocardiogram QT prolonged	CCI					
Alanine aminotransferase increased	CCI					
Aspartate aminotransferase increased	CCI					
Neutrophil count decreased	CCI					
Nervous system disorders	CCI					
Dizziness	CCI					
Headache	CCI					
Blood and lymphatic system disorders	CCI					
Anaemia	CCI					
Thrombocytopenia	CCI					
Skin and subcutaneous tissue disorders	CCI					
Pruritus	CCI					
Vascular disorders	CCI					
Hot flush	CCI					
Orthostatic hypotension	CCI					
Musculoskeletal and connective tissue disorders	CCI					
Arthralgia	CCI					
Psychiatric disorders	CCI					

Preferred terms and SOCs are per MedDRA version 21.1.

MedDRA=Medical Dictionary for Regulatory Activities; SOC=system organ class.

Source: Study D8530C00001 preliminary data (DCO: CCI).

The most commonly reported AEs that were considered AZD9833-related by the Investigator were visual disturbances and bradycardia and both are now considered adverse drug reactions by AstraZeneca.

A dose-dependent prolongation of QT interval corrected for heart rate by Fridericia's formula (QTcF) was also observed. These are described in detail below.

Three patients experienced DLTs, which are listed as follows:

- CTCAE Grade 3 QTcF prolongation (300 mg; onset on Cycle 1 Day 8; recovered to Grade 1 following dosing interruption from Cycle 1 Day 8 to Cycle 1 Day 16, then restarted at 150 mg)
- CTCAE Grade 3 vomiting (450 mg; progression from Grade 1 onset on Cycle 1 Day 3 to Grade 3 on Cycle 1 Day 21 despite antiemetic therapy. Dosing interrupted from Cycle 1 Day 21 to Cycle 2 Day 1 then restarted at 300 mg)
- CTCAE Grade 2 visual changes (verbatim term) and Grade 2 nausea (450 mg; necessitating dose interruption from Cycle 1 Day 8 until Cycle 1 Day 15 when restarted at 300 mg)

Visual disturbances

Reported AEs considered to represent visual disturbances included the following Investigator-reported terms: intermittent flashing lights, visual disturbances, visual alterations, blurry vision, photopsia and vision problems. The events were intermittent during AZD9833 dosing and not continuous throughout the day; but if they occurred, they were generally reported throughout the study period with unchanged severity. There was a preliminary association with variable lighting conditions (eg, dawn or dusk).

Data pertaining to patients who discontinued from AZD9833 treatment and for whom follow-up visit data is available included [redacted] patients who experienced visual disturbance-related AEs while on treatment with AZD9833. [redacted] of these [redacted] patients experienced resolution of visual disturbance while still receiving AZD9833 (75 mg), while the other 5 patients confirmed resolution of visual disturbances at the 28-day follow-up. In at least [redacted] cases, visual disturbance AEs resolved within [redacted] hours of drug discontinuation.

During study, it was recommended that patients reporting visual disturbances be referred for ophthalmological examination; the resultant available information has not revealed any physical abnormalities of the eye attributable to trial participation.

Expert ophthalmological opinion indicates that these events most likely represent a phenomenon of illusory palinopsia (Gersztenkorn and Lee 2015). The precise mechanism whereby AZD9833 caused visual disturbance is not understood. Similar visual disturbances are associated with other endocrine therapies, including tamoxifen, exemestane and clomiphene. [redacted].

The number of patients with visual disturbances by dose level is summarised in Table 5.

Table 5 Summary of visual disturbances

Number (%) of patients with	AZD9833, assigned starting dose				
	25 mg (N=12)	75 mg (N=12)	150 mg (N=13)	300 mg (N=11)	450 mg (N=4)
Visual disturbances	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• leading to dose reduction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• leading to dose discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• leading to dose interruption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Visual disturbances include the MedDRA (version 21.1) preferred terms of visual impairment, vision blurred, and photopsia.

MedDRA=Medical Dictionary for Regulatory Activities.

Source: Study D8530C00001 preliminary data (DCO: [redacted]).

No patients required treatment discontinuation but [redacted] patient in the [redacted] mg cohort experienced a [redacted] due to a combination of [redacted] (verbatim term) and Grade 2 nausea. The patient experienced [redacted] on Cycle 1 Day 2, which progressed to Grade 2 by Cycle 1 Day 8. As it occurred in combination with [redacted], it required dose interruption. The patient restarted AZD9833 treatment with dose reduction to [redacted] mg at Cycle 1 Day 15.

Bradycardia

The number of patients reporting bradycardia as an AE is shown by dose level in Table 6. Although both 'bradycardia' and 'sinus bradycardia' were reported by Investigators, the preferred terms are clinically interchangeable (as all instances of bradycardia were in sinus rhythm) and are thus summed in Table 6. Furthermore, all reported AEs of bradycardia or sinus bradycardia were CTCAE Grade 1 (asymptomatic).

Table 6 Summary of bradycardia events

Number (%) of patients with preferred term	AZD9833, assigned starting dose					
	25 mg (N=12)	75 mg (N=12)	150 mg (N=13)	300 mg (N=11)	450 mg (N=4)	Total (N=52)
Bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted])
Sinus bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Combined bradycardia and sinus bradycardia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Study D8530C00001 preliminary data (DCO: [redacted]).

Heart rate and standard ECG parameters were also measured in Study D8530C00001 by centrally read digital ECGs collected in triplicate throughout the study. The ECG-derived bradycardia data is shown in Table 7 as an absolute reduction from baseline and as a percentage change from baseline, along with the number of patients at each dose level with on-study observations of heart rate below [redacted] beats per minute (bpm), respectively.

Table 7 Summary of heart rate data

	AZD9833, assigned starting dose				
	25 mg (N=12)	**75 mg (N=12)**	**150 mg (N=13)**	**300 mg (N=11)**	**450 mg (N=4)**
Subject mean [a] change from baseline for all timepoints from Day 15					
mean absolute change (bpm) 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
mean percent change 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients with maximum heart rate value [b]					
[redacted] absolute value (pre-dose)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] absolute value (post-dose)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] absolute value (pre-dose)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] absolute value (post-dose)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] absolute value (pre-dose)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] absolute value (post-dose)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] For each patient, the mean of absolute and percent change from baseline measured for all timepoints from Day 15 onwards was calculated.

[b] Heart rate threshold values [redacted]) are calculated based on the individual patient maximum absolute value. This is defined as the maximum absolute reduction of the mean of the triplicate values at any timepoint post first dose.

Source: Study D8530C00001 preliminary data (DCO: [redacted]).

AZD9833-related bradycardia exhibits a time-dependent onset, with a gradual decrease in heart rate over a period of approximately [redacted] days, reaching a stable nadir at that time. There does not appear to be a [redacted] of heart rate during dosing beyond [redacted] days, but no further reductions in rate are observed from that time onwards. Events of bradycardia were [redacted] on cessation of treatment, with [redacted] (to above [redacted] of the baseline value). The [redacted] patient [redacted] was in the [redacted] mg cohort and had a heart rate of [redacted] bpm at screening, a pre-dose baseline of [redacted] bpm, a stable nadir of [redacted] bpm, a heart rate of [redacted] bpm at the discontinuation visit and a heart rate of [redacted] bpm at [redacted] days post-discontinuation.

Table 8 Recovery of bradycardia after treatment discontinuation

	AZD9833, assigned starting dose					
	25 mg (N=12)	75 mg (N=12)	150 mg (N=13)	300 mg (N=11)	450 mg (N=4)	Total (N=52)
Number of discontinued patients	CCI					
Number of discontinued patients with at least 1 post-discontinuation follow-up visit	CCI					
Number (%) of patients with heart rate above CCI of baseline	CCI					

Source: Study D8530C00001 preliminary data (DCO: CCI).

AZD9833-related bradycardia was not associated with other changes in ECG variables other than QT interval (see below) and CCI ; nor was it observed to be associated with significant changes in either supine diastolic or systolic blood pressure.

CCI patient required CCI for bradycardia. The CCI in the CCI mg cohort experienced a reduction in resting heart rate from CCI bpm pre-dosing on Cycle 1 Day 1 to CCI bpm on Cycle 1 Day 15; due to CCI CCI the dose was CCI to CCI mg on Cycle 2 Day 1. No patients required dose interruption or discontinuation for AEs of bradycardia. Investigators have reported that patients with bradycardia are able to increase heart rate on exercise, although formal exercise tolerance testing has not been performed in this metastatic cancer population.

To better understand the relationship of dose-dependent bradycardia to general symptomology all reported AEs that might relate to bradycardia were considered. They included the following preferred terms; dizziness, dyspnoea, dyspnoea exertional, fall, orthostatic hypotension and presyncope. Table 9 details these AEs, expressing collectively and individually their relationship to bradycardia for each dose studied. Due to the sustained nature of observed heart rate changes, the table is further split to consider the same AEs when experienced for 7 days or more.

Table 9 Summary of AEs potentially related to bradycardia symptoms

	AZD9833, assigned starting dose				
Number (%) of patients with	25 mg (N=12)	75 mg (N=12)	150 mg (N=13)	300 mg (N=11)	450 mg (N=4)
Bradycardia and sinus bradycardia	CCI				
Any symptoms [a]	CCI				
Dizziness	CCI				
Dyspnoea	CCI				
Dyspnoea exertional	CCI				

Table 9 Summary of AEs potentially related to bradycardia symptoms

Number (%) of patients with	AZD9833, assigned starting dose				
	25 mg (N=12)	75 mg (N=12)	150 mg (N=13)	300 mg (N=11)	450 mg (N=4)
Fall	CCI	[redacted]	[redacted]	[redacted]	[redacted]
Orthostatic hypotension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Presyncope	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Any symptoms [a] lasting ≥7 days	CCI	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	CCI	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea exertional	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Orthostatic hypotension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia/sinus bradycardia including any other symptoms [a]	CCI	[redacted]	[redacted]	[redacted]	[redacted]
Bradycardia/sinus bradycardia including any other symptoms [a] lasting ≥7 days	[redacted]	[redacted]	[redacted]	[redacted]	**0**

[a] Any symptoms include the MedDRA (version 21.1) preferred terms of dyspnoea, dyspnoea exertional, dizziness, fall, presyncope, orthostatic hypotension. The AE reporting period is any time from 1st dose, including the safety follow-up period.

MedDRA=Medical Dictionary for Regulatory Activities.

Source: Study D8530C00001 preliminary data (DCO: CCI [redacted]).

Patients with AEs of bradycardia and who also experienced at least 1 AE of at least 7-day duration that might relate to bradycardia across the 25, 75, 150, 300 and 450 mg cohorts numbered CCI [redacted] respectively. Of the CCI [redacted] patients in the CCI [redacted] mg cohort, CCI [redacted] patient experienced 2 transient episodes of CCI [redacted] that resolved on the same day (Cycle 1 Day 28 and midway through Cycle 5), CCI [redacted] from Cycle 2 Day 1 onwards and transient CCI [redacted] midway through Cycle 6. The CCI [redacted] patient in the 150 mg cohort experienced CCI [redacted] and CCI [redacted] from Cycle 1 Day 8 onwards. The patient in the 300 mg cohort experienced an AE of CCI [redacted] from Cycle 1 Day 5 until Cycle 2 Day 1. Two further patients were identified with AEs of CCI [redacted] and AEs of any duration that might relate to bradycardia. CCI [redacted] patient assigned to the CCI [redacted] mg cohort had CCI [redacted] prior to Cycle 4 Day 1 dosing while a patient assigned to the CCI [redacted] mg cohort experienced CCI [redacted] from Cycle 1 Day 1 to Cycle 1 Day 2.

Taken altogether, it would appear from the data available that AZD9833-induced bradycardia is generally asymptomatic with little association between the degree of bradycardia and potential bradycardia-related symptoms.

There was CCI [redacted] report of CCI [redacted] and CCI [redacted] (CTCAE Grade 1) CCI [redacted] CCI [redacted] possibly related to AZD9833 during Cycle 1 Day 1 in the CCI [redacted] mg cohort; no

relevant past medical history or concomitant medications. No similar event was captured either before or subsequently for this patient, nor for any other study subject.

CCI

AZD9833 appears to be associated with a CCI increase in CCI, as summarised in Table 10.

Table 10 CCI values and change from baseline in CCI

	AZD9833, assigned starting dose				
	25 mg (N=12)	**75 mg (N=12)**	**150 mg (N=13)**	**300 mg (N=11)**	**450 mg (N=4)**
Maximum increase from baseline in QTcF (msec)					
Median (95% CI)	CCI				)
Mean (95% CI)	CCI				
Min, Max	CCI				3
Patients with CCI					
CCI absolute value	CCI				
CCI absolute value	CCI				
CCI absolute value	CCI				
CC change from baseline	CCI				
CC change from baseline	CCI				
CCI change from baseline	CCI				
CC change from baseline	CCI				

[1] QTcF threshold values are calculated based on the individual patient maximum absolute value occurring at any time after the 1st dose.

Source: Study D8530C00001 preliminary data (DCO: CCI)

The time course of onset of CCI appears similar to that of CCI, raising the possibility that the CCI represents an artefact of the CCI, rather than a true effect on CCI rate *per se*. Investigation into the CCI is ongoing.

One patient in the CCI mg cohort experienced a CCI from CCI msec on Cycle 1 to CCI msec on Cycle 1 Day 8 (central ECG trace; local site ECG trace 502 msec), which was regarded as a DLT (mean CCI) was CCI msec at the same study timepoint). The mean heart rate on Cycle 1 Day 8 was CCI bpm (representing a decrease of CCI bpm from pre-dosing ECGs on Cycle 1 Day 1). The mean heart rate on Cycle 1 Day 8 was CCI bpm (representing a decrease of CCI bpm from

pre-dosing ECGs on Cycle 1 Day 1. The patient's dose was CCI to CCI mg following a treatment interruption of CCI days.

No patients with CCI while on treatment were observed to have CCI CCI. One patient in the CCI mg cohort still had CCI at CCI msec above baseline following treatment discontinuation.

Table 11 Recovery of CCI after treatment discontinuation

	AZD9833, assigned starting dose					
	25 mg (N=12)	75 mg (N=12)	150 mg (N=13)	300 mg (N=11)	450 mg (N=4)	Total (N=52)
Number of discontinued patients	CCI					
Number of discontinued patients with at least 1 post-discontinuation follow-up visit	CCI					
Number (%) of patients with CCI	CCI					

[a] CCI

Source: Study D8530C00001 preliminary data (DCO: CCI).

CCI

CCI

CCI

CCI

CCI

CCI

CCI [redacted]

Summary

Overall, based on the emerging safety data from D8530C00001, AZD9833 CCI [redacted] CCI [redacted] daily appears to be tolerated in patients with ER-positive advanced breast cancer. Dosing with AZD9833 is associated with bradycardia, CCI [redacted] and visual disturbances, with lower doses showing lesser degrees of bradycardia and CCI [redacted], and inducing visual disturbances in a lower proportion of patients exposed.

2.2.2.2 Pharmacokinetics

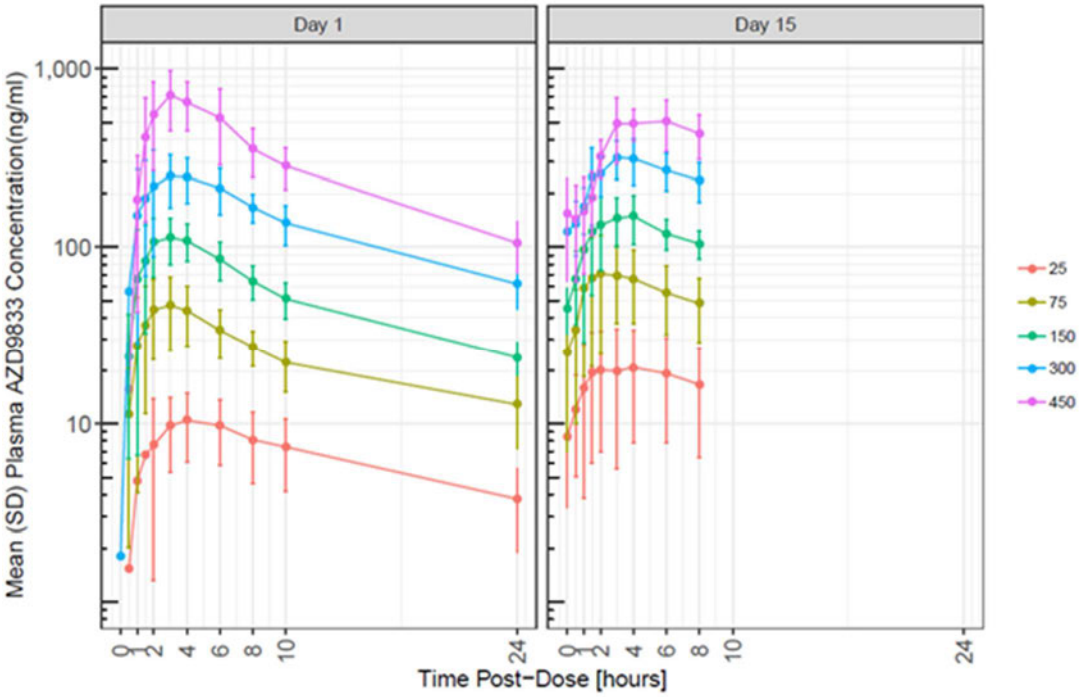
Pharmacokinetics after the 1st dose

After a single AZD9833 dose, the time to reach maximum plasma concentration (t_{max}) was achieved approximately 2 to 4 hours post-dose (Figure 2). Following t_{max}, plasma concentrations declined with a median terminal elimination half-life ($t_{1/2}$) of approximately 9 to 13 hours across all dose groups (Table 12). Exposure increased more than in proportion to dose over the range 25 to 450 mg, with geometric means of the dose-normalised maximum plasma drug concentration (C_{max}) and area under the plasma concentration-time curve from time of dose to 24 hours (AUC_{0-24h}) values for AZD9833 450 mg being 3.7 and 2.6-fold higher respectively than the dose-normalised values for AZD9833 25 mg.

Pharmacokinetics after multiple doses

After 15 days of repeat dosing, the t_{max} was achieved approximately 2 to 6 hours post-dose. After multiple dosing, there was evidence of accumulation at the lower dose levels with the C_{max} Day 15/Day 1 ratios being 1.8 and 1.4 for the 25 and 75 mg cohorts respectively. However, at 150, 300 and 450 mg doses, the C_{max} Day 15/Day 1 ratios reduced to 1.2, 1.1 and 0.7, respectively. After 15 days of once daily dosing, exposure in terms of C_{max} and area under the plasma concentration-time curve from time of dose to 8 hours (AUC_{0-8h}) increased broadly in proportion to dose between 75 and 300 mg.

Figure 2 **Mean plasma AZD9833 PK time course Day 1 versus Day 15 of Cycle 1**



Solid dots/vertical bars represent mean concentration/standard deviation (SD) at each timepoint for each dose
Source: Study D8530C00001 preliminary data (DCO: CCI [redacted]).

Table 12 **Preliminary plasma PK parameters of AZD9833 in humans**

Dose (mg)	Day	N	C_{max} [a] ng/mL	t_{max} [b] hour	$AUC_{0\text{-}last}$ [a,c] ng.h/mL	$AUC_{0\text{-}inf}$ [a] ng h/mL	$t_{1/2}$ [b] hour
25	**1**	12	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
25	**15**	11	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
75	**1**	12	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
75	**15**	12	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
150	**1**	14 [d]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
150	**15**	12	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 12 Preliminary plasma PK parameters of AZD9833 in humans

Dose (mg)	Day	N	C_{max} [a] ng/mL	t_{max} [b] hour	$AUC_{0\text{-}last}$ [a,c] ng.h/mL	$AUC_{0\text{-}inf}$ [a] ng h/mL	$t_{1/2}$ [b] hour
300	1	11	CCI				
300	15	7	CCI				
450	1	4	CCI				
450	15	3	CCI				

[a] reported geometric mean (geometric coefficient of variation)

[b] reported median (minimum-maximum)

[c] last timepoint where PK sample taken. Day 1=Nominal 24 hours. Day 15=Nominal 8 hours.

[d] CCI

$AUC_{0\text{-}inf}$=area under the plasma concentration-time curve from time of dose to infinity; $AUC_{0\text{-}last}$=area under the plasma concentration-time curve from time of dose to last timepoint when PK sample taken; ND=not determined.
Source: Study D8530C00001 preliminary data (DCO: CCI).

2.2.2.3 Biological activity and clinical efficacy

Patients enrolled in Study D8530C00001, who were eligible and consented to have paired tumour biopsies, were analysed by immunohistochemistry for ER, the progesterone receptor (PgR) and Ki-67. At the DCO date of CCI , 8 patients across 4 dose cohorts (25, 75, 150, and 300 mg once daily) had evaluable tumour biopsy samples. All patients, across all doses, displayed pharmacodynamic effects and reduction of ER following treatment with AZD9833. Modulation of ER downstream transcriptional target (ie, PgR) and functional proliferation biomarker (Ki-67) was also observed across the dose cohorts. Pharmacodynamic biomarker modulation is summarised in Table 13.

Table 13 Mean percent change in ER and PgR H-scores and Ki-67 score

	AZD9833, assigned starting dose				
	25 mg (N=1)	**75 mg (N=3)**	**150 mg (N=3)**	**300 mg (N=1)**	**450 mg (N=0)**
Lesion site (n)					
Liver	1	1	2	1	-
Subcutaneous skin	-	2	1	-	-
Mean % change in ER H-score (range)	-11%	-56% (-69, -34)	-32% (-40, -25)	-38%	-
Mean % change in PgR H-score (range)	-63%	-68% (-83, -52)	-74% (-100, -47)	-91%	-
Mean % change in Ki-67 score (range)	-0%	-35% (-98, +50)	-36% (-76, 0)	-98%	-

[a] One patient had a PgR negative status, so not included in the calculation for mean percent change in PgR H-score.

Source: Study D8530C00001 preliminary data (DCO: CCI [redacted]).

All patients enrolled in Study D8530C00001 had CCI [redacted] ctDNA and tumour marker CCI [redacted] analysed pre and on-treatment, there was evidence of ctDNA suppression across all dose levels following AZD9833. Patients with RECIST responses had the largest level of reduction of ctDNA levels and CCI [redacted] levels.

Patients with measurable and non-measurable disease were enrolled to D8530C00001. The RECIST objective response rate (ORR) in patients with measurable disease at baseline along with clinical benefit rate at 24 weeks (CBR_{24}) is summarised in Table 14.

For patients with measurable disease in advanced breast cancer and treated with fulvestrant monotherapy, response rates range from 11 to 14% (Di Leo et al 2010, Turner et al 2015, André et al 2019, Jones et al 2019).

Table 14 Objective response rate and clinical benefit rate at 24 weeks

n/m (%)	AZD9833, assigned starting dose					
	25 mg (N=12)	75 mg (N=12)	150 mg (N=13)	300 mg (N=11)	450 mg (N=4)	Total (N=52)
ORR (based upon measurable disease at baseline only) [a]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CBR_{24} (based upon measurable or non-measurable disease at baseline) [b]	CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] For the ORR, n=number of responders; m=number of patients who have a DCO date - date of 1st dose ≥17 weeks or 2nd post-treatment scan ≥15 weeks.

[b] For the CBR_{24}, n=number of patients who have confirmed response or SD for ≥23 weeks post-treatment; m=number of patients who have a DCO date - date of 1st dose ≥24 weeks or ≥23 weeks post-treatment scan.

SD=stable disease.

Source: Study D8530C00001 preliminary data (DCO: CCI [redacted]).

Overall, the observed modulation of key pharmacodynamic markers along with the durations on study, the CBR_{24} and ORR are considered to be strong indicators of clinical efficacy for doses of AZD9833 of 75 mg once daily and above in this Phase 1 setting, and that warrant further investigation in a Phase 2 progression-free survival study.

In light of the overall safety and efficacy findings summarised above, further investigation of AZD9833 at doses of 75 mg, 150 mg and 300 mg once daily is planned in a randomised Phase 2, second-line ER-positive setting versus the standard-of-care SERD fulvestrant.

A detailed and updated description of the chemistry, pharmacology, efficacy, and safety of AZD9833 is provided in the Investigator's Brochure.

2.3 Benefit/risk assessment

Patients enrolled in the study will be randomly assigned in a 1:1:1:1 ratio to receive one of the following 4 treatments:

- AZD9833 (75 mg, PO, once daily)
- AZD9833 (150 mg, PO, once daily)
- AZD9833 (300 mg, PO, once daily)
- Fulvestrant (500 mg, IM, on Day 1, Day 15, Day 29, and 4-weekly thereafter)

As of December 2020, the Sponsor stopped enrolment to the 300 mg treatment arm. Ongoing patients in the 300 mg treatment arm may continue treatment as planned.

2.3.1 Fulvestrant

Fulvestrant is approved for the treatment of ER-positive, locally advanced or metastatic breast cancer in post-menopausal women (not previously treated with endocrine therapy, or with disease relapse on or after adjuvant anti-oestrogen therapy, or disease progression on anti-oestrogen therapy) and is considered standard-of-care treatment for ER-positive breast cancer (Cardoso et al 2018).

Detailed information about the known and expected benefits and risks and reasonably expected AEs of fulvestrant may be found in the local product information of fulvestrant.

2.3.2 AZD9833

2.3.2.1 Potential benefits

There is no certainty that AZD9833 will provide clinical benefit to patients, although the biological hypothesis, non-clinical data and preliminary clinical efficacy and safety data from the Phase 1 study (D8530C00001) support further evaluation of AZD9833 in the proposed patient population.

2.3.2.2 Potential risks

Based on non-clinical toxicology studies, cardiovascular effects, CCI [redacted]), neurological effects and reproductive system effects were identified as potential risks. The Phase 1 study has identified visual disturbances and bradycardia as new important risks, and CCI [redacted] as a new risk as described in detail above. CCI [redacted] and reproductive symptom effects were not observed in the Phase 1 study. CCI [redacted] Further information about non-clinical toxicology data is provided in the Investigator's Brochure.

Visual disturbances

Patients with uncontrolled central nervous system (CNS) metastatic disease are excluded from the study. Patients with spinal cord compression and/or brain metastases may be enrolled if definitively treated (eg, surgery or radiotherapy) and stable off steroids for at least 4 weeks prior to start of study treatment (see Section 5.2, exclusion criterion 3).

Patients experiencing neurological AEs (including visual disturbances) should be fully assessed by the Investigator and appropriately managed as per standard local practice, including ophthalmological examination if indicated.

Patients will be carefully monitored for the development of visual disturbance AEs through conventional AE collection and reporting. Specific patient-centric questionnaires and interviews in relation to visual disturbances are detailed in Section 8.1.4.3.

Patients experiencing visual disturbances will be counselled regarding driving and operating machinery, particularly under conditions of variable lighting.

See Section 6.6 for patient-level dose reduction and stopping rules in relation to visual disturbances.

Bradycardia and CCI

The study will exclude patients with clinically important cardiac conditions and factors that increase the risk of CCI or arrhythmia (see Section 5.2, exclusion criterion 5):

Cardiovascular monitoring will be performed regularly during the study (see SoA, Table 1). Vital signs (including blood pressure and pulse rate, see Section 8.2.3) and 12-lead centralised ECGs (see Section 8.2.4.1) will be recorded weekly for the first 3 weeks of Cycle 1, on Day 1 of every cycle up to Cycle 6 and then every 2 cycles. A 24-hour ambulatory ECG will also be performed at screening and once during treatment (see Section 8.2.4.2).

Patients will be carefully monitored for the development of potential bradycardia-related symptoms through conventional AE collection and reporting. Patients experiencing cardiovascular AEs should be fully assessed by the Investigator and appropriately managed as per standard local practice.

See Section 6.6 for patient-level dose reduction and stopping rules in relation to bradycardia and/or CCI.

Drugs that are known to prolong QT and have a known risk of torsade de pointe are not permitted, as indicated in Appendix B 1. Advice regarding drugs known to reduce heart rate is provided in Appendix B 4.

CCI

Minimal to moderate CCI was observed in CCI female rats dosed at CCI mg/kg/day (mid dose) and CCI female rats dosed at CCI mg/kg/day (high dose) after six months administration of AZD9833. There were no accompanying clinical signs and no evidence of effect on CCI). There were no histopathological findings in other CCI examined. Patients will have regular monitoring of CCI , CCI) at the same frequency as the safety laboratory assessments (see section 8.2.1). CCI will also be performed at CCI monthly whilst on treatment with AZD9833 and upon discontinuation (see section 8.2.4.3). Furthermore, patients with a

baseline left ventricular ejection fraction (LVEF) of <50% will be excluded from the study (see Section 5.2).

CCI and CCI in the CCI

Moderate or marked CCI was observed in the CCI of female rats dosed at CCI mg/kg/day (high dose) (increased severity of a previously identified finding). This was accompanied by mild mixed CCI and CCI, co-localised with CCI and an increase in CCI (new findings). Patients will be carefully monitored for the development of relevant symptoms through conventional AE collection and reporting.

CCI

CCI were observed in rats (CCI/15 dosed at CCI mg/kg/day [high dose]) and dogs (CCI/4 dosed at CCI mg/kg/day [low dose] and 1/4 dosed at CCI mg/kg/day [high dose]). In rats only, the findings correlated with CCI macroscopically observed in the CCI at necropsy. Mild or moderate CCI was observed in 5 rats dosed at CCI mg/kg/day (high dose) and at a moderate severity in CCI rat dosed at CCI mg/kg/day (low dose) and 1 rat dosed at CCI mg/kg/day (mid dose). Moderate severity CCI CCI was present in CCI 4 dogs dosed at CCI mg/kg/day (high dose). CCI CCI) were considered to be a precursor to the CCI CCI

Patients will be carefully monitored for the development of relevant symptoms through conventional AE collection and reporting.

Drug-drug interactions

Drugs which may be of risk of drug-drug interactions should be avoided as per the guidance provided in Appendices B 2 and B 3.

CCI

2.3.3 Overall benefit-risk and ethical assessment

The patients in this study will have advanced ER-positive breast cancer and have experienced disease progression on endocrine therapy for ER-positive breast cancer. There is an unmet clinical need for new therapeutic agents for patients in this disease setting. Although there can be no certainty of clinical benefit to patients from AZD9833 at the proposed doses, the

biological hypothesis, non-clinical data, and preliminary clinical data described above and in the Investigator's Brochure support its potential benefit in the proposed study population.

The dose-ranging aspect of this Phase 2 study permits a detailed evaluation of the overall benefit-risk profile at each of the tolerated AZD9833 doses associated with clinical benefit in the Phase 1 study.

Provision is made for appropriate safety and futility interim analyses during the study to enable modification of the study if required. Rolling 6-monthly interim safety analyses will be performed by a SRC throughout the study and which will permit re-evaluation of potential risks during study conduct. The SRC remit will make provision for modification of the study (eg, modification of assessment schedule, closure of experimental study arms, or the study overall) if required. Interim futility analyses described in Section 9.5.1 and conducted by a DMC will minimise patient exposure to AZD9833 should the anticipated benefits not materialise. The remit and conduct of the SRC and DMC will be described in separate charter documents which will be finalised prior to the 1st patient's randomisation.

Detailed patient-level dose de-escalation plans and stopping rules are provided for the key AZD9833-related AEs identified in the Phase 1 study (see Section 6.6).

Fulvestrant has been selected as an appropriate comparator in this randomised study and is used in accordance with the local product information.

The investigation of AZD9833 versus fulvestrant in this patient population is considered to be acceptable based upon the data presented above, the lack or limitations of effective alternative monotherapy treatments available, the limited life expectancy of the study population due to malignant disease. The overall benefit/risk assessment for this Phase 2 study is considered to be favourable.

See Section 9.5.1 and Appendix A for information regarding the DMC and the SRC.

3 OBJECTIVES AND ENDPOINTS

Table 15 Study objectives

Primary Objective:	**Endpoint/Variable:**
To determine the clinical efficacy (as assessed by PFS) of AZD9833 when compared to fulvestrant in women with advanced ER-positive HER2-negative breast cancer	PFS assessed by the Investigator as defined by RECIST version 1.1
Secondary Objectives:	**Endpoints/Variables:**
To determine anti-tumour effect of AZD9833 when compared to fulvestrant in women with advanced ER-positive HER2-negative breast cancer	Based on tumour response assessed by the Investigator, as defined by RECIST version 1.1: • ORR • DoR • Best percentage change in tumour size and percentage change in tumour size at 16 weeks
To determine the effect of AZD9833 on survival and clinical benefit when compared to fulvestrant in women with advanced ER-positive HER2-negative breast cancer	• OS • CBR_{24}
To evaluate the PK of AZD9833 in this patient population at steady state	Plasma concentrations of AZD9833 and, if appropriate, metabolite(s) on Day 15 (pre- and post-dose) and Day 29 (pre-dose)
To evaluate the pharmacodynamics of AZD9833 and fulvestrant in a subgroup of patients with advanced ER-positive HER2-negative breast cancer	• Percent change from baseline in ER and PgR expression assessed by the manual H-score method. • Percent change from baseline in Ki67 labelling index
To evaluate the effect of AZD9833 and fulvestrant on the patients' HRQoL, as assessed by patient-completed HRQoL questionnaires	Changes from baseline in total/subscale scores of the EORTC QLQ-C30, EORTC QLQ-BR23, NEI VFQ-25, and EQ-5D-5L
Safety Objective:	**Endpoints/Variables:**
To evaluate the safety and tolerability of AZD9833 when compared to fulvestrant in women with advanced ER-positive HER2-negative breast cancer	• AEs/SAEs • Vital signs, ECGs, clinical chemistry, haematology, urinalysis parameters

Table 15 Study objectives

CCI	**Endpoints/Variables:**
To investigate predictive markers of response and/or acquired resistance to AZD9833 and fulvestrant	• Change from baseline in amount and mutation status of cancer-associated genes in ctDNA, CCI
To assess the impact of CCI	• Subgroup analysis of CCI • CCI during treatment
To evaluate the effect of AZD9833 and fulvestrant on th CCI	• CCI
To examine overall CCI	CCI
Optional CCI : To collect and store CCI according to each country's local and ethical procedures for future exploratory research into CCI that may influence response to treatment	Results from future exploratory research may be reported outside of the CSR.

CBR_{24}=clinical benefit rate at 24 weeks; ctDNA=circulating tumour DNA; DoR=duration of response; ECG=electrocardiogram; EORTC=European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30=EORTC quality of life questionnaire – core questionnaire, EORTC QLQ-BR23=EORTC quality of life questionnaire – breast cancer module; EQ-5D-5L=EuroQol 5 Dimension 5 level; NEI VFQ-25=National Eye Institute 25-Item Visual Function Questionnaire; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; CCI PgR=progesterone receptor.

4 STUDY DESIGN

4.1 Overall design

This is a randomised, open-label, parallel-group, multicentre Phase 2 study to compare the efficacy and safety of daily PO AZD9833 versus IM fulvestrant in women with advanced ER-positive HER2-negative breast cancer. Post-menopausal women with histologically or cytologically confirmed metastatic or loco-regionally recurrent disease before randomisation and fulfilling all of the inclusion criteria and none of the exclusion criteria will be included. Randomisation will be stratified according to the prior use of CDK4/6 inhibitors and the presence of liver and/or lung metastases.

After the screening visit and confirmation of eligibility, patients will be randomly assigned in a 1:1:1:1 ratio to receive 1 of the following 4 treatments, consisting in 4-week treatment cycles until disease progression (assessed by the Investigator as defined by RECIST version 1.1):

- AZD9833 (75 mg, PO, once daily)
- AZD9833 (150 mg, PO, once daily)
- AZD9833 (300 mg, PO, once daily) closed for recruitment as of December 2020
- Fulvestrant (500 mg IM, Day 1, Day 15, Day 29, and 4-weekly thereafter)

As of December 2020, the Sponsor stopped enrolment to the 300 mg treatment arm. Ongoing patients in the 300 mg treatment arm may continue treatment as planned.

During the treatment period, patients will attend visits on:

- Day 1, Day 8, and Day 15 of Cycle 1
- Day 1 of each subsequent cycles until treatment discontinuation

After the treatment period, patients will attend 2 safety follow-up visits (at the time of treatment discontinuation and 28 days later) and will continue to be followed for survival.

Throughout the study, patients will be asked to report AEs and the use of concomitant medication.

Safety assessments (physical examination, vital signs, ECGs, clinical safety laboratory assessments) will be performed at screening, on Day 1 of every cycle (up to Cycle 6) and every 2 cycles (from Cycle 6) and at the EOT visit. Safety assessments will also be performed on Cycle 1 Day 8 (vital signs and triplicate ECGs), Cycle 1 Day 15 (vital signs, ECGs, clinical chemistry, haematology, and urinalysis), at the 28-day safety follow-up (physical exam, vital signs, triplicate ECGs and echocardiogram).

Tumour imaging will be performed for the assessment tumour response according to RECIST version 1.1 at screening and every 8 weeks from Week 9 until disease progression.

Patients will complete HRQoL questionnaires on Day 1 of Cycles 1, 2, and 4, then 8-weekly (Day 1 of every 2nd cycle) from Week 25 (Cycle 7) to coincide with tumour imaging, at the EOT and/or disease progression, and at the 28-day safety follow-up.

Blood and plasma samples for ctDNA and CCI analyses will be collected at screening, on Day 1 and Day 15 of Cycle 1, on Day 1 of Cycles 2 to 5, 8-weekly (Day 1 of every 2nd cycle) from Week 25 (Cycle 7) to coincide with tumour imaging, at the EOT and/or disease progression.

Blood samples for CCI will be collected at screening, on Day 1 of Cycles 1, 2, and 4, and at the EOT.

For patients receiving AZD9833, blood samples will be collected for PK assessments on Cycle 1 Day 15 and Cycle 2 Day 1.

For patients who provide specific consent, the following optional assessments will be performed:

- Up to 12 patients per treatment group will be selected such that they are suitable for providing 1 pre-treatment and 1 on-treatment paired tumour biopsy sample. If provision of paired biopsies becomes clinically unfeasible for a selected patient during the course of her care, the patient may be replaced until up to 12 evaluable biopsy pairs are collected within each treatment group.
- An optional blood sample will be collected at pre-dose on Day 1 of Cycle 1 or later during the study for future CCI research.

For an overview of the study design see Figure 1, Section 1.3. For details on treatments given during the study, see Section 6.1 Treatments Administered.

For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

4.2 Scientific rationale for study design

This Phase 2 study is designed to investigate the efficacy and safety of AZD9833 compared with fulvestrant for the treatment of ER-positive HER2-negative advanced breast cancer. The study will enrol post-menopausal women with histologically or cytologically confirmed metastatic or loco-regionally recurrent disease. Fulvestrant, the active comparator selected for the study, is approved in this patient population and considered standard-of-care (Cardoso et al 2018).

The primary endpoint for this study is PFS (defined by RECIST version 1.1). The anti-tumour efficacy will be further evaluated with secondary endpoints (ie, ORR, duration of response [DoR], percent change in tumour size). The OS and CBR_{24} will also be assessed.

Patients will be randomly assigned to 1 of the 4 treatment groups, or from December 2020, to 1 of the 3 treatment groups via an interactive web response system (IWRS). An open-label design is adopted due to the impracticality and patient impact in administering dummy IM injections 4-weekly for the 3 groups of patients randomised to AZD9833. The potential assessment biases of an open-label design are mitigated by a BICR sensitivity analysis for PFS.

Randomisation will be stratified according to the following:

- Prior use of CDK4/6 inhibitors (yes/no), controlled such that between 32 and up to a maximum of 40 patients per treatment group are enrolled for each strata
- Presence of liver and/or lung metastases at baseline (yes/no)

It is currently unknown how prior use of CDK4/6 inhibitors will affect the overall PFS in this patient population, and therefore a capped stratification (as described above) will be implemented to allow approximately equal proportions of patients with or without prior use of CDK4/6 inhibitors to be recruited. However, given the rapidly evolving treatment landscape with accelerating usage of CDK4/6 inhibitors in this disease setting, in the event that the availability of patients without prior of CDK4/6 inhibitor use becomes limited, then the Sponsor may choose to modify the cap limit.

Presence of lung/liver metastases is known as an important prognostic factor in women with advanced breast cancer and therefore it is important to balance this disease characteristic across the treatment groups.

Sparse PK samples will be collected on Day 15 (pre-dose, 2 and 4 hours post-dose) and Cycle 2 Day 1 (pre-dose only) to measure pre-dose and post-dose plasma concentrations of AZD9833 and, if appropriate, metabolite(s). The 2 and 4 hours post-dose reflect timepoints around absorption phase and t_{max}. Pre-dose values at Day 15 and Cycle 2 Day 1 will confirm steady state.

For patients who provide specific consent, up to 12 patients per treatment group will be selected such that they are suitable for providing 1 pre-treatment and 1 on-treatment paired tumour biopsy sample. In the event that a subject has been selected for provision of paired biopsies, and this becomes clinically unfeasible during the course of their care, the individual treatment groups may be expanded by recruiting additional biopsy-eligible subjects until up to 12 evaluable biopsy pairs in each treatment group have been collected.

The study will also include exploratory investigations into variations in pharmacodynamics and exploratory biomarker profiles and their relationship to drug effect. These biomarkers may be derived from CCI [redacted], and may include CCI [redacted]. There are many potential benefits of this exploratory research, including the possibility to identify patients most likely to benefit from treatment, explain outliers or non-responders, and identify adverse reactions related to drug exposure. This research may result in an understanding of the impact of variation between individuals and how it can be utilised to bring better drugs to the clinic. The ability to acquire appropriate consent to collect biological samples is of utmost importance to establish an archive and allow future meta-analysis of data derived from this and future studies with AZD9833.

AstraZeneca intends to perform CCI [redacted] research in the broader AZD9833 clinical development programme to explore how CCI [redacted] may affect the clinical parameters associated with AZD9833. This may result in improvements in the design and interpretation of future clinical studies and, potentially, the development of CCI [redacted] guided treatment strategies.

4.3 Justification for dose

The selected dose of fulvestrant is the dose recommended in its product information for this patient population.

The selection of the 3 dose levels of AZD9833 to be tested is supported by the PK and safety data collected during the first-in-human study of AZD9833 (Protocol D8530C00001, see Section 2.2). Rules for AZD9833 dose modifications in case of toxicity are summarised in Section 6.6

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last patient undergoing the study.

A patient is considered to have completed the study when she has completed the 28-day follow-up visit after discontinuation of study treatment. After this visit, the patient will continue to be followed for survival and may have further tumour assessments until disease progression is confirmed.

For the purpose of the primary efficacy analysis, the DCO will be after enrolment is complete and when a minimum of 108 events is observed for the pairwise comparison of 75 mg and 150 mg AZD9833 doses versus fulvestrant (corresponding to approximately 75% PFS maturity for the best performing dose level). At the time of this DCO, the database will be locked, the data analysis will be performed, and the Clinical Study Report (CSR) written. Following the decision to stop enrolment to the 300 mg AZD9833 treatment arm, data from

this arm will be reported in the same CSR when the DCO is reached for the remaining treatment arms.

After the primary DCO, efficacy and safety data may continue to be collected. Additional DCOs may be defined for PFS and OS follow-up analyses. If these additional DCOs are reached, the database will be locked, further limited data analysis will be performed and an addendum or addenda to the CSR will be written to document the results. The last DCO may be when CCI OS maturity is reached (see Section 9.4, Table 22 for the definition of DCOs).

See Appendix A 6 for guidelines for the dissemination of study results.

5 STUDY POPULATION

Prospective approval of protocol deviations to inclusion/exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to assigned/randomised to a study intervention. Patients who are enrolled and do not meet the entry requirements are screen failures, refer to Section 5.4.

In this protocol, “enrolled” patients are defined as those who sign informed consent. “Randomised” patients are defined as those who undergo randomisation and receive a randomisation number.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3.

5.1 Inclusion criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1 Provision of signed and dated, written informed consent prior to any mandatory study-specific procedures, sampling, and analyses. Patients are also required to consent to the provision of archival tumour biopsies.

2 For patients who consent, provision of signed and dated written CCI informed consent prior to collection of sample for CCI analysis.

Age and gender

3 Female patients aged at least 18 years.

Menopausal status

4 Post-menopausal defined as meeting at least 1 of the following criteria:

(a) Have undergone a bilateral oophorectomy.

(b) Age ≥60 years.

(c) Age ≥50 years and with cessation of regular menses ≥12 months and with an intact uterus in the absence of gonadotropin-releasing hormone (GnRH) agonist, oral contraception or hormone replacement therapy.

(d) Age <50 years and with cessation of regular menses ≥12 months and follicle stimulating hormone (FSH) and oestradiol levels in the post-menopausal range (utilising ranges from the local laboratory facility) and with an intact uterus in the absence of gonadotropin-releasing hormone (GnRH) agonist, oral contraception or hormone replacement therapy.

Disease characteristics

5 Histologically or cytological confirmation of adenocarcinoma of the breast.

6 Documented ER-positive status of primary or metastatic tumour tissue, according to the local laboratory parameters and where those laboratory parameters are in accordance with accepted diagnostic guidelines (eg, American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer, [Hammond et al 2010]).

7 Documented HER2-negative status defined as an immunohistochemistry (IHC) Score 0 or 1+ or negative by in situ hybridisation (ISH; FISH/CISH/SISH); if IHC 2+, ISH negativity is required. Where available, assessment of ER and HER2 status should be based on the most recent tumour biopsy sample. according to the local laboratory parameters and where those laboratory parameters are in accordance with accepted diagnostic guidelines (eg, American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer, [Hammond et al 2010]).

8 Metastatic disease or loco-regionally recurrent disease suitable for treatment with fulvestrant.

9 Radiological or other objective evidence of progression on or after the last systemic therapy prior to starting study treatment. Tumour marker progression alone is not considered objective evidence of progression.

10 Patients must have:

(a) at least 1 lesion, not previously irradiated, that can be measured accurately at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements, or

in absence of measurable disease as defined above, at least 1 lytic or mixed (lytic+sclerotic) bone lesion that is amenable to serial assessment by CT or MRI; patients with sclerotic/osteoblastic bone lesions only in the absence of measurable disease are not eligible.

11 Eastern Cooperative Oncology Group (ECOG)/World Health Organisation (WHO) performance status 0 to 1, with no deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks.

Prior chemotherapy, endocrine therapy and other anti-cancer therapy

12 Prior endocrine therapy as follows:

(a) Recurrence or progression on at least one line of endocrine therapy.

(b) No more than 1 line of endocrine therapy for advanced disease.

(c) No more than 1 line of chemotherapy for advanced disease. A chemotherapy line in advanced disease is an anti-cancer regimen(s) that contains at least one cytotoxic chemotherapy agent and given for 21 days or longer. If a cytotoxic chemotherapy regimen was discontinued for a reason other than disease progression and lasted less than 21 days, then this regimen does not count as a prior line of chemotherapy. Repeat administration of the same anti-cancer regimen on a separate occasion does not count as a new line of chemotherapy.

(d) Prior treatment with CDK4/6 inhibitors is permitted.

(e) No prior treatment with fulvestrant, oral SERD, or related therapies (eg, ER, proteolysis targeting chimeras [PROTACs], selective ER covalent antagonists [SERCAs] in the metastatic setting).

Inclusion criteria for the paired tumour biopsy research subgroup

1 Disease suitable for paired baseline and on-treatment tumour biopsies.

2 Washout from prior tamoxifen: 4 months to elapse from last tamoxifen dose to pre-dose on-study biopsy.

3 Provision of signed, written, and dated informed consent for tumour biopsies.

5.2 Exclusion criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled:

Prior/concomitant therapy

1 Intervention with any of the following:

(a) Any cytotoxic chemotherapy, investigational agents or other anti-cancer drugs for the treatment of breast cancer from a previous treatment regimen or clinical study within 14 days of the first dose of study treatment.

(b) Use of systemic oestrogen-containing hormone replacement therapy within 6 months prior to the first dose of study treatment.

(c) Medications or herbal supplements known to be strong inhibitors/inducers of cytochrome P450 CCI sensitive CCI substrates (commonly prescribed drugs are listed in Appendix B), and drugs which are substrates of CCI and/or CCI which have a narrow therapeutic index ie, CCI and CCI or inability to stop use within the washout period as specified in Appendix B prior to receiving the first dose of study treatment.

(d) Drugs that are known to prolong QT and have a known risk of torsades de pointes, as indicated in Appendix B 1.

(e) Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of study treatment, and/or radiation to more than 30% of the bone marrow or a wide field of radiation within 4 weeks of the first dose of study treatment.

(f) Major surgical procedure or significant traumatic injury, as judged by the Investigator, within 4 weeks of the first dose of study treatment, CCI

Medical conditions

2 Any unresolved toxicities from prior therapy greater than CTCAE Grade 1 at the time of starting study treatment, with the exception of alopecia and chemotherapy-related peripheral neuropathy.

3 Presence of life-threatening metastatic visceral disease or uncontrolled CNS metastatic disease as judged by the Investigator. Patients with spinal cord compression and/or brain metastases may be enrolled if definitively treated (eg, surgery or radiotherapy) and stable off steroids for at least 4 weeks prior to start of study treatment.

4 Any of the following criteria:

(a) Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, or eg, infection requiring intravenous antibiotic therapy, which in the Investigator's opinion makes it undesirable for the patient to participate in the study or which would jeopardise compliance with the protocol,

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

(c) Patients with known active hepatitis (ie, heapatitis B or C)

5 Any of the following cardiovascular criteria:

(a) Mean resting QTcF >470 msec obtained from screening triplicate ECG.

(b) Resting heart rate <45 bpm

(c) Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG (eg, complete left bundle branch block, second- and third-degree heart

block), or clinically significant sinus pause, or sick sinus syndrome. Patients with controlled atrial fibrillation can be enrolled.

(d) Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as symptomatic heart failure, congenital long QT syndrome, immediate family history of long QT syndrome, or unexplained sudden death at <40 years of age; hypertrophic cardiomyopathy and clinically significant stenotic valve disease; clinically significant hypokalaemia, hyperkalaemia, hypo- and hyper-magnesaemia, hypo- and hyper-calcaemia.

(e) Left ventricular ejection fraction <50%, and/or experience of any of the following procedures or conditions in the preceding 6 months: coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, unstable angina pectoris, congestive heart failure New York Heart Association (NYHA) Grade ≥2, cerebrovascular accident, or transient ischaemic attack.

(f) Uncontrolled hypertension. Hypertensive patients may be eligible, but blood pressure must be adequately controlled at baseline. Patients may be rescreened regarding the blood pressure requirement.

(g) Symptomatic hypotension

6 Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:

(a) Absolute neutrophil count (ANC) $<1.5\times10^9$/L

(b) Platelet count $<100\times10^9$/L

(c) Haemoglobin (Hb) <90 g/L

(d) Alanine aminotransferase (ALT) >2.5×the upper limit of normal (ULN)

(e) Aspartate aminotransferase (AST) >2.5×ULN

(f) Total bilirubin (TBL) >1.5×ULN or >3×ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinaemia)

(g) Estimated glomerular filtration rate (eGFR) <50 mL/min

7 Refractory nausea and vomiting, uncontrolled chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption of AZD9833.

Other exclusions

8 History of hypersensitivity to active or inactive excipients of AZD9833 or fulvestrant.

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

10 Previous randomisation in the present study.

11 Judgement by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

12 Male patients are excluded from this study.

13 Women of childbearing potential are excluded from this study.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

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

There are no food restrictions for AZD9833 (ie, AZD9833 may be taken with or without food). There are no food restrictions for fulvestrant.

5.4 Screen failures

Screen failures are defined as patients who are enrolled (ie, signed the informed consent form [ICF] to participate in the clinical study) but do not meet entry requirements and therefore are not subsequently randomly assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reasons for screen failure (captured in the screening log), and any SAE.

Screen failures may be rescreened. Rescreened patients should be assigned the same patient number as for the initial screening. However, rescreening should be documented so that its effect on study results, if any, can be assessed.

Patients have to re-consent to the study and all screening procedures out of screening period window must be repeated. Laboratory values re-tested within the 28-day screening period are not considered rescreening and are allowed. In case of multiple laboratory data within the screening period, the most recent data should be used to confirm eligibility.

Patients failing screening should have the reason for study withdrawal recorded in the case report form (CRF).

6 STUDY TREATMENTS

Study treatment is defined as any product(s) (including marketed product comparator) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to AZD9833, and to fulvestrant.

6.1 Treatments administered

6.1.1 Investigational products

Table 16 Study treatments

	Treatment 1	Treatment 2	Treatment 3	Treatment 4
Treatment name	AZD9833			Fulvestrant
Dosage formulation	25-mg and 100-mg tablets			250 mg/5 ml solution for IM injection
Dosage level(s)	75 mg once daily	150 mg once daily	300 mg once daily	500 mg Day 1, Day 15, Day 29, and 4-weekly thereafter
Route of administration	PO			IM injection
Dosing instructions	3×25-mg tablets	2×25-mg tablets + 1×100-mg tablet	3×100-mg tablets	2 consecutive 250-mg injections from 2 prefilled syringes (1 in each buttock)
	AZD9833 should be taken in the morning, with or without food, at approximately the same time.			
Packaging and labelling	AZD9833 will be provided in bottles. Each bottle will be labelled in accordance with country regulatory requirements.			Fulvestrant will be packed into single-dose cartons containing 2 labelled prefilled syringes. Each carton will be labelled in accordance with country regulatory requirements.
Provider	AstraZeneca			Commercial fulvestrant (Faslodex) will be provided by AstraZeneca.

Missed doses of AZD9833

The patient should make every reasonable effort to take the AZD9833 tablet(s) at the same time of day. Table 17 below provides advice in the event of missed AZD9833 doses. If a patient needs to take the dose earlier, for whatever reason, the patient can take the dose up to 2 hours earlier than the scheduled dose time.

Patients should not attempt to take a replacement dose of AZD9833 should they vomit shortly after attempting to swallow the tablet(s). Rather, they should wait and take their next

scheduled dose of AZD9833. The patient should make every reasonable effort to take AZD9833 on time.

Table 17 Missed doses of AZD9833

Issue	Action
Patient misses dose of AZD9833, but remembers within 6 hours of their normal scheduled dosing time	Patient should take the missed dose of AZD9833
Patient misses dose of AZD9833, but remembers more than 6 hours after their normal scheduled dosing time	Patient should wait and take their next scheduled dose of AZD9833

6.2 Preparation/handling/storage/accountability

Fulvestrant must be stored in a refrigerator (2°C to 8°C) in the original packaging, to protect from light.

AZD9833 should be stored in the pack provided, protected from light and at the recommended storage condition of below 30°C, and used according to the instructions on the label.

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

Only patients enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments 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 study personnel at the investigational sites will account for all drugs dispensed and for appropriate destruction. Certificates of delivery and destruction should be signed.

If the investigational site does not have the capabilities for destroying unused drugs, the drugs will be sent to a third-party vendor for proper disposal. Certificates of delivery and return should be signed.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

6.3 Measures to minimise bias: randomisation and blinding

This is an open-label study. All patients will receive active treatment.

As the Investigators will not be blinded to study treatments, a BICR of tumour scans will be performed to provide independent tumour response assessment in addition to response evaluation by Investigator.

To reduce potential bias during the study, eligible patients will be randomly allocated at a 1:1:1:1 ratio to receive 1 of the 4 study treatments. As of December 2020, the Sponsor stopped enrolment to the 300 mg treatment arm.

Patients will be randomised as they become eligible. Once the eligibility of a patient has been confirmed, the Investigator (or designee) will notify the centralised IWRS. Randomisation should take place as close to the start of study treatment as possible, with a maximum delay of 3 days. The randomisation will be stratified based on 2 stratification factors:

- prior use of CDK4/6 inhibitors in any setting (yes/no)
- presence of lung and/or liver metastases (yes/no)

The 1st factor (ie, prior use of CDK4/6 inhibitors) will be controlled such that between 32 and up to a maximum of 40 patients per treatment arm (out of 72 planned patients) are included in each stratum, to ensure approximately 50% of patients in each treatment group at the final analysis will be naïve to CDK4/6 inhibitors. The cap will allow a maximum number of 40 patients to be enrolled per stratum, but will not exceed the total planned per treatment group. There will be no cap imposed on the 2nd stratification factor (ie, presence of lung and/or liver metastases). Given the rapidly evolving treatment landscape with accelerating usage of CDK4/6 inhibitors in this disease setting, the Sponsor may choose to modify the cap limit if the availability of patients without prior of CDK4/6 inhibitor use becomes limited.

If a patient withdraws from the study, then her enrolment/randomisation code cannot be reused. For information relating to withdrawn patients, see Section 7.1 Discontinuation of study treatment.

6.4 Treatment compliance

The study treatment should only be used as directed in this protocol. Details of study treatment for each patient will be recorded in the CRF. Any change from the dosing schedule, dose interruptions, dose reductions, dose discontinuations should be recorded in the CRF.

Patients should return all unused study treatment and empty containers to the Investigator. The Investigator is responsible for ensuring that the patient has returned all unused study treatment.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

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

6.5.1 Drugs affecting CCI metabolism

Strong inhibitors and strong inducers of CCI should not be combined with AZD9833 and are not allowed in this study (see Section 5.2 Exclusion criteria).

Strong inhibitors or inducers of CCI should be stopped at least 2 weeks before the first dose of AZD9833 (3 weeks for CCI).

Moderate inhibitors and inducers of CCI are permitted but, caution should be exercised and patients monitored closely for possible drug interactions.

Guidelines regarding potential interactions of AZD9833 with concomitant medications, including lists of drugs known to be inhibitors or inducers of CCI are provided in Appendix B 2.

For fulvestrant, the current local product information should be followed, as appropriate for the study site region.

6.5.2 CCI substrates

6.5.2.1 Sensitive CCI substrates

Sensitive CCI substrates (eg, CCI) should be stopped at least 2 weeks before the 1st dose of AZD9833.

6.5.2.2 CCI and CCI substrates

Drugs which are substrates of CCI and/or CCI which have a narrow therapeutic index ie, CCI hould not be combined with AZD9833. These drugs should be stopped at least 2 weeks before the 1st dose of AZD9833 and not used for at least two weeks after the last dose of AZD9833.

Guidelines regarding drugs whose exposure may be affected by AZD9833, including lists of known drugs which are substrates of CCI and CCI are provided in Appendix B 3

6.5.3 CCI [redacted] Substrates

Preliminary PK data from Part CCI [redacted] of SERENA-1 suggest there is a possibility that AZD9833 may effect clinically relevant CCI [redacted].

Guidelines regarding drugs whose exposure may be affected by AZD9833, including lists of known drugs that are substrates of CCI [redacted] are provided in Appendix B 3.

6.5.4 Medications that prolong QT and have a known risk of torsades de pointes

Drugs that are known to prolong QT and have a known risk of torsades de pointes should not be combined with AZD9833, as indicated in Appendix B 1.

6.5.5 Medications known to reduce heart rate

Drugs that are known to reduce heart rate are allowed, but new prescriptions or dose increments while on study should be discussed with the clinical study team, as indicated in Appendix B 4.

6.5.6 Anti-cancer treatments

- Patients requiring radiotherapy or surgery for breast cancer to manage worsening of disease after randomisation will generally be considered to have progressed. If radiation or surgery is performed for breast cancer for reasons other than objective disease progression, the patient may continue to receive study medication and be followed for objective disease progression.
- Bisphosphonate/denosumab therapy for the prevention of skeletal related events in patients with bone metastases must be started at least 14 days prior to the first dose of study treatment. Patients who have commenced randomised study treatment and are considered to require treatment with denosumab or bisphosphonates will need to be discussed with the Sponsor.
- Patients must not receive any other anti-cancer therapy, including investigational agents, while on study.

CCI [redacted]

6.5.8 Drugs containing sex hormones or affecting sex hormone status

Sex hormone containing drugs such as hormone replacement therapy, progestational agents (megestrol acetate), dehydroepiandrosterone, other androgens (eg, oxandrolone) and selective ER modulators (eg, raloxifene [Evista®]) are not permitted during the study. In cases where

patients suffer severe menopausal symptoms, management with non-hormonal agents (eg, clonidine or venlafaxine) is recommended. In cases of atrophic vaginitis the use of non-hormonal vaginal moisturising or lubricating gels or creams is recommended. Use of oestrogen-containing vaginal creams or other topical preparations is not allowed on the study, but use of controlled-release vaginal rings (eg, Estring®) may be considered at the Investigator's discretion in severe cases or where all the other treatment possibilities have been exhausted.

In addition, other drugs than those mentioned above which may affect sex hormone status or disease response, such as systemic ketoconazole, systemic corticosteroids and adrenocortical suppressants are not allowed to begin after randomisation into the study. However, the patient can continue to receive such drugs if they were taken before randomisation and the Investigator is satisfied that the patient's hormonal status is stable. Hormone antagonists and related agents (eg, soyisoflavones) are not allowed.

6.5.9 Other concomitant treatment

Treatments other than those described above, which are considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

The use of herbal or traditional remedies should be discouraged while patients are on study treatment.

Details of all subsequent breast cancer therapies received from the time of objective disease progression on randomised treatment in this study and, up to the date of DCO for the CCI survival analysis (or final database closure whichever is the earliest) must be collected.

6.6 Dose modification

6.6.1 AZD9833

For AZD9833, guidance for dose modifications (dose interruption, reduction and/or discontinuation) in case of toxicities that are not attributable to the disease or disease-related processes and considered to be possibly related to AZD9833 by the investigator is summarised in Table 18.

Table 18 AZD9833 dose interruption, reduction and/or discontinuation guidance

CTCAE (version 5.0) toxicity	Details	Actions
Sinus bradycardia	CCI	
QT prolongation	CCI	
Other cardiac events	CCI	
Blurred visions, flashing lights, photopsia, eye disorder – Other	CCI	

Table 18 AZD9833 dose interruption, reduction and/or discontinuation guidance

CTCAE (version 5.0) toxicity	Details	Actions
Other AEs considered related to AZD9833	CCI [redacted]	[redacted]
	[redacted]	[redacted]

[a] Permitted dose reduction levels are CCI mg and/or CCI mg once daily. In the event that a patient receiving CCI mg once daily requires a dose reduction, any further reduced dose level should be discussed with the Sponsor.

[b] The following (non-exhaustive) list details actions that may aid in the identification of alternative causative factors for the QTcF prolongation:

- Investigate for electrolyte disturbance; to include hypokalaemia, hyperkalaemia, hypomagnesaemia, hypermagnesaemia, hypocalcaemia and hypercalcaemia.
- Investigate for thyroid abnormality
- Interrogate concomitant medication including new prescriptions and/or dose alterations to existing prescriptions

ADL=activities of daily living; CTCAE=Common Terminology Criteria for Adverse Events; QTcF=QT interval corrected for heart rate by Fridericia's formula.

6.6.2 Fulvestrant

Dose reductions for fulvestrant are not permitted.

6.7 Treatment after the end of the study

Subsequent anti-cancer treatment (after study treatment discontinuation) will be at the discretion of the patient's treating physician and should be recorded in the CRF.

7 DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

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

- Patient decision: The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- AE.
- Severe non-compliance with the clinical study protocol, as judged by the Investigator and/or AstraZeneca.
- Confirmed disease progression.
- Patients incorrectly initiated on study treatment (see Section 7.1.1 Procedures for handling patients incorrectly initiated on study treatment).

See the SoA (Table 1) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Temporary discontinuation and rechallenge

As described in Section 6.6.1, temporary discontinuations of AZD9833 are recommended for the management of some toxicities (see Table 18).

7.1.2 Procedures for handling subjects incorrectly initiated on study treatment

When patients who do not meet the eligibility criteria are enrolled in error or incorrectly started on study treatment, the Investigator should inform the AstraZeneca Study Physician immediately for consideration of the reasonableness of continuing study treatment.

7.1.3 Procedures for discontinuation of study treatment

Patients are at any time free to withdraw consent from study treatment without prejudice to further treatment. The Investigator should instruct the patient to contact the site before or at the time if study treatment is stopped. A patient that 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 CRF. All study treatment should be returned by the patient at their next on-site study visit or unscheduled visit. If possible, they will be seen by an Investigator and undergo the assessments and procedures scheduled for the post-study assessment.

Patients who have withdrawn from study treatment cannot be re-enrolled.

7.2 Lost to follow-up

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

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

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient or next of kin (eg, by repeat telephone calls, certified letter to the patient´s last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient be unreachable at the end of the study the patient should be considered lost to follow-up with unknown survival status at end of study.

7.3 Withdrawal from the study

A patient may withdraw from the study (eg, withdraw consent), at any time at her own request, without prejudice to further treatment. Patients who are withdrawn from the study will not be replaced.

A patient may withdraw from providing biopsy samples at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study. These patients may be replaced until up to 12 evaluable biopsy pairs are collected in each treatment group.

If the patient 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 patient withdraws from the study, she may request destruction of any samples taken, and the Investigator must document this in the site study records.

AstraZeneca or its delegate will request Investigators to collect information on patients' survival status (dead or alive; date of death when applicable).

See SoA (Table 1) for data to be collected at the time of study discontinuation and 28-day follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (Table 1).

The Investigator will ensure that data are recorded on the CRFs. The web-based data capture (WBDC) system will be used for data collection and query handling.

The Investigator ensures the accuracy, completeness, legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed CRFs. A copy of the completed CRFs will be archived at the study site.

Immediate safety concerns should be discussed with the Sponsor upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study requirements, including those specified in the SoA (Table 1), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure.

Procedures conducted as part of the patient's routine clinical management 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 (Table 1).

The total amount of mandatory blood samples collected from each patient up to Week 24 is estimated to a maximum of 305 mL. From Week 25 to the EOT and/or disease progression, a maximum of 27 mL will be collected 8-weekly (Table 19). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 19 Blood sample volumes

Blood volume (mL)	Type of samples						
Visit / Cycle /Weeks	**Safety** [c]	**PK**	**ctDNA**	**CCI**	**CCI**	**CCI** [d]	**Total**
Screening / Week -4 to -1	15 +2		20	2	10		49
Cycle 1 / Week 1 to 4	2×15+2	3×2	2×10	2×2	10	(6 optional)	72 (+6 optional)
Cycle 2 / Week 5 to 8	15+2	2	10	2	10		41
Cycle 3 / Week 9 to 12	15		10	2			27
Cycle 4 / Week 13 to 16	15		10	2	10		37
Cycle 5 / Week 17 to 20	15		10	2			27
Cycle 6 / Week 21 to 24	15						15
EOT	15		10	2	10		37
Total up to Week 24 + EOT assessments							
• **Mandatory**	**141**	**8**	**90**	**16**	**50**	-	**305**
• **Optional**	-	-	-	-	-	6	**6**
From Week 25 onward (8-weekly)	15 until EOT	-	10 until progression	2 until progression	-	-	27

[c] A volume of 15 mL is estimated for safety, assuming 6 mL clinical chemistry and 9 mL haematology per visit with 2 mL added for coagulation tests for a subset of visits. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. The number of samples/blood volumes is therefore subject to site-specific change.

[d] If the CCI sample is not drawn prior to dosing (for any reason), it may be taken at any visit until the last study visit.

CCI ; ctDNA=circulating tumour DNA.

8.1 Efficacy assessments

8.1.1 Assessment of tumour response

The assessment of tumour response per RECIST version 1.1 will be used to determine the clinical activity (assessed by PFS) and anti-tumour activity (assessed by ORR, clinical benefit rate [CBR]) of AZD9833 and fulvestrant.

8.1.1.1 Tumour imaging

Tumour imaging should be performed per the SoA (Table 1). The imaging modalities to be used for the assessment of tumour response per RECIST version 1.1 are summarised in Appendix G 3.

Baseline tumour assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Baseline assessments should be performed no more than 28 days before the start of study treatment, ideally, as close as possible to the start of study treatment.

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 visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

8.1.1.2 Investigator's assessment of tumour response per RECIST version 1.1

Tumour response will be assessed by the Investigators per RECIST version 1.1 (Eisenhauer et al 2009). Guidelines for the evaluation of measurable, non-measurable, TLs and non-target lesions (NTLs) and the objective tumour response per RECIST version 1.1 are presented in Appendix G.

From the Investigator's review of the imaging scans, the evaluation of TLs, NTLs and new lesions will be used to determine the overall visit response for each patient. Overall visit responses for each visit will then be used to determine if and when a patient has progressed in accordance with RECIST and their best objective response to study treatment.

8.1.1.3 Blinded Independent Central Review of tumour assessments

Coded copies of all imaging assessments (regardless of modality and including unscheduled visit scans) will be sent to an AstraZeneca-appointed Contract Research Organisation (CRO) for central analysis. Results of this independent review will not be communicated to Investigators, and the management of patients will be based solely upon the results of the RECIST assessment conducted by the Investigator.

The imaging scans will be reviewed by 2 independent radiologists using RECIST version 1.1 and will be adjudicated, if required (ie, 2 reviewers will review the scans and, in case of a disagreement, adjudication is performed by a separate reviewer). The independent reviewers will be blinded to study treatment.

The BICR will be conducted on an ongoing basis throughout the study. Where possible scans will be batched, and an in-patient series of assessments read together.

For each patient, the BICR will define the overall visit response (ie, the response obtained overall at each visit by assessing TLs, NTLs, and new lesions) and no programmatic derivation of overall visit response is necessary.

Further details of the BICR will be documented in the BICR Charter.

8.1.2 Bone scan or skeletal survey

All patients should have a baseline bone scan or skeletal survey performed no more than 12 weeks before and as close as possible to the start of study treatments.

Additional on-study bone scans or skeletal surveys may be performed, if clinically indicated.

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray should be recorded as NTLs and followed by the same method (CT, MRI, or X-ray), as indicated in the SoA (Table 1).

8.1.3 Survival follow-up

After discontinuation of study treatment, the survival status of the patients will continue to be followed every 12 weeks via phone until closure of the clinical study database. Any new anti-cancer therapies commenced by the patient during the survival follow-up period will be documented in the clinical database.

A survival follow-up phone call will be made in the week following the DCO date for each survival analysis.

8.1.3.1 Post Primary Analysis

At the time of final analysis, the clinical study database will close to new data. Patients are, however, permitted to continue to receive study treatment beyond the closure of the database if, in the opinion of the Investigator, they are continuing to receive benefit from study treatment.

8.1.4 Clinical outcome assessments

8.1.4.1 Performance status

Performance status will be assessed at the visits indicated in the SoA (Table 1), according to ECOG/WHO criteria as follows:

0 Fully active, able to carry on all pre-disease activities without restrictions.

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).

2 Ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

8.1.4.2 Health-related quality of life questionnaires

PRO measures will be used to examine the impact of treatment on symptoms, functioning, and HRQoL and aid in understanding the benefit/risk evaluation from the patient's perspective. The following PRO measures will be administered in this study in accordance with the SoA (Table 1), and in the following order:

1 European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire - core questionnaire (EORTC QLQ-C30)

2 EORTC quality of life questionnaire – breast cancer module (EORTC QLQ-BR23)
3 National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25)
4 EuroQol 5-Dimension 5-level (EQ-5D-5L)
5 CCI [redacted]
6 CCI [redacted]
7 CCI [redacted]
8 CCI [redacted]

The PRO measures will be self-administered by patients using an electronic device per the SoA (Table 1). PRO measures will be provided in the language of the country in which they will be administered.

Each centre must allocate the responsibility for the administration of the questionnaires to a specific individual (eg, a research nurse, study coordinator) and if possible assign a back-up to cover absence.

Approximately 25 minutes are required for patients to complete the questionnaires.

The below instructions should be followed:

- The research nurse or appointed site staff must explain to the patient the value and importance of completing PRO questionnaires, so they are motivated to comply with questionnaire completion. The patient should be informed that these questions are being asked to find out directly from them how they feel, and the information they provide is critical to the success of the study.
- It is vital that the PRO reporting is initiated at the baseline visit (Cycle 1, Day 1), as specified in the study plan to capture the effect of study treatment. The electronic device must be charged and fully functional at the beginning of the baseline visit to ensure that the PROs can be completed at the start of the visit.
- PRO questionnaires must be completed prior to treatment administration and ideally before any discussions of health status, to avoid biasing the patient's responses to the questions. As feasible, site staff should also ensure PRO questionnaires are completed prior to other study procedures (eg, collection of laboratory samples) to further minimise bias.
- PRO questionnaires should be completed by the patient in a quiet and private location. The patient should be given the time they need to complete the questionnaires at their own speed.
- The research nurse or appointed site staff should stress that the information is not routinely shared with study staff. Therefore, if the patient has any medical problems, they should discuss them with the doctor or research nurse separately from the PRO assessment.

- The research nurse or appointed site staff must train the patient on how to use the electronic PRO (ePRO) device, using the materials and training provided by the ePRO vendor.
- All questionnaires must be completed using the ePRO device; paper questionnaires are not allowed in this study.
- The research nurse or appointed site staff must remind the patient that there are no right or wrong answers and avoid introducing bias by not clarifying questions for the patient. If the patient is uncertain about the meaning of a question, the site staff should ask the patient to answer based on what they think the item means.
- The patient should not receive help from relatives, friends, or clinic staff in choosing answers on the PRO questionnaires.
- If a patient uses visual aids (eg, spectacles or contact lenses) for reading and does not have them when attending the clinic, the patient will be exempted from completing the PRO questionnaires at that clinic visit.
- Site staff must not read or complete the PRO questionnaires on behalf of the patient. If the patient is unable to read the questionnaire (eg, is blind, illiterate or does not speak the available language), the patient is exempted from completing PRO questionnaires but may still participate in the study. Patients exempted in this regard should be flagged appropriately by the site staff in the source documents and CRF.
- Site staff must administer questionnaires available in the language that the patient speaks and understands.
- If a patient's compliance drops to 85% or below, they will be flagged in the routine compliance report generated by the ePRO system. For missed questionnaires, the reason(s) for missing the assessment should be documented in the CRF.

A short description of each questionnaire is provided below and sample questionnaires are included in a separate Quality of Life Manual.

European Organisation for Research and Treatment of Cancer quality of life questionnaire - core questionnaire

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group to assess HRQoL, functioning, and symptoms in cancer clinical trials. It has undergone extensive testing and validation and has been translated and linguistically and culturally validated in numerous languages (Aaronson et al 1993). It is a 30-item self-administered questionnaire for all cancer types. Questions are grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social), 3 multi-item symptom scales (fatigue, pain, and nausea/vomiting), a 2-item global health status/quality of life (QoL) scale, 5 single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation, and diarrhoea), and 1 item on the financial impact of the disease. All but 2 questions are rated on a 4-point verbal rating scale: “Not at all,” “A little,” “Quite a bit,” and “Very much.” The 2 questions concerning global health status and QoL have 7-point scales with ratings ranging from “Very poor” to “Excellent.” For each of the

15 domains, final scores are transformed such that they range from 0 to 100, where higher scores indicate better functioning, better QoL, or worse symptoms (Aaronson et al 1993).

European Organisation for Research and Treatment of Cancer quality of life questionnaire - breast cancer module

The EORTC QLQ-BR23 is a validated breast cancer-specific module used in conjunction with the core QLQ-C30 to assess breast cancer-specific HRQoL (Sprangers et al 1996). The self-administered instrument includes 23-items and yields 5 multi-item scores (body image, sexual functioning, arm symptoms, breast symptoms, and systemic therapy side effects). Items are scored on a 4-point verbal rating scale: "Not at All," "A Little," "Quite a Bit," and "Very Much". Scores are transformed to a 0 to 100 scale, where higher scores indicate better functioning, better HRQoL, or greater level of symptoms.

National Eye Institute 25-Item Visual Function Questionnaire

The NEI VFQ-25 is a valid and reliable instrument capturing vision-related health status. It consists of 25 vision-targeted questions representing 11 vision-related subscales, plus an additional single-item general health rating question (Mangione et al 2001). The subscales include: global vision rating (1 item), difficulty with near vision activities (3 items), difficulty with distance vision activities (3 items), limitations in social functioning due to vision (2 items), role limitations due to vision (2 items), dependency to others due to vision (3 items), mental health symptoms due to vision (4 items), driving difficulties (3 items), limitations with peripheral (1 item), colour vision (1 item), ocular pain (2 items), and general health rating question.

EuroQol 5-dimension 5-level

The EQ-5D-5L will be used to explore the impact of treatment and disease state on health state utility for use in economic analyses. The EQ-5D-5L, developed by the EuroQol Group, is a generic questionnaire that provides a descriptive profile of health and a single index value for health status for economic appraisal (Herdman et al 2011, EuroQol Group 1990). The questionnaire comprises 6 questions that cover 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Respondents also assess their health today using the EQ-VAS (visual analogue scale), which ranges from 0 (worst imaginable health) to 100 (best imaginable health).

CCI [redacted]

CCI

[redacted]

[redacted]

[redacted]

CCI

[redacted]

[redacted]

[redacted]

CCI

CCI

[redacted]

CCI [redacted]

8.2 Safety assessments

Planned timepoints for all safety assessments are provided in the SoA (Table 1).

8.2.1 Clinical safety laboratory assessments

See Table 20 for the list of clinical safety laboratory tests to be performed and to the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the Laboratory Manual and the SoA.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. 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 8.3.7.

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

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

Table 20 Laboratory safety variables

Haematology (whole blood)	**Clinical chemistry (serum or plasma)**
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total (TBL)
B-Haematocrit	S/P-Conjugated bilirubin
B-Red blood cell count	S/P- Unconjugated bilirubin
B-Leukocyte differential count (absolute count)	S/P-Alkaline phosphatase (ALP)
Neutrophils	S/P-Aspartate transaminase (AST)
Lymphocytes	S/P-Alanine transaminase (ALT)
Monocytes	S/P-Creatine kinase (CK)
Basophils	S/P-Albumin
Eosinophils	S/P-Calcium, total
B-Platelet count	S/P-Potassium
	S/P-Sodium
Coagulation parameters	S/P-Glucose
activated partial thromboplastin time (aPTT)	S/P-Magnesium
international normalised ratio (INR)	S/P-Phosphate
	S/P-Urea nitrogen
Urinalysis	S/P-Protein, total
U-Glucose	S/P-Troponin
U-Protein	S/P-NT-proBNP
U-Blood	

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

B=blood; S/P=serum/plasma; U=urine; ULN=upper limit of normal.

8.2.2 Physical examinations

A complete physical examination, including a standard neurological examination, will be performed at the visits indicated in the SoA (Table 1), including body weight and height at screening and weight on Day 1 of each cycle.

Investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as AEs, see Section 8.3.7 for details.

8.2.3 Vital signs

Temperature, pulse rate, and blood pressure will be assessed at the timepoints indicated in the SoA (Table 1) as follows:

- Blood pressure and pulse measurements will be assessed in supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 10 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the CRF.

8.2.4 Electrocardiograms

8.2.4.1 Triplicate 12-lead digital ECGs

Triplicate 12-lead digital ECGs will be obtained as outlined in the SoA (Table 1) using standardised ECG machines that automatically calculate the heart rate and measure RR, PR, QRS, QT, and QTcF intervals:

- e-Research Technology (ERT), as the responsible company for the centralised ECG assessments, will provide the study sites with standardised ECG equipment and supplies, specific training and written instructions.
- The ECGs will be collected after 10 minutes of rest in supine position, before vital signs and PK sampling.
- At each timepoint, 3 individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes.
- Following an acquisition of a quality ECG tracing, the Investigator or designee will electronically transfer the data to ERT.

The ECG parameters to be determined will include (but will not be limited to) the following:

- Heart rate
- RR interval: duration in msec between 2 R peaks of 2 consecutive QRS complexes
- PR interval: duration in msec from the beginning of wave P to onset of ventricular depolarisation (Q and R)
- QRS interval: duration in msec of the QRS complex
- QT interval: duration in msec from the beginning of Q wave to the end of the T-wave
- QTcF: QT interval corrected for heart rate using Fridericia's formula ($QT[msec]/RR[sec]^{1/3}$)

Any abnormal finding in the ECG tracing will be evaluated by the Investigator and will be specifically documented and registered in the CRF. Throughout the study, clinically relevant new findings or worsening of a pre-existing finding in the ECGs (parameters or abnormal findings in the tracing) must be considered an AE and must be recorded in the AE CRF form.

For information on how AEs based on ECG results should be recorded and reported, see Section 8.3.7. For ECG-related treatment modifications, see Section 6.6.1 (Table 18).

8.2.4.2 Ambulatory ECG

Ambulatory 24-hour ECG recordings will be performed during screening and once while on study at any time between Cycle 1 Day 15 and Cycle 2 Day 1. The ambulatory 24-hour ECG can be fitted and worn by the patient for 26 hours to allow 24 hours of recorded data to be extracted.

Study sites will be provided with the necessary equipment and training for performing ambulatory ECGs. Data will be acquired and centrally analysed through a vendor supplying ambulatory ECG services.

The SRC may recommend cessation of 24-hour ambulatory ECG assessment at any time following their 1st safety review of the study.

8.2.4.3 Echocardiogram

This will be a focused study to assess left ventricular ejection fraction (LVEF; Biplane Modified Simpson's method) and left ventricular end-systolic (LVES) and end-diastolic (LVED) dimensions.

The echocardiogram will be conducted on all patients at:

- Screening
- Cycle 2 Day 1 (+/- 7 days)
- Cycle 5 Day 1 (+/- 7 days)
- D1 of every 3rd cycle thereafter (+/- 7 days)
- 28-day follow-up (+/- 7 days)

The schedule of echocardiogram assessment may be modified at any time during the study, if supported by emerging data and with the agreement of the SRC.

8.2.5 Other safety assessments

Other safety assessments include ECOG/WHO performance status. For details, see Section 8.1.4.

8.3 Collection of adverse events

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

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

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

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow up AEs see Section 8.3.3.

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting AE and SAE information

AEs will be collected from time of signature of ICF, throughout the treatment period and including the safety follow-up period (28 days after last dose of study treatment).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix C. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the Investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix C.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All AEs/SAEs will be followed until resolution, stabilisation, the event is otherwise explained, or the patient is lost to follow-up

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF.

AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade (version 5.0)
- Whether the AE is serious or not
- Investigator causality rating against the study treatment (yes or no)
- Action taken with regard to study treatment
- Outcome.

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

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

8.3.5 Causality collection

The Investigator will assess causal relationship between study treatments 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 will 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 C.

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study site staff: *'Have you/the patient had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7 Adverse events based on examinations and tests

The results from the protocol-mandated laboratory tests, ECG and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values, ECG and vital signs should therefore be reported as AEs if they are assessed as clinically significant by the investigator, or if they fulfil any of the SAE criteria or are the reason for discontinuation of study treatments.

If deterioration in a laboratory value/ECG/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/ECG/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 Hb 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 sections 8.3.9 and 8.310.

8.3.8 Hy's law

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

8.3.9 Disease progression

Disease progression can be considered as a worsening of a patient'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.

New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least 1 of the seriousness criteria. New cancers are those that are not the primary reason for the administration of the study treatments and have been identified after the patient's inclusion in this study. They do not include metastases of the original cancer.

Handling of deaths

All deaths that occur during the treatment period including the 28-day safety follow-up period should be reported as follows:

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

Deaths that occur after the treatment period during the survival follow-up period should be reported on the survival log on the CRF.

8.4 Safety reporting and medical management

8.4.1 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 CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform 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 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 1 calendar day (ie, immediately but **no later than 24 hours**) of when he or she becomes aware of it.

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

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

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

Regulatory reporting requirements for SAEs
Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

For all studies except those utilising medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure or and will notify the IRB/IEC, if appropriate according to local requirements.

For further guidance on the definition of a SAE, see Appendix C.

8.4.2 Pregnancy

As patients participating in the study are post-menopausal women, no pregnancies are expected during the study.

8.4.3 Overdose

All 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 CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

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

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

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.3.2. For other overdoses, reporting must occur within 30 days.

8.4.3.1 AZD9833

For this study, any dose of AZD9833 greater than the intended dosage (ie, 75 mg, 150 mg or 300 mg per day) will be considered an overdose.

AstraZeneca does not recommend specific treatment for an overdose. Any patient who receives a dose higher than intended should be monitored closely, managed with appropriate supportive care.

8.4.3.2 Fulvestrant

There are only isolated reports of overdose with fulvestrant in humans; if it occurs, symptomatic supportive treatment is recommended.

8.4.4 Medication error

If any 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 8.3.2) and within 30 days for all other medication errors.

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

8.5 Pharmacokinetics

Venous blood samples of approximately 2 mL will be collected from patients receiving AZD9833 for measurement of plasma concentrations of AZD9833 and, if appropriate, metabolite(s) as specified in the SoA (Table 1).

Samples may be collected at additional timepoints or no longer collected during the study if warranted and agreed upon between the Investigator and the Sponsor. Instructions for the collection and handling of biological samples will be provided by the Sponsor or analytical test site. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for analyses of AZD9833 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study (ie, PK samples may be repurposed if required).

Any changes in the timing, addition or removal of timepoints, for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files, but will not constitute a protocol amendment.

8.5.1 Determination of drug concentration

Samples for determination of drug/metabolite concentration in plasma will be analysed by analytical test sites by or on behalf of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

8.5.2 Storage and destruction of pharmacokinetic samples

Details on sample processing, handling, shipment, and storage are provided in the Laboratory Manual. Samples containing AZD9833 for analysis should be protected from light to avoid photo-degradation.

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

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

8.6 Pharmacodynamics

Pharmacodynamic measurements are described in Section 8.8.

CCI [redacted]

8.7.1 Optional exploratory CCI sample

Patients will be offered the possibility to participate in optional CCI exploratory research. Collection and storing of CCI will be according to each country's local and ethical procedures for future exploratory research into CCI that may influence response to treatment.

After signing a separate consent for optional CCI research, a 6-mL CCI sample will be collected in accordance with the inclusion criteria and SoA (Table 1). If for any reason the CCI sample is not CCI on Day 1 according to the SoA, it may be taken at any time up until the last study visit. Although the genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an AE, such subjects would be important to include in any CCI analysis. Only 1 sample should be collected per subject for CCI research during the study.

A record of the date the subject consented to the CCI research and the date and time of the CCI sample collection will be recorded in the CRF. Samples will be collected, handled, labelled, stored and shipped as detailed in the Laboratory Manual.

See Appendix E for information regarding CCI research. Details on processes for collection and shipment and destruction of these samples can be found in Appendix E or in the Laboratory Manual.

8.7.2 Storage and destruction of CCI samples

The processes adopted for the coding and storage of samples for CCI analysis are important to maintain patient confidentiality. Samples may be stored for a maximum of 15 years or as per local regulations from the date of the last patient's last visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

No personal details identifying the individual will be available to AstraZeneca or designated organisations working with the DNA

8.8 Biomarkers

Biomarkers will be tested in plasma, blood and tumour samples for the secondary and exploratory objectives to investigate predictive markers of response and/or acquired resistance to AZD9833 and to assess the impact of tumour mutation status on response to treatment and acquired resistance.

The following samples for biomarker research are required and will be collected from all patients in this study as specified in the SoA (Table 1):

- Blood and plasma samples for ctDNA
- Blood samples for tumour marker [redacted]
- Blood samples for [redacted]
- Archival tumour tissue samples

The following samples for biomarker research are optional and will collected from patients in the study where possible as specified in the SoA (Table 1):

- Paired tumour biopsy samples; pre- and on-treatment. Samples will be collected for patients with tumours amenable to biopsies in up to 12 patients per treatment group.
- Additional tumour biopsy samples may be collected at time of progression.

8.8.1 Blood samples for circulating tumour DNA

One 20-mL whole blood sample will be taken at screening, for the isolation of plasma and buffy coat to enable the assessment, analysis and interpretation of circulating tumour DNA. 10-mL blood sample will be taken at all of the other timepoints indicated in the SoA (Table 1) to provide plasma only.

The samples will be used for the extraction and analysis of ctDNA for the analysis of predictive and pharmacodynamic biomarkers to interrogate changes in frequency, level, specific genetic alterations and potential mechanisms of resistance.

8.8.2 Blood samples for [redacted]

A blood sample of approximately 2 mL will be taken for [redacted] assessment at each of the timepoints indicated in the SoA (Table 1). The sample will be analysed 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.

8.8.3 [redacted]

One 10-mL blood sample will be taken at each of the timepoints as indicated in the SoA (Table 1). These samples will be taken to obtain a preliminary assessment of AZD9833 activity in the tumour by evaluation of [redacted], which may include but are not limited to total counts, and expression levels of [redacted]

8.8.4 Archival tumour tissue

Formalin-fixed archival tumour tissue embedded in paraffin blocks are to be retrieved for all patients, where available. If baseline biopsy samples can also be collected, retrieval of the

archival diagnostic tumour material is still required to provide data on how the tumour has evolved since diagnosis. The archival samples can be derived from the primary tumour and/or metastatic site and, where possible, the most recently acquired archival sample is required.

If this is not possible, a minimum of 20 slides of freshly prepared unstained 5-micron sections from the archival tumour block are accepted, if tumour blocks cannot be submitted. From submitted archival tumour blocks, cores may be removed to construct tissue microarrays for later biomarker analysis. The remaining part of the tumour block may be returned to the institution.

8.8.5 Tumour biopsy in selected patients

Optional paired tumour biopsies will be collected from up to 12 eligible patients in each treatment group.

The paired tumour biopsies will be obtained from patients with accessible tumours and who consent to provide biopsy samples. Accessible lesions are defined as tumour lesions that are amenable to repeat biopsy. Paired biopsies of bone tissue are not permitted.

The pre-treatment biopsy may be taken during screening as close as possible to starting treatment, ideally no greater than 6 weeks prior to treatment start. The on-treatment biopsy sample may be taken on Day 1 (±7 days) of Cycle 2, but both pre- and on -treatment samples can be taken outside this time window, if agreed with AstraZeneca. The pre-dose and on-treatment biopsies should be taken from the same tumour lesion. Biopsies should be taken within 1 to 12 hours of the last AZD9833 dose where possible. A further tumour biopsy may also be taken on disease progression or at the end of treatment.

The biomarkers to be investigated using tumour samples may include, but will not necessarily be limited to: ER, PgR, Ki67, genomic/genetic alterations, and other ER-regulated gene expression. Where feasible, collection of a tumour biopsy at disease progression is encouraged. This sample will be used to investigate changes in pathway signalling and potential mechanisms of resistance (ie, genetic alterations or evidence of alternative pathway activation).

8.8.6 Storage, re-use and destruction of biomarker samples

Samples will be stored for a maximum of 15 years from the date of the last patient's last visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

The results of this biomarker research may be pooled with biomarker data from other studies with the study treatment to generate hypotheses to be tested in future research.

8.9 Medical Resource Utilisation and Health Economics

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

9 STATISTICAL CONSIDERATIONS

As of December 2020, the Sponsor stopped enrolment to the 300 mg treatment arm. Ongoing patients in the 300 mg treatment arm may continue treatment as planned.

In the following sections, the primary analysis, which is a formal comparison of AZD9833 versus fulvestrant, only applies to AZD9833 75 mg and 150 mg treatment groups and pairwise comparisons only refer to AZD9833 doses 75 mg and 150 mg. Data accrued from the AZD9833 300 mg treatment group will be summarised and reported as appropriate, and will not contribute to the event triggers for the analysis timepoints in the following sections.

9.1 Statistical hypotheses

For the primary analysis, the null hypothesis to be tested is that there is no treatment effect, (ie, there is no difference in PFS between patients treated with any dose of AZD9833 and patients treated with fulvestrant).

- H_0: PFS HR $_{AZD9833/fulvestrant}=1$
- H_1: PFS HR $_{AZD9833/fulvestrant}\neq 1$

Each dose of AZD9833 of interest will be compared with fulvestrant in a pairwise comparison. As this is a Phase 2 study, no adjustments for multiplicity will be made.

9.2 Sample size determination

A sample size of approximately 288 patients, randomised in equal proportions to the 4 treatment groups will be required to observe a total of at least 108 PFS events for each pairwise comparison against fulvestrant. As of December 2020, and the decision to stop enrolment to the AZD9833 300 mg arm, the resulting total sample size across the 3 enrolling treatment arms is approximately 216, with approximately an additional 20 patients from the AZD9833 300 mg arm enrolled up to recruitment closure of this arm. The primary analysis will only be triggered when a minimum of 108 events is observed for the pairwise comparison of 75 mg and 150 mg AZD9833 doses versus fulvestrant.

A HR of 0.59 for each pairwise treatment comparison versus fulvestrant is of interest. Under the assumption that a 5-month median PFS will be observed on fulvestrant, this is equivalent to a 3.5-month increase in median PFS over fulvestrant. A minimum of 108 events for the pairwise comparison of each AZD9833 dose of interest versus fulvestrant will provide 86% power at the 2-sided 10% significance level if the assumed true treatment effect is HR = 0.59.

For each treatment arm comparison, PFS events will be tracked by an unblinded team at the CRO on an ongoing basis throughout the study and will be used to estimate when the primary

analysis for PFS should occur. The Sponsor will have knowledge of the total number of events which have accrued but will not know the allocation between treatment groups.

The primary endpoint will be based on the Investigator assessment of progression. A sensitivity analysis based on the BICR of scans will be conducted. Due to the different methods of declaring progression, it is expected that the number of events declared via the 2 methods will be different.

Two interim analyses will be conducted at approximately CCI PFS maturity and CCI PFS maturity in the best performing dose group. The interim analyses will be triggered when the best performing pair hit a minimum of CCI events and CCI events (based on the Investigators assessment), respectively. At the interim analyses, each AZD9833 dose level of interest will be compared in a pairwise comparison against fulvestrant to assess both futility and efficacy. Each dose level (75 mg and 150 mg) will be tested to assess whether the dose passes the futility hurdle and then whether the dose meets the pre-defined acceleration criteria. This assessment for efficacy will be used for internal future development purposes only. All boundaries will be pre-specified in the DMC charter.

Sample size within subgroups of patients with/without prior use of CDK4/6 inhibitors

As per Section 6.3, patients will be stratified for prior use of CDK4/6 inhibitors. Assuming the cap limit is maintained, the study will randomise between 32 and up to a maximum of 40 patients per stratum in each treatment group. Under this scenario, approximately equal proportions (ie, 36 patients per stratum in each treatment group) are expected.

Controlling the sample size in this way will allow for approximately 54 events for the pairwise comparison at the primary analysis (under the assumption that the event rates are the same in the subgroups of patients with or without prior use of CDK4/6 inhibitor). Fifty-four events for the pairwise comparison of each AZD9833 dose versus fulvestrant will provide 86% power at the 1-sided 20% significance level if the assumed true treatment effects are HR = 0.59.

9.3 Populations for analyses

For purposes of analysis, the following populations are defined in Table 21. Full details of the analysis populations and reporting will be provided in the statistical analysis plan (SAP).

Table 21 Study populations

Population	Description
Enrolled	All patients who sign the ICF.
Full analysis set (FAS)	All randomised patients, with treatment groups assigned in accordance with the randomisation, regardless of the treatment actually received. Patients who are randomised but do not subsequently receive treatment will be included in the FAS. The analysis of data using the FAS therefore follows the principles of ITT.
Safety analysis set	All patients who received any amount of study treatment (AZD9833 or fulvestrant), regardless of whether that was the randomised therapy intended or whether they received therapy without being randomised and for whom any post-dose data are available. Patients randomised to AZD9833 who received only fulvestrant will be accounted for in the fulvestrant treatment group. Safety data will not be formally analysed but summarised using the safety analysis set, according to the treatment/ AZD9833 dose level actually received.
Pharmacokinetics (PK) analysis set	All patients who receive at least 1 dose of AZD9833 per the protocol, for whom there is at least 1 reportable PK concentration.
Pharmacodynamic analysis set	All patients who received at least 1 dose of AZD9833 or fulvestrant per the protocol, and who: • had evaluable paired tumour samples by central pathology assessment • had no major protocol deviations that impacted the biomarkers analysis.

ICF=informed consent form; ITT=intention-to-treat.

9.4 Statistical analyses

All Sponsor personnel involved in the the study will remain blinded to the aggregate efficacy data until after database lock for the primary analysis. Following database lock for the primary analysis, all study team members will become unblinded.

Analyses will be performed by AstraZeneca or its representatives, including CROs. A comprehensive SAP will be developed and finalised prior to the first patient treated and will describe the patient populations to be included in the analyses, the analyses including any subgroup analyses or sensitivity analyses, and the procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan which occur prior to the database lock for the primary analysis will be included in the SAP. Those which occur post-database lock for the primary analysis will be reported in the CSR.

Table 22 details which data will be analysed at each timepoint.

Table 22 Summary of analyses and data cut-off triggers

Analysis	Trigger	Data type included
Interim analysis 1	At least CCI events for each of the pairwise treatment comparisons between each dose of AZD9833 (75 mg and 150 mg) and fulvestrant	Efficacy data (including PFS, ORR and BoR). Safety data may be included in this analysis, depending on how recently the latest SRC has been conducted
Interim analysis 2	At least CCI events for the each of the pairwise treatment comparisons between each dose of AZD9833 (75 mg and 150 mg) and fulvestrant	Efficacy data (including PFS, ORR and BoR). Safety data may be included in this analysis, depending on how recently the latest SRC has been conducted
PFS primary analysis (approximately 75% maturity in the best performing dose group)	At least 108 events for each of the pairwise treatment comparisons between each dose of AZD9833 (75 mg and 150 mg) and fulvestrant	All data (including summary OS data available at the time of primary analysis) [b]
Survival follow-up analysis [a] **(CCI and CCI maturity)**	Further survival analyses may be conducted at approximately CCI and CCI OS maturity, or other maturities as may be appropriate	OS[b]
Safety update	At clinical database closure	Key safety data (including SAEs)

[a] The PFS and OS analysis may be combined if there is sufficient maturity in the OS data at the time of the primary PFS analysis.

[b] The safety update may be combined with the OS follow-up analysis if the decision is made to close the study database at this time. A PFS analysis may also be conducted at this timepoint.

BoR = Best objective response; PFS = Progression-free survival; ORR = Objective response rate; OS = Overall survival; SAE = Serious adverse event; SRC = Safety review committee.

9.4.1 Efficacy analyses

All efficacy analyses will be performed on the FAS. The primary analysis, which is a formal comparison of AZD9833 to fulvestrant, only applies to AZD9833 75 mg and 150 mg treatment arms and pairwise comparisons only refer to AZD9833 doses 75 mg and 150 mg. Results of all statistical analyses will be presented using 90% CIs and 2-sided p-values. The treatment comparison of interest is each dose level of AZD9833 versus fulvestrant. Data accrued from the AZD9833 300 mg treatment arm will be summarised and reported as appropriate.

Investigator's assessment of tumour response per RECIST version 1.1

From the Investigators review of the imaging scans, the measurement of TLs (where appropriate), assessment of NTLs and new lesions will be used to determine the overall visit response of each patient according to RECIST version 1.1: patients will be programmatically

assigned an overall visit response of complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) depending on the status of their disease compared with baseline and previous assessments (see Appendix G 4).

The efficacy endpoints of PFS, CBR_{24}, ORR and DoR will be derived programmatically from the overall visit responses determined for each visit.

The endpoint of percentage change in sum of TLs will be derived programmatically from the TL tumour measurements.

Blinded independent central review of tumour response

A sensitivity analysis for the primary endpoint for this study will be based on the BICR of the radiological scans.

For each patient, the BICR will define the overall visit response (ie, the response obtained overall at each visit by assessing TLs, NTLs and new lesions) data and no programmatic derivation of visit response is necessary.

PFS will be derived programmatically from the overall visit responses determined for each visit.

A BICR of all patients will be performed for the final database lock for the primary analysis of PFS. The BICR will cover all available scans up to the respective DCO.

Further details of the BICR will be documented in the BICR Charter.

9.4.1.1 Primary endpoint: progression-free survival

The analysis of the primary endpoint of PFS (as assessed by the Investigator) will occur when recruitment to the study has completed and at least 108 events have occurred for the pairwise comparison of each AZD9833 dose versus fulvestrant (approximately 75% maturity). A further analysis of PFS may also be conducted at a later timepoint based on more mature data, particularly in the subgroups of interest.

The PFS is defined as the time from date of randomisation to date of objective disease progression or death (by any cause in the absence of progression), regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to progression (ie, date of PFS event or censoring – date of randomisation + 1).

Patients 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 assessment (per RECIST version 1.1). However, if the patient progresses or dies immediately after 2 or more consecutive missed visits, the patient will be censored at the time of the latest evaluable assessment (per RECIST

version 1.1) prior to the 2 missed visits. The PFS time will always be derived based on scan/assessment dates and not on visit dates.

PFS will be analysed based on the FAS using a Cox proportional hazards model, allowing for the effect of treatment and including terms for the stratification factors; prior use of CDK4/6 inhibitors (yes/no) and presence of lung and/or liver metastases (yes/no). A stratified log-rank test adjusting for prior use of CDK4/6 inhibitors and presence of lung and/or liver metastases will be used to compare all AZD9833 doses against fulvestrant.

The stratification variables in the statistical modelling will be based on the values entered into the IWRS at randomisation, even if it is subsequently discovered that these values were incorrect. If considered necessary, a sensitivity analysis may be conducted based on the correct assignment.

The HRs for each treatment comparison against fulvestrant will be estimated along with their 90% CIs and 2-sided p-values.

Kaplan-Meier plots of PFS will be presented by treatment arm. Summaries of the number and percentage of patients experiencing a PFS event, and the type of event (progression or death) will be provided along with the median PFS, and the proportion of patients progression-free at 6 months and 1 year for each treatment arm.

The assumption of proportionality will be assessed, should evidence of non-proportionality exist a time-dependent covariate will be fitted to assess the extent to which this represents random variation. Full details will be provided in the SAP.

As a sensitivity analysis to the primary endpoint, the above analysis methods will be repeated based on the BICR.

Collected RECIST version 1.1 data (Investigator determined and BICR) will be listed for all randomised patients.

Subgroup analyses

The primary endpoint will also be summarised and analysed for the subgroups of patients with prior use of CDK4/6 inhibitors (yes/no), provided there are enough events available for a meaningful analysis; if not, descriptive summaries will be provided. Further subgroups of interest may be defined based on patient characteristics at baseline, these will be illustrated in a forest plot comparing the HR and 90% CIs. The subgroups of interest, along with any sensitivity analyses will be fully defined in the SAP.

9.4.1.2 Secondary endpoints

Objective response rate

The ORR is defined as the percentage of patients with at least 1 Investigator-assessed visit response of CR or PR prior to any evidence of progression. The ORR will be based on a subset of the FAS with measurable disease at baseline. A response does not need to be confirmed to be included in the calculation of ORR.

The ORR will be compared between AZD9833 (each dose level) and fulvestrant using a logistic regression model adjusting for prior use of CDK4/6 inhibitors and presence of lung and/or liver metastases. The results of the analysis will be presented in terms of an odds ratio for each treatment comparison together with its associated profile likelihood 90% CI and 2-sided p-values (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

Summaries will be produced that present the number and percentage of patients with a tumour response (CR/PR), these will include frequencies of confirmed complete responses and partial responses, in addition to unconfirmed complete and partial responses, stable disease, progressive disease and not evaluable.

Duration of response

The DoR will be defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR. If a patient does not progress or die following a response, then their DoR will use the PFS censoring time.

Descriptive data will be provided for the duration of response in responding patients, including the associated Kaplan-Meier curves.

Change in tumour size

One of the secondary outcome variables for this study is percentage change from baseline in the sum of TL diameters at 16 weeks. The percentage change in tumour size at 16 weeks will be obtained for each patient, based on RECIST measurements taken at baseline and at 16 weeks. Tumour size is the sum of the longest diameters of the TLs. TLs are measurable tumour lesions. Baseline for RECIST is defined to be the last evaluable assessment prior to randomisation.

Best percentage change

The absolute change and percentage change from baseline in the sum of tumour size at each visit will be calculated. The best change in tumour size (ie, depth of response) is the largest decrease from baseline or the smallest increase from baseline in the absence of a reduction and

will include all assessments prior to the earliest of death in the absence of progression, any evidence of progression, the start of subsequent anti-cancer therapy or the last evaluable RECIST assessment if the patient has not died, progressed or started subsequent anti-cancer therapy.

The absolute value, the change in tumour size from baseline and the percentage change in tumour size from baseline will be summarised using descriptive statistics and presented at each timepoint and by randomised treatment group.

The change from baseline in tumour size at 16 weeks and best change from baseline in tumour size will also be summarised and presented by randomised treatment group.

Normality of the data will be assessed and if appropriate the effect of AZD9833 on percentage change in tumour size will be estimated from an analysis of covariance (ANCOVA) model. The number of patients, unadjusted mean and least squares means (LSmeans) for each treatment group will be presented, together with the difference in LSmeans, 90% CI and corresponding 2-sided p-values. If the assumptions do not hold, an appropriate transformation of the data will be investigated, full details of which will be provided in the SAP.

Tumour size will also be presented graphically using waterfall plots and spider plots split by treatment as appropriate.

Overall survival

The OS is defined as the time from the date of randomisation until death due to any cause regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Note: Survival follow-up phone calls will be made in the week following the date of DCO for the analysis, and if patients are confirmed to be alive or if the death date is after the DCO date these patients will be censored at the date of DCO.

The OS data will be analysed at the time of the primary analysis of PFS and will use the same methodology and model (provided there are enough events available for a meaningful analysis [>20% maturity in OS], if not, descriptive summaries will be provided). Further survival analyses may be conducted after CCI and CCI of patients have died.

Clinical benefit rate at 24 weeks

The CBR_{24} is defined as the percentage of patients who have a best objective response (BoR) of CR or PR in the first 25 weeks (to allow for a late assessment within the assessment window) or who have SD (without subsequent cancer therapy) for at least 23 weeks after start

of treatment (to allow for an early assessment within the assessment window). The CBR will be defined based on the Investigator's assessment of RECIST.

The CBR_{24} will be summarised by treatment group and analysed using a logistic regression model (similarly to the analysis for the ORR).

9.4.2 Safety analyses

All safety analyses will be performed on the safety analysis set. Safety data will not be analysed formally.

Safety and tolerability will be assessed in terms of AEs (including SAEs), deaths, laboratory data, vital signs and ECGs. These will be collected for all patients. Additional subgroup analyses of safety data may be performed, as specified in the SAP.

9.4.2.1 Adverse events

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

Events will be defined as treatment-emergent if they onset or worsen (by Investigator report of a change in intensity), during the treatment period (defined from date of 1st dose of any study treatment to the date of the last dose of any study treatment) or during the safety follow-up period (28 days after last dose of study treatment). The MedDRA (version 22.1 or later) will be used to code AEs.

Summary tables for AEs will only include only treatment-emergent adverse events (TEAEs). AEs occurring prior to dosing or starting more than 28 days after discontinuation of study treatment will be listed separately but not included in the summaries. Any AE occurring after initiation of the first subsequent therapy following discontinuation of study treatment will be flagged in the data listings.

9.4.2.2 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to treatment discontinuation. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant AEs (OAEs) and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

9.4.2.3 Other safety data

Duration of exposure will be summarised appropriately.

Clinical chemistry, haematology, urinalysis, vital signs and echocardiogram data will be listed individually by patient and appropriately summarised. For all laboratory variables that are included in the CTCAE (version 5.0), the CTCAE grade will be calculated.

The ECG parameters (PR, QRS, RR, QT, QTcB, and QTcF) obtained from the central review will be summarised over time in terms of absolute values and change from baseline.

Details of any death will be listed for all patients.

Visualisations of the safety data over time may also be produced as appropriate. Full details of the analysis of safety data will be provided in the SAP.

9.4.3 Other analyses

The PK, pharmacodynamic, demographic, safety, and tumour response data collected in this study may also be combined with similar data from other studies and explored using population PK and/or pharmacokinetic-pharmacodynamic methods. The results of any such analyses will be presented separately from the main CSR.

9.4.3.1 Pharmacokinetic data

Pre and post-dose PK concentrations of AZD9833 at steady state will be summarised by AZD9833 dose level, and PK concentration data will be listed for each patient in the PK analysis set. If applicable, AZD9833 metabolites will be summarised appropriately.

9.4.3.2 Pharmacodynamic data

The secondary endpoints; percentage change from baseline in ER and PgR expression as assessed by manual H-score method and percentage change in Ki67 labelling index will be listed and summarised appropriately. An ANCOVA model will be fitted to each endpoint, with baseline value, day of biopsy and treatment group included in the model. Estimates of the treatment effect will be calculated together with confidence intervals. It is expected that the distribution of the Ki67 index data will not be normally distributed (Robertson et al 2013), hence, Ki67 index data will be naturally log transformed before being analysed.

9.4.3.3 Health-related quality of life assessments

Patient-reported HRQoL data from the EORTC QLQ-C30, EORTC QLQ-BR23, NEI VFQ-25 and EQ-5D-5L questionnaires will be analysed by descriptive summaries and graphical data presentations.

Descriptive summaries and figures may include the following, which will be produced for each questionnaire by randomised treatment group:

- Summary of compliance of subjects to the PRO instruments
- Summary statistics of the change from baseline in total and subscale scores at each visit
- Plots of mean change from baseline in total and subscale scores over time with indicators of number of subjects at each visit (eg, n and error bars)

Further analyses using mixed effects model for repeated measures data may be utilised if there are sufficient data and further exploratory of the HRQoL data is required, these analyses will look at the effect of treatment on the change in total or subscale score of each HRQoL score over time. The analysis population will be the subset of the FAS with baseline and at least 1 follow-up assessment. Full details will be included in the SAP.

9.4.3.4 Exploratory analyses

All exploratory endpoints will be reported outside of the CSR.

9.4.4 Methods for multiplicity control

As this is a Phase 2 study, there will be no adjustment for multiplicity.

9.5 Interim analyses

Interim analyses and safety review of the data are planned throughout the study, which may be combined or conducted separately.

9.5.1 AstraZeneca data monitoring committee

An independent AstraZeneca DMC will undertake interim analyses for this study.

Two interim analyses will be conducted at approximately CCI PFS maturity and CCI PFS maturity in the best performing dose group. These interim analyses will assess the primary endpoint for both futility and efficacy. PFS based on the Investigator assessment will be analysed using a Cox proportional hazards model, as described above. The data will be reviewed by the DMC, who will make a recommendation based on pre-defined decision criteria. The DMC may include a recommendation to continue the study as planned, stop an AZD9833 dose level (or dose levels) for futility, or accelerate future planning activities. The clinical project team within AstraZeneca will remain blinded to the aggregate efficacy data and will only be informed of the final decision of the DMC, should there be a requirement to change study conduct. Full details of the DMC remit will be provided in the DMC charter.

Section A 5 provides more details on the rationale for and the remit of the committee.

9.5.2 Safety Review Committee

A review of the safety data will be conducted by the SRC approximately every 6 months up to the primary analysis for PFS, and thereafter at the discretion of the SRC. Other safety reviews outside of this may be conducted either at the request of the SRC, based on the emerging

profile of the drug (either within or outside of this clinical trial) or at the Sponsor's discretion. At each review the SRC will review the accumulated safety data available at that point in time. Based on the SRC's review of the data, the SRC will make a recommendation to the AZ study team: this may include to continue study as planned, to modify the study, or to consider dropping one or more doses from the study based on the tolerability profile.

The SRC will consist of:

- AstraZeneca physician who will chair the committee
- AstraZeneca safety physician
- 2 external Investigator clinicians who are independent of the study

The full remit, membership and conduct of the SRC will be described in the SRC charter.

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11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/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 approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A 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.

A 3 Informed consent process

The Investigator or his/her representative will explain the nature of the study to the patient or her legally authorised representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients 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 patient was enrolled in the study and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Patients 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 patient or the patient's legally authorised representative.

If a patient declines to participate in any voluntary exploratory CCI research component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.

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

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorised designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The patient will give a separate agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analysed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data protection

Each patient will be assigned a unique identifier by the Sponsor. Any patient records or data sets transferred to the Sponsor will contain only the identifier; patient names or any information which would make the patient identifiable will not be transferred.

The patient 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 must also be explained to the patient.

The patient 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.

A 5 Committees structure

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

An independent AstraZeneca data monitoring committee (DMC, see Section 9.5.1) and a Safety Review Committee (SRC, see Section 9.5.2) will be convened.

A 6 Dissemination of clinical study data

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

A 7 Data quality assurance

All patient data relating to the study will be recorded on electronic CRF 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 CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients 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.

A 8 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Source data includes all information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

A 9 Study and Site Closure

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. The study may be stopped if, in the judgement of AstraZeneca, trial patients are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study treatment
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests

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

A 10 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a co-ordinating Investigator will be designated by mutual agreement.

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

Appendix B Guidelines regarding potential interactions of AZD9833 with concomitant medications

There are currently no data confirming that there is a PK interaction between any concomitant medication and AZD9833. Potential interaction is considered on the basis of preclinical data only.

For a complete overview of the preclinical Drug Metabolism and Pharmacokinetics (DMPK) work conduct, including the drug-drug interaction liability of AZD9833, please refer to the Investigator's Brochure.

B 1 Guidance for drugs that prolong QT and have a known risk of torsades de pointes

Drugs that are known to prolong QT and have a known risk of torsades de pointes (according to the CredibleMeds® list [www.crediblemeds.org]) should not be combined with AZD9833.

B 2 Restrictions regarding drugs affecting CCI metabolism

It is probable that AZD9833 is predominantly eliminated via CCI Therefore, inhibitors or inducers of CCI may increase or decrease exposure to AZD9833, respectively.

Strong inhibitors and strong inducers of CCI should not be combined with AZD9833.

Moderate inhibitors and inducers of CCI are permitted, but caution should be exercised and patients monitored closely for possible drug interactions.

Strong inhibitors or inducers of CCI should be stopped at least 2 weeks before the first dose of AZD9833 (3 weeks for CCI).

The lists below provide examples of CCI inhibitors and inducers. These lists are not intended to be exhaustive, and similar restrictions will apply to other drugs that are known to modulate CCI activity. Appropriate medical judgement is required. Please contact AstraZeneca with any queries you have on this issue. Please refer to full prescribing information for all drugs prior to co-administration with AZD9833.

If the Investigator feels that concomitant administration of medications or herbal supplements that strongly modulate CCI is essential (eg, to treat AEs) AZD9833 treatment should be discontinued.

Table 23 Drugs known to be inhibitors of CCI

Strong CCI **(should not be combined)**	**Moderate** CCI **(permitted with caution)**
CCI	CCI

[a] CCI

Table 24 Drugs known to be inducers of CCI

Strong CCI inducers (should not be combined)	Moderate CCI inducers (permitted with caution)
CCI	CCI

[a] Not available on the US market

[b] CCI has dual effects of simultaneous CCI inhibition and induction; the net PK outcome during chronic ritonavir therapy is inhibition of CCI activity.

B 3 Guidance for drugs whose exposure may be affected by AZD9833

In vitro studies have shown that AZD9833 is a time-dependent inhibitor of CCI and CCI CCI and may increase the exposure of drugs which are substrates of CCI and CCI.

CCI and CCI substrates:

Drugs which are substrates of CCI and/or CCI which have a narrow therapeutic index ie, CCI should not be combined with AZD9833.

Drugs which are substrates of CCI and/or CCI which have a narrow therapeutic index ie, CCI should be stopped at least 2 weeks before the first dose of AZD9833 and not used for at least 2 weeks after the last dose of AZD9833.

Other drugs which are substrates of CCI and/or CCI are permitted, but guidance for dose adjustments when combining with CCI and/or CCI inhibitors should be followed in accordance with their labels.

No drugs have been identified as being contraindicated for combination with CCI and/or CCI inhibitors, however if any are identified they should not be combined with AZD9833.

Concomitant medication should be given in accordance with its prescribing information.

Examples of CCI and CCI substrate drugs are provided in Table 25 This list is not exhaustive.

Table 25 Examples of CCI and CCI substrate drugs.

CYP enzymes	Sensitive drug substrate[2]	Drug with narrow therapeutic range[1]
CCI	[redacted]	[redacted]
[redacted]	[redacted]e	-

[1] The University of Washington Drug Interaction Database https://www.druginteractionsolutions.org/

[2] Guidance for Industry. Drug Interaction Studies, Study Design, Data Analysis, Implications for Dosing, and Labelling Recommendations: Draft Guidance 2012

In vitro, it has been shown that AZD9833 is an inhibitor of CCI.

CCI **substrates:**
Sensitive CCI **substrates should not be combined with AZD9833 (eg,** CCI **).**
Sensitive CCI **substrates should be stopped at least 2 weeks before the first dose of AZD9833.**

Preliminary PK data from Part CCI [redacted] of SERENA-1 are unable to exclude the possibility that AZD9833 may affect drugs that are sensitive to CCI inhibition. Therefore, prescribing advice for drugs that are known CCI substrates and which have specific label advice regarding combination with CCI inhibitors should be consulted. Examples of such drugs in clinical practice are provided in Table 26; please note drugs already excluded by other concomitant medication restrictions may not be listed below.

Table 26 CCI substrates with label advice regarding combination with CCI inhibitors

Drug	USPI	SmPC
CCI [redacted]	*No label comment*	See label advice
CCI [redacted]	See label advice	See label advice
CCI [redacted]	See label advice	See label advice
CCI [redacted]	See label advice	*No label comment*
CCI [redacted]	See label advice	See label advice
CCI [redacted]	See label advice	See label advice
CCI [redacted]	See label advice	*No label comment*

CCI [redacted]; SmPC = Summary of product characteristics; USPI = United States prescribing information.

B 4 Drugs known to reduce sinus heart rate

Patients already taking drugs known to reduce sinus heart rate can be enrolled onto study provided that cardiovascular-related eligibility criteria are satisfied. New prescriptions or dose increments of such drugs while on study should be discussed with the clinical study team, ideally before the new drug or increment is commenced,

Drugs known to reduce sinus heart rate include, but are not limited to, the following:

Beta blockers, including non-selective and β1-selective beta-adrenoreceptor antagonists
Non-dyhdropyridine calcium-channel blockers (eg, verapamil, diltiazem)
Cardiac glycosides (eg, digoxin)
Ivabradine

Appendix C Adverse event definitions and additional safety information

C 1 Definition of adverse events

An AE is the development of any untoward medical occurrence in a patient or clinical study patient 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.

C 2 Definitions of serious adverse event

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

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

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..

This 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 investigational product 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.

C 3 Life-threatening

'Life-threatening' means that the patient 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 patient'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).

C 4 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 patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

C 5 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 patient 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

C 6 Intensity rating scale

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

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 C 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 C 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 C 2.

C 7 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 patient 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.
- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

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

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

The causality assessment is performed based on the available data including enough information to make an informed judgement. With limited or insufficient information in the case, it is likely that 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.

C 8 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 treatment 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 recognise 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 (excluding IWRS errors)
- Wrong drug administered to participant (excluding IWRS errors)

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

- Errors related to or resulting from IWRS – including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) (eg, forgot to take medication)
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard-of-care medication in open-label studies, even if an AZ product

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

Appendix D Handling of human biological samples

D 1 Chain of custody of biological samples

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 patients while in storage at the centre until shipment or disposal (where appropriate).

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 documentation of receipt of arrival.

AstraZeneca 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 AZ-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire 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.

D 2 Withdrawal of Informed Consent for donated biological samples

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

The Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

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

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

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:

- are to be packed and shipped in accordance with IATA Instruction 602.

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, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. 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 – all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient
- Temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

CCI

E 1 Use/analysis of CCI

CCI variation may impact a patient's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for CCI analysis from consenting patients.

AstraZeneca intends to collect and store CCI for CCI research to explore how CCI variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. CCI research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of CCI samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to CCI guided treatment strategies.

CCI research may consist of the analysis of the structure of the patient´s CCI (ie, the entire genome).

The results of CCI analyses may be reported in the CSR or in a separate study summary.

The Sponsor will store the CCI samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on AZD9833 continues but no longer than 15 years or other period as per local requirements.

E 2 CCI research plan and procedures

Selection of CCI research population

Study selection record

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

Inclusion criteria

For inclusion in this CCI research, patients must fulfil all of the inclusion criteria described in the main body of the CSP and: Provide informed consent for the CCI sampling and analyses.

Exclusion criteria

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

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

Withdrawal of consent for genetic research

Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7 of the main CSP.

Collection of samples for CCI research

The blood sample for CCI research will be obtained from the patients at Visit 2. Although CCI is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE, such patients would be important to include in any CCI analysis. If for any reason the sample is not drawn at Visit 1, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for CCI during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and storage of CCI samples

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

An additional second code will be assigned to the blood either before or at the time of CCI extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca CCI laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the CCI).

The link between the patient enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant CCI samples for analysis, facilitate correlation of CCI results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this CCI research component, are outlined in Appendix C.

Informed consent

The CCI component of this study is optional and the patient may participate in other components of the main study without participating in the CCI component. To participate in the CCI component of the study the patient must sign and date both the consent form for the main study and the CCI component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely withdrawal from the CCI aspect of the study at any time.

Patient data protection

AstraZeneca will not provide individual CCI results to patients, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent CCI data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the CCI data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and also have access to his or her CCI data. In addition, Regulatory authorities may require access to the relevant files, though the patient's medical information and the CCI files would remain physically separate.

Data management

Any CCI data generated in this study will be stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples.

AstraZeneca and its designated organisations may share summary results (such as CCI differences from groups of individuals with a disease) from this CCI research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual patient data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the CCI data in a suitable secure environment separate from the clinical database.

Statistical methods and determination of sample size

The number of patients that will agree to participate in the [redacted] research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A SAP may be prepared where appropriate.

Appendix F Actions required in cases of increases in liver biochemistry and evaluation of Hy's law

F 1 Introduction

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

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient 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 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 IP.

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

F 2 Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3× ULN **together with** total bilirubin (TBL) ≥ 2×ULN 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 ≥ 3×ULN **together with** TBL ≥ 2×ULN, where no other reason, other than the study treatment, 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 time frame within which the elevations in transaminases and TBL must occur.

F 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 patient who meets any of the following identification criteria in isolation or in combination:

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

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

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Appendix F 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

F 4 Follow-up

F 4.1 Potential Hy's Law criteria not met

If the patient does not meet PHL criteria the Investigator will:

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

F 4.2 Potential Hy's Law criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For patients that met PHL criteria prior to starting study treatment, the Investigator is not required to submit a PHL SAE unless there is a significant change in the patient's condition.

  Note: A 'significant' change in the patient'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.

- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.
  - Complete the 3 Liver CRF Modules as information becomes available.

F 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 study treatment, 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 patient 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 CRF.
- If the alternative explanation is an AE/SAE, update the previously submitted PHL SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AZ standard processes.

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

- 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 PHL, (report term now 'Hy's law case') ensuring causality assessment is related to study treatment 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.

F 6 Actions required for repeat episodes of potential Hy's Law

This section is applicable when a patient 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)?

If **No**: Follow the process described in Appendix F 4.2 for reporting PHL as an SAE.

If **Yes**: Determine if there has been a significant change in the patient'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 Appendix F 4.2 for reporting PHL as an SAE.

Note: A 'significant' change in the patient'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.

REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'

Appendix G Guidelines for evaluation of objective tumour response using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1

G 1 INTRODUCTION

This appendix details the implementation of RECIST version 1.1 Guidelines (Eisenhauer et al 2009) for study D8530C00002 with regards to Investigator assessment of tumour burden including protocol-specific requirements for this study.

G 2 Definition of measurable, non-measurable, target and non-target lesions

Measurable disease is defined by the presence of at least one measurable lesion which has not been previously irradiated and not chosen for biopsy during the screening period.

Measurable:

A lesion, not previously irradiated and not chosen for biopsy during the screening period, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with CT or MRI and which is suitable for accurate repeated measurements. If only one measurable lesion exists, it is acceptable to be used (as a TL) as long as it has not been previously irradiated and baseline tumour assessment scans are done at least 14 days after the screening biopsy is performed.

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis at baseline).

  Note: Nodes with <10 mm short axis are considered non-pathological and should not be recorded or followed as NTL.
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated lesions

  Note: Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and must be selected as NTLs at baseline and followed up as part of the NTL assessment.
- Skin lesions assessed by clinical examination
- Brain metastasis
- Lesions biopsied within the screening period

  Exception: if only 1 measurable lesion exists, it is acceptable to be used (as a target lesion [TL]) as long as it has not been previously irradiated and baseline tumour assessment scans are done at least 14 days after the screening biopsy is performed.

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 as TLs.

Target lesions:

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

Non-target lesions:

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

G 3 Methods of assessment

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

A summary of the methods to be used for RECIST assessment is provided below and those excluded from tumour assessments for this study are highlighted, with the rationale provided.

Table 27 Summary of Methods of Assessment

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

CT=computed tomography; FDG-PET=fluorodeoxyglucose-positron emission tomography; MRI=magnetic resonance imaging

G 3.1 CT and MRI

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

It is recommended that CT examinations of the chest and abdomen (including liver and adrenal glands), will be used to assess tumour burden at baseline and follow-up visits. CT examination with intravenous (iv) contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For brain lesion assessment, MRI is the preferred method although CT is acceptable.

G 3.2 Clinical examination

Clinical examination will not be used for assessment of TLs. Clinically detected lesions can be selected as TLs if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTLs and to identify the presence of new lesions.

G 3.3 X-ray

Chest X-ray

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

Plain X-ray

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

G 3.4 Ultrasound

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

G 3.5 Endoscopy and laparoscopy

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

G 3.6 Tumour markers

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

G 3.7 Cytology and histology

Histology will not be used as part of the tumour response assessment as per RECIST version 1.1.

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

G 3.8 Isotopic bone scan

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

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

G 3.9 FDG-PET scan

Fluorodeoxyglucose-positron emission tomography (FDG-PET) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

Note: A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

G 4 Tumour response evaluation

G 4.1 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 patients and should be performed no more than 28 days before the start of study treatment (refer to Table 1 and Section 8.1.1 of the CSP). Follow-up

assessments will be performed every 8 weeks (±1 week) after randomisation until objective disease progression as defined by RECIST version 1.1 even if a patient discontinues treatment prior to progression or receives other anti-cancer treatment. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

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

G 4.2 Target lesions

G 4.2.1 Documentation of target lesions

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

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

Special cases:

- For TLs measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into 2 or more parts, then record the sum of the diameters of those parts.
- If 2 or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.

- When a TL has had any intervention (eg, radiotherapy, embolisation, surgery, etc) during the study, the size of the TL should still be provided where possible.

G 4.2.2 Evaluation of target lesions

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

Table 28 Evaluation of target lesions

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

CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease; TL=target lesion.

G 4.3 Non-target lesions

G 4.3.1 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 29 Evaluation of non-target lesions

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 1 or more NTL.
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.

CR	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
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 patients 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.

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; NE=not evaluable; NA=not applicable (only relevant if there were no NTLs 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 SD or PR in TLs, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

G 4.4 New lesions

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

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

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

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

G 4.5 Symptomatic deterioration

Symptomatic 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 evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

G 4.6 Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in Table 30.

Table 30 Overall Visit Response

TLs	NTLs	New lesions	Overall response
CR	CR	No	CR
CR	NA	No	
CR	Non-CR / Non-PD	No	PR
CR	NE	No	
PR	Non-PD or NE	No	
SD	Non-PD or NE	No	SD
NE	Non-PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	
Any	Any	Yes	

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

G 5 Central review

The CRO appointed by AstraZeneca to perform the independent central review for this study will provide specification for radiological imaging protocols in standard acquisition guidelines documentation.

G 6 References

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 H Abbreviations

Abbreviation or special term	Explanation
AE	adverse event
AI	aromatase inhibitor
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC_{0-8h}	area under the plasma concentration-time curve from time of dose to 8 hours
AUC_{0-24h}	area under the plasma concentration-time curve from time of dose to 24 hours
AUC_{0-inf}	area under the plasma concentration-time curve from time of dose to infinity
AUC_{0-last}	area under the plasma concentration-time curve from time of dose to last timepoint when PK sample taken
BICR	Blinded Independent Central Review
BoR	Best objective response
bpm	beat per minute
CCI	[redacted]
CBR	clinical benefit rate
CBR_{24}	clinical benefit rate at 24 weeks
CDK4/6	cyclin-dependent kinase 4 and 6
CI	confidence interval
CIOMS	Council for International Organisations of Medical Sciences
CK	creatine kinase
C_{max}	maximum plasma drug concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRF	case report form (electronic/paper)
CRO	Contract Research Organisation
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	computed tomography

Abbreviation or special term	Explanation
CTC	circulating tumour cell
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	circulating tumour deoxyribonucleic acid
CCI	[redacted]
DCO	data cut-off
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
DMPK	Drug Metabolism and Pharmacokinetics
DNA	deoxyribonucleic acid
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	EORTC quality of life questionnaire – core questionnaire
EORTC QLQ-BR23	EORTC quality of life questionnaire – breast cancer module
EOT	end of treatment
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQol 5-Dimension 5-level
ER	oestrogen receptor
ERα	oestrogen receptor alpha
ERT	E-Research Technology
ESR1	oestrogen receptor 1
FAS	full analysis set
FDG-PET	fluorodeoxyglucose-positron emission tomography
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
Hb	haemoglobin
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HL	Hy's law
HR	hazard ratio

Abbreviation or special term	Explanation
HRQoL	health-related quality of life
IATA	International Airline Transportation Association
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (formerly International Conference on Harmonisation)
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IM	intramuscular
INR	international normalised ratio
IRB/IEC	Institutional Review Boards/Independent Ethics Committees
ITT	intention-to-treat
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the Investigators and/or activities internationally.
ISH	in situ hybridisation
IWRS	interactive web response system
LSmeans	least squares means
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NEI VFQ-25	National Eye Institute 25-Item Visual Function Questionnaire
NTL	non target lesion
OAE	other significant adverse event
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
CCI	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CCI	[redacted]
PgR	progesterone receptor
PHL	potential Hy's law
PK	pharmacokinetic(s)
PR	partial response

Abbreviation or special term	Explanation
PRO	patient-reported outcome
QoL	quality of life
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SERD	selective oestrogen receptor degrader
SmPC	Summary of product characteristics
SoA	Schedule of Activities
SOC	system organ class
SRC	Safety Review Committee
$t_{1/2}$	terminal elimination half-life
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TL	target lesion
t_{max}	time to reach maximum plasma concentration
ULN	upper limit of normal
USPI	United States prescribing information
WBDC	web-based data capture
WHO	World Health Organisation

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