Clinical Study Protocol	
Drug Substance	AZD9833 (INN: camizestrant)
Study Code	D8530C00003
Version	3.0
Date	04 July 2022

A Randomised, Open-Label, Parallel-Group, Pre surgical Study to Investigate the Biological Effects of AZD9833 in Women with ER-positive, HER2-negative Primary Breast Cancer (SERENA-3)

Sponsor Name: AstraZeneca

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

Regulatory Agency Identifier Number(s)

EudraCT number: 2020-001079-33

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

Protocol Number: D8530C00003

Amendment Number: 2

Study Intervention: AZD9833
Study Phase: Phase 2

Short Title: A Randomised, Pre-surgical Study to Investigate the Biological Effects of AZD9833 in Women with ER-positive, HER2 negative Primary Breast Cancer

SERENA-3

Medical Monitor Name and Contact Information will be provided separately

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Version 3.0 (Global Amendment 2)	04-Jul-2022
Version 2.0 (Global Amendment 1)	28-Sep-2021
Original Protocol	11-Jun-2020

Overall Rationale for Amendment 2.0:

This global amendment has been issued in order to investigate longer duration dosing of AZD9833 and in order to implement recommendations made by the SDMC.

Section Number	Description of Change	Brief Rationale	Substantial/ Non-substantial
Sections 1.1; 1.2; 1.3; 2.1; 2.2.2; 2.3.2; 3; 4.1; 4.3	Text has been amended to allow for addition of Stage 3 of the CSP, with a longer duration of 12 to 15 days. Assessments and text related to the addition of Stage 3 have been added throughout	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 1.1	Text has been added to account for increased duration of treatment (12 to 15 days) in Stage 3 of the CSP. This includes updates to show change in sampling times for Stage 3, given longer treatment period, updated sample size to account for addition of Stage 3 and requirement for patients in Stage 3 to show a CCI [redacted] CCI [redacted]	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 1.2	New schema added (Figure 3) with accompanying text added to describe Stage 3	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 1.3	New SoA added (Table 2) to describe Stage 3	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 2.1	Rationale updated to confirm current status of SERENA-3 study and rationale for addition of Stage 3	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 2.2.2	Paragraph relating to preliminary data from SERENA-1 study deleted	Data are superseded by updated data from SERENA-1, new data from SERENA-2 and interim data from Stages 1 and 2 of the SERENA-3 study	Substantial

Section Number	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 2.2.2.1	Section updated using data from a pooled analysis of SERENA-1, and SERENA-2	Safety data in larger population included to provide more confidence on the safety profile for AZD9833.	Substantial
Section 2.2.2.3	New section providing data for the pool of data for SERENA-1 and SERENA-2 at the 15-day exposure timepoint	Safety data at longer exposures added to provide more confidence on the safety profile for AZD9833.	Substantial
Section 2.2.2.8	New section from the interim analysis of PD data from Stages 1 and 2 of the SERENA-3 study.	Biological activity data provided for a treatment period of 5 to 7 days with AZD9833, to justify that a longer treatment is needed, to achieve maximal PD effect	Substantial
Section 2.2.2.9	New section from the interim analysis of safety data from Stages 1 and 2 of the SERENA-3 study.	Data provided for Stages 1 and 2 of the SERENA-3 study CCI [redacted]	Substantial
Section 2.3.2	Section updated to require patients in Stage 3 CCI [redacted] Section also updated to show change in sampling times for Stage 3, given longer treatment period and updated sample size to account for addition of Stage 3	CCI [redacted]	Substantial
Section 3	Objectives table updated to account for addition of Stage 3 to the study	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 4.1	Design updated to account for addition of Stage 3 to the study	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 4.1.3	New subsection to describe Stage 3	As per, or as a consequence of, recommendations by the SDMC	Substantial

Section Number	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 4.3	Justification of dose updated to account for longer treatment period allowed in Stage 3 to the study	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 5.2	Exclusion criterion 5b updated to require patients in Stage 3 CCI CCI	Change based on CCI CCI summarised which showed the potential for a higher proportion of patients to be impacted by an CCI risk of AEs of CCI	Substantial
Section 6.1.1	Updated to confirm investigational product to be used in Stage 3	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 6.6.1	New table of dose modifications added for Stage 3	Change based on CCI CCI summarised which showed the potential for a higher proportion of patients to be impacted by an CCI risk of AEs of CCI.	Substantial
Section 8.6	Updated to show change in sampling times for Stage 3, given longer treatment period	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 9.2	Updated sample size for Stage 3	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 9.2.1	Confirmation of definition of an evaluable patient for Stage 3	As per, or as a consequence of, recommendations by the SDMC	Substantial

AE = Adverse event; bpm = Beats per minute; CSP = Clinical study protocol; CSR = Clinical study report; ERα = Oestrogen receptor alpha; PD = Pharmacodynamic(s); PK = Pharmacokinetics; SDMC = Safety and Data Monitoring Committee; SoA = Schedule of Activities.

Additionally, minor changes were made throughout the protocol to clarify the SoAs to be used for Stage 1 and 2 and for Stage 3 where appropriate.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A Randomised, Open-Label, Parallel-Group, Pre-surgical Study to Investigate the Biological Effects of AZD9833 in Women with ER positive, HER2 negative Primary Breast Cancer (SERENA-3).

Short Title: A Randomised, Pre-surgical Study to Investigate the Biological Effects of AZD9833 in Women with ER positive, HER2 negative Primary Breast Cancer (SERENA-3).

Rationale:

The oestrogen receptor alpha (ERα) is a well-established drug target in ER-positive breast cancer and anti-hormonal endocrine therapies have become the mainstay of treatment (Early Breast Cancer Trialists' Collaborative Group 2005). The selective oestrogen receptor down-regulator and degrader (SERD) fulvestrant is used as a standard-of-care treatment for ER positive metastatic breast cancer, both alone and in combination with cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors (Cardoso et al 2018).

While fulvestrant has demonstrated superior clinical efficacy to other endocrine therapies and is approved for use in the metastatic breast cancer 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 patients with ER-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer.

A first-in-human study (SERENA-1, D8530C00001, NCT03616587) evaluating AZD9833 in women with advanced breast cancer has completed its monotherapy dose escalation phase. This study evaluated multiple ascending doses of AZD9833 administered once daily to pre- or post-menopausal women. Subsequent parts of this study are examining AZD9833 in several combinations. Study D8530C00001 established that AZD9833 doses of 25, 75, 150, 300 and 450 mg administered once daily were safe and exhibited dose-dependent tolerability in that population. Indications of efficacy were observed with AZD9833, with evidence of clinical benefit and target engagement observed at all dose levels, including patients pre-treated with CDK4/6 inhibitors and fulvestrant, and those with oestrogen receptor 1 (ESR1) mutations (Hamilton et al 2020).

SERENA-2 (D8530C00002, NCT04214288) is a global Phase 2, randomised, open-label study enrolling post-menopausal women who are suitable for fulvestrant therapy and with

disease progression after no more than one line of endocrine therapy for advanced disease, no more than one line of chemotherapy for advanced disease, and no prior fulvestrant or other oral SERD in the advanced disease setting. The study will evaluate the efficacy and safety of AZD9833 monotherapy doses once daily versus fulvestrant (administered according to its label). The primary objective is to determine the clinical efficacy of AZD9833 versus fulvestrant, as assessed by progression-free survival (PFS). Secondary objectives include objective response rate (ORR), duration of response, clinical benefit rate at 24 weeks (CBR24) and overall survival (OS). Effects of AZD9833 and fulvestrant on patients' health-related quality of life (HRQoL) will also be assessed. Exploratory endpoints include analysis of serially sampled circulating tumour DNA (ctDNA) and CCI .

This study, SERENA-3 (D8530C00003) is a randomised, open-label, parallel-group, pre-surgical study to investigate the biological effects of different doses of AZD9833 in post-menopausal (and potentially pre-menopausal) women with primary breast cancer. Stage 1 of the study will examine the effects of AZD9833 at 75 and 150 mg administered once daily for 5 to 7 days. An on-treatment tumour biopsy will be assessed for ER, progesterone receptor (PgR) and Ki-67 expression by immunohistochemistry (IHC) and compared with the diagnostic biopsy assessed by the same IHC method.

A Safety and Data Monitoring Committee (SDMC) will review the data from Stage 1 with reference to the SDMC charter, where guidelines regarding progress to, and dose-selection in, Stage 2 will be provided. Stage 2 will only occur in the United Kingdom after approval of a substantial protocol amendment including details of the rationale, the doses of AZD9833 and/or fulvestrant, and the study populations that will be evaluated in Stage 2 as recommended by the SDMC. In general, if Stage 1 doses produce a high degree of pharmacodynamic (PD) modulation versus historical fulvestrant control data, Stage 2 will likely focus on lower AZD9833 doses. Conversely, if Stage 1 doses produce a similar or lower degree of PD modulation compared with historical fulvestrant control data, Stage 2 will likely focus on higher AZD9833 doses. An alternative scenario is that the precision of the estimate of the primary endpoint from Stage 1 is insufficient, and the inclusion of additional patients in Stage 2 at the same doses from Stage 1 will provide additional clarity. Therefore, Stage 2 of the study makes provision for the examination of the biological effects of several different dose levels of AZD9833, or to evaluate additional patients at the dose levels examined in Stage 1.

A fulvestrant control group was not included in Stage 1, as several pre-surgical studies have been conducted, which include a fulvestrant control or experimental arms (eg, Robertson et al 2013, Robertson et al 2019), allowing a cross-study comparison of AZD9833 with fulvestrant historical control data. Provision was made in Stage 2 for a supplementary fulvestrant control group, if the SDMC advise that a concurrent fulvestrant control group would add to the scientific understanding of the study in Stage 2.

Randomisation to Stage 1 was completed on 10 March 2021 and the SDMC met on 6 July 2021 to review the overall Stage 1 data in detail. On the basis of that review, the SDMC has advised that Stage 2 will comprise: 1) additional patients at both the 75 and 150mg doses of AZD9833, and 2) an additional arm examining a higher dose of 300mg AZD9833. The details and justification for these Stage 2 doses is given in Sections 2.2.2.6 and 2.2.2.7.

Randomisation to Stage 2 (Georgia & Mexico) was completed on 08 Dec 2021. Patients were dosed at the following 3 doses of AZD9833: 75mg, 150mg and 300mg.

The UK portion of Stage 2 is currently ongoing at the following 2 doses of AZD9833; 75mg and 150mg.

The SDMC met on 27 June 2022 to review data arising from Stage 1 and 2. The SDMC has advised that an additional Stage 3 of the study will examine the effects of AZD9833 at 75 and 150 mg administered once daily for 12 to 15 days.

The details and justification for Stage 3 are given in Section(s) 2.2.2.8 ,and 2.2.2.9; and Section 6.1.1.

SERENA-3 is key to understanding the PD dose-response relationship for AZD9833, and in concert with the clinical efficacy and safety determined from SERENA-2, will support dose selection for further clinical development.

Objectives and Endpoints

Objectives	**Endpoint/Variable**
Primary	
• To explore the ER PD effects of AZD9833 between pre- and on-treatment tumour samples in women with early breast cancer after 5 to 7 days and 12 to 15 days of AZD9833 treatment.	• Change from baseline in ER expression between pre and on-treatment tumour samples measured by IHC and assessed by the manual H-score method.
Secondary	
• To explore the PgR and Ki-67 PD effects of AZD9833 between pre- and on-treatment tumour samples in women with early breast cancer after 5 to 7 days and 12 to 15 days of AZD9833.	• Change from baseline in PgR expression between pre and on-treatment tumour samples measured by IHC and assessed by the manual H-score method. • Change from baseline in Ki-67 labelling index between pre and on-treatment tumour samples measured by IHC.
• To evaluate the safety and tolerability of AZD9833 in this patient population.	• Adverse events (AEs)/Serious adverse events (SAEs). • Vital signs, electrocardiograms (ECGs).

• To evaluate the PK of AZD9833 in this patient population.	• Plasma concentrations of AZD9833 on the biopsy day.

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

Overall Design

This is a three-stage, randomised, open-label, parallel-group, multicentre study to investigate the biological effects of different doses of daily, orally administered (PO) AZD9833 in women with primary breast cancer awaiting curative-intent surgery. Women with histologically proven, ER-positive, HER2-negative invasive breast cancer involving a palpable tumour of any size, or a tumour with an ultrasound of ≥ 1.0 cm and fulfilling all the inclusion criteria and none of the exclusion criteria will be enrolled in the study.

Stage 1 of the study will include 2 treatment groups, to which post-menopausal patients will be randomised 1:1.

Stage 2 of the study will include 3 treatment groups (post-menopausal women; 3 AZD9833 groups).

Stage 3 of the study will include 2 treatment groups, to which post-menopausal patients will be randomised 1:1.

Stage 1:

After the screening visit and confirmation of eligibility, patients will be randomly assigned in a 1:1 ratio to receive one of the following two treatments for 5 to 7 days:

- Group 1: AZD9833 75 mg once daily (n = 12 evaluable post-menopausal patients)
- Group 2: AZD9833 150 mg once daily (n = 12 evaluable post-menopausal patients)

The SDMC will convene to review the Stage 1 data, potentially alongside the ongoing Phase 1 and 2 studies. The SDMC will make a decision as to whether to proceed to Stage 2, based on the SDMC charter, where guidelines regarding progress to, and dose-selection for Stage 2 will be provided.

Stage 2:

The SDMC reviewed the Stage 1 data and advised that Stage 2 will comprise:

- Group 1: AZD9833 Dose 75 mg once daily; approximately n = 24 evaluable patients
- Group 2: AZD9833 Dose 150 mg once daily; approximately n = 24 evaluable patients
- Group 3: AZD9833 Dose 300 mg once daily; approximately n = 12 evaluable patients

The randomisation will be stratified by country such that the UK will recruit approximately 24 evaluable patients across Groups 1 and 2, and Georgia and Mexico will recruit approximately 36 evaluable patients across Groups 1, 2, and 3.

Patients will attend a study visit on Day 5, 6, or 7 for an on-treatment imaging-guided biopsy. Following a washout period of a minimum of 5 days, the patients will undergo curative-intent surgery.

Stage 3:

The SDMC has advised that an additional Stage 3 will evaluate the biological effects of AZD9833 with longer duration of AZD9833 treatment (12 to 15 days) at doses of 75 and 150 mg once daily.

Stage 3 will comprise:

- Group 1: AZD9833 Dose 75 mg once daily; approximately n = 24 evaluable patients
- Group 2: AZD9833 Dose 150 mg once daily; approximately n = 24 evaluable patients

Patients will attend a study visit on Day 12, 13, 14, or 15 for an on-treatment imaging-guided biopsy. Following a washout period of a minimum of 5 days, the patients will undergo curative-intent surgery.

Safety Assessments

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

Stages 1 and 2:

Safety assessments (physical examination, vital signs) will be performed at screening. Clinical safety laboratory assessments will be performed at screening and on the biopsy visit day. ECGs and supine blood pressure measurement will be performed at screening (to ensure CCI [redacted] at screening), on the day of biopsy (Day 5 to 7; ie, Visit 3) and on the day of surgery (to ensure CCI [redacted] prior to surgery). Patients will wear a heart rate monitor from Day 1 to the Surgery Visit day.

Stage 3:

Safety assessments (physical examination, vital signs) will be performed at screening. Clinical safety laboratory assessments will be performed at screening and on the biopsy visit day. ECGs and supine blood pressure measurement will be performed at screening (to ensure CCI [redacted] at screening), on the day of biopsy (Day 12 to 15; ie, Visit 4), and on the day of surgery (to ensure CCI [redacted] prior to surgery). In Stage 3 an additional safety assessment will be performed on Day 7 (+3 days), specifically to assess heart

rate (by triplicate ECG) and blood pressure. Patients will wear a heart rate monitor from Day 1 to the Surgery Visit day.

Blood and Plasma Samples

Stages 1 and 2:

Blood and plasma samples for ctDNA will be collected at screening, on the day of the biopsy (Day 5 to 7), and the day of surgery. Where a decision to perform surgery is delayed for any reason (eg, neoadjuvant therapy, COVID-19-related reasons, adverse drug reaction) the 'surgery day' visit should be conducted on Day 13 (+ 3 days). Blood samples for exploratory circulating biomarkers will be collected at screening, on the day of the biopsy (Day 5 to 7), and the day of surgery.

Stage 3:

Blood and plasma samples for ctDNA will be collected at screening, on the day of the biopsy (Day 12 to 15) and the day of surgery. Where a decision to perform surgery is delayed for any reason (eg, neoadjuvant therapy, COVID-19-related reasons, adverse drug reaction), the 'surgery day' visit should be conducted on the 6th day following the last dose of AZD9833 (with a + 3 day window). Blood samples for exploratory circulating biomarkers will be collected at screening, on the day of the biopsy (Day 12 to 15), and the day of surgery.

All Stages

Blood samples will be collected for assessment of pharmacokinetics (PK) on the day of the biopsy, one sample prior to the biopsy and the other sample 1 to 3 hours after biopsy.

For patients who provide optional consent, an additional blood sample will be collected at screening, Day 1, or day of biopsy for future genetic research.

Study Period:

Estimated date of first patient enrolled: Q3 2020.

Estimated date of last patient completed (end of Stage 3): Q2 2023.

Number of Participants:

In Stage 1 of the study, approximately 28 post-menopausal patients will be screened (assuming a screen failure rate of approximately 15%), in order to randomise 24 evaluable patients into two treatment groups in a 1:1 ratio. Non-evaluable patients may be replaced.

In Stage 2 of the study, approximately 70 post-menopausal patients will be screened (assuming a screen failure rate of approximately 15%), in order to randomise up to 60 evaluable post-menopausal patients into 3 treatment groups. Non-evaluable patients may be replaced.

In Stage 3 of the study, approximately 56 post-menopausal patients will be screened (assuming a screen failure rate of approximately 15%), in order to randomise approximately 48 evaluable post-menopausal patients into 2 treatment groups. Non-evaluable patients may be replaced.

Treatments and Treatment Duration:

In Stages 1 and 2 patients will receive AZD9833 for 5 to 7 days.

In Stage 1, AZD9833 will be administered PO once daily in the morning at the same time:

- 75 mg: CCI tablets
- 150 mg: CCI tablet + CCI tablets

In Stage 2, AZD9833 will be administered once daily in the morning at the same time at the doses selected by the SDMC, ie:

- 75 mg: CCI tablets
- 150 mg: CCI tablet + CCI tablets
- 300 mg: CCI tablet

In Stage 3, patients will receive AZD9833 for 12 to 15 days. AZD9833 will be administered PO once daily in the morning at the same time:

- 75 mg: CCI tablets
- 150 mg: CCI tablet + CCI tablets

Safety and Data Monitoring Committee:

An independent AstraZeneca SDMC was to consider the Stage 1 data from this study prior to commencing Stage 2.

Stage 2 will only start enrolling in the UK after approval of a substantial protocol amendment including details of the rationale, the doses of AZD9833 and the study population that will be evaluated in Stage 2 as recommended by the SDMC.

The SDMC convened on 06 July 2021 and reviewed the Stage 1 data. The SDMC decided to proceed with Stage 2, based on the guidelines outlined in the charter and, selected three treatment groups as noted above. The charter is provided as a separate document.

The SDMC met on 27 June 2022 to review data arising from Stage 1 and 2. The SDMC has advised that an additional Stage 3 of the study will examine the effects of AZD9833 at 75 and

150 mg administered once daily for 12 to 15 days. The details and justification for Stage 3 are given in Section(s) 2.2.2.8 and 2.2.2.9; and Section 6.1.1.

Statistical Methods:

Statistical methods for the study will be as described in Section 9.

1.2 Schema

The general study design for Stage 1 is summarised in Figure 1. The study design for Stage 2 is shown in Figure 2 and the study design for Stage 3 is shown in Figure 3.

Figure 1 Study Design: Stage 1

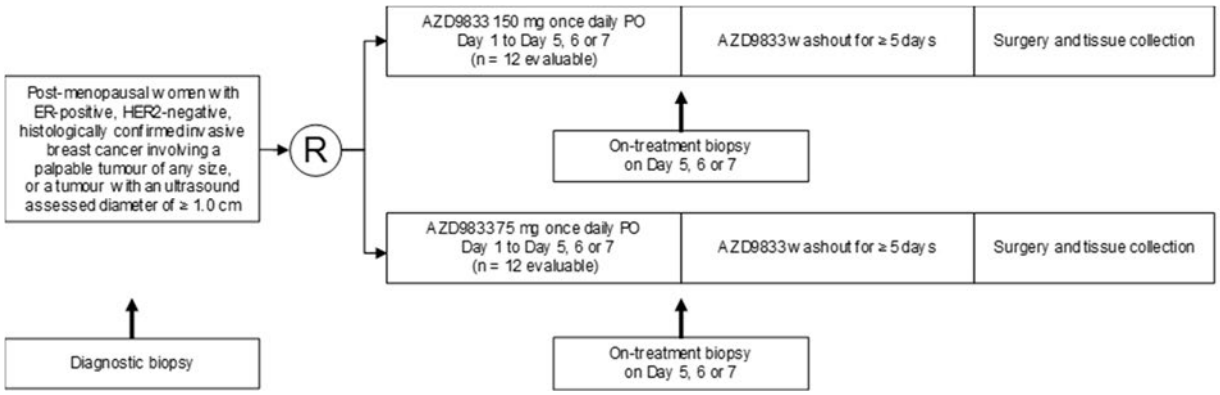


Figure 2 Study Design: Stage 2

The SDMC has advised Stage 2 should be conducted as follows:

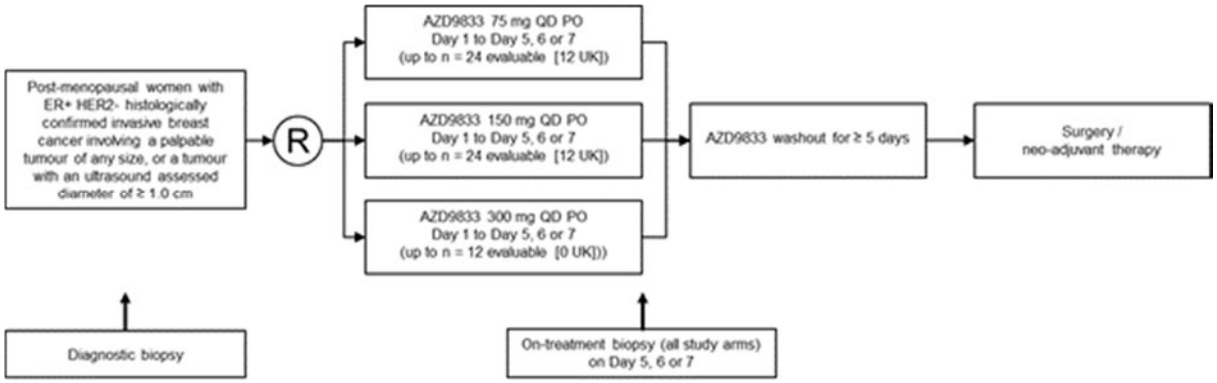
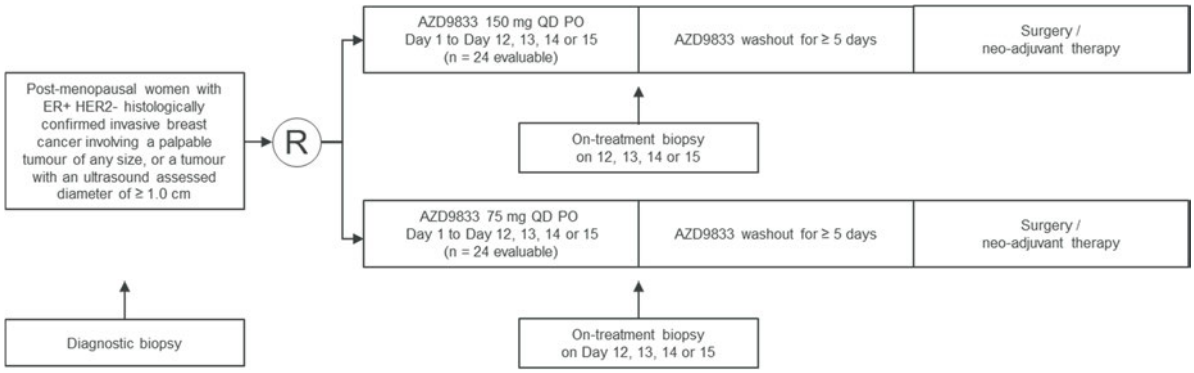


Figure 3 Study Design: Stage 3

The SDMC has advised Stage 3 should be conducted as follows:



1.3 Schedule of Activities

Table 1 indicates the Schedule of Activities throughout the study for Stage 1 and Stage 2.
Table 2 indicates the Schedule of Activities throughout the study for Stage 3.

Table 1 Schedule of Activities: Stages 1 and 2

Stage 1 and 2	Screening	Day 1	Biopsy day	Surgery day[a]	28-day safety	CSP section
Visit	1	2	3	4	5[b]	
Study Day	-21 to 1	1	5 to 7	≥ 11	28 ± 3	
Informed consent and eligibility criteria	X					5.1, 5.2
Demography, medical/surgical history, baseline disease characteristics (including ECOG)	X					5.1, 8.1.1
Clinical chemistry, haematology, urinalysis	X		X			8.2.1
Troponin and NT-proBNP	X		X			8.2.1
Physical examination, neurological exam, weight, height, temperature, pulse rate	X					8.2.2
Triplicate digital ECG[c] + supine blood pressure	X		X	X		8.2.4
Wearable heart rate monitor		Continuous				8.2.5
Randomisation	X					6.3
AZD9833 (allocated dose PO)		Daily				6.1.1
Concomitant medications	At every visit					6.5
Adverse events	At every visit					8.3
AZD9833 PK sample pre-biopsy			X			8.5.1
AZD9833 PK sample post-biopsy (1 to 3 hours)			X			8.5.1
Diagnostic tumour tissue retrieval	X					8.6.3
Tumour biopsy	(X)[d]		X			8.6.3
Blood sample for ctDNA	X		X	X		8.6.1
Blood sample for exploratory biomarkers	X		X	X		8.6.2
Genetic blood sample	(X)					8.7

[a] Surgery must be scheduled after a minimum of 5 days washout period from the last dose of study medication. In the event that a patient is undergoing longer-term neoadjuvant therapy rather than surgery, the 'surgery day' visit should be conducted on Day 13 (+ 3 days).

[b] Adverse events and concomitant medications information may be collected by telephone at the safety follow-up visit.

[c] Heart rate will be assessed by central review of the mean of triplicate ECG at all assessment timepoints except on the day of surgery, where it will be assessed by the treating physician prior to planned surgery.

[d] Mandatory tumour biopsy if diagnostic biopsy taken > 6 weeks prior to the screening visit date or patients consent to biopsy for fresh tumour tissue.

Table 2 Schedule of Activities: Stage 3

Stage 3	Screening	Day 1	Day 7	Biopsy day	Surgery day[a]	28-day safety	CSP section
Visit	1	2	3	4	5	6[b]	
Study Day	-21 to 1	1	7 (+ 3 days)	12 to 15	≥ 18[a]	28 ± 3 days after last dose	
Informed consent and eligibility criteria	X						5.1, 5.2
Demography, medical/surgical history, baseline disease characteristics (including ECOG)	X						5.1, 8.1.1
Clinical chemistry, haematology, urinalysis	X			X			8.2.1
Troponin and NT-proBNP	X			X			8.2.1
Physical examination, neurological exam, weight, height, temperature, pulse rate	X						8.2.2
Triplicate digital ECG[c] + supine blood pressure	X		X	X	X		8.2.4
CCI		Continuous					8.2.5
Randomisation	X						6.3
AZD9833 (allocated dose PO)		Daily					6.1.1
Concomitant medications		At every visit					6.5
Adverse events	At every visit						8.3
AZD9833 PK sample pre-biopsy				X			8.5.1
AZD9833 PK sample post-biopsy (1 to 3 hours)				X			8.5.1
Diagnostic tumour tissue retrieval	X						8.6.3
Tumour biopsy	(X)[d]			X			8.6.3
Blood sample for ctDNA	X			X	X		8.6.1
Blood sample for exploratory biomarkers	X			X	X		8.6.2
Genetic blood sample		(X)					8.7

[a] Surgery must be scheduled after a minimum of 5 days washout period from the last dose of study medication. In the event that a patient is undergoing longer-term neoadjuvant therapy rather than surgery, the 'surgery day' visit should be conducted on the 6th day following the last dose of AZD9833 (with a + 3 day window).

[b] Adverse events and concomitant medications information may be collected by telephone at the safety follow-up visit.

[c] Heart rate will be assessed by central review of the mean of triplicate ECG at all assessment timepoints except on the day of surgery, where it will be assessed by the treating physician prior to planned surgery.

[d] Mandatory tumour biopsy if diagnostic biopsy taken > 6 weeks prior to the screening visit date or patients consent to biopsy for fresh tumour tissue.

2 INTRODUCTION

2.1 Study Rationale

Anti-hormonal endocrine therapies targeting ERα have become treatments of choice in breast cancer (Early Breast Cancer Trialists' Collaborative Group 2005). The SERD fulvestrant is used as a standard-of-care treatment for ER positive metastatic breast cancer (Cardoso et al 2018).

While fulvestrant has demonstrated superior clinical efficacy to other endocrine therapies and is approved for use in the metastatic breast cancer 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 patients 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 (SERENA-1, D8530C00001, NCT03616587) evaluating multiple ascending doses of AZD9833 established that doses of 25, 75, 150, 300, and 450 mg once daily were safe and exhibited dose-dependent tolerability in pre- and post-menopausal women. Indications of efficacy were observed with AZD9833, with evidence of clinical benefit and target engagement observed at all dose levels, including patients pre-treated with CDK4/6 inhibitors and fulvestrant, and those with ESR1 mutations (Hamilton et al 2020).

SERENA-2 (D8530C00002, NCT04214288) is a global Phase 2, randomised, open-label study evaluating the efficacy and safety of AZD9833 monotherapy versus fulvestrant. The primary objective is to determine the clinical efficacy of AZD9833 versus fulvestrant, as assessed by PFS. Secondary endpoints include ORR, duration of response, CBR24 and OS. Exploratory endpoints include analysis of serially sampled ctDNA and CTCs. This study started recruiting patients in Q2 2020 and aims to enrol 288 patients in approximately 100 sites in up to 16 countries.

This study, SERENA-3 (D8530C00003) is a randomised, open-label, parallel-group, pre-surgical study to investigate the biological effects of different doses of AZD9833 in post-menopausal (and potentially pre-menopausal) women with primary breast cancer. Stage 1 will examine AZD9833 at 75 and 150 mg once daily for 5 to 7 days. An on-treatment tumour biopsy will be assessed for ER, PgR and Ki-67 expression by IHC, and compared with the diagnostic biopsy assessed by the same IHC method. The SDMC will review the data from Stage 1 to decide whether to proceed to Stage 2, in line with the SDMC charter, where guidelines regarding progress to and dose-selection will be provided. Stage 2 of the study may examine the biological effects of different dose levels of AZD9833 or provide an option for

further patients at the dose levels examined in Stage 1. Stage 2 will only occur in the UK after approval of a substantial protocol amendment including details of the rationale, the doses of AZD9833, and the study populations that will be evaluated in Stage 2 as recommended by the SDMC.

Randomisation to Stage 1 was completed on 10 March 2021 and the SDMC met on 06 July 2021 to review the overall Stage 1 data in detail. On the basis of that review, the SDMC has advised that Stage 2 will comprise of: 1) additional patients at both the 75 and 150 mg doses of AZD9833, and 2) an additional arm examining a higher dose of 300 mg AZD9833. The details and justification for these Stage 2 doses is given in Sections 2.2.2.6, 2.2.2.7 and Section 6.1.1.

Randomisation to Stage 2 (Georgia and Mexico) was completed on 08 December 2021. Patients were dosed at the following 3 doses of AZD9833: 75, 150, and 300 mg. The UK portion of Stage 2 is currently ongoing at the following 2 doses of AZD9833: 75 and 150 mg.

The SDMC met on 27 June 2022 to review data arising from Stage 1 and 2. The SDMC has advised that an additional Stage 3 of the study will examine the effects of AZD9833 at 75 and 150 mg administered once daily for 12 to 15 days. Stage 3 of the study will examine the effects of AZD9833 at 75 and 150 mg administered once daily for 12 to 15 days. An on-treatment tumour biopsy will be assessed for ERα, PgR, and Ki-67 expression by IHC and compared with the diagnostic biopsy assessed by the same IHC method. The details and justification for these Stage 3 doses and treatment duration are given in Sections 2.2.2.8 and 2.2.2.9; and Section 6.1.1.

SERENA-3 is key to understanding the PD dose response for AZD9833, and in concert with the clinical efficacy and safety determined from SERENA-2, will support dose selection for further clinical development in the early and advanced breast cancer settings.

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 that 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 a risk of recurrence 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 that the preferred first-line endocrine therapy for post-menopausal women with advanced disease is an 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 (INN: camizestrant) is a selective, non-steroidal, and potent SERD that can be administered orally. Pre-clinically, the drug has demonstrated equivalent maximal ERα degradation to fulvestrant in a panel of ER-positive breast cancer cell lines and complete antagonism of oestradiol induced gene expression changes in vitro. Furthermore, AZD9833 did not cause any agonism of ER activity in the absence of oestradiol in ER-positive breast cancer nor in uterine endothelial models in vitro and in vivo. AZD9833 caused significant anti-tumour effects in several patient-derived xenograft models of ER-positive breast cancer, including those bearing clinically relevant mutations in ESR1, the gene that encodes ERα.

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 (SERENA-1) (Hamilton et al 2020).

The AZD9833 programme has now recruited CCI patients; the safety information presented below, and in the current version of the Investigator's Brochure remains representative.

2.2.2.1 Safety and Tolerability

Safety and Efficacy in Humans

To-date, evaluation of AZD9833 monotherapy has occurred in study D8530C00001 (SERENA-1) and study D8530C00002 (SERENA-2) in patients with advanced breast cancer. The clinical safety data summarised below are described separately, as follows:

- AZD9833 safety at doses of 75 to 300 mg, administered daily in patients with advanced breast cancer (irrespective of duration of exposure); (N = CCI; SERENA-1 and SERENA-2).
- AZD9833 safety at doses of 75 to 300 mg, administered daily for the first 7 days only (N = CCI; SERENA-1 study).
- AZD9833 safety at doses of 75 to 300 mg, administered daily for the first 15 days only. (N = CCI; SERENA-1 and SERENA-2)

The short duration safety data (7-day and 15-day exposure) is of most clinical relevance to the exposure and, in turn, the likely safety profile that will be observed in SERENA-3, where AZD9833 will be administered for a period of 5 to7 or 12 to 15 days.

The primary objective of SERENA-1 (D8530C00001) was to investigate the safety and tolerability of AZD9833, and to define the doses for further clinical evaluation by assessment of 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 to study withdrawal if that occurred before disease progression. The DLT evaluation period was 28 days.

The primary objective of SERENA-2 (D8530C00002) was to determine the clinical efficacy (as assessed by PFS) of AZD9833 at 75, 150 and 300 mg once daily when compared to fulvestrant in women with advanced ER-positive HER2-negative breast cancer. SERENA-2 is ongoing. While the study is open-label, it is blinded to the study team in terms of aggregate efficacy.

Overall Safety: AZD9833 Monotherapy (SERENA-1 and SERENA-2)

Durations of exposure at each dose level are provided in Table 3.

Table 3 Duration of Exposure – AZD9833 Monotherapy (SERENA-1 and SERENA-2)

	AZD9833 monotherapy			
	75 mg	**150 mg**	**300 mg**	**Total (monotherapy)**
Subject exposure, days	CCI			
Mean				
SD				
Median				
Min				
Max				
Months n (%)				
< 3 months				
3 to 6 months				
≥ 6 months				

DCO = Data cut-off; SD = Standard deviation.

Source: Studies D8530C00001 (SERENA-1) and D8530C00002 (SERENA-2) combined preliminary data (DCO: CCI).

The observed AE profile is described in Table 4 and Table 5 below.

Table 4 Summary of Adverse Events in Study AZD9833 monotherapy (SERENA-1 and SERENA-2)

	75 mg	150 mg	300 mg	Total (monotherapy)
Any AE	CCI			
Any causally related AE[a]				
Any AE of CTCAE Grade 3 or higher				
Any causally related AE[a] of CTCAE grade 3 or higher				
Any AE leading to dose interruption				
Causally related AE[a] leading to dose interruption				
AE leading to dose reduction				
Causally related AE[a] leading to dose reduction				
AE leading to discontinuation				
Causally related AE[a] leading to discontinuation				
Any SAE				
Causally related SAE[a]				
Any AE with outcome = death				
Causally related AE[a] with outcome = death				

[a] Causally related to AZD9833, as assessed by the Investigator.

The AEs are reported if occurred during period from first dose to the end of safety follow-up or got worse during treatment.

AE = Adverse event; CTCAE = Common terminology criteria for adverse events; DCO = Data cut-off; SAE = Serious adverse event.

Source: Studies D8530C00001 (SERENA-1) and D8530C00002 (SERENA-2) combined preliminary data (DCO: CCI).

Table 5 AZD9833-related AEs (Investigator Opinion) Occurring in ≥10% (SERENA-1 and SERENA-2)

	AZD9833 monotherapy							
	Number of Patients (%)				Number of Patients			
	75 mg	150 mg	300 mg	Total	Max Grade 1	Max Grade 2	Max Grade 3	Max Grade 4/5
CCI	CCI				CCI			
CCI								
CCI [a]								
CCI [b]								
CCI								
CCI [c]								

[a] CCI includes the preferred terms: CCI ' and CCI '.

[b] CCI includes the preferred terms: CCI ' and CCI '

[c] CCI is a 'concept' AE term incorporating the following reported preferred terms: CCI ' and CCI '.

Source: Studies D8530C00001 (SERENA-1) and D8530C00002 (SERENA-2) combined preliminary data (DCO: CCI).

The highest dose tested in SERENA-1 was 450 mg once daily; following review of the safety data described, the SRC for that study declared 300 mg once daily was likely to be highest dose appropriate for long-term dosing in future clinical development with advanced/metastatic breast cancer. SERENA-2 and SERENA-3 investigate doses of 75, 150 and 300 mg once daily. CCI [redacted] In addition, CCI [redacted] associated with AZD9833 was observed, including following CCI [redacted]; this is also considered in further detail below.

2.2.2.2 Safety from Short Duration AZD9833 Monotherapy (7 days): Stages 1 and 2

This section has been left unchanged to reflect the data available at the start of the study and where the planned SERENA-3 exposure period was 5 to 7 days.

AZD9833 will be evaluated in a short duration (5 to 7 days) window of opportunity study in patients with newly diagnosed breast cancer. To optimally characterise the safety profile of AZD9833 after a short duration of exposure, the safety data in 80 patients treated with AZD9833 at doses of 25, 75, 150, 300 and 450 mg administered for 7 days in the ongoing Phase 1 AZD9833 monotherapy study was evaluated.

At the time of writing Version 1 of this CSP, it had not been decided which doses (if any) might be evaluated in Stage 2 of the SERENA 3 window of opportunity study; and that this would be determined after Stage 1 by the SDMC. In Stage 1 AZD9833 doses of 75 and 150 mg only were evaluated. In Stage 2 up to 60 patients may be evaluated with AZD9833 including doses unchanged, higher or lower than those in Stage 1 (75 and 150 mg). As described in Section 6.1.1, the SDMC has advised doses of AZD9833 of 75, 150, and 300 mg once daily for Stage 2.

In total, in the Phase I, SERENA-1 study, CCI [redacted] %) patients had an AZD9833 causally related AE during 7 days of treatment. CCI [redacted] respectively. The patient with CCI [redacted]

The most commonly occurring AZD9833-related AEs by system organ class term were CCI [redacted] and CCI [redacted] occurring in CCI [redacted] %) and CCI [redacted] %) of patients, respectively. The most common AZD9833-related AEs during 1-7 days of treatment occurring in ≥ 2 patients were: CCI [redacted] and CCI [redacted].

CCI
CCI PPD
PPD

A summary of AZD9833 causally related AEs occurring during the first 7 days of treatment is detailed below (Table 6).

Table 6 Summary of Causally Related AEs by SOC/PT in Study DC8530C0001 – First 7 Days of Treatment

MedDRA SOC [a]/PT [b]	AZD9833 monotherapy					
	25 mg	75 mg	150 mg	300 mg	450 mg	Total
CCI						

Table 6 Summary of Causally Related AEs by SOC/PT in Study DC8530C0001 – First 7 Days of Treatment

MedDRA SOC [a]/PT [b]	AZD9833 monotherapy					
	25 mg	75 mg	150 mg	300 mg	450 mg	Total
CCI						

Table 6 Summary of Causally Related AEs by SOC/PT in Study DC8530C0001 – First 7 Days of Treatment

MedDRA SOC [a]/PT [b]	AZD9833 monotherapy					
	25 mg	75 mg	150 mg	300 mg	450 mg	Total
CCI						

[a] SoC number represents the number of patients with AEs (eg, with AZD9833 150 mg, CCI),

[b] Preferred term number represents the number of AEs reported in patients (eg, with AZD9833 150 mg, CCI AEs were reported in CCI).

Source: t 36b_caus_rel_AE_soc_7d_V.

AZD9833 Monotherapy (7-days Exposure): CCI [1]

CCI

CCI

CCI

CCI PPD .

CCI

[1] This has now changed to 'CCI '; Refer to the AZD9833 IB (version 4.0) for justification of this change.

Table 7 CCI

	25 mg CCI	75 mg CCI	150 mg CCI	300 mg CCI	450 mg CCI	Total CCI	Patients with AE	Max Grade 1	Max Grade 2	Max Grade 3
CCI										
n (%)										

Source: ae_tab_AB_7d.

AZD9833 Monotherapy (7-days Exposure): CCI

The number of patients with CCI was defined based on CCI
CCI
CCI

CCI
PPD
PPD

Table 8 CCI [redacted]

	AZD9833 monotherapy					
	25 mg	**75 mg**	**150 mg**	**300 mg**	**450 mg**	**Total**
CCI [redacted]						

Source: CCI [redacted]

AZD9833 Monotherapy (7-days Exposure): CCI

CCI

Table 9 CCI

	AZD9833 monotherapy					
	25 mg	75 mg	150 mg	300 mg	450 mg	Total
CCI						

CCI

CCI

Source: CCI

2.2.2.3 Safety from Short Duration AZD9833 Monotherapy (15 days): Stage 3

This section has been updated using the most recently available data to provide a description of the safety profile over a 15-day exposure period, which supports Stage 3 of SERENA-3.

AZD9833 will be evaluated in a 12 to 15 day duration in Stage 3 of this window of opportunity study in patients with newly diagnosed breast cancer. To optimally characterise the safety profile of AZD9833 after a 1 to 15-day exposure (ie, longer than the 5 to 7 days examined in Stages 1 and 2) the safety data in 251 patients treated with AZD9833 at doses of 75, 150, and 300 mg administered for 1 to 15 days in the ongoing SERENA-1 and SERENA-2 studies were evaluated.

A summary of AZD9833 causally related AEs occurring during the first 15 days of treatment is detailed below (Table 10).

Table 10 Summary of Most Common (≥ 5% in Total for any SOC) Causally Related AEs by SOC/PT (SERENA-1 and SERENA-2); First 15 Days of Treatment

MedDRA SOC [a]/PT	AZD9833 monotherapy Number (%) of patients			
	75 mg	150 mg	300 mg	Total
CCI				

Table 10 Summary of Most Common (≥ 5% in Total for any SOC) Causally Related AEs by SOC/PT (SERENA-1 and SERENA-2); First 15 Days of Treatment

MedDRA SOC [a]/PT	AZD9833 monotherapy Number (%) of patients			
	75 mg	150 mg	300 mg	Total
CCI [redacted]				

Table 10 Summary of Most Common (≥ 5% in Total for any SOC) Causally Related AEs by SOC/PT (SERENA-1 and SERENA-2); First 15 Days of Treatment

MedDRA SOC [a]/PT	AZD9833 monotherapy Number (%) of patients			
	75 mg	150 mg	300 mg	Total
CCI				

[a] SoC number represents the number of patients with AEs (eg, with AZD9833 150 mg, CCI patients had CCI),
AE = Adverse event; DCO = Data cut-off; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred term; SOC = System organ classification.
Source: Studies D8530C00001 (SERENA-1) and D8530C00002 (SERENA-2) combined preliminary data (DCO: CCI).

AZD9833 Monotherapy (15-days Exposure): CCI

CCI

Table 11 CCI

	AZD9833 monotherapy Number (%) of patients			
	75 mg	150 mg	300 mg	Total
CCI				

CCI

CCI

Source: Studies D8530C00001 (SERENA-1) and D8530C00002 (SERENA-2) combined preliminary data (DCO: CCI).

AZD9833 Monotherapy (15-days Exposure): CCI

As above, the number of patients with CCI

CCI

CCI

Table 12 CCI [redacted]

	AZD9833 monotherapy			
	75 mg	150 mg	300 mg	Total
CCI [redacted]				

CCI [redacted]

Source: Studies D8530C00001 (SERENA-1) and D8530C00001 (SERENA-2) combined preliminary data (DCO: CCI [redacted]).

AZD9833 Monotherapy (15-days Exposure): CCI

An AZD9833-related CCI

CCI

CCI , during the first 15 days of treatment (Table 13).

Table 13 CCI

	AZD9833 monotherapy			
	75 mg	**150 mg**	**300 mg**	**Total**
CCI				

CCI

CCI

Source: Studies D8530C00001 (SERENA-1) and D8530C00001 (SERENA-2) combined preliminary data (DCO: CCI).

2.2.2.4 Pharmacokinetics

After a single AZD9833 dose, the time to reach t_{max} was achieved approximately 2 to 4 hours post-dose, with a $t_{1/2}$ of approximately 11 to 15 hours across all dose groups.

After 15 days of repeat daily dosing, the t_{max} was achieved approximately 2 to 4 hours post-dose (for detailed PK data see the Interim Clinical Summary or the Investigator's Brochure, Section 1.2.2).

2.2.2.5 Biological Activity and Clinical Efficacy from D8530C00001 (SERENA-1)

Patients enrolled in SERENA-1 Parts A and B, who were eligible and consented to have paired tumour biopsies, were analysed by IHC for ERα, PgR, and Ki-67. On

28 February 2020, 11 patients across 5 dose cohorts (25, 75, 150, 300 and 450 mg once daily) had evaluable tumour biopsy samples. All patients, across all doses, displayed PD effects and reduction of ERα following treatment with AZD9833. Reduction of the ER downstream transcriptional target PR and functional proliferation biomarker (Ki-67) was also observed across the dose cohorts.

RECIST ORR in patients with measurable disease at baseline, along with CBR24 for those evaluable, indicate ORR ranges from 11.1% at 25 mg to 20.0% at 300 mg, and CBR24 ranges from 23.1% for 300 mg to 50.0% for 450 mg.

Overall, the observed modulation of key PD markers, along with evidence of clinical efficacy is considered to be a strong indicator of the potential clinical utility of AZD9833 in this Phase 1 setting, and that warranted further investigation in a Phase 2 SERENA-2 study. SERENA-3 will further characterise the modulation of key PD markers in an early breast cancer context in patients without prior therapy.

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

2.2.2.6 Biological Activity from Stage 1 of SERENA-3, and Justification for Stage 2 Dose Selection

CCI [redacted]
CCI [redacted]
CCI [redacted] PPD [redacted]
PPD [redacted]

Biopsy pairs from 3 patients were not evaluated due to:

- failure to process the on-treatment biopsy correctly (n = 1).
- technical reasons in relation to biopsy processing (n = 1).
- on-treatment biopsy taken > 12 hours after the final AZD9833 dose (n = 1).

Additionally, one patient was determined to be HER2-positive by central assessment and was therefore excluded from further analysis. This resulted in 11 evaluable paired biopsies from patients treated with 75 mg AZD9833, and 10 from patients treated with 150 mg AZD9833.

Paired pre-treatment/on treatment biopsies were analysed by IHC for ERα, PgR, and Ki-67 and the data are presented in Figure 4 and Table 14.

These data demonstrate that both doses of AZD9833 examined in Stage 1 caused ERα degradation, and PgR and Ki-67 downregulation. CCI [redacted]
CCI [redacted]

CCI
CCI
CCI (middle panel of Figure 4 and Table 14). CCI
CCI

Furthermore, CCI
CCI
CCI These data indicate that CCI
CCI

CCI
The SDMC therefore regarded CCI
CCI
to be an important goal for Stage 2.

Figure 4 Pharmacodynamic Effect of 5 to7 Days Treatment with 75 mg or 150 mg AZD9833 on ERα, PgR, and Ki-67 Expression.

CCI

Table 14 ANCOVA Analysis for ERα, PgR, and Ki-67 (Adjusted for Key Covariates)

	75 mg AZD9833			150 mg AZD9833		
	n	LS mean	80% CI	n	LS mean	80% CI
% change from baseline in ERα H-score	11	CCI	CCI	10	CCI	CCI
% change from baseline in PgR H-score	8	CCI	CCI	8	CCI	CCI
% change from baseline in Ki67 % positive [a]	8	CCI	CCI	10	CCI	CCI

[a] Back transformed from log scale

Note: Table contents sourced from SERENA-3 Stage 1 PD data.

Least squares means were derived from an ANCOVA model adjusting for day of biopsy, baseline score, and treatment.

Note: Patients with a baseline H-score <10 on PgR or baseline labelling index <5% for Ki67 were excluded from the PgR or Ki-67 analysis, respectively.

CI = Confidence interval; ERα = Oestrogen receptor alpha; Ki-67 = Antigen Ki-67; PgR = Progesterone receptor.

The SDMC additionally recognised CCI
CCI
CCI
CCI The SDMC advised that it would be scientifically valuable to examine the CCI . Therefore, the SDMC advised that it was key to increase the precision of the estimates of the PD effects at the 75 and 150 mg doses and examine the PD effect of a higher dose.

The appropriate higher dose for Stage 2 is considered to be 300 mg. The linear dose-exposure relationship of AZD9833 over the dose range 25 to 300 mg means that increasing the dose from 150 mg to 300 mg would represent a doubling of exposure which could reasonably be expected to cause an observable increase in PD effect.

The SDMC specifically considered how many patients might be included in the 300 mg dose group and advised that 12 patients would be appropriate. This could be expected to provide sufficient understanding regarding the shape of the dose-response curve beyond 150 mg.

CCI

The examination of AZD9833 in a pre-menopausal population remains scientifically desirable. However, given the optimal dose to assess biological activity is not clear from Stage 1, the SDMC considers that delineation of the dose-response curve should be the key focus for Stage 2. CCI [redacted] CCI [redacted] CCI Therefore, based on SDMC recommendations, pre-menopausal patients will not be included in Stage 2.

The SDMC considered that given the comparability of the Stage 1 recruited population to recent historical studies which included a fulvestrant control arm (Robertson et al 2020b), in terms of tumour size, histology, grade, and TNM status, the addition of a fulvestrant comparator arm in SERENA-3 is not of key importance at this point.

All patients in Stage 1 were recruited from Georgia. While recruitment of Stage 2 only in Georgia would be appropriate, the SDMC considered that the inclusion of significant numbers of patients from UK and/or Mexico in Stage 2 would add robustness to the dataset. The SDMC proposed that an appropriate and practical way of assessing the homogeneity of the dose-response curve in a wider geographic population was to mirror the number of patients entered in Stage 1 in Georgia in a single county (either the UK or Mexico). For reasons of study centre readiness, and the historical linkage to fulvestrant data which has been generated mainly in the UK, the mirror will be prosecuted in the UK. Mexico will be permitted to contribute recruitment alongside Georgia in Stage 2.

2.2.2.7 Safety Data from Stage 1 of SERENA-3, and Justification for Stage 2 Dose Selection

Preliminary PK data for all PK-evaluable patients (n=25) was as expected, with no indication of under-exposure in any patient.

CCI [redacted]

There were no AEs reported that resulted in any form of surgical or anaesthetic impact or delay. CCI [redacted] CCI CCI

CCI [redacted]

CCI [redacted] The SDMC considered that the 5-day washout period is safe, reasonable, and sufficient for Stage 2 conduct as proposed.

2.2.2.8 Biological Activity from Stage 1 and 2 of SERENA-3, and Justification for Selection Stage 3 Dose and Duration of Dosing

CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted] PPD [redacted]
PPD [redacted]
PPD [redacted]

Biopsy pairs from 4 patients were not evaluated due to:

- Failure to process the on-treatment biopsy correctly (n = 1).
- Insufficient tumour in the on-treatment sample (n=2).
- On-treatment biopsy taken > 12 hours after the final AZD9833 dose (n = 1).

This resulted in 24 evaluable paired biopsies from patients treated with 75 mg AZD9833, 25 from patients treated with 150 mg AZD9833 and 11 from patients treated with 300 mg AZD9833. Additionally, one patient treated at 75mg was determined to be HER2-positive by central assessment and was therefore excluded from further analysis.

Paired pre-treatment/on treatment biopsies were analysed by IHC for ERα, PgR, and Ki-67 and the data are presented in Figure 5 and Table 15.

These data demonstrate that all doses of AZD9833 examined in Stage 1 and Stage 2 (Georgia and Mexico) caused ERα degradation, and PgR and Ki-67 downregulation. They also suggest that, while there is no apparent difference between the degree of ERα degradation nor the reduction in PgR expression caused by the different doses of AZD9833, 150 mg and 300 mg may be more effective than 75 mg AZD9833 at reducing Ki-67 levels.

Figure 5 Pharmacodynamic Effect of 5 to7 Days Treatment with 75 mg, 150 mg or 300 mg AZD9833 on ERα, PgR, and Ki-67 Expression

Note: In lower graphs of the above plot, line represents least squares mean and error bars 80% confidence interval.
+ve = positive; ERα = Oestrogen receptor alpha; Ki67 = Antigen Ki-67; PgR = Progesterone receptor.

Table 15 ANCOVA Analysis for ERα, PgR, and Ki-67 (Adjusted for Key Covariates)

	75 mg AZD9833			150 mg AZD9833			300 mg AZD9833		
	n	LS mean	80% CI	n	LS mean	80% CI	n	LS mean	80% CI
% change from baseline in ERα H-score	23	CCI	CCI	25	CCI	CCI	11	CCI	CCI
% change from baseline in PgR H-score	17	CCI	CCI	20	CCI	CCI	8	CCI	CCI
% change from baseline in Ki-67 % positive[a]	15	CCI	CCI	23	CCI	CCI	11	CCI	CCI

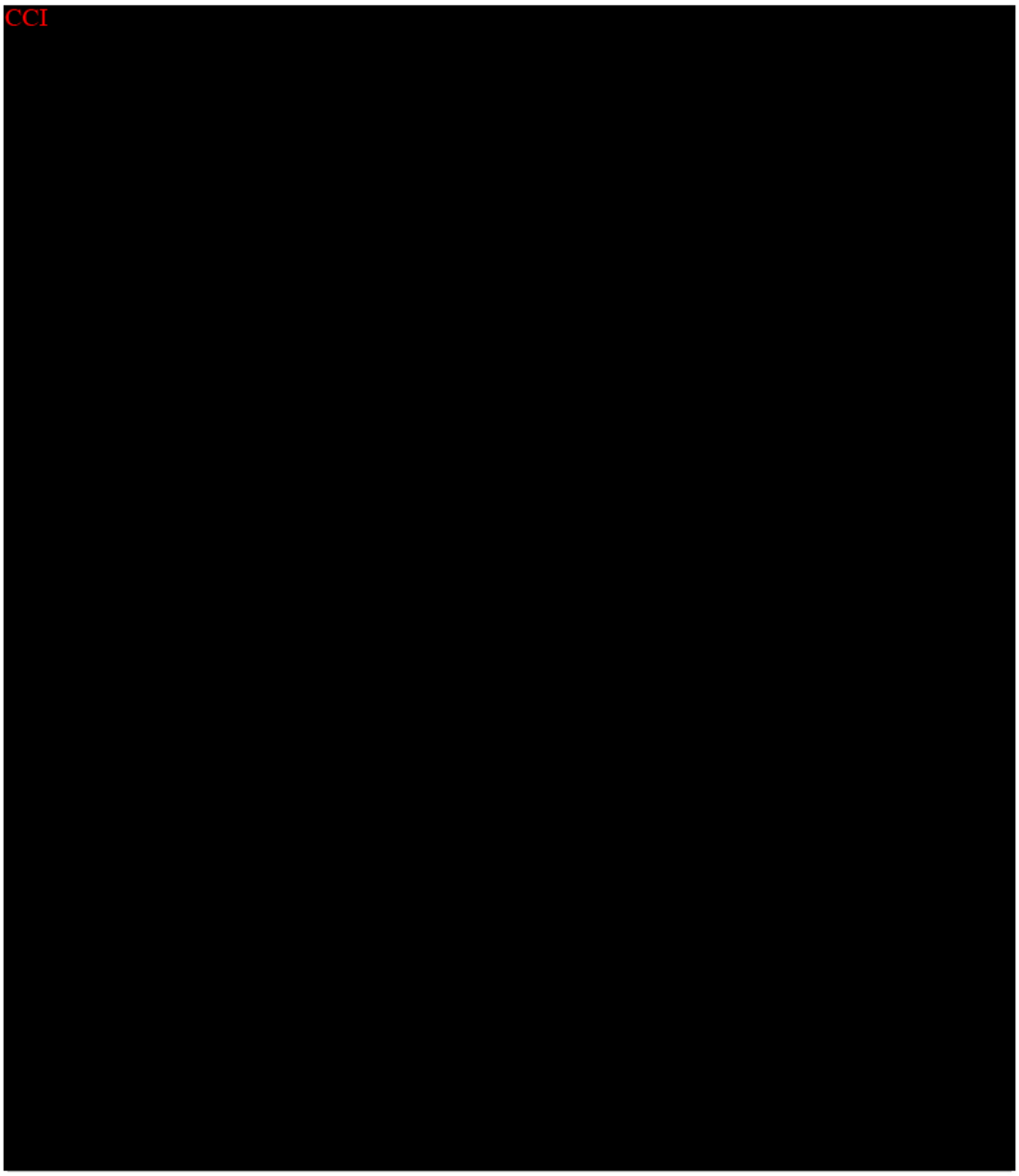
[a] Back transformed from log scale

Least squares means were derived from an ANCOVA model adjusting for day of biopsy, baseline score, and treatment. Note: Patients with a baseline H-score <10 on PgR or baseline labelling index <5% for Ki-67 were excluded from the PgR or Ki-67 analysis, respectively.

ANCOVA = Analysis of covariance; CI = Confidence interval; ERα = Oestrogen receptor alpha; Ki-67 = Antigen Ki-67; LS = Least squares; PD = Pharmacodynamic(s); PgR = Progesterone receptor.

Note: Table contents sourced from SERENA-3 Stage 1 + 2 interim analysis PD data.

Figure 6 **Percent Change from Baseline of ERα, PgR, and Ki-67 Expression Upon treatment with 75 mg, 150 mg or 300 mg AZD9833** CCI



Line represents the median. PgR % change data where baseline PgR H-score <10 and Ki67 % change data where baseline Ki67 % +ve <5 have been removed.

+ve = positive; ERα = Oestrogen receptor alpha; Ki67 = Antigen Ki-67; PgR = Progesterone receptor.

CCI

CCI [redacted] These data suggest that the maximal PD effect of AZD9833 may not have been achieved when tumour biopsies were collected on Day 5 to 7 of treatment, which may be a confounding factor in interpreting the effect of different doses of AZD9833. Therefore, the SDMC have advised to examine the PD effect of different doses of AZD9833 at longer treatment durations. CCI [redacted] CCI [redacted] the SDMC recommended that it would be appropriate to test the extended dosing period at 75 and 150 mg AZD9833.

In the IMPACT study, the effect of the endocrine therapies anastrozole, tamoxifen and the combination of the two agents on reductions in Ki-67 expression after 2 and 12 weeks of treatment was assessed (Dowsett et al 2005). While these are two drugs that target ER indirectly and directly respectively, there was no difference between the level of Ki-67 reduction seen at 2 and 12 weeks for either drug, suggesting that the maximal PD effect of ER inhibition is achieved after 2 weeks of dosing. As changes in Ki-67 is the most distant from target engagement of the 3 biomarkers assessed in SERENA-3, it is considered that a 12 to 15 day treatment period with AZD9833 is sufficient to achieve maximal PD effect on all three biomarkers.

2.2.2.9 Safety data from Stage 1 and 2 of SERENA-3, and Justification for Stage 3 Dose Selection and Duration of Exposure

No safety concerns were identified during the conduct of Stages 1 and 2. Table 16 and Table 17 below show the key AE data from the interim analysis of Stages 1 and 2. CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted]

Table 16 Summary of Adverse Events from Interim Analysis of Data for Stage 1 and Stage 2 of SERENA-3 Study

	AZD9833 Monotherapy Number (%) of patients			
	75 mg	150 mg	300 mg	Total
	CCI			
Any AE				
Any AE possibly related [a] to treatment				
Any AE of CTCAE Grade 3 or higher				
Any AE of CTCAE Grade 3 or higher possibly related[a] to treatment				
Any AE with outcome = death				
AE[a] with outcome = death possibly related to treatment				
Any SAE (including events with outcome = death)				
Any AE leading to discontinuation of treatment				
Any AE leading to discontinuation of treatment, possibly related[a] to treatment				
Any AE leading to dose modification of treatment				

a Possibly related to AZD9833, as assessed by the Investigator.

AE = Adverse event; CTCAE = Common terminology criteria for adverse events; DCO = Data cut-off.

Source: Table 14.3.2.1 Study D8530C00003 (SERENA-3) interim analysis (DCO: CCI).

Table 17 Summary of Causally Related Adverse Events from Interim Analysis of Data for Stage 1 and Stage 2 of SERENA-3 Study

	AZD9833 Monotherapy Number (%) of patients			
	75 mg	150 mg	300 mg	Total
Any AE possibly related [a] to treatment	CCI			

a Possibly related to AZD9833, as assessed by the Investigator.
AE = Adverse event; DCO = Data cut-off; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred term; SOC = System organ class.
Source: Table 14.3.2.8 Study D8530C00003 (SERENA-3) interim analysis (DCO: CCI).

No AEs of CCI were reported. CCI
CCI
CCI

Figure 7

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

2.3 Benefit/Risk Assessment

2.3.1 AZD9833

2.3.1.1 Potential Benefits

AZD9833 is unlikely to provide clinical benefit to patients in this pre-surgical window setting. The data presented above support potential benefit in a wider ER positive breast cancer setting at the doses under investigation in this study.

2.3.1.2 Potential Risks

Risks Identified in Pre-clinical Studies

Based on non-clinical toxicology studies, CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

Further information regarding non-clinical toxicology data is provided in the Investigator's Brochure.

Risks Identified in Clinical Studies

The Phase 1 study has identified CCI [redacted], as important risks, as described in detail above. CCI [redacted] Please refer to the Investigator's Brochure for further information regarding the potential risks for AZD9833 in a clinical setting.

2.3.2 Overall Benefit/Risk and Ethical Assessment

Whilst biomarker changes may be observed in tumours from these patients receiving 5 to 15 days of AZD9833, there is no data to support that short-term pre-/peri-operative changes in biomarkers translate into clinical benefit in patients with primary breast cancer. As such, short-term administration of endocrine therapy prior to surgery for primary breast cancer is not considered a standard-of-care treatment.

Similar smaller window-of-opportunity studies of other anti-hormonal or growth factor inhibitor agents in patients with early stage ER-positive breast cancer have been conducted (De Friend et al 1994, Robertson et al 2013, Robertson et al 2019, Robertson et al 2020a, Robertson et al 2020b) and found to be acceptable to the planned patient population. These studies have been central to the clinical development of SERDs, in particular to appropriate dose selection for later-phase clinical studies.

The investigation of AZD9833 in women with primary ER-positive HER2-negative breast cancer is considered acceptable, based upon:

- The clinical safety and efficacy data obtained from D8530C00001, D8530C00002 and D8530C00003
- The short duration of treatment with AZD9833 of 5 to 15 days in terms of side effect profile, CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

- The strength and importance of the scientific hypothesis under evaluation

Overall, the study provides an important clinical and scientific opportunity to investigate the PD effect of a new oral SERD at different doses. The study has the potential to substantially impact on the later clinical development of AZD9833 and other new endocrine treatments for women with breast cancer. There is an unmet clinical need for new therapeutic agents for patients with breast cancer and this study substantially facilitates rational drug development in that field. On balance, it is considered that the study presents an overall positive risk/benefit profile.

Stage 1 data support the overall risk/benefit and ethical assessment above, and the statements are unmodified for the conduct of Stage 2.

The combined Stage 1 and 2 data support the overall risk/benefit and ethical assessment above, and the statements are modified where appropriate to support the conduct of Stage 3.

3 OBJECTIVES AND ENDPOINTS

Table 18 Objectives and Endpoints

Objectives	Endpoints/Variables
Primary	
• To explore the ER PD effects of AZD9833 between pre- and on-treatment tumour samples in women with early breast cancer after 5 to 7 days and 12 to 15 days of AZD9833 treatment.	• Change from baseline in ER expression between pre- and on-treatment tumour samples measured by IHC and assessed by the manual H-score method.
Secondary Objectives	
• To explore the PgR and Ki-67 PD effects of AZD9833 between pre- and on-treatment tumour samples in women with early breast cancer after 5 to 7 and 12 to 15 days of AZD9833.	• Change from baseline in PgR expression between pre- and on-treatment tumour samples measured by IHC and assessed by the manual H-score method. • Change from baseline in Ki-67 labelling index between pre- and on-treatment tumour samples measured by IHC.
• To evaluate the safety and tolerability of AZD9833 in this patient population.	• AEs/SAEs. • Vital signs, ECGs.
• To evaluate the PK of AZD9833 in this patient population.	• Plasma concentrations of AZD9833 on the biopsy day.
Exploratory	
• To assess the effects of AZD9833 in tumour tissue on ER, PgR and Ki-67 assessed by image analysis of pathological specimens.	• Change from baseline in ER and PgR expression and Ki-67 labelling index, assessed by image analysis after 5 to 7 days and 12 to 15 days treatment.
• To assess the effects of AZD9833 in tumour tissue on ER, PgR and Ki-67 in patient subgroups including, but not limited to, baseline (pre-surgical) Ki-67 expression and CCI [redacted] CCI	• Change from baseline in ER, PgR, and Ki-67, as assessed by manual and computerized methods after 5 to 7 days and 12 to 15 days of treatment in patients according to other baseline characteristics, for example CCI [redacted].
• To assess the effects of AZD9833 on ER expression and PgR expression in tumour tissue, based on alternative methods of analysis, such as, but not limited to, Western blot and mass spectrometry methods.	• Change from baseline in ER and PgR expression, based on alternative methods of analysis such as, but not limited to, Western blot and mass spectrometry methods.
• To assess the effects of AZD9833 on mRNA expression of ESR1 and a panel of oestrogen-regulated genes in tumour tissue.	• Change from baseline in mRNA expression of ESR1 and a panel of oestrogen-regulated genes after 5 to 7 days and 12 to 15 days of treatment.
• To assess the effects of AZD9833 on other tumour biomarkers including DNA, mRNA or proteins in tumour tissue.	• Change from baseline in tumour tissue markers and circulating biomarkers, such as tumour DNA, mRNA, proteins or immune biomarkers (eg, autoantibodies).
• To explore the relationship between AZD9833 plasma exposure and changes in tumour tissue	• PK/PD modelling of AZD9833 plasma exposure and changes in tumour tissue markers and

Table 18 Objectives and Endpoints

markers and circulating biomarkers such as tumour DNA, mRNA, proteins or immune biomarkers (eg, autoantibodies).	circulating biomarkers such as tumour DNA, mRNA, proteins, or immune biomarkers.
• To collect and store plasma and serum samples for possible retrospective exploratory biomarker analysis which may include, but will not be limited to, understanding mechanisms of response to treatment (where response is defined broadly to include biomarker change, tolerability, or safety). This may include the analysis of tumour-specific and circulating biomarkers such as tumour DNA, proteins, antibodies or metabolites.	• Results from future exploratory biomarker analysis may be reported outside of the CSR.
• To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to AZD9833 and/or susceptibility to breast cancer.	• Results from future exploratory research may be reported outside of the CSR.

4 STUDY DESIGN

4.1 Overall Design

This is a three-stage, randomised, open-label, parallel-group, multicentre study to investigate the biological effects of different doses of daily PO AZD9833 in post-menopausal women with primary breast cancer. Participants will be newly diagnosed with histologically ER-positive, HER2-negative invasive breast cancer involving a palpable tumour of any size, or a tumour with an ultrasound of ≥ 1.0 cm and fulfilling all the inclusion criteria and none of the exclusion criteria will be included. Stage 1 of the study comprises two treatment groups, to which post-menopausal patients will be randomised (Figure 1). Stage 2 of the study may include up to four optional treatment groups, in which post-menopausal patients will be randomised in an allocation ratio to be determined (Figure 2). Stage 3 of the study comprises two treatment groups, to which post-menopausal patients will be randomised (Figure 3). All efficacy and safety assessments will be performed as described in the SoA for Stages 1 and 2 (Table 1), and the SoA for Stage 3 (Table 2) and Section 8.

4.1.1 Stage 1

After the screening visit (up to Da 21ys prior to randomisation) and confirmation of eligibility, patients will be randomly assigned in a 1:1 ratio to receive one of the following two treatments for 5 to 7 days:

- AZD9833 (75 mg, PO, once daily for 5 to 7 days)
- AZD9833 (150 mg, PO, once daily for 5 to 7 days)

During the treatment period, patients will attend study visits on:

- Day 1
- Day of biopsy (Day 5, 6 or 7)
- Day of surgery (following a washout from AZD9833 for at least 5 days; ie, if AZD9833 was taken for the last time on morning of Day 5, then Days 6, 7, 8, 9 and 10 are washout days and surgery can be scheduled for Day 11 onwards). In the event that a patient is undergoing longer-term neoadjuvant therapy rather than surgery, the 'surgery day' visit should be conducted on Day 13 (+ 3 days).

A treatment window of 5 to 7 days, along with a washout period of 5 days is considered to permit curative intent surgery within existing standard of care timeframes.

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

Safety assessments (physical examination, vital signs, ECGs, clinical safety laboratory assessments) will be performed at screening. An additional ECG and supine blood pressure measurement will be performed on the day of biopsy (Day 5 to 7; ie, Visit 3) and on the day of surgery.

Patients will wear a portable heart rate monitor continuously from Day 1 to the Surgery Visit day.

Blood and plasma samples for ctDNA will be collected at screening, on day of biopsy and the day of surgery. An additional blood sample (plasma and serum) to assess exploratory biomarkers will also be collected at screening, on the day of biopsy and on the day of surgery.

Patients may be replaced until 12 evaluable paired biopsies are collected within each treatment group (see Section 9.2.1 for definition of an evaluable patient).

Blood samples will be collected for PK assessment on the day of biopsy. CCI [redacted]
CCI [redacted]
CCI [redacted]

After the treatment period, patients will have a telephone 28-day safety follow-up visit to report any AEs and the use of concomitant medication.

4.1.2 Stage 2

Following the completion of the last patient visit in Stage 1 and availability of the IHC data, the SDMC will convene to review the Stage 1 data, potentially alongside the emerging data from any relevant ongoing AZD9833 studies. The SDMC will make a decision on whether to proceed with Stage 2, based on the guidelines outlined in the charter. If the decision is to proceed, the SDMC will then select the number of treatment groups in Stage 2 and at which doses, and confirm whether a pre-menopausal patient treatment group should be included, and at which dose of AZD9833. Stage 2 will only occur in the UK after approval of a substantial protocol amendment including details of the rationale, the doses of AZD9833 and/or fulvestrant, and the study populations that will be evaluated in Stage 2 as recommended by the SDMC.

See Section 2.2.2.6and 2.2.2.7 for a summary of Stage 1 data, and the SDMC recommendations.

After the screening visit (up to 21 days prior to randomisation) and confirmation of eligibility, patients will be randomly assigned in a 1:1 or 1:1:1 ratio to receive one of the following two or three treatments (based on the geographical stratification factor) for 5 to 7 days:

- AZD9833 (75 mg, PO, once daily for 5 to 7 days)

- AZD9833 (150 mg, PO, once daily for 5 to 7 days)
- AZD9833 (300 mg, PO, once daily for 5 to 7 days)

During the treatment period, patients will attend study visits on:

- Day 1
- Day of biopsy (Day 5, 6 or 7)
- Day of surgery (following a washout from AZD9833 for at least 5 days; ie, if AZD9833 was taken for the last time on morning of Day 5, then Days 6, 7, 8, 9, and 10 are washout days and surgery can be scheduled for Day 11 onwards). In the event that a patient is undergoing longer-term neoadjuvant therapy rather than surgery, the 'surgery day' visit should be conducted on Day 13 (+ 3 days)

A treatment window of 5 to 7 days, along with a washout period of 5 days is considered to permit curative intent surgery within existing standard of care timeframes. Throughout the study, patients will be asked to report AEs and the use of concomitant medications.

Safety assessments (physical examination, vital signs, ECGs, supine blood pressure, and clinical safety laboratory assessments) will be performed at screening. An additional ECG and supine blood pressure measurement will be performed on the day of biopsy (Day 5 to 7; ie, Visit 3) and on the day of surgery. Additional clinical safety laboratory assessments will be performed on the day of biopsy. Patients will wear a portable heart rate monitor continuously from Day 1 to the day of surgery, or the Day 13 'surgical visit' in the case of patients proceeding to neoadjuvant therapy rather than surgery. Blood and plasma samples for ctDNA will be collected at screening, on day of biopsy, and the day of surgery. An additional blood sample (plasma and serum) to assess exploratory biomarkers will also be collected at screening, on the day of biopsy, and on the day of surgery. Patients may be replaced until approximately 12 or 24 evaluable paired biopsies are collected within each treatment group (see Section 9.2.1 for definition of an evaluable patient). Blood samples will be collected for PK assessment on the day of biopsy. CCI [redacted] CCI [redacted] CCI [redacted]

After the treatment period, patients will have a telephone 28-day safety follow-up visit to report any AEs and the use of concomitant medication.

4.1.2.1 Post-menopausal Women

After the screening visit and confirmation of eligibility, post-menopausal women with a pre-treatment diagnostic biopsy will be randomly assigned to one of up to 3 treatment groups (three AZD9833 dose groups). Following the SDMC recommendation, patients will be randomised to one of two (UK) or one of three (Georgia and Mexico) AZD9833 dose groups.

Treatment will be administered for 5 to 7 days using exactly the same inclusion/exclusion criteria and schedule of assessments as in Stage 1.

4.1.3 Stage 3

After the screening visit (up to 21 days prior to randomisation) and confirmation of eligibility, patients will be randomly assigned in a 1:1 ratio to receive one of the following two treatments for 12 to 15 days:

- AZD9833 (75 mg, PO, once daily for 12 to 15 days)
- AZD9833 (150 mg, PO, once daily for 12 to 15 days)

During the treatment period, patients will attend study visits on:

- Day 1
- Day 7 (+ 3 days)
- Day of biopsy (Day 12, 13, 14, or 15)
- Day of surgery (following a washout from AZD9833 for at least 5 days; ie, if AZD9833 was taken for the last time on morning of Day 12, then Days 13, 14, 15, 16, and 17 are washout days and surgery can be scheduled for Day 18 onwards). In the event that a patient is undergoing longer-term neoadjuvant therapy rather than surgery, the 'surgery day' visit should be conducted on the 6th day following the last dose of AZD9833 (with a + 3 day window).

If, at the Day 7 (+ 3 days) visit, a patient is observed to have a mean of triplicate heart rate of < 50 bpm, she will be scheduled to undergo her biopsy day visit at Day 12; she will then commence her washout from AZD9833 following her daily dose on Day 12. In the event that it is not possible to schedule her biopsy on Day 12, the patient will begin her washout immediately at the Day 7 (+ 3 days) visit and will not be required to undergo biopsy. Patients may be replaced until approximately 24 evaluable paired biopsies are collected within each treatment group of Stage 3.

A treatment window of 12 to 15 days, along with a washout period of 5 days is considered to permit curative intent surgery within existing standard of care timeframes.

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

Safety assessments (physical examination, vital signs, ECGs, clinical safety laboratory assessments) will be performed at screening. An additional ECG and supine blood pressure measurement will be performed at the Day 7 (+ 3 days) visit, on the day of biopsy (Day 12 to 15 ie, Visit 3) and on the day of surgery.

Patients will wear a portable heart rate monitor continuously from Day 1 to the Surgery Visit day.

Blood and plasma samples for ctDNA will be collected at screening, on the day of biopsy and the day of surgery. An additional blood sample (plasma and serum) to assess exploratory biomarkers will also be collected at screening, on the day of biopsy and on the day of surgery.

Patients may be replaced until approximately 24 evaluable paired biopsies are collected within each treatment group (see Section 9.2.1 for definition of an evaluable patient).

Blood samples will be collected for PK assessment on the day of biopsy. CCI [redacted]
CCI [redacted]
CCI [redacted]

After the treatment period, patients will have a telephone 28-day (± 3 days) safety follow-up visit to report any AEs and the use of concomitant medication.

4.1.3.1 Post-menopausal Women

After the screening visit and confirmation of eligibility, post-menopausal women with a pre-treatment diagnostic biopsy will be randomly assigned to one of two AZD9833 dose groups. Treatment will be administered for 12 to 15 days. The SOA for patients participating in Stage 3 is described in Table 2.

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

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2] or similar pandemic infection), which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during the COVID-19 outbreak, temporary changes may be implemented to ensure the safety of study patients, maintain compliance with GCP, and minimise risks to study integrity.

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

- Obtaining consent for the mitigation procedures (note, in the case of verbal consent, the ICF should be signed at the patient's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened patients (see Section 5.5).
- Home or remote visit: Performed by a site-qualified HCP or HCP provided by a third party vendor (TPV).
- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home study treatment administration: Performed by a site-qualified HCP, HCP provided by a TPV, or by the patients or the patient's caregiver, if possible. Additional information related to the visit can be obtained via telemedicine.

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

4.2 Scientific Rationale for Study Design

An open-label clinical design is adopted to minimise patient tablet burden and given that the primary endpoint is measurement of tumour biopsy pharmacodynamics, where the IHC reading will be conducted blinded to group allocation and sequence (diagnostic versus on treatment).

The primary endpoint for this study is percent change from baseline in ER expression, measured by IHC and assessed by the manual H-score method. The PD relationship will be further evaluated with secondary endpoints (ie, percent change from baseline in PgR H-score and Ki-67 labelling index measured by IHC). Ki-67 labelling index will be calculated as the number of Ki-67 stained nuclei counted/total number of all invasive nuclei counted. These PD endpoints have proven informative for the clinical development of the SERDs (Robertson 2007, Robertson et al 2020b) and are considered appropriate here.

4.3 Justification for Dose

The selection of the two dose levels of AZD9833 (75 and 150 mg) for Stage 1 is supported by the PK, PD, safety and efficacy data collected during D8530C00001, and represent the lower two of the three doses selected for the Phase 2 PFS study (D8530C00002).

The initial two-stage design provides flexibility to obtain an early read-out on what are considered to be the most-likely AZD9833 doses for further clinical development, whilst preserving the option to investigate further doses in Stage 2, as informed by the results of Stage 1.

The maximum daily dose to be considered for Stage 2 will not exceed 450 mg, which is the maximum dose examined in D8530C00001.

The absence of a control arm in Stage 1 has been explained earlier. The provision for a supplementary fulvestrant control arm has been justified above.

Pre-menopausal women with ER-positive breast cancer require induction of either surgical or medical menopause when a third generation AI is being prescribed. Furthermore, women with high risk, hormone receptor-positive, primary breast cancer have been shown to benefit by adding medical ovarian ablation to tamoxifen in the adjuvant setting. SERDs that are sufficiently potent to be able to obviate this requirement for ovarian ablation in pre-menopausal patients would present a substantial improvement in standard of care.

The Stage 1 and 2 on-treatment interval of 5 to 7 days prior to biopsy is based on a) PK modelling in relation to time for AZD9833 to reach steady-state exposure, and b) pre-clinical PD modelling relating to the rate of onset of ER expression reduction, and is set to be as short as feasible, ie, 5 days. This is also consistent with the recent STAKT study in the same setting where short-term treatment, albeit with a different class of agent, demonstrated significant dose-dependent PD effects that could be measured after 4.5 days of drug administration (Robertson et al 2020a). Dosing up to 7 days allows flexibility in clinical scheduling to ensure that both the Day 1 on-treatment visit and the biopsy day visit can occur on weekdays.

Data emerging from Stages 1 and 2 indicated that PD steady state, particularly in relation to Ki-67 at the 75 mg dose, may not have been reached and it is important to understand this potential time-dependency to fully characterise the PD effect at longer exposure intervals, ie, the 12-to-15-day exposure period stipulated for Stage 3. Detailed justification is given in Sections 2.2.2.8 and 2.2.2.9; and Section 6.1.1.

CCI [redacted]

See Sections 2.2.2.6 and 6 for a summary of Stage 1 data and SDMC recommendations. There is no change to the justification text above as a consequence of the readout of data from Stage 1.

4.4 End of Study Definition

The end of study is defined as the last expected visit or 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.

5 STUDY POPULATION

5.1 Inclusion Criteria

Informed Consent

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

3 For patients who consent, provision of signed and dated written genetic informed consent prior to collection of samples for genetic analysis

Age and Gender

4 Female patients aged at least 18 years

Menopausal Status

5 Post-menopausal status defined as meeting at least one of the following criteria:

(a) Have undergone a bilateral oophorectomy

(b) Age ≥ 60 years

(c) Age ≥ 50 and < 60 years and with cessation of menses ≥ 12 months and 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 oral contraception or hormone replacement therapy prior to the diagnosis of breast cancer

Disease Characteristics

6 Female patients with newly diagnosed primary breast cancer scheduled to undergo treatment with curative intent by surgery and irrespective of clinical node status

(a) Patients who are scheduled to start neoadjuvant therapy can still participate in the study but must have their core tumour biopsies performed before commencing neoadjuvant therapy

7 Histologically confirmed invasive breast cancer involving a palpable tumour of any size, or a tumour with an ultrasound assessed diameter of ≥ 1.0 cm

8 Multifocal tumours (including bilateral tumours) are allowed, assuming one lesion is designated as the ‘target lesion’ (at the Investigator’s discretion) and tumour evaluations and pre- and on-treatment biopsies are performed on that lesion

9 Patients with adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumours curatively treated with no evidence of disease for ≥ 3 months can be considered for the study

(a) Any endocrine or other anti-cancer therapies must have been received at least 12 months prior to enrolment

10 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]) patients must have (where available, assessment of ER and HER2 status should be based on the most recent tumour biopsy sample):

(a) ER positive breast cancer

(b) HER2-negative breast cancer, defined as an IHC Score 0 or 1+ or negative by in situ hybridisation (ISH; FISH/CISH/SISH); if IHC 2+, ISH negativity is required

11 ECOG performance status 0 to 1

5.2 Exclusion Criteria

Prior/Concomitant Therapy

1 Previous systemic or local treatment for the new primary breast cancer currently under investigation (including surgery, radiotherapy, cytotoxic and endocrine treatments)

2 Intervention with any of the following:

(a) Use of sex-hormone-containing drugs within 6 months prior to the first dose of study treatment (including oral contraceptive pills, hormone replacement therapy, oestrogen-containing vaginal creams or other topical preparations, and controlled-release vaginal rings and sex hormone-containing intra-uterine systems)

(b) Medications or herbal supplements known to be strong inhibitors/inducers of CYP3A4/5, sensitive CYP2B6 substrates (commonly prescribed drugs are listed in Appendix A), and drugs which are substrates of CYP2C9 and/or CYP2C19 which have a narrow therapeutic index ie, CCI [redacted] as specified in Appendix A, prior to receiving the first dose of study treatment

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

Medical Conditions

3 Inflammatory breast cancer

4 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, or active infection including hepatitis B, hepatitis C, and HIV

Note: Active viral infection is defined as requiring antiviral therapy. Screening for chronic conditions is not required

5 Any of the following cardiovascular criteria:

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

(b) Resting heart rate of < 50 bpm, obtained from central review of the average of triplicate ECGs taken at screening for Stages 1 and 2;
Resting heart rate of < 60 bpm, obtained from central review of the average of triplicate ECGs taken at screening for Stage 3

(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 hypermagnesemia, hypo- and hypercalcaemia

(e) Known 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 re-screened 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) ANC < 1.5×10^9/L

(b) Platelet count < 100×10^9/L

(c) Hb < 90 g/L

(d) ALT > 2.5 × ULN)

(e) AST > 2.5 × ULN

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

(g) 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 drugs with a similar chemical structure or class to AZD9833.

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. Women of childbearing potential are excluded from Stage 1.

5.3 Enrolled and Randomised Patients

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. Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned/randomised to a study intervention. Patients who are enrolled and do not meet the entry requirements are screen failures, refer to Section 5.5.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.1.2. Prospective approval of protocol deviations to inclusion/exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

5.4 Lifestyle Considerations

5.4.1 Contraceptive Measures

All Stages will include post-menopausal women only. If a woman has had bilateral oophorectomy, alone or along with hysterectomy and/or bilateral salpingectomy, she would be regarded as having been rendered post-menopausal.

5.4.2 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).

5.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but 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 CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria and any serious adverse event (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 must re consent to the study and all screening procedures out of screening period window must be repeated. Laboratory values re-tested within the 21-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 CRF.

6 STUDY INTERVENTION

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

6.1 Study Interventions Administered

6.1.1 Investigational Products

Details of the investigational products are provided in Table 19 (Stage 1 and Stage 3) and Table 20 (Stage 2).

Table 19 Study Treatments in Stage 1 and Stage 3

	Treatment 1	Treatment 2
Treatment name	AZD9833	
Dosage formulation	CCI [redacted] tablets	
Dosage level(s)	75 mg once daily	150 mg once daily
Route of administration	PO	
Dosing instructions	CCI [redacted] tablets	CCI [redacted] tablet CCI [redacted] tablets

Table 19 Study Treatments in Stage 1 and Stage 3

	Treatment 1	Treatment 2
Packaging and labelling	AZD9833 will be provided in bottles. Each bottle will be labelled in accordance with country regulatory requirements.	
Provider	AstraZeneca	

Table 20 Study Treatments in Stage 2

	Treatment 1	Treatment 2	Treatment 3
Treatment name	AZD9833		
Dosage formulation	CCI [redacted] tablets		
Dosage level(s)	75 mg once daily	150 mg once daily	300 mg once daily
Route of administration	PO		
Dosing instructions	CCI [redacted] tablets	CCI [redacted] tablet CCI [redacted] tablets	CCI [redacted] tablets
Packaging and labelling	AZD9833 will be provided in bottles. Each bottle will be labelled in accordance with country regulatory requirements.		
Provider	AstraZeneca		

6.1.2 Medical Devices

No medical devices are planned for use in this study. A portable heart rate monitor will be used in all patients to record heart rate (see Section 8.2.5). Data will be collected from the heart monitor on an ongoing basis but will be reviewed only at the end of each stage of the study, ie, data will not be available in real-time.

6.2 Preparation/Handling/Storage/Accountability of Interventions

1 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.

2 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.

3 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.

4 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.

5 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.

6 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.

To reduce potential bias during the study, eligible patients will be randomly allocated at a 1:1 ratio to receive one of the two study treatments in Stage 1 and 3.

In Stage 2, eligible patients will be randomly allocated to one of two (UK) or three (Georgia and Mexico) treatment groups. The randomisation will be stratified based on country (UK / Georgia and Mexico). As per the SDMC recommendation the randomisation will be controlled such that approximately 24 evaluable patients are randomised in the UK across Groups 1 and 2, and approximately 36 evaluable patients are randomised in both Georgia and Mexico across Groups 1, 2 and 3.

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.

Biopsies will be scored in a blinded manner both in terms of which arm of the study the patient was allocated to and also which is the pre- and the on-treatment biopsy being assessed, and the data will be read out at the end of Stage 1, at the end of Stage 2, if applicable, and at the end of Stage 3.

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 Intervention.

6.4 Study 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, or 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 CCI

CCI

6.5.2 CCI

CCI

6.5.3 CCI

CCI

CCI

6.5.4 Medications that CCI

CCI

Drugs that are known CCI

6.5.5 Medications Known to CCI

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

6.5.6 Anti-cancer Treatments

Patients must not receive any other anti-cancer therapy, including investigational agents, while on study.

6.5.7 CCI

CCI

6.5.8 Drugs Containing Sex Hormones or Affecting Sex Hormone Status

Sex hormone-containing drugs such as oral contraceptive pills, hormone replacement therapy, progestational agents (megestrol acetate), dehydroepiandrosterone, other androgens (eg, oxandrolone) and selective ER modulators (eg, raloxifene [Evista®]) are not permitted during treatment (Day 1 to the biopsy day). 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 during treatment.

In addition, drugs other 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 up the biopsy day. 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, soy isoflavones) 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.

6.6 Dose Modification

6.6.1 Dose Modification for AZD9833

For AZD9833, guidance for dose modifications (dose discontinuation) in case of toxicities that are not attributable to the disease or disease-related processes is summarised in Table 21 (for Stages 1 and 2) and Table 22 (for Stage 3).

Table 21 AZD9833 Dose Discontinuation Guidance (AZD9833-related); Stages 1 and 2

Toxicity	Details	Actions
CCI	CCI	CCI
	CCI	CCI
CCI	CCI	CCI
CCI	CCI	CCI
	CCI	CCI
Any CTCAE Grade ≥ 3 or clinically significant AE (considered to be possibly related to AZD9833 by the Investigator)		Discontinue AZD9833

Table 22 AZD9833 Dose Discontinuation Guidance (AZD9833-related); Stage 3

Toxicity	Details	Actions
CCI	CCI	CCI
	CCI	CCI
	CCI	CCI
CCI	CCI	CCI
CCI	CCI	CCI
	CCI	CCI
Any CTCAE Grade ≥ 3 or clinically significant AE (considered to be possibly related to AZD9833 by the Investigator)		Discontinue AZD9833

6.7 Intervention after the End of the Study

Subsequent treatment will be at the discretion of the patient's treating physician.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

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.
- Patients incorrectly initiated on study treatment (see Section 7.1.2, Procedures for Handling Patients Incorrectly Initiated on Study Treatment).

See the SoA tables (Table 1 and Table 2) 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 Re-challenge

Not applicable.

7.1.2 Procedures for Handling Patients 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 Participant Withdrawal from the Study

A participant may withdraw from the study (eg, withdraw consent), at any time at her own request, without prejudice to further treatment. Participants who are withdrawn from the study will be replaced.

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.

See the SoA tables (Table 1 and Table 2) for data to be collected at the time of study discontinuation and 28-day follow-up.

7.3 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.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in SoA tables (Table 1 and Table 2).

The Investigator will ensure that data are recorded on the CRFs. A WBDC system will be used for data collection and query handling.

The Investigator will ensure 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 tables, 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.

The total amount of mandatory blood samples collected from each patient is estimated to a maximum of 103 mL (Table 23). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 23 Blood Sample Volumes

Visit	Safety[a]	PK (AZD9833)	ctDNA	Exploratory biomarkers	CCI	CCI
Screening	15 + 2		CCI			
Day 1	6[c]					
Day of biopsy	6[c]					
AZD9833 treatment groups		2 × 2				
Day of surgery						

[b] A volume of 15 mL is estimated for the Safety samples, assuming 6 mL for clinical chemistry, and 9 mL for haematology. In addition, 2 mL will be drawn for coagulation tests. 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.

CCI

CCI

8.1 Efficacy Assessments

Not applicable.

8.1.1 Performance Status

Performance status will be assessed at the visits indicated in the SoA tables (Table 1 and Table 2), 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.

8.2 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA tables (Table 1 and Table 2).

8.2.1 Clinical Safety Laboratory Assessments

See Table 24 for the list of clinical safety laboratory tests to be performed and 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 assess the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at each site 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 analysis 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 24 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
Coagulation parameters	S/P-Sodium
Prothrombin time (PTT)	S/P-Glucose
Activated partial thromboplastin time (aPTT)	S/P-Magnesium
International normalised ratio (INR)	S/P-Phosphate
Urinalysis (dipstick)	S/P-Urea or Urea Nitrogen
U-Glucose	S/P-Protein, total
U-Protein	S/P-Troponin
U-Blood	CCI [redacted]

NB. In case a patient shows an AST **or** ALT ≥ 3× ULN together with total bilirubin ≥ 2× ULN please refer to Appendix C 'Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law', for further instructions.

8.2.2 Physical Examinations

A complete physical examination, including a standard neurological examination, body weight, and height, will be performed at screening, as indicated in the SoA tables (Table 1 and Table 2).

Investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as AEs, see Section 8.3.6 for details.

8.2.3 Vital Signs

Vital signs (including blood pressure, pulse rate, and body temperature), will be assessed at the timepoints indicated in the SoA (Table 1 and Table 2) 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, body temperature, 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 one pulse and three blood pressure measurements (three consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the three blood pressure readings will be recorded on the CRF.
- Following screening only blood pressure will be measured prior to blood collection for laboratory tests and the ECG.

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 using standardised ECG machines that automatically calculate the heart rate and measure RR, PR, QRS, QT, and QTcF intervals:

- 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, where applicable before blood pressure, PK and ctDNA sampling.
- At each timepoint, three 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 (ERT mean of triplicate ECG).
- RR interval: duration in msec between two R peaks of two 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.

8.2.5 CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI [redacted]

8.3 Adverse Events and Serious Adverse Events

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

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

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).

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

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix D. 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 AEs or SAEs 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 shall, without undue delay, report the SAE to the Sponsor.

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

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 SAE
- Date Investigator became aware of SAE
- AE is serious due to (state reason)
- 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 D.

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 and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of study treatments or are considered to be clinically relevant as judged by the Investigator (which may include, but not limited to, consideration as to whether treatment or non-planned visits were required or other action was taken with the study treatment, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low 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 8.3.11.

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 $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ ULN may need

to be reported as SAEs. Please refer to Appendix C 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 participant's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of ER-positive HER2-negative breast cancer should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

8.3.10 Deaths

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

- 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.

8.3.11 Reporting of Serious Adverse Events

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

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

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE

within one calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

If the WBDC system is not available, then the Investigator or other study site staff will report 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 treatment 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 treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

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

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it 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 D.

8.3.12 Medication Error

If any medication error occurs in the course of the study, then the Investigator or other site personnel will 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 will work 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 8.3.12) and within 30 days for all other medication errors.

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

8.4 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 will inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all 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.

8.4.1 AZD9833

For this study, any dose of AZD9833 greater than the intended dosage will be considered an overdose.

AstraZeneca does not recommend specific treatment for an AZD9833 overdose. Any patient who receives a dose higher than intended should be monitored closely, managed with appropriate supportive care.

8.5 Human Biological Samples

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

8.5.1 Pharmacokinetics

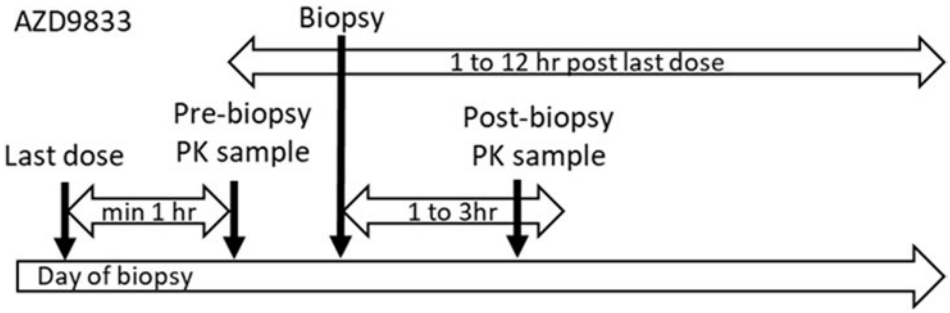
Venous blood samples of approximately 2 mL will be collected from patients receiving AZD9833 for measurement of plasma concentrations of AZD9833 as specified in the SoA.

For AZD9833, two PK blood samples will be taken as illustrated in Figure 8:

- One PK sample will be taken at least 1 hour post-dose, and as close to the biopsy as possible.

- The second PK sample should be taken 1 to 3 hours post biopsy.

Figure 8 Schematic Illustrating the Relative Timings and Windows for Biopsy and PK Sampling



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 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.

8.5.1.1 Determination of Drug Concentration

Samples for determination of AZD9833 drug 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.

8.5.1.2 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.

In the event that PK samples destruction is required, they may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK

samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

8.5.2 Pharmacodynamics

PD measurements are described in Section 8.6.

8.6 Human Biological Sample Biomarkers

Biomarkers (ER, PgR and Ki-67) will be tested in tumour samples using a variety of methods for the primary, secondary and exploratory objectives.

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

- Diagnostic tumour tissue and tumour biopsy (Stage 1 and 2: Day 5 to 7; Stage 3: Day 12 to 15) for analysis of biomarkers including, but not limited to, ER, PgR, and Ki-67 protein levels and ER-regulated genes and mutational profile, as follows:
  - Blood samples for ctDNA
  - Blood samples for exploratory biomarkers

8.6.1 Blood Samples for Circulating Tumour DNA

Two 10 mL whole blood samples will be taken at screening, for the isolation of plasma and buffy coat to enable the assessment, analysis and interpretation of ctDNA. One 10 mL blood sample will be taken at all of the other timepoints indicated in the SoA to provide plasma only.

8.6.2 Blood Samples for Exploratory Biomarkers

Two 5 mL blood samples will be taken at each of the three timepoints indicated in the SoA to provide one sample of plasma and one sample of serum per timepoint. The samples will be collected and stored to permit retrospective exploratory biomarker analysis which may include, but will not be limited to, understanding mechanisms of response and resistance to treatment (where response is defined broadly to include biomarker change, tolerability or safety) and for diagnostic purposes. This may include the analysis of circulating biomarkers, such as tumour DNA, mRNA, proteins, metabolites or immune biomarkers (eg, autoantibodies).

8.6.3 Tumour Biopsy

Paired tumour biopsies will be collected from a minimum of 12 patients in each treatment group in Stage 1, approximately 12 (300 mg Stage 2 arm) or 24 (75 and 150 mg Stage 2 arms) evaluable patients in each treatment group in Stage 2, and approximately 24 patients in each treatment group in Stage 3.

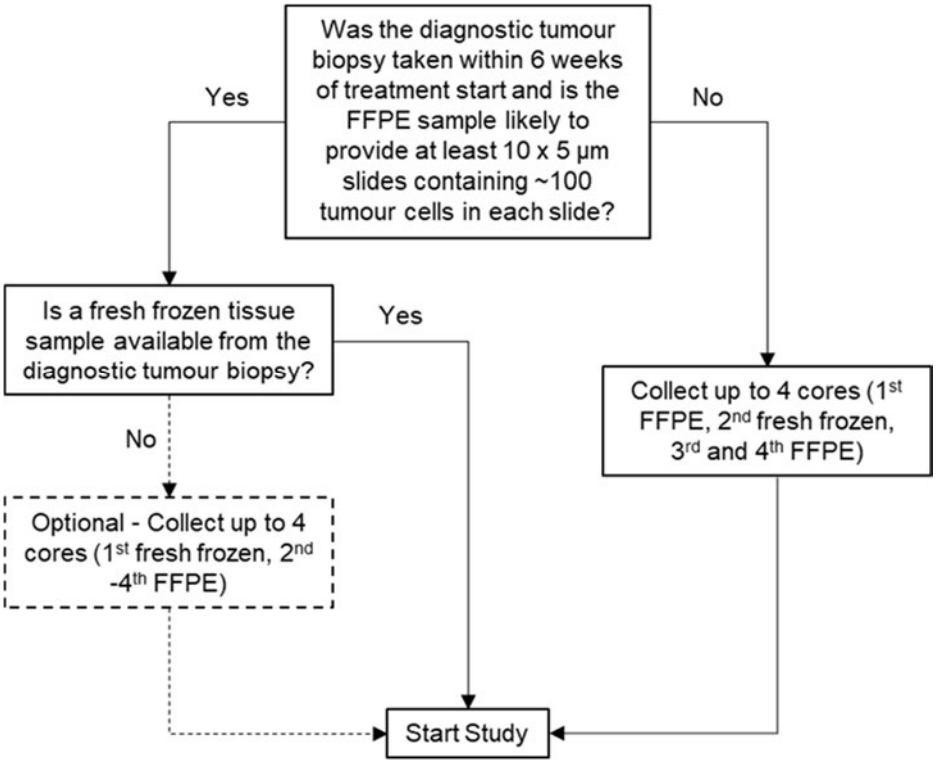
The paired tumour biopsies will be the diagnostic tumour tissue and an on-treatment biopsy sample, taken on Day 5, 6, or 7 of treatment for Stages 1 and 2, and Day 12, 13, 14, or 15 of treatment for Stage 3. All biopsies should be taken from the same tumour lesion.

The diagnostic tumour tissue sample will have been taken from tumour tissue using a core cut or tru cut device as a standard hospital diagnostic procedure at baseline. Patients must consent to the use of their diagnostic FFPE biopsy sample and fresh frozen tissue sample (if available) if the biopsy was taken within 6 weeks of the planned start of study treatment.

If the diagnostic biopsy was taken ≥ 6 weeks prior to starting treatment or was taken within 6 weeks but was not likely to provide adequate tissue sections for the biomarker assays (eg, technical artefact or too little tumour present in the diagnostic core), patients will require a new biopsy to be taken prior to starting treatment. Up to four core cut or tru cut biopsy samples will be taken via imaging-guided biopsy. The first core should be processed for FFPE, the second as fresh frozen and the third and fourth for FFPE. If fewer than 4 cores are obtained, the first core should be processed for FFPE the second as fresh frozen and any subsequent cores as FFPE.

If the diagnostic biopsy was taken within 6 weeks prior to starting treatment, but a fresh frozen tissue sample is not available from the initial diagnostic biopsy, patients may also consent to an optional new pre-treatment biopsy to provide a fresh frozen tissue sample. Up to four core cut or tru cut biopsy samples will be taken via imaging-guided biopsy. The first core should be processed for fresh frozen tissue and subsequent cores processed for FFPE. These possibilities are summarised in Figure 9.

Figure 9 Diagnostic Biopsy Decision Tree



Diagnostic FFPE tumour samples will preferably be in the form of a FFPE block. If this is not possible, freshly prepared unstained slides (minimum of 10, but preferably 20) 5 micron sections from the tumour block will be accepted if tumour blocks cannot be submitted. Fresh frozen core biopsies will be used for research purposes, unless the fresh frozen biopsy is required for initial diagnostic purposes.

The treatment biopsy samples should be taken on treatment Day 5, 6, or 7 for Stages 1 and 2, and on treatment Day 12, 13, 14, or 15 for Stage 3. In AZD9833-treated groups this should preferably be 2 to 4 hours after the last dose of AZD9833 but must be between 1 and 12 hours after the last dose of AZD9833. Up to four core cut or tru cut biopsy post-treatment samples will be taken via imaging-guided biopsy. The first core should be processed for FFPE, the second as fresh frozen and the third and fourth for FFPE. If fewer than 4 cores are obtained, the first core should be processed for FFPE the second as fresh frozen and any subsequent cores as FFPE.

The date and exact time of AZD9833 last dose and date and exact time of collection of on-treatment tumour biopsies and PK samples must be carefully recorded in the CRFs.

All tissues should be either formalin-fixed, or fresh frozen, immediately following biopsy. Routine paraffin-wax embedding of formalin fixed biopsies will be carried out at the local investigational site (general guidance is provided in the Laboratory Manual).

The date and exact time of the last dose AZD9833, and date and exact time of collection of on-treatment tumour biopsies and PK samples must be carefully recorded in the CRFs.

All tissues should be either formalin-fixed or fresh frozen immediately following biopsy. Routine paraffin-wax embedding of formalin fixed biopsies will be carried out at the local investigational site. Full details regarding the collection, processing, labelling, storage and shipping of FFPE and fresh frozen samples is provided in the Laboratory Manual.

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(s) to generate hypotheses to be tested in future research.

8.7 CCI

CCI

CCI

CCI

8.8 Medical Resource Utilization and Health Economics

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

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary objective is to obtain an estimation of the change in ER following treatment with different doses of AZD9833.

9.2 Sample Size Determination

The study is designed as an exploratory estimation of ER knockdown of different AZD9833 doses, as assessed by the manual H-score method. The sample size is based on the primary endpoint, percent change from baseline in ER expression in each dose group. Assuming a drop-out rate of 15%, approximately 14 patients will be recruited per treatment group, to allow 12 evaluable patients per treatment group for the analysis of the primary endpoint at the end of Stage 1.

For Stage 1, a total of 12 evaluable patients per treatment group will provide an 80% chance of obtaining an 80% CI, where one half of the CI is at most 14 for the mean percent change from baseline in ER. This is under the assumption of a true standard deviation of 29 (Robertson et al 2020a, Robertson et al 2020b).

For Stage 2, following the SDMC review of Stage 1 data, approximately 24 evaluable patients will be recruited to each of Group 1 (AZD9833 75 mg) and Group 2 (AZD9833 150 mg), and approximately 12 evaluable patients to Group 3 (AZD9833 300 mg). For completeness, with further patients recruited to the same two dose groups under Stage 2 of the study, approximately 36 evaluable patients may be included. A total of 36 evaluable patients per treatment group will provide an 80% chance of obtaining an 80% CI where one half of the CI is at most 7 for the mean percent change from baseline in ERα.

As per Sections 2.2.2.6 and 6, in Stage 2 of the study, approximately 12 patients in Group 1 (AZD9833 75 mg) and Group 2 (AZD9833 150 mg) will be recruited from the UK to enable additional understanding of the homogeneity of the dose-response curves across the two geographies. The operating characteristics with 12 patients per dose group will mirror the Stage 1 precision above.

For Stage 3, a total of 24 evaluable patients per treatment group will provide an 80% chance of obtaining an 80% CI, where one half of the CI is at most 9 for the mean percent change from baseline in ER. This is under the assumption of a true standard deviation of 29 (Robertson et al 2020a; Robertson et al 2020b). In relation to the key secondary endpoint of Ki-67, a total of 24 evaluable patients per treatment group will provide an 80% chance of obtaining an 80% CI, where one half of the CI is at most 0.312 on the log scale, which if a geometric mean of -80% for Ki-67 was observed, the expected CI would be (-85%, -73%). CCI [redacted] CCI [redacted]

9.2.1 Definition of an Evaluable Patient

A patient is evaluable for the primary endpoint if:

1 Patient has taken a minimum of 5 consecutive daily doses of AZD9833 (as per Section 6.1.1) for Stages 1 and 2, and a minimum of 12 consecutive daily doses prior to, and including, the biopsy day for Stage 3.

2 Patient received the last dose of AZD9833 within 12 hours of on-treatment biopsy

3 Biopsy pair evaluable as below:

(a) The diagnostic and on-treatment biopsy pair is considered evaluable by central pathology assessment, defined as containing >100 tumour cells in each FFPE biopsy and

(b) A minimum of 2 slides to allow measurement of ER

4.Has no protocol deviations that may impact the biomarker analysis

On an ongoing basis and prior to final database lock, patient data will be reviewed on a case-by-case basis to determine if the patient is evaluable. Non-evaluable patients may be replaced.

9.3 Populations for Analyses

Analysis populations are defined in Table 25. Full details of the analysis populations and reporting will be provided in the SAP:

Table 25 Study Populations

Population	Description
Primary endpoint analysis set	See Section 9.2.1
Safety analysis set	All patients who received at least one dose of AZD9833
Pharmacokinetics (PK) analysis set	All patients who received at least one dose of AZD9833 and had at least one reportable plasma concentration

9.4 Statistical Analyses

Analyses will be performed by AstraZeneca or its representatives, including CROs. All data will be summarised by treatment group and time point. The data from all stages will be combined and reported together where appropriate. Continuous data will be reported using n (number of observations), mean, standard deviation (SD), median, minimum, and maximum values. Categorical data will be reported using number and percentage of patients. A comprehensive SAP will be developed and finalised before database lock and will describe the patient populations to be included in the analyses, and 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 at each stage of the study. 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 will be reported in the CSR.

9.4.1 Definition of Endpoints

Derivation of Biomarker Variables

The following primary biomarker variable will be calculated:

- Percent change from baseline in ER expression assessed by the manual H-score method after 5 to 7 consecutive days of AZD9833 treatment for Stage 1 and 2, and after 12 to 15 consecutive days for Stage 3.

The following secondary biomarker variables will be calculated:

- Percent change from baseline in PgR expression as assessed by manual H-score method after 5 to 7 consecutive days of AZD9833 treatment for Stage 1 and 2, and after 12 to 15 consecutive days for Stage 3.
- Percent change from baseline in Ki-67 labelling index after 5 to 7 days of consecutive AZD9833 treatment for Stage 1 and 2, and after 12 to 15 consecutive days for Stage 3.

Other exploratory variables may be investigated.

9.4.2 Pharmacodynamic Analyses

The primary endpoint (percent change from baseline in ER expression) and the secondary endpoints (percent change from baseline in PgR expression and change in Ki-67 labelling index) will be listed and summarised appropriately, based on the PD analysis set. If data permit, an ANCOVA model will be fitted to each endpoint, with baseline value, day of biopsy and dose group included in the model. Estimates of the LS mean percent change taken from the model will be presented together with 80% CIs. Normality of the data will be assessed, and if it is judged that the data do not adequately follow a normal distribution, then the use of the natural log transformed data (ratio), or a non-parametric approach could replace the untransformed analysis as the primary approach. It is expected that the distribution of the Ki-67 index data will not be normally distributed (Robertson et al 2013, Robertson et al 2020b), hence Ki-67 index data will be naturally log-transformed before being analysed.

Sensitivity analyses, eg, a non-parametric approach may be performed as necessary and will be fully detailed in the SAP, along with any subgroup analyses.

9.4.3 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. Appropriate summaries of these data will be presented.

9.4.3.1 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 first 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 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.

9.4.3.2 Other Significant Adverse Events (OAEs)

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 OAEs and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data and other safety assessments 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.

9.4.3.3 Other Safety Data

Duration of exposure will be summarised appropriately.

Clinical chemistry, haematology, urinalysis, and vital signs 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) will be summarised over time in terms of absolute values and change from baseline.

Details of any death will be listed for all patients.

9.4.4 Pharmacokinetic Analyses

PK concentrations of AZD9833 will be summarised by treatment group, and PK concentration data will be listed for each patient in the PK analysis set. Data will be summarised by timepoint using appropriate descriptive statistics. Geometric mean (± geometric SD) concentration-time data will be presented (if applicable).

AZD9833 plasma concentration data from this study may be combined with data from other studies to conduct population PK exploratory analysis and may be detailed in a separate PK plan and reported separately.

9.4.5 Other Analyses

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

9.4.5.1 Exploratory Analyses

Exploratory endpoints will not be reported in the CSR.

9.4.6 Methods for Multiplicity Control

Not applicable.

9.5 Interim Analyses

There will be no interim statistical analyses during the conduct of Stage 1, except that which will be planned and reviewed by the SDMC at the completion of Stage 1. In Stage 2, there may be an interim analysis conducted once all patients have completed treatment in Georgia/Mexico (and with provision to include any patients who have been recruited from the UK at the date of data cut off) and on completion of recruitment. Analyses will be defined in the SAP.

9.6 Safety and Data Monitoring Committee

The SDMC will undertake review of the Stage 1 data prior to Stage 2 commencing. The doses, specific arms and sample size for Stage 2 will be determined by the SDMC based on data from Stage 1 and potentially using data on AZD9833 from other studies. A SDMC charter will include further detail outlining the membership and guidelines for transition from Stage 1 to Stage 2. Stage 2 will only occur in the UK after approval of a substantial protocol amendment including details of the rationale, the doses of AZD9833 and the study populations that will be evaluated in Stage 2 as recommended by the SDMC. Note that a fulvestrant arm will not be included in Stage 2 as decided by the SDMC.

In general, if Stage 1 doses produce a high degree of PD modulation versus historical fulvestrant control data, Stage 2 will likely focus on lower AZD9833 doses. Conversely, if Stage 1 doses produce a similar or lower degree of PD modulation compared with historical fulvestrant control data, Stage 2 will likely focus on higher AZD9833 doses. An alternative scenario is that the precision of the estimate of the primary endpoint from Stage 1 is insufficient, and the inclusion of additional patients in Stage 2 at the same doses from Stage 1 will provide additional clarity. Therefore, Stage 2 of the study makes provision for the examination of the biological effects of several different dose levels of AZD9833, or to evaluate additional patients at the dose levels examined in Stage 1.

Analysis of tumour samples will be batched and the resulting data reviewed on an ongoing basis throughout the study.

The rationale for the remit and scope of the SDMC will be summarised in the SDMC charter. The key data from Stage 1, and the SDMC advice is summarised in Sections 2.2.2.6 and 6.

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11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

It is advised that systemic atropine and systemic atropine-containing medicines are not administered to patients currently receiving AZD9833.

A 1 CCI [redacted]

Drugs that are known CCI [redacted] CCI [redacted] CCI [redacted] should not be combined with AZD9833.

A 2 Restrictions Regarding Drugs Affecting CCI [redacted] Metabolism

It is probable that AZD9833 is CCI [redacted] CCI [redacted] may increase or decrease exposure to AZD9833, respectively.

CCI [redacted] **should not be combined with AZD9833.**
CCI [redacted] **are permitted, but caution should be exercised, and patients monitored closely for possible drug interactions.**
CCI [redacted] **should be stopped at least 2 weeks before the first dose of AZD9833** CCI [redacted] **.**

The lists below provide examples of CCI [redacted]. These lists are not intended to be exhaustive, and similar restrictions will apply to other drugs that are known to modulate CCI [redacted]. 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 CCI [redacted] is essential (eg, to treat AEs) AZD9833 treatment should be discontinued.

Table 26 Drugs Known to be [redacted]

Strong [redacted] **(should not be combined)**	**Moderate [redacted]** **(permitted with caution)**
[redacted] [redacted]	[redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted] [redacted]

[redacted]

Table 27 Drugs Known to be CCI

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

CCI

A 3 Guidance for Drugs Whose Exposure May Be Affected by AZD9833

In vitro studies have shown that AZD9833 is CCI
CCI
CCI

Drugs which are CCI
CCI
should not be combined with AZD9833 and 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 CCI are permitted, but guidance for dose adjustments when combining with CCI should be followed, in accordance with their labels.

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

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

Table 28 below provides examples of CCI drugs. This list is not exhaustive.

Table 28 Examples of CCI Drugs

CCI	CCI	CCI
CCI	CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI	CCI CCI
CCI	CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI	-
CCI		

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

CCI	
CCI	**should not be combined with AZD9833 CCI .**
CCI	**should be stopped at least 2 weeks before the first dose of AZD9833.**

Preliminary PK data from CCI of SERENA-1 CCI Therefore, prescribing advice for drugs that are known CCI

CCI should be consulted. Examples of such drugs in clinical practice are provided in Table 29; please note drugs already excluded by other concomitant medication restrictions may not be listed below.

Table 29 CCI CCI with Label Advice Regarding Combination with CCI

Drug	USPI	SmPC
CCI	*No label comment*	See label advice
CCI	See label advice	See label advice
CCI	See label advice	See label advice
CCI	See label advice	*No label comment*
CCI	See label advice	See label advice
CCI	See label advice	See label advice
CCI	See label advice	*No label comment*

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

A 4 Drugs Known to Reduce Heart Rate

Patients already taking drugs known to reduce 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:

- CCI
- CCI
- CCI
- CCI

Appendix B Regulatory, Ethical and Study Oversight Considerations

B 1 Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines
- Applicable ICH and GCP Guidelines
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator's 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 Title 21 of the 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.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

- For all studies except those utilizing medical devices investigator safety reports must be prepared for 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 and will notify the IRB/IEC, if appropriate according to local requirements.

B 2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

B 3 Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the 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 Title 21 of the CFR 50, local regulations, ICH guidelines, 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.

CCI [redacted]

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

CCI [redacted]

B 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.

B 5 Committees Structure

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

An independent AstraZeneca SDMC will consider the Stage 1 data from this study, and prior to commencing Stage 2.

B 6 Dissemination of Clinical Study Data

A description of this clinical study will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical study 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.

B 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.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data. The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).

Study monitors will perform ongoing source data verification to confirm that data entered into the 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.

B 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.

B 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 treatment development.

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

B 10 Publication Policy

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

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data.

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

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

C 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 DILI caused by the study treatment.

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

C 2 Definitions

Potential Hy's Law (PHL)

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

Hy's law (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.

C 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 C 2 for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory CRF.

C 4 Follow-Up

C 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.

C 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 TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study 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.

C 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 AstraZeneca standard processes.

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

C 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 C 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 C 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 TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

REFERENCES

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

Appendix D Adverse Event Definitions and Additional Safety Information

D 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.

D 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. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious** AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new malignant tumour (ie, it is not the tumour for which entry into the study is a criterion and that

is being treated by the 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.

All SAEs must be recorded and reported to the Sponsor or designee within 24 hours.

D 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).

D 4 Hospitalisation

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

D 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 intravenous 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.

D 6 Intensity Rating Scale

The grading scales found in the revised National Cancer Institute CTCAE latest version (at the start of the study) will be utilised for all events with an assigned CTCAE grading. This version will be used throughout the study, irrespective of whether a later version becomes available. 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 D 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 D 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 D 2.

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

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

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

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

The causality assessment is performed based on the available data including enough information to make an informed judgement. With 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.

D 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 recognised that could have led to an error.

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

- Drug name confusion.
- Dispensing error (eg, medication prepared incorrectly) even if it was not actually given to the participant.
- Drug not administered as indicated, for example, wrong route or wrong site of administration.
- Drug not taken as indicated (eg, tablet dissolved in water when it should be taken as a solid tablet).
- Drug not stored as instructed (eg, kept in the fridge when it should be at room temperature).
- Wrong participant received the medication (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 E Handling of Human Biological Samples

E 1 Chain of Custody of Biological Samples

A full chain of custody is maintained for all samples throughout their life-cycle.

The Investigator at each site keeps full traceability of collected biological samples from the patients while in storage at the site 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 AstraZeneca-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.

E 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, the action documented, and the signed document returned to the study site.

E 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, HIV 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.

Appendix F Genetics

F 1 Use/Analysis of DNA

Genetic 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 DNA analysis from consenting patients.

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

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

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

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

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

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

F 2 Genetic Research Plan and Procedures

Selection of Genetic Research Population

Study Selection Record

All patients will be asked to participate in this genetic 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 genetic research, patients must fulfil all of the inclusion criteria described in the main body of the CSP and provide informed consent for the genetic sampling and analyses.

Exclusion Criteria

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

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

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 Genetic Research

The blood sample for genetic research will be obtained from the patients at screening or on Day 1. Although DNA 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 genetic analysis. If for any reason the sample is not drawn at screening or on Day 1, it may be taken at any visit until the day of surgery. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and Storage of DNA Samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain 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. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated

organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).

The link between the 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 DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

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

Informed Consent

The genetic component of this study is optional, and the patient may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study and the genetic 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 site. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely withdraw from the genetic aspect of the study at any time.

Patient Data Protection

AstraZeneca will not provide individual genotype 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 genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic 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 genetic data. In addition, Regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

Data Management

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

Statistical Methods and Determination of Sample Size

The number of patients that will agree to participate in the genetic 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. An SAP may be prepared where appropriate.

Appendix G Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis, including COVID19 Outbreak

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

G 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections G 2 to G 5. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

G 2 Rescreening of Participants to Reconfirm Study Eligibility

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

In addition, during study disruption there may be a delay between confirming eligibility of a participants and either enrolment into the study or commencing of dosing with study intervention. If this delay is outside the screening window specified in Section 1.3 the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to rescreen a participant in addition to that detailed in Section 5.5. The procedures detailed in Section 5.5 must be undertaken to confirm eligibility using the same randomisation number as for the participant.

G 3 Home or Remote Visit to Replace On-site Visit (Where Applicable)

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

G 4 Telemedicine Visit to Replace On-site Visit (Where Applicable)

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

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs and concomitant medication to be reported and documented.

G 5 Data Capture During Telemedicine or Home/Remote Visits

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

G 6 COVID-19 Risk Assessment

The safety of participants is of primary importance. Any potential risks of participating in the study, particularly with the added challenges due to the COVID-19 outbreak, should be weighed against the anticipated benefit (see also principle 2.2 of ICH GCP). Investigators are advised to use clinical judgment in determining infection prevention precautions for study participants.

The emergence of SARS-CoV-2 presents a potential safety risk for cancer patients. Participants enrolling in this study may require more frequent visits to the site for study treatment administration and for study assessments compared to participants receiving standard of care. Therefore, several risk mitigation factors have been implemented related to study conduct during the COVID-19 outbreak, for patient management in an event of COVID-19, and actions to be taken on study treatment (see Section G 9).

Notably, participants with active COVID-19 infection confirmed by local laboratory testing will not be eligible for study enrolment (see CSP Section 5.2, Exclusion Criterion 4).

G 7 Potential Risks During COVID-19

Every effort should be made to follow the CSP. Section G 10 provides a dose modification and management plan for participants with confirmed or suspected COVID-19 who are being treated with study intervention AZD9833. The risk-benefit assessment should be carefully considered for each participant enrolling in the study based on the known safety risks related to COVID-19, individual needs, and local guidelines and restrictions. Investigators must continue to use their best clinical judgment in determining the most optimal care for participants and utmost diligence in determining their eligibility for study participation, continued study treatment, and overall assessment of benefit/risk of study treatment or participation.

The Sponsor must be promptly notified of a site's inability to perform study activities due to COVID-19 outbreak in order to minimise any potential risks.

G 8 New Participant Enrolment

Study sites may continue to recruit new participants into the study provided the following activities to preserve study integrity can be met:

- Upon discussion with the site monitor, the study site has confirmed the ability to enrol and manage new participants effectively and in compliance with the protocol.
- Data will continue to be entered into the eCRF and queries resolved in a timely manner.

Per CSP Exclusion Criterion 4 (see CSP Section 5.2), participants with severe or uncontrolled systemic diseases, including but not limited to, ongoing or active infection are not eligible for the study participation and hence such participants (including those who have confirmed COVID-19) should not be included for study participation.

G 9 Study Treatment Administration

If an AE or SAE is associated with COVID-19, the investigator should determine whether the participants' treatment with investigational product should continue, be interrupted, or be discontinued in accordance with the CSP.

Adverse events, SAEs, cycle delays, and/or treatment suspensions associated with COVID-19 along with logistical issues should be reported according to the eCRF Completion Guidelines.

For dosing discontinuations, where applicable, the dosing discontinuation guidelines should be followed, and the End of Treatment Form(s) completed

G 10 Ongoing Participants

Participants receiving study intervention should continue to undergo safety assessments prior to dosing in accordance with the CSP. In case it is not feasible to perform safety assessments, study intervention should be interrupted until such assessments can be completed.

G 10.1 If a Participant has an Event Suspected to be COVID-19

Delay or omit study intervention as appropriate and test for COVID-19 per local health authority or institutional guidance.

- Signs and symptoms of COVID-19 include but are not limited to new onset of fever, new or worsening cough, shortness of breath, difficulty breathing, and sometimes abnormal chest imaging and may be similar to those of an imAE.
- In accordance with the CSP and the TMGs for imAEs, thorough evaluation should be performed to accurately identify the underlying pathology in case an AE is encountered for a participant.
- If COVID-19 is ruled out, study intervention may be resumed per the CSP.
- If COVID-19 **is confirmed or diagnosis still suspected after evaluation**, manage COVID-19 per local guidance until full recovery.

G 10.2 Participants with Confirmed COVID-19

Participants with confirmed COVID-19 (by local laboratory testing and/or combination of key symptoms) should have study intervention withheld and COVID-19 managed per local guidance.

In case of confirmed COVID-19 and a simultaneous imAE requiring treatment, investigators are advised to apply clinical judgement regarding the use of corticosteroids. This also includes the consideration of alternate immunosuppressive agents other than corticosteroids for imAE management, depending on the individual participant's presentation (Curigliano et al 2020).

G 10.3 Restarting Study Intervention

Study intervention must not be resumed until recovery from COVID-19 (eg, confirmed by imaging, lab testing, and/or absence of symptoms) and COVID-19-specific treatment has been completed per local guidance.

The study clinical lead should be contacted if any additional guidance or clarification is needed.

G 10.4 Vaccination Against COVID-19

Protocol restrictions applying to live attenuated vaccines are relevant for live attenuated COVID-19 vaccines as well. Investigators should apply their discretion assessing the risk-benefit of other types of COVID-19 vaccines for participants in clinical trials. Ideally, administration of the vaccine should be done on a different day other than the day of study drug administration to differentiate any potential AEs seen from the vaccine and study drug. The administration of the vaccine and any potential AEs associated with the vaccine are to be documented on the concomitant medication and AE eCRFs, respectively.

G 11 References

Curigliano et al 2020
Curigliano G, Banerjee S, Cervantes A, Garassino MC, Garrido P, Girard N, et al. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. Ann Oncol. 2020;31(10):1320-35.

Appendix H Abbreviations

Abbreviation or special term	Explanation
ADL	Activities of daily living
AE	Adverse event
AI	Aromatase inhibitor
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
$AUC_{0\text{-}8h}$	Area under the plasma concentration-time curve from time of dose to 8 hours
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve from time of dose to 24 hours
$AUC_{0\text{-}inf}$	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
B	Blood
bpm	Beats per minute
CBR	Clinical benefit rate
CBR_{24}	Clinical benefit rate at 24 weeks
CDK4/6	Cyclin-dependent kinase 4 and 6
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organisations of Medical Sciences
CISH	Chromogenic in situ hybridization
CK	Creatine kinase
C_{max}	Maximum plasma drug concentration
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus 2019 disease
CRF	Case report form (electronic/paper)
CRO	Contract Research Organisation
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CCI	CCI [redacted]
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	Circulating tumour DNA

Abbreviation or special term	Explanation
CYP	Cytochrome P450
DCO	Data cut-off
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
DMPK	Drug Metabolism and Pharmacokinetics
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
ER	Oestrogen receptor
ERα	Oestrogen receptor alpha
ERT	E-Research Technology
ESR1	Oestrogen receptor 1
FAS	Full analysis set
FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescence in situ hybridization
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
Hb	Haemoglobin
HCP	Health care professional
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
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
imAE	Immune-mediated adverse event
INN	International Non-proprietary Name
INR	International normalised ratio

Abbreviation or special term	Explanation
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
IRB/IEC	Institutional Review Boards/Independent Ethics Committees
ITT	Intention-to-treat
ISH	In situ hybridisation
IWRS	Interactive web response system
Ki-67	Antigen Ki-67
LS mean	Least-squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency
mRNA	Messenger ribonucleic acid
NEI VFQ-25	National Eye Institute 25-Item Visual Function Questionnaire
CCI	CCI
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamic(s)
PFS	Progression-free survival
PGI-BR	Patient Global impression of Benefit-Risk
PGIC	Patient Global Impression of Change
PGIS	Patient global impression of severity
PGI-TT	patient global impression of treatment tolerability
CCI	CCI
PgR	Progesterone receptor
PHL	Potential Hy's law
PK	Pharmacokinetic(s)
PO	Per os (oral administration)
QD	Once daily
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 Tumors
SAE	Serious adverse event

Abbreviation or special term	Explanation
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SDMC	Safety and Data Monitoring Committee
SERD	Selective oestrogen receptor down-regulator/degrader
SISH	Silver in situ hybridisation
SoA	Schedule of Activities
SmPC	Summary of product characteristics
SOC	System organ class
SOP	Standard operating procedure
S/P	Serum/plasma
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reactions
$t_{1/2}$	Terminal elimination half-life
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
t_{max}	Time to reach maximum plasma concentration
TPV	Third party vendor
U	Urine
ULN	Upper limit of normal
USPI	United States prescribing information
WBDC	Web-based data capture
WHO	World Health Organization

Appendix I Protocol Amendment History

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

Amendment 1 (28 Sep 2021)

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

This global amendment has been issued in order to implement recommendations made by the SDMC and to consolidate into the global CSP, local changes made to the CSP in response to requests from the MHRA.

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Sections 1.1; 1.3 (Table 1); 2.1; 2.3.2; 3; 4.1.1; 4.1.2; 4.1.2.1; 6.1.1; 8 (text and Table 14); 8.5.1 (text and Figure 4); 9.2.1; 9.3 (Table 16); 9.4.4; and 9.6	Text has been amended to confirm Stage 2 will only occur in the UK after approval of a substantial protocol amendment including details of the rationale, the doses of AZD9833 and/or fulvestrant, and the study populations that will be evaluated in Stage 2 as recommended by the SDMC. Assessments and text related to the Stage 2 fulvestrant arm have been deleted.	As advised by the MHRA	Substantial
Sections 1.1 and 3 (Table 10)	The objectives have been modified to remove fulvestrant treatment from the first of the secondary objectives and the last of the exploratory objectives.	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 1.1	The number of patients randomised to each dose group has been updated.	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 1.1, 6.3, and 4.1.2.1	The randomisation will be stratified based on country (UK / Georgia and Mexico).	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 1.1	The estimated date of last patient completed (end of Stage 2) has been updated to Q1 2023.	To reflect current recruitment timelines	Non-substantial
Sections 1.1 and 4.1.1	Heart rate monitor text reworded for consistency with the SoA and Section 8.2.5.	To improve clarity	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Sections 1.1; 1.3 (Table 1); and 4.1.1 and 4.1.2.	Clarification regarding the timing of the follow-up visit after the biopsy visit for patients going on to subsequent neoadjuvant therapy is provided.	To provide clarification on the timing of the follow-up visit in patients planned to receive neoadjuvant therapy prior to planned surgery.	Non-substantial
Sections 1.1; 1.2 (Figure 2); 1.3 (Table 1); 4.1; 4.1.2.2; 5.1; and 6.3.	Text/sections regarding the optional treatment group in pre-menopausal women in Stage 2 of the study have been removed.	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 1.2 (Figure 2)	Figure has been amended to show the Stage 2 doses as advised by the SDMC for Stage 2.	As per, or as a consequence of, recommendations by the SDMC	Substantial
Sections 1.1; 1.3 (Table 1); and 2.3.2	'Study entry' updated to 'the screening visit date'/ 'screening'.	To provide clarification	Non-substantial
Sections 2.1; 2.2.2.2; 2.2.2.5; 2.2.2.6; 4.1.2; 6.1.1 (Table 12); and 9.2	Updated to include details of the rationale and the doses of AZD9833 that will be evaluated in Stage 2.	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 2.2.2	Clarification that safety information remains representative despite recruiting over 500 patients to the study.	To provide clarification	Non-substantial
Section 2.2.2.3	After a single AZD9833 dose, the time to reach t_{max} was achieved approximately 2 to 4 hours post-dose, with a $t_{1/2}$ of approximately 11 (previously 10) to 15 (previously 13) hours across all dose groups.	Updated data	Non-substantial
Sections 2.2.2.4 and 9.2	ER updated to ERα.	For clarification	Non-substantial
Section 2.3.2 Fulvestrant (applicable to Stage 2 only); Section 6.6.2 Dose Modification for Fulvestrant; Section 6.5.1 Drugs Affecting CCI [redacted] CCI [redacted]; and Section 8.4.2 Fulvestrant	Sections/text deleted.	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 2.3.2 Overall Benefit/Risk and Ethical Assessment (previously Section 2.3.3)	Text updated to confirm that Stage 1 data support the overall risk/benefit and ethical assessment above, and the statements are unmodified for the conduct of Stage 2.	Updated information	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 4.1.2	Section heading moved to include final paragraph of Section 4.1.1. Text added to explain Stage 2 of the study.	As per, or as a consequence of, recommendations by the SDMC	Substantial
Sections 4.1.3 and 11 (Appendix G)	New sections added to provide guidance on changes related to mitigation of study disruptions due to cases of civil crisis, natural disaster, or public health crisis, including COVID 19 outbreak.	As per revised AZ template	Substantial
Section 5.2 (Exclusion criterion 8)	'History of hypersensitivity to active or inactive excipients of fulvestrant for Stage 2 if relevant' has been deleted.	As per, or as a consequence of, recommendations by the SDMC	Non-substantial
Section 5.4.1	Text relating to contraceptive measures has been deleted in line with the removal of pre-menopausal women from the protocol.	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 5.4.2	'There are no food restrictions for fulvestrant (if applicable in Stage 2).' was deleted.	As per, or as a consequence of, recommendations by the SDMC	Non-substantial
Sections 6.2; 8.5.1.1; and 8.5.1.2.	Text relating to the storage of fulvestrant, and the handling of samples for fulvestrant PK analyses have been deleted.	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 6.3	Text related to the randomisation of patients for Stage 2 has been updated.	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 6.5.3 CCI CCI	New section added presenting preliminary PK data from SERENA-1 suggesting the possibility that AZD9833 may CCI	New information	Substantial
Section 6.5.8	Text modified to clarify that sex hormone containing drugs or other drugs that may affect sex hormone status or disease response are not permitted during treatment (Day 1 to the biopsy day).	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 8.3.12 Pregnancy	Section deleted. Note this has resulted in the Medication Error section being renumbered to 8.3.12.	As per, or as a consequence of, recommendations by the SDMC	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 8.6.3	Additional details on the number of patients for whom paired tumour biopsies will be collected has been added for Stage 2 of the study. Reference to the collection of biopsy samples in Stage 2 patients receiving fulvestrant has been deleted.	As per, or as a consequence of, recommendations by the SDMC	Substantial
Sections 1.1 and 9.2	Update of the sample size determination in line with the revised dose groups to be included in the study.	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 9.4.5.1	Confirmation that exploratory endpoints will not be reported in the CSR.	Correction of typo	Non-substantial
Section 9.5	It has been added that an interim analysis may be conducted once all patients have completed treatment in Georgia/Mexico (and with provision to include any patients who have been recruited from the UK at the date of data cut off) and on completion of recruitment.	As per, or as a consequence of, recommendations by the SDMC	Substantial
Section 10 References	The reference list has been moved from Section 11 to come before the appendices (Supporting Documentation and Operational Considerations)	To maintain consistency with the AstraZeneca CSP template	Non-substantial
Section 11 (Appendix A3)	The appendix has been modified to provide advice regarding the concomitant use of CCI [redacted].	New information	Substantial
Section 11 (Appendix D2)	The wording in this section has been modified to change 'congenital abnormality or birth defect' to 'congenital anomaly or birth defect'.	To maintain consistency within the document	Non-substantial
Section 11 (Appendix I)	A new appendix has been created which will be used to include the details of any prior global amendment.	To maintain consistency with the AstraZeneca CSP template	Non-substantial

CSR = Clinical study report; CCI [redacted]; ERα = Oestrogen receptor alpha; MHRA =Medicines and Healthcare Products Regulatory Agency; Q1 = Quarter 1; CCI [redacted]; PK = Pharmacokinetics; SDMC = Safety and Data Monitoring Committee; SoA = Schedule of Activities; t½ = Terminal elimination half-life; t_{max} = Time to reach maximum plasma concentration; UK = United Kingdom

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Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
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