Parexel International

AstraZeneca

D8530C00003

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)

Statistical Analysis Plan

Version: Final 4.0

Parexel Project Number: 247887

TABLE OF CONTENTS

1 INTRODUCTION 8

2 STUDY OBJECTIVES 8

2.1 PRIMARY OBJECTIVE 8
2.2 SECONDARY OBJECTIVES 9
2.3 EXPLORATORY OBJECTIVES 9

3 INVESTIGATIONAL PLAN 10

3.1 STAGE 1 10
3.2 STAGE 2 11
3.3 STAGE 3 12
3.4 END OF STUDY 13
3.5 PLANNED ANALYSIS 13

4 STATISTICAL METHODS 14

4.1 DATA QUALITY ASSURANCE 14
4.2 GENERAL DATA PRESENTATION CHARACTERISTICS 14
4.3 GENERAL VARIABLES 15
4.3.1 Study Day Definitions 15
4.3.2 Handling missing data 16
4.4 SOFTWARE 17
4.5 ANALYSIS SETS 17
4.6 STUDY PATIENTS 19
4.6.1 Disposition of Patients 19
4.6.2 Protocol Deviations 19
4.6.3 Demographic and Other Baseline Characteristics 20
4.7 MEDICAL AND SURGICAL HISTORY 21
4.8 CONCOMITANT MEDICATIONS AND TREATMENT 21
4.9 CURATIVE INTENT SURGERY 22
4.10 PHARMACODYNAMIC EVALUATION 22
4.10.1 ER and PgR 22
4.10.2 Ki-67 Labelling Index 24
4.11 SAFETY EVALUATION 25
4.11.1 Extent of Exposure 25
4.11.2 Adverse Events 26
4.11.3 Deaths 27
4.11.4 Clinical Laboratory Evaluation 27
4.11.5 Physical Examination findings 28
4.11.6 Vital Signs 29
4.11.7 ECG Variables 29
4.11.8 CCI *30*
4.12 PHARMACOKINETIC EVALUATION 30
4.13 SAMPLE SIZE CONSIDERATIONS 31
4.14 SDMC ANALYSIS AND REPORTING 32
4.15 INTERIM ANALYSIS 33
4.16 OTHER ANALYSIS 33

5 REFERENCES 33

REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	13 Nov 2020	New document
2.0	4 Apr 2022	Updated throughout to remove reference to fulvestrant and clarify Stage 2 design following protocol Version 2.0 Section 4.3.1; Table 2 Corrected the Visit 5, Analysis visit as 'Follow-up' Section 4.5; Table 5 Updated footnote to clarify reporting analysis sets. Section 4.6.3 The age group categories revised to < 50, 50-59, 60-69, ≥ 70. 'breast' is added as primary cancer location. The presentation of neurological assessment was updated to 'listing only'. Section 4.8 'concomitant procedures' were added to the summary list. Section 4.9 New section 4.9 Curative intent surgery was added. Section 4.10 Updated the section with the strategy to handle multiple tumour blocks data at a single visit. Section 4.10.1 Additional sensitivity analyses for HER2 positive patients were added. Section 4.10.2 Additional sensitivity analysis criteria for Ki67 was added. Section 4.11.2 References to treatment emergent adverse events or TEAEs were updated to adverse events or AEs throughout. All references to 'casually' related AEs were updated to 'possibly' related AEs. Section 4.11.7 The section has been updated to include box plots for percentage change from baseline

		Appendix A Appendix A: Table of contents with the list of deliverables was added.
3.0	03 Jan 2023	Section 1 Added the treatment duration for Stage 3 Added the sample collection strategies for Stage 3. Updated the CSP version to 3.0 Updated eCRF version to 7 (Sep 5, 2022) Section 2 Updated with Stage 3 treatment objective (12 to 15 days of treatment) Section 3 Updated with Stage 3 investigational plan. Added figure 3. Section 3.5 Corrected the number of patients for interim analysis to 60 in Table 1 Section 4.2 Added a paragraph explaining how the data from Stage 1 , 2 and 3 will be summarised and presented. Section 4.3.1 Added analysis visit mapping table for Stage 3 Section 4.6.1, 4.6.3, 4.10.1, 4.10.2, 4.11, 4.11.6, 4.11.7, 4.12 Elaborated how the respective data from Stages 1,2 and 3 will be summarized. Section 4.10.1, 4.10.2 Added how the percentage change from baseline in biomarker scores will be analysed and least square means will be presented. Section 4.15 Added the following sentence No formal interim analysis will be performed during Stage 3.
4.0	Date of last signature	Section 4.10.2 Added the following sensitivity analysis to the Ki67 labelling index • Any patients with an ER H-score < 10 on their pre-treatment biopsy.

		• Any patients with an ER H-score < 10 on their pre-treatment biopsy or any patients with a Ki-67 labelling index < 5% from their pre-treatment biopsy. Added a new Table 4 summary of deviations and actions. Updated the table number of subsequent tables. Updated the eCRF version with the latest version number and date. Added Final stage 3 analysis to Table 1 summary of analyses during study conduct. <u>Section 4.5</u> Elaborated the conditions for subjects to be included in the PD analysis set

LIST OF ABBREVIATIONS

AEs	adverse events
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine transaminase
ANCOVA	analysis of covariance
AST	aspartate transaminase
AZ	AstraZeneca
BLQ	below the limit of quantification
BMI	body mass index
CI	confidence interval
CK	creatine kinase
cm	centimetres
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse events
CV	coefficient of variation
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic Case Report Form
ER	oestrogen receptor
ESR 1	oestrogen receptor 1
FAS	full analysis set
GE	Georgia
HER2	epidermal growth receptor 2
IHC	immunohistochemistry
kg	kilogram
LLoQ	lower limit of quantification
MedDRA	Medical Dictionary or Regulatory Affairs
mmHg	millimeter of mercury
mRNA	messenger ribonucleic acid
MX	Mexico
NC	not calculable
NE	not evaluable
NQ	not quantifiable
NR	not reportable
NS	no sample
OAEs	other significant adverse events
PD	pharmacodynamic
PgR	progesterone receptor
PK	pharmacokinetic
PO	orally administered
PT	preferred term

PTT	prothrombin time
PXL	PAREXEL®
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RDI	Relative Dose Intensity
SAEs	serious adverse events
SBP	systolic blood pressure
SD	standard deviation
SDMC	Safety and Data Monitoring Committee
SOC	system organ class
TBL	total bilirubin
TEAE	treatment emergent adverse events
TMF	trial master file
UK	United Kingdom
ULN	upper limit of normal
ULoQ	upper limit of quantification
WHO	World Health Organisation
WHODD	World Health Organisation Drug Dictionary

1 INTRODUCTION

This is a randomised, open-label, parallel-group, multicentre study which has three stages to help investigating the biological effects of different doses of AZD9833 orally administered (PO) once daily (QD), in women with primary breast cancer awaiting curative-intent surgery, for 5 to 7 days consecutively in Stage 1 and 2; for 12 to 15 days consecutively in Stage 3. Women with histologically proven, oestrogen receptor-positive (ER-positive), human epidermal growth receptor 2-negative (HER2-negative) invasive breast cancer involving a palpable tumour of any size, or a tumour with an ultrasound assessed diameter ≥ 1.0 cm and fulfilling all the inclusion criteria and none of the exclusion criteria will be enrolled in the study.

In Stage 1, approximately twenty-four evaluable post-menopausal women will be randomly assigned in a 1:1 ratio to two dose groups (75 mg PO QD for 5 to 7 days and 150 mg PO QD for 5 to 7 days) of AZD9833. Following completion of Stage 1 and availability of immunohistochemistry (IHC) data, the Safety and Data Monitoring Committee (SDMC) will review the Stage 1 data, potentially alongside the emerging data from any relevant ongoing AZD9833 studies and decide whether to proceed with Stage 2 based on the guidelines provided in the SDMC charter.

Following the review of the Stage 1 data, the SDMC has advised that Stage 2 will comprise of approximately thirty-six evaluable post-menopausal women from Georgia (GE) and Mexico (MX), randomly assigned in a 1:1:1 ratio to three dose groups (75 mg PO QD for 5 to 7 days, 150 mg PO QD for 5 to 7 days and 300 mg PO QD for 5 to 7 days) of AZD9833 and approximately twenty-four post-menopausal women from the United Kingdom (UK) randomly assigned in a 1:1 ratio to two AZD9833 dose groups (75 mg PO QD for 5 to 7 days and 150 mg PO QD for 5 to 7 days).

Following the interim analysis after Georgia and Mexico completed recruitment in Stages 1 and 2, the SDMC has advised that Stage 3 of the study should be conducted to include forty-eight evaluable post-menopausal women from Georgia (GE) and Mexico (MX), randomly assigned in a 1:1 ratio to two AZD9833 dose groups (75 mg PO QD for 12 to 15 days, 150 mg PO QD for 12 to 15).

This statistical analysis plan (SAP) provides the technical elaboration of the statistical analysis of pharmacodynamic (PD), safety and pharmacokinetic (PK) data.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 3.0 (04 July 2022)
- electronic Case Report Form (eCRF), D8530C00003 Version 8.0 (Nov 30, 2022)

Specifications for tables, figures and listings are contained in a separate document.

2 STUDY OBJECTIVES

2.1 Primary Objective

Primary Objective:	**Endpoint/Variable:**
To explore the ER pharmacodynamic effects of AZD9833 between pre- and on-treatment tumour samples in women with early breast cancer after 5 to 7 consecutive days of AZD9833 treatment for Stage 1 and 2, and after 12 to 15	Change from baseline in ER expression between pre- and on-treatment tumour samples measured by immunohistochemistry (IHC) and assessed by the manual H-score method.

consecutive days of AZD9833 treatment for Stage 3.

2.2 Secondary Objectives

Secondary Objectives:	Endpoint/Variables:
To explore the progesterone receptor (PgR) and Ki-67 pharmacodynamic effects of AZD9833 between pre- and on-treatment tumour samples in women with early breast cancer after 5 to 7 consecutive days of AZD9833 treatment for Stage 1 and Stage 2, and after 12 to 15 consecutive days of AZD9833 treatment for Stage 3.	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 (ECG).
To evaluate the PK effect of AZD9833 in the patient population.	Plasma concentrations of AZD9833 on the biopsy day.

2.3 Exploratory Objectives

Exploratory Objectives:	Endpoint/Variables:
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 of AZD9833 treatment for Stage 1 and Stage 2; and 12 to 15 days of AZD9833 of treatment for Stage 3.
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 [redacted]	Change from baseline in ER, PgR, and Ki-67, as assessed by manual and computerized methods after 5 to 7 days of AZD9833 for Stage 1 and Stage 2; and 12 to 15 days of AZD9833 treatment for Stage 3 in patients according to other baseline characteristics, for example [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 messenger ribonucleic acid (mRNA) expression of	Change from baseline in mRNA expression of ESR1 and a panel of oestrogen-regulated genes

oestrogen receptor 1 (ESR1) and a panel of oestrogen-regulated genes in tumour tissue.	after 5 to 7 days of AZD9833 treatment for Stage 1 and Stage 2; and 12 to 15 days of AZD9833 treatment for Stage 3.
To assess the effects of AZD9833 on other tumour biomarkers including deoxyribonucleic acid (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 (e.g. autoantibodies).
To explore the relationship between AZD9833 plasma exposure and changes in tumour tissue markers and circulating biomarkers such as tumour DNA, mRNA, proteins or immune biomarkers (e.g. autoantibodies).	PK/PD modelling of AZD9833 plasma exposure and changes in tumour tissue markers and 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 clinical study report (CSR).
To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (i.e., 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.

All exploratory endpoints will be reported outside of the CSR and are therefore not described further within this SAP.

3 INVESTIGATIONAL PLAN

3.1 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)

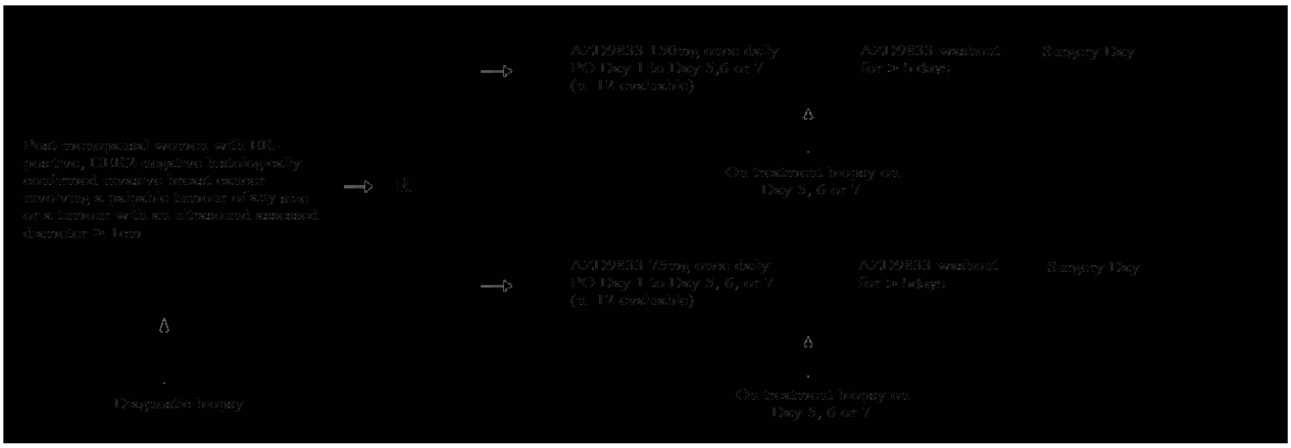
During the treatment period the patients will attend visits on:

Day 1
Day 5, 6 or 7 for an on-treatment imaging-guided biopsy
Day of surgery (following a washout period of at least 5 days after taking the last dose of AZD9833 on Day 5, 6 or 7, the patients will undergo curative-intent surgery i.e. study day ≥ 11)

28 day safety follow-up (after last dose of the study treatment for AZD9833)

The general study design of Stage 1 is summarised in Figure 1

Figure 1 : Study Design Stage 1



3.2 Stage 2

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:

Group 1: AZD9833 (75 mg, PO, once daily for 5 to 7 days; approximately 24 evaluable patients [12 UK])
Group 2: AZD9833 (150 mg, PO, once daily for 5 to 7 days; approximately 24 evaluable patients [12 UK])
Group 3: AZD9833 (300 mg, PO, once daily for 5 to 7 days; approximately 12 evaluable patients)

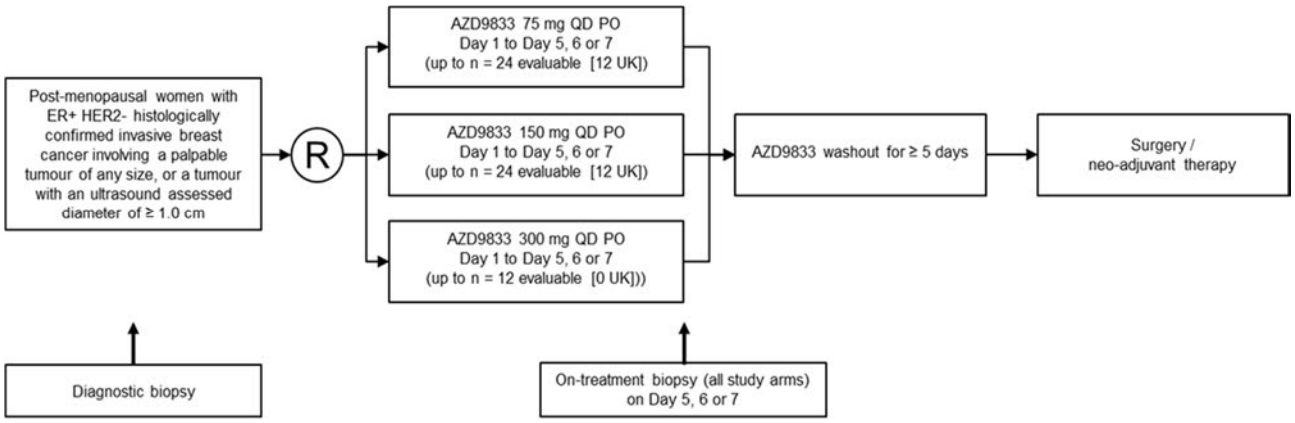
During the treatment period, patients will attend study visits on:

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)
28 day safety follow-up (after last dose of the study treatment for AZD9833)

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.

The general study design of Stage 2 is summarised in Figure 2.

Figure 2: Study Design Stage 2



3.3 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. 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:

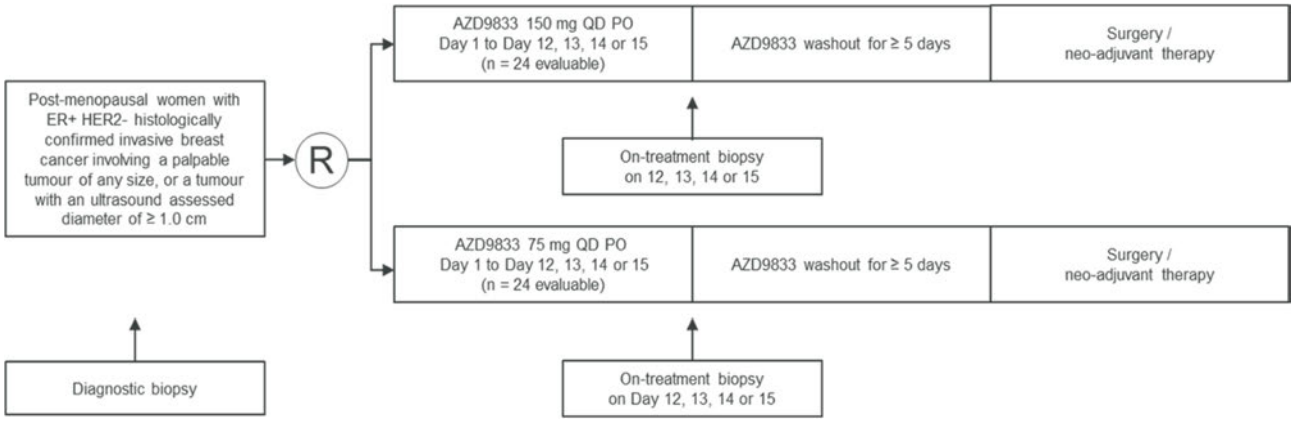
Group 1: AZD9833 (75 mg, PO, once daily for 12 to 15 days; approximately 24 evaluable patients).
Group 2: AZD9833 (150 mg, PO, once daily for 12 to 15 days; approximately 24 evaluable patients).

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

Day 1
Day 7
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 6th day following the last dose of AZd9833 (with a +3 day window).
28 day safety follow-up (after last dose of the study treatment for AZD9833)

The general study design of Stage 3 is summarised in Figure 3

Figure 3: Study Design Stage 3



3.4 End of Study

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.

3.5 Planned Analysis

The study is open-label, and so all AstraZeneca (AZ) and Parexel (PXL) team members involved in this study will be unblinded throughout. The details of the analyses planned during the conduct of this study are outlined in Table 1.

Table 1: Summary of Analyses during Study Conduct

Analysis	Trigger/Timepoint	Data included
End of Stage 1: Review by the SDMC	Upon completion of Stage 1 and availability of IHC data.	Data from Stage 1, including: Primary endpoint Key secondary endpoints Key safety data
Interim analysis Stage 2	Upon study completion of all patients recruited from Georgia and Mexico	Key data from Stage 1 and Stage 2, to include approximately 60 patients from Georgia and Mexico, and any available data from the UK patient population. Data to include: Primary endpoint Key secondary endpoints Key safety data
Final Stage 3 analysis[a]	Upon study completion of all patients recruited from Georgia and Mexico	Key data from Stage 3, to include approximately 48 patients from Georgia and Mexico, and any available data from the UK patient population. Data to include: Primary endpoint

		Key secondary endpoints Key safety data
Final analysis and CSR[a]	Following completion of the study and final database lock	All data from Stage 1, Stage 2 and Stage 3

[a] In the event that UK stage 2 completes ahead of stage 3, a UK stage 2 specific interim analysis may be performed; Final stage 3 analysis and final analysis may be combined if appropriate

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity and in accordance with standard Parexel procedures.

4.2 General Data Presentation Characteristics

The data from all countries and stages will be combined and reported together. Stage 1 and Stage 2 data combined and Stage 3 data alone will also be reported separately. All data will be summarised by treatment group and timepoint.

Continuous data will be summarised using descriptive statistics (the number of patients [n], mean, standard deviation [SD], median, 25^{th} and 75^{th} percentiles [where appropriate], minimum and maximum unless otherwise stated). For log-transformed data it is more appropriate to present geometric mean (gmean), geometric coefficient of variation (CV), median, minimum and maximum.

For continuous data, the mean, median and gmean will be rounded to one additional decimal place compared to the original data. The SD and geometric CV will be rounded to two additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data. The maximum number of decimal places reported will be four for any summary statistic.

Categorical data will be summarised in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. Percentages will not be presented for zero counts. Unless otherwise stated, percentages will be calculated using the number of patients included in the analysis set for that treatment group as denominator and presented to one decimal place.

Confidence intervals (CIs), when presented, will generally be constructed at the 2 sided 80% level. CIs will be presented to one additional decimal place compared to the original data.

For safety, PD, and PK endpoints the last observation prior to the first dose of study treatment will be considered the baseline measurement unless otherwise specified. For assessments on the day of first dose where time is not captured, a nominal pre-dose indicator, if available, will serve as evidence that the assessment occurred prior to first dose. Assessments on the day of first dose where neither time nor a nominal pre-dose indicator are captured will be considered prior to first dose if such procedures are required by the protocol to be conducted before first dose.

Any information taken after first dose/administration of study medication will be regarded as post baseline information. If two visits are equally eligible to assess patient status at baseline (e.g., screening and baseline assessments both on the same date prior to first dose/administration), the average should be taken as the baseline value. For non-numeric laboratory tests (i.e. some of the urinalysis parameters) where taking an average is not possible then the best value will be taken as baseline as this is the most conservative. Where safety data are summarised over time, study day will be calculated in relation to date of first treatment. If no value exists before the first dose/administration, then the baseline value will be treated as missing.

In all summaries:

Change from baseline = post-baseline value - baseline value.
Percent change from baseline = (post-baseline value - baseline value)/baseline value × 100

For any variable subject to log transformation, the back transformed change from baseline, calculated and summarised on the log scale, will be presented as 'baseline scaled ratio' (BSR). Percentage change will then be calculated as (BSR – 1) x 100.

4.3 General Variables

4.3.1 Study Day Definitions

Study day 1 is defined as the date of first dose of study treatment.
For visits (or events) that occur on or after first dose of study treatment:
Study day = Date of visit [event] – Date of first dose of study treatment + 1.

For visits (events) that occur prior to first dose:
Study day = Date of visit [event] – Date of first dose of study treatment.

There is no study day 0 defined for this study.

For listings (such as AEs) that include the derivation "Days since last dose", days will be defined as:
Days since last dose = Event date – Date of last dose.

Where "Date of last dose" is defined as the date of dosing immediately preceding the event occurrence. Events that occur on the same day as the last dose of study treatment will therefore be described as occurring zero days from last dose of study treatment.

All visit-based summaries will use eCRF visits as shown in Table 2. There won't be any visit windowing defined for on-treatment visits for this study. If there is more than one value per patient within an analysis visit then the closest value to the intended visit date will be summarised, or the earlier, in the event the values are equidistant from the protocol intended visit date. The 28th day safety follow-up is from the last day of dose administration of AZD9833. Any adverse event and concomitant medication data collected after the last dose of study treatment until 28 ± 3 days will be included in the relevant summaries. For summaries of the minimum or maximum observed value whilst on treatment, all data recorded at any time point (including unscheduled visits) will have the potential to be summarised. All results will be presented by treatment group and by visit with descriptive statistics appropriate to the nature of the variables.

Table 2: Analysis visit mapping

For Stage 1 and Stage 2

eCRF visit	Protocol visit	Protocol visit window	Analysis visit
Visit 1	Screening[a]	Day -21 to Day 1 (pre-dose)	Baseline
Visit 2	First day of dosing[a]	Day 1 (pre-dose)	
Visit 3	Biopsy Day	Day 5, Day 6 or Day 7	Biopsy day
Visit 4	Surgery Day	≥ Day 11	Surgery day
Visit 5	28 Day follow-up after the last dose of the study treatment	≥Biopsy Day +25 days to ≤Biopsy Day +31 days	Follow-up

[a] The last non missing value obtained prior to the first dose/administration of study medication will be considered as baseline.

For Stage 3

eCRF visit	Protocol visit	Protocol visit window	Analysis visit
Visit 1	Screening[a]	Day -21 to Day 1 (pre-dose)	Baseline
Visit 2	First day of dosing[a]	Day 1 (pre-dose)	
Visit 3	Day 7	Day 7 (+ 3 days)	Day 7
Visit 4	Biopsy day	Day 12, Day 13, Day 14 or Day 15	Biopsy day
Visit 5	Surgery Day	≥ Day 18	Surgery day
Visit 6	28 Day follow-up after the last dose of the study treatment	≥Biopsy Day +25 days to ≤Biopsy Day +31 days	Follow-up

[a] The last non missing value obtained prior to the first dose/administration of study medication will be considered as baseline.

Listings will display all values contributing to a time point for a patient. The values used in the summary table for a patient will be highlighted, wherever applicable.

4.3.2 Handling missing data

Missing safety data will not be imputed.

Missing pharmacodynamics biomarker data will not be imputed since no missing data are expected for the primary pharmacodynamics biomarker variables. Patients are required to have evaluable paired tumour samples for the primary endpoint by central pathology assessment, patients who don't meet this criterion will be replaced.

In general, other than for the below described, or where otherwise specified in the particular analysis, missing data will not be imputed and will be treated as missing.

4.3.2.1 Imputation of Adverse Event and Concomitant Medication Start Date

Missing day: impute with the 1st of the month unless month and year are same as month and year of first dose of study drug then impute first dose date.
Missing day and month: impute with 1st January unless year is the same as first dose date then impute first dose date.
Completely missing: impute with date of first dose of study treatment, unless the end date suggests it could have started prior to this in which case impute with 1st January of the same year as the end date.

When imputing a start date ensure that the new imputed date is sensible i.e. is prior to the end date of the AE or medication.

4.3.2.2 Imputation of Adverse Event and Concomitant Medication End Date

Missing day: impute with the last day of the month, unless month and year are the same as month and year of last dose of study treatment, then impute with the last treatment date in that month.
Missing day and month: impute with 31st of December unless the year is the same as the year of last dose of the study treatment, then impute with the last treatment date of that year.
Completely missing: assume the event is still ongoing and do not impute any date.

Generally, the imputation of dates is to decide if an observation is treatment emergent for AEs or concomitant for medications. Flags will be retained in the database indicating where any

programmatic imputation has been applied, and in such cases, durations and study days will not be calculated.

4.3.2.3 Imputation of Laboratory Values Outside of Quantification Range

Values of the form of "< x" (i.e., below the lower limit of quantification [LLoQ]) or > x (i.e. above the upper limit of quantification [ULoQ]) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the listings. Values of "≤ x" or "≥ x" will be imputed as well.

4.4 Software

All report outputs will be produced using SAS® version 9.4 or later in a secure and validated environment

4.5 Analysis Sets

The Enrolled Analysis Set will include all patients who sign the informed consent form.

The **Full Analysis Set (FAS)** is defined as all randomised patients, with treatment groups assigned in accordance with the randomisation, regardless of the actual treatment received. Patients who are randomised, but do not subsequently receive treatment will be included in the FAS. If a patient is allocated the incorrect study treatment as per the study randomisation list, patients will be summarised and analysed 'as randomised' i.e., by randomised treatment group.

There will be not statistical analyses of the FAS dataset as the primary endpoint analysis and summaries will be based on the PD analysis set.

PD analysis set.

A patient is considered to be evaluable for the PD analysis set if:

- the patient has taken a minimum of 5 consecutive daily doses of AZD9833 for Stage 1 and Stage 2; and the patient has taken a minimum of 12 consecutive daily doses of AZD9833 for Stage 3.
- the patient received the last dose of AZD9833 within 12 hours of on-treatment biopsy;
- the diagnostic and on-treatment biopsy pair are considered evaluable as below:
    - 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
    - A minimum of 2 slides to allow measurement of ER
- has no protocol deviations that may impact the biomarker analysis.

The PD analysis set will include all patients who have a pair of any of ER, PgR or Ki67 results and will show a missing category when no results are available for an individual biomarker. Note that, from Stage 1 and Stage 3, all evaluable patients were evaluable for all 3 markers. For all non-evaluable patients, all were non-evaluable for all 3 biomarkers, e.g. no tumour tissue.

For the PD analysis set, if a patient is allocated the incorrect study treatment as per the study randomisation list, patients will be summarised 'as treated', i.e., patients randomised to AZD9833 who received an incorrect AZD9833 dose at the randomisation visit, will be accounted for in the treatment group corresponding to the first AZD9833 dose they received.

The **Safety Analysis Set** is defined as all patients who received any amount of study treatment, regardless of whether that was the randomised therapy intended or whether they received therapy without being randomised. If a patient is allocated the incorrect study treatment as per the study

randomisation list, patients will be summarised 'as treated' i.e., patients randomised to AZD9833 who received an incorrect AZD9833 dose at the randomisation visit will be accounted for in the treatment group corresponding to the first AZD9833 dose they received. The safety summaries will be based on safety analysis set. Safety data will not be formally analysed.

PK summaries will be based on the **PK Analysis Set**. The PK Analysis Set is defined as all patients who received at least one dose of AZD9833 per protocol, for whom there is at least one reportable PK concentration. If a patient is allocated the incorrect study treatment as per the study randomisation list, patients will be summarised 'as treated' i.e., patients randomised to AZD9833 who received an incorrect AZD9833 dose at the randomisation visit, will be accounted for in the treatment group corresponding to the first AZD9833 dose they received.

Upon database release, protocol deviation and analysis set outputs will be produced and will be sent to AZ and the ICI for review. Prior to database lock, an analysis set classification meeting will be arranged, involving AZ and the ICI, to discuss the outputs and decide which patients and/or patient data will be excluded from certain analyses, these decisions will be documented. A similar review to determine PD analysis set classification will take place prior to the production of outputs for the SDMC and the Stage 2 interim analysis.

A summary on which analysis set will be used for each outcome variable is provided in Table 3.

Table 3: Summary of Outcome Variables and Analysis Sets

Outcome Variable	**Analysis Set**
Study Population/Demography Data	
Disposition of patients	Enrolled
Demography characteristics	FAS*/Safety
Baseline and disease characteristics	FAS*/Safety
Important protocol deviations	FAS*/Safety
Medical/surgical history	FAS*/Safety
Previous anti-cancer therapy	FAS*/Safety
Concomitant medications/procedures	Safety
Subsequent anti-cancer therapy	Safety
PK Data	
PK concentrations	PK
Pharmacodynamic Data	
ER, PgR, Ki-67	PD Safety**
Safety Data	
Exposure	Safety
AEs	Safety
Laboratory measurements	Safety
Vital signs	Safety
ECGs	Safety

ER = oestrogen receptor; FAS = Full Analysis Set; PgR = progesterone receptor; PK = pharmacokinetic.
*Summary will be provided for safety analysis set; listings will be produced for the FAS analysis set.
**Pharmacodynamic data summaries will be based on PD analysis set, but listings will be provided for safety analysis set

4.6 Study Patients

4.6.1 Disposition of Patients

Patient disposition will be summarized by treatment group for all patients byStage 1 and Stage 2 combined, Stage 3 alone and by stages 1, 2 and 3 combined. Important protocol deviations and analysis sets will be tabulated using the safety analysis set (see Section 4.5). The number and percentages of patients will be presented for the following categories:

- All enrolled
- Randomised to study treatment
- Not randomised to study treatment (and reason)
- Received study treatment
- Did not receive study treatment (and reason)
- Completed study treatment
- Discontinued from study treatment (and reason)
- Completed study
- Prematurely withdrawn from study (and reason).

The number of patients recruited in each country and each centre will be presented by treatment group and total.

Additional listings and summaries on patients affected by the COVID-19 pandemic will also be presented.

4.6.2 Protocol Deviations

Important protocol deviations are defined as those deviations from the protocol likely to have a large impact on the interpretation of any analysis based on addressing the primary and secondary objectives of the trial.

The following general protocol deviation categories will be programmatically derived from the electronic case report form (eCRF) data. These deviations will be reviewed and assessed on a case-by-case basis by the study team to determine importance. Deviations considered to be important will be listed and discussed in the CSR as appropriate. All decisions on importance will be made ahead of database lock and will be documented prior to the analysis being conducted. Deviations will include, but are not limited to:

- Patients who deviate from inclusion /exclusion criteria per the Clinical Study Protocol (CSP) (Deviation 1).
- Patients who fail to sign the correct informed consent form, except the genetic informed consent form, before randomisation (Deviation 2).
- Patients whose baseline safety assessments as per CSP are missing (Deviation 3).
- Patients who received prohibited medications during the study (Deviation 4). Refer to the CSP Section 6.5 for those medications that are detailed as being ‘excluded’ from permitted use during the study. This will be used as a guiding principle for the physician review of all medications prior to database lock.
- Patients who don’t have a baseline biopsy (Deviation 5).
- Patients who don’t have an on-treatment biopsy (Deviation 6).
- Patients randomised who received an incorrect dose to that which they were randomised to (Deviation 7).
- Received AZD9833 and had an on-treatment biopsy more than 12 hours after last AZD9833 dose (Deviation 8).

- Pre- or on-treatment FFPE samples contain ≤ 100 tumour cells (Deviation 9).
- No on-treatment FFPE blocks provided (Deviation 10).
- Received AZD9833 and had an on-treatment biopsy without a minimum of 5 consecutive dosing days (Deviation 11).
- A minimum of 2 slides are not available from either the baseline or on-treatment biopsy (Deviation 12).

The following will be checked for analysis purposes and will not be included as part of the deviations to be recorded in the protocol deviations log during the study:

- Patients randomised but who did not receive any study treatment (Deviation 13).
- Patient vomits on the day of PK sampling and within 8 hours of AZD9833 dosing (Deviation 14). These will be reviewed on a case-by-case basis to determine whether any exclusion from the PK analysis set is deemed necessary.
- Non-invasive tumour biopsy scorings (Deviation 15).

Patients who received the wrong treatment at any time will be included in the analysis set as described in Section 4.5. During the study, decisions on how to handle errors in treatment dispensing (with regards to continuation/discontinuation of study treatment or, if applicable, analytically) will be made on an individual basis with written instruction from the study team leader and/or statistician.

Important protocol deviations will be listed and summarised by randomised treatment group. Important protocol deviations related to COVID-19 will be summarised separately.

Table 4: Summary of Deviations and Actions

Deviation	Action
Deviation 13	Exclusion from the Safety Analysis Set
Deviations 5, 6, 8-11 and 12	Patient becomes non-evaluable and to exclusion from the PD analysis set
Deviation 15	Exclusion of non-invasive tumour biopsy scorings from analysis
Other/further deviations	Will not lead to patients being excluded from the analysis sets described in Section 4.5 unless the deviation is considered to impact upon pharmacodynamic data. Non-evaluable patients will be replaced.

A per-protocol analysis excluding patients with specific important protocol deviations is not planned, however a sensitivity analysis may be performed on the key PD endpoints if > 10% of patients in any treatment group have any other significant deviation deemed to affect the primary endpoint which haven't already led to exclusion from the PD analysis set.

The need for such a sensitivity analysis will be determined following review of the protocol deviations ahead of database lock and will be documented prior to the analysis being conducted.

In addition to the programmatic determination of deviations above, other study deviations captured from the eCRF module for inclusion/exclusion criteria will be tabulated and listed. Any other deviations from monitoring notes or reports will be reported in an appendix to the CSR.

A full list of protocol deviations can be found in the study-specific Protocol Deviation Specification.

4.6.3 Demographic and Other Baseline Characteristics

No formal statistical analysis of baseline data will be provided for this study. Demographic and other baseline disease characteristics will be summarised and listed by treatment group for all patientsby

Stage 1 and Stage 2 combined, Stage 3 alone, and by Stages 1, 2 and 3 combined in the safety analysis set as follows:

- Demographics (age [years], age group[<50; 50-59; 60-69; ≥ 70], sex [only female patients are expected in this study], race and ethnicity).
- Patient characteristics at baseline (height [cm], weight [kg], and body mass index [BMI] [kg/m^2]).
- Previous non-breast related treatment modalities.
- Disease characteristics at baseline (Eastern Cooperative Oncology Group [ECOG] performance status, primary tumour location (breast), histology type, tumour grade, tumour stage /AJCC stage, receptor status [ER/PgR/Ki67/HER2]).
- Tumour, node and metastasis (TNM) classification at baseline.
- Neurological assessment (listed only).
- Time from diagnosis of primary breast cancer to randomisation.

4.7 Medical and Surgical History

Disease related medical history and relevant surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All disease related medical history (past and current) will be listed and the number and percentage of patients with any disease related medical history will be summarised for the safety analysis set by system organ class (SOC) and preferred term (PT).

All relevant surgical history will be listed and summarised similarly.

4.8 Concomitant Medications and Treatment

Information on any treatment that the patient is receiving at the time of enrolment and all concomitant treatments given up to 28 days after discontinuation of study treatment, with reasons for the treatment will be recorded in the eCRF. Any form of anti-cancer treatments, investigational agents, disallowed medications and radiotherapy should not be given while the patient is on study treatment. See Section 6.5 of CSP for a list of prohibited medications and anti-cancer treatments.

Treatments (including surgery), received prior to, concomitantly, or post-treatment will be coded using the Word Health Organisation (WHO) Drug Dictionary (WHODD) Anatomical Therapeutic Chemical (ATC) classification codes. Concomitant medications will be summarised for the safety analysis set by ATC classification codes.

For the inclusion in prior and/or concomitant medication or treatment summaries, incomplete medication or treatment start and stop dates will be imputed as detailed in Section 4.3.2.1 and Section 4.3.2.2.

- Prior medications are those taken prior to study treatment with a stop date prior to first dose of study treatment.
- Concomitant medications are those with a stop date on or after the first dose date of study treatment (and could have started prior to or during treatment).
- Post treatment medications are those with a start date after the last dose date of study treatment.

The following summaries will be produced:

- Cancer therapies prior to this study.
- Disallowed concomitant medications (as identified during physician review described in Section 4.6.2, deviation 4).

- Allowed concomitant medications.
- Concomitant procedures.
- Post-discontinuation cancer therapy.

The number and percentage of patients who took any previous cancer treatments will be summarised by therapy class (i.e. immunotherapy, hormonal therapy, cytotoxic chemotherapy, systemic therapy and other). The prior cancer (non-breast) therapy regimens will be listed.

Listings of prior, concomitant and post treatment medications, will be provided; and the timing of the medications will be marked clearly as 'prior', 'concomitant' or 'post'.

4.9 Curative intent surgery

Curative intent surgery details will be listed. If the reasons for no surgery/delay in surgery for a patient is not collected on CRF, data management lead will provide the reasons in a separate MS Excel sheet after contacting study sites, which will subsequently be reviewed and approved by study medical monitor. This excel sheet will be used for curative intent surgery listings and excel sheet will be filed in the TMF at the end of the study.

4.10 Pharmacodynamic Evaluation

Biopsy samples will be sectioned and assessed for tumour content. Pathologist scoring for ER, PgR and Ki-67 expression will be carried out at a contracted external good clinical practice (GCP) accredited laboratory. Sections will be scored for ER, PgR and Ki-67 expression in tumour by a contracted independent pathologist who will be blinded to treatment groups.

For patients where more than one tumour block has been provided for a single timepoint, a weighted mean score based on the percentage (%) of tumour cells in each section will be used as the score for that timepoint. Non-invasive tumour biopsy scorings will be excluded from the PD summaries and listings.

For example: If i=1, 2, 3 …n is the number of tumour blocks provided for a single patient for a particular tumour assessment visit; and the sample has corresponding percentage tumour tissues t_i and H-scores h_i (total H-score for ER and PgR expressions, and percentage tumour cells with positive nuclei for Ki-67 expression), then the weighted mean score for that patient for that particular visit is calculated as follows:

$$\sum_{i=1}^{n} \left(\frac{t_i}{\sum_{i=1}^{n} t_i} \right) h_i \quad \text{where i=1,2, 3….n}$$

The weighted mean score will be used as is in the analyses, where the score will be rounded off to the nearest integer before presenting in the summary tables.

Pathology scoring will be summarised and listed by treatment group for all patients by Stage 1 and Stage 2 combined, Stage 3 alone, and by Stages 1, 2 and 3 combined by actual treatment group and by visit.

The receptor status will be listed for safety analysis set by ER and PgR total H-score, Ki67 labelling index, and HER2 IHC positive staining.

4.10.1 ER and PgR

ER and PgR expression will be determined by the percentage of positively stained tumour nuclei in each staining category, i.e., negative '-/-', weak '+', moderate '++', strong '+++'. The sum of the

percentages of these 4 staining categories will be 100%. Then, ER and PgR expression will be assessed using the following manual H-score method, which yields to a manual H-score range of 0 to 300.

H-score = (1 * % of +) + (2 * % of ++) + (3 * % of +++).

When a biopsy contains only 0-100 tumour cells, then H-score is not reported and not evaluable (NE) will be stated.

The primary and secondary pharmacodynamic biomarker variables of percentage change from baseline in ER and PgR expressions after 5 to 7 days of AZD9833 treatment for Stage 1 and Stage 2; and after 12 to 15 days of AZD9833 treatment for Stage 3 will be listed and summarised based on the PD analysis set (see Section 4.5).

The primary objective of the study will be assessed using percent change in ER expression, however data will be summarised and analysed for the percent change and absolute change from baseline, and will also be analysed based on the log transformed values. This is to ensure comparability with the different methods of reporting used within the literature. For all summaries and analyses, baseline values equal to zero will be set to one and corresponding biopsy day ER expression value will be incremented by 1. The same will hold for the reporting of PgR expression. For listings, original values will be reported.

For percent change in ER, and PgR expression, if data permits, three separate analyses of covariance (ANCOVA) models will be fitted, one utilizing data from stage 1 and 2 only (5-7 days exposure), one utilizing data from stage 3 only (12-15 days exposure) and one utilizing data from all stages combined with on-treatment biomarker expression score as a dependent variable, baseline expression score as a covariate, and day of biopsy and treatment group as fixed effects.

An exploratory analysis utilizing data from all stages may also be performed with on-treatment biomarker expression score as a dependent variable, baseline expression score as a covariate, day of biopsy and treatment group as fixed effects and an interaction between day of biopsy and treatment group. Other covariates such as stage and country may be explored as well as interactions between covariates.

Least squares means (LS-means) estimates of the treatment effect will be calculated together with 80% CIs for all treatment durations (5 to 7 consecutive days of AZD9833 treatment for stage 1 and stage 2, and 12 to 15 consecutive days of AZD9833 treatment for stage 3), as per the model fitted. To calculate the percentage change, mean changes from baseline will be converted to percentage of initial staining by dividing mean changes by the overall mean score at baseline (Robertson et al 2013). The three ANCOVA models will be repeated based on the absolute change from baseline.

If the distribution of ER and PgR expressions manual H-score is normal, these data will be analysed as described previously and this will form the primary analysis. If data does not adequately follow a normal distribution, then the use of the natural log transformed data (i.e., ratio) will replace the untransformed analysis as the primary approach. Log transformed ANCOVA analyses will be produced including the same covariates as specified for the untransformed analyses, but with the log transformed baseline value replacing the untransformed value. The estimated treatment effect and its 80% CIs will be back transformed to the original scale prior to reporting. The values equal to zero (0) on the original scale will be set to 1, and corresponding baseline / biopsy day expressions scores will be incremented by 1 before natural log transformation.

The normality of the distribution of the data will be tested using a Shapiro-Wilk test. In case of a two-sided p-value > 0.20, there will be evidence that the data is normally distributed. Additional plots and

statistics will be provided to measure the severity of the deviations from normality if necessary.***Sensitivity analyses for ER and PgR***

If necessary, the following sensitivity analysis will be conducted on a subset of the PD analysis set by excluding:

From ER analysis

- Any patients who are HER2 positive by central assessment.
- Any patients with an ER H-score < 10 on their pre-treatment biopsy.

From PgR analysis

- Any patients who are considered to be HER2 positive by central assessment.
- Any patients with a PgR H-score < 10 on their pre-treatment biopsy.

If considered necessary, further cuts and sensitivity analyses may be performed.

If following transformation of the data an ANCOVA model is still not appropriate, a non-parametric approach may be considered.

4.10.2 Ki-67 Labelling Index

Ki-67 labelling index will be assessed and expressed as the average percentage of tumour cells with counted positive nuclei, following the International Ki-67 in Breast Cancer Working Group Recommendations. Ki-67 labelling index will be scored by increments of 1% and can range from 0 – 100. When the number of tumour cells per section for a counted biopsy is less than 100 tumour cells, then the Ki-67 labelling index is not reported and NE will be stated.

The secondary pharmacodynamic biomarker variables of change from baseline in Ki-67 labelling index after 5 to 7 days of AZD9833 treatment for Stage 1 and Stage 2; and after 12 to 15 days of AZD9833 treatment for Stage 3 will be listed and summarised based on the PD analysis set (see Section 4.5).

It is expected that the distribution of the Ki-67 labelling index data will not be normally distributed (Robertson et al 2013, Robertson et al 2020b), hence Ki-67 labelling index data will be naturally log-transformed before being analysed. Ki-67 will be analysed similarly to ER and PgR, using a parametric ANCOVA on natural log transformed data. Values equal to zero on the original scale will be set to one (1), and one will be added to the corresponding baseline/biopsy day labelling index value before natural log transformation. Log transformed baseline score will be included as a covariate, and day of biopsy and treatment group included as fixed effects. The estimated treatment effect together with 80% CIs for all treatment durations (5 to 7 consecutive days of AZD9833 treatment for stage 1 and stage 2, and 12 to 15 consecutive days of AZD9833 treatment for stage 3), as per the model fitted will be back transformed to the original scale for reporting. For listings, original values will be reported.

Sensitivity analyses for Ki-67 labelling index

If necessary, sensitivity analysis will be conducted on a subset of the PD analysis set by excluding:

- Any patients who are considered to be HER2 positive by central assessment.
- Any patients with a Ki-67 labelling index < 5% from their pre-treatment biopsy.
- Any patients with an ER H-score < 10 on their pre-treatment biopsy.
- Any patients with an ER H-score < 10 on their pre-treatment biopsy or any patients with a Ki-67 labelling index < 5% from their pre-treatment biopsy.

If considered necessary, further cuts and sensitivity analyses may be performed.

If, following transformation of the data, an ANCOVA model is still not appropriate, a non-parametric approach may be considered.

4.11 Safety Evaluation

All safety summaries will be based upon the Safety Analysis Set and presented for all patients by Stage 1 and Stage 2 combined, Stage 3 alone and Stages 1, 2 and 3 combined by actual treatment group.

4.11.1 Extent of Exposure

Extent of exposure for AZD9833 will be defined in terms of the number of days the treatment is received.

Exposure (i.e., duration of treatment) will be defined as follows:

Total exposure = min (last day of dosing, date of death, date of withdrawal) – first dose date + 1.

Actual exposure = total exposure of study treatment – total duration of dose interruptions

where total exposure will be calculated as above, and a dose interruption is defined as any length of time (number of days) where the patient has not taken any of the planned daily dose. This should be taken from the patient diary cards.

RDI is defined as the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation. Relative dose intensity will be calculated as follows:

$$\text{RDI}(\%)=\frac{d}{D}\times 100,$$

where

d the actual cumulative dose delivered (which will be taken from the patient diary card)
D the intended cumulative dose (duration of intended dose will be calculated from Day 1 to the planned biopsy day. D is the total dose that would have been delivered if there were no modification to dose or schedule).

If a patient permanently discontinues study treatment, then the date of last administration of study medication recorded on eCRF will be used to program the RDI. If a patient permanently discontinues study treatment during a treatment interruption, then the date of last administration of study medication recorded on the eCRF will be used to program the RDI.

Summaries

The exposure data will be summarised and listed for the safety analysis set including all data from the diary card (see Section 4.5).

For AZD9833 treatment groups, actual treatment duration, total treatment duration, RDI, and the number and percentage of patients that received at least 5 consecutive days of dosing for Stage 1 and Stage 2; and at least 12 consecutive days of treatment for Stage 3 will be summarised. In addition, the number and percentage of patients who received the planned starting dose of AZD9833, with no interruption, with dose interruption or discontinuation and with both dose interruption and discontinuation will be presented. Reason for dose interruption and dose discontinuation will also be summarised.

4.11.2 Adverse Events

AEs and SAEs will be collected throughout the study from date of informed consent until the end of the safety follow-up period (28 days after last dose of study treatment). The latest version of MedDRA will be used to code the AEs. AEs will be graded according to the National Cancer Institute of Common Terminology Criteria for AEs (CTCAE) version 5.0.

Events will be defined as treatment-emergent AEs, and reported in the summary tables if they onset or worsen (by investigator report of a change in CTCAE grade), during the treatment period as defined in the CSP or during the 28-day safety follow-up period. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of study treatment) will be flagged in the data listings.

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

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

Some clinical concepts (including some selected individual preferred terms and higher-level terms) are considered to be "AEs of special interest" (AESIs). AESIs represent pre-specified risks that are considered to be of importance to a clinical development program. These AESIs, if applicable, will be identified as a list of categories provided by the patient safety team.

Reviews will take place prior to database lock to determine whether any AE should be classified as AESIs. The review will identify which higher-level terms, and which preferred terms should contribute to each AESI.

In general, all AE summary tables include only TEAEs. AEs occurring prior to dosing or starting more than 28 days after discontinuation of study drug will be flagged in listings and will not be included in any summaries.

All reported AEs will be listed along with the actual treatment received at the time of onset, date of onset, date of resolution (if AE is resolved), investigator's assessment of CTCAE grade, relationship to study treatment, action taken and outcome. Frequencies and percentages of patients reporting each preferred term will be presented (i.e., multiple events per patient will not be accounted for, except for event level summaries).

Summaries of adverse events (the number and percentage of patients by treatment) by MedDRA System Organ Class (SOC) and Preferred Term (PT) will include but are not limited to:

- All AEs
- All AEs possibly related to study treatment
- AEs of CTCAE grade 3 or higher
- AEs of CTCAE grade 3 or higher, possibly related to treatment
- AEs with outcome of death
- All SAEs
- All SAEs possibly related to study treatment
- AEs leading to discontinuation of treatment

- AEs leading to discontinuation of treatment, possibly related to treatment
- SAEs leading to discontinuation of treatment
- SAEs leading to discontinuation of treatment, possibly related to treatment
- Other significant AEs (if applicable)
- AESIs (if applicable)

An overall summary of the number and percentage of patients in each of the above categories will be presented, as well as an overall summary of number of events in each of the above categories. In addition, a truncated AE table of most common AEs, showing all events that occur in at least 5% of patients overall will be summarised by PT, by decreasing frequency.

Additionally, an event level summary will be presented for all AEs by PT.

Summaries of the number and percentage of patients with AEs will also be produced by maximum reported CTCAE grades, SOC and PT.

All AESI PTs, if applicable, searched for in this study will be presented. Summaries of AESIs will be presented by maximum reported CTCAE grade, by AE outcome, including time of resolution (on-treatment, follow-up or post-treatment), whether treatment was received (yes/no) and action taken.

In addition, AEs with outcome death, SAEs, AEs leading to discontinuation of treatment and OAEs will be listed separately.

Covid-19 AEs will also be collected and reported by MedDRA System Organ Class.

4.11.3 Deaths

A summary of deaths will be provided with number and percentage of patients, categorised as:

- Related to disease under investigation only
- AE outcome = death only
- Both related to disease under investigation and with AE outcome = death
- Other deaths.

A corresponding listing will also be produced.

4.11.4 Clinical Laboratory Evaluation

All laboratory results collected will be listed.

Summaries for safety laboratory will only include the parameters specified in Table 5.

All values will be classified as low (below range), normal (within range), or high (above range) based on local laboratory reference ranges. Results will be converted to standard units and graded with CTCAE version 5.0.

Table 5: Laboratory safety variables

Haematology (whole blood)	Clinical chemistry (serum or plasma)
B-Haemoglobin	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	S/P-Magnesium
International normalised ratio	S/P-Phosphate
Urinalysis (dipstick)	S/P-Urea or Urea nitrogen
U-Glucose	S/P-Protein, total
U-Protein	S/P-Troponin I
U-Blood	S/P-Troponin T
	S/P-NT-proBNP

If the same parameter is found as measured in serum and in plasma, then the summaries will not distinguish between them (e.g., values from plasma albumin and serum albumin will be summarised under albumin). If the same parameter is found as measured in serum and in plasma within the same patient, which would be a rare case, then the change from baseline will only be calculated for those post-baseline values using the same source, i.e., only within plasma or serum. If one patient has multiple toxicity grades, because they are derived separately from serum and plasma then the maximum value of the two will be considered.
Corrected calcium will be calculated as:
Corrected calcium (mg/dL) = 0.8 × (normal albumin - patients albumin) + total serum calcium
or
Corrected calcium (mmol/L) = 0.02 × (normal albumin - patients albumin) + total serum calcium
depending on the unit used.

For all continuous laboratory assessments, absolute value, change from baseline and percentage change from baseline will be summarised using descriptive statistics at each scheduled assessment time by actual treatment group.

For clinical chemistry and haematology, shift tables will present movements from baseline to worst value on-treatment (defined from start of treatment to biopsy day) according to reference range classification. CTCAE grade changes from baseline to on-treatment will also be provided. Corresponding shift tables ("Negative", "Trace", "Positive", "0", "+", "++", "+++") will be produced for urinalysis. In addition, the number of patients with ≥ 2 CTCAE grade changes and CTCAE grade changes to 3 or 4 will be summarised by actual treatment group for clinical chemistry and haematology parameters.

Plots for both maximum post-baseline alanine transaminase (ALT) and aspartate transaminase (AST) versus the maximum post-baseline total bilirubin (expressed as multiples of their upper limit of normal [ULN] reference range) will be produced with reference lines at 3 x ULN for ALT and AST and 2 x ULN for total bilirubin. Box plots of absolute values and change from baseline values for all haematology and clinical chemistry parameters will also be presented.

Liver biochemistry test results over time for patients who show elevated ALT or AST (≥ 3 x ULN) and elevated bilirubin (≥ 2 x ULN) (elevated results do not need to be present at the same visit) or ALT or AST of ≥ 5 x ULN, will be tabulated and plotted.

4.11.5 Physical Examination findings

A complete physical examination will be performed at screening; all data will be listed.

4.11.6 Vital Signs

All vital signs data collected will be listed.

Changes from baseline in vital signs to each post-baseline assessment will be calculated. Absolute values, changes from baseline and percentage change from baseline will be summarised for all patients by Stage 1 and Stage 2 combined, Stage 3 alone and Stages 1, 2 and 3 combined by actual treatment group and by visit. Box plots of absolute values and change from baseline values and percentage change from baseline for all vital sign variables will also be presented.

There will be no imputation for missing values. Observed values and changes from baseline will be compared to the relevant AstraZeneca defined reference ranges for vital signs (see Table 6) and clinically important change criteria and all values (observed and change) falling outside the reference ranges will be flagged in the listings.

Table 6: AstraZeneca defined reference ranges for vital signs variables

Vital sign (unit)	Outside AZ defined reference range lower limit if	Outside AZ defined reference range upper limit if	Treatment emergent decrease if	Treatment emergent increase if
SBP (mmHg)	<100	>160	<-30	>30
DBP (mmHg)	<60	>100	<-15	>15
Pulse	<40	>100	<-20	>20
Height (cm)	<140	>220		
Weight (kg)	<40	>200		

SBP- systolic blood pressure; DBP-diastolic blood pressure
mmHg-millimeter of mercury; cm-centimeter; kg-kilogram

4.11.7 ECG Variables

All ECG data received will be presented in data listings.

Absolute values, changes from baseline and percentage change from baseline to each scheduled visit will be summarised for all patients Stage 1 and Stage 2 combined, Stage 3 alone and Stages 1, 2 and 3 combined by actual treatment group and by visit for the following ECG variables: heart rate, QT interval corrected for heart rate using Fridericia's formula (QTcF) and Bazett's formula (QTcB), RR, PR, QRS, and QT.The average of the three individual tracings will be used in summaries. However, the individual tracing values will be given in the data listings.

Box plots of observed values, changes from baseline and percentage change from baseline by treatment group will also be presented for each ECG variable with reference lines indicating the limits of the AstraZeneca Cardiac SKG reference ranges (see Table 7), when available.

Table 7: AstraZeneca defined reference ranges for ECG variables

ECG Parameter	Outside AZ defined reference range lower limit if	Outside AZ defined reference range upper limit if
Heart rate (bpm)	< 40	> 100
RR (msec)	< 600	> 1200
PR (msec)	< 120	> 200
QRS (msec)	< 60	> 109
QT, QTcF, and QTcB (msec)	< 300	> 450

Cut-off values for categorical analyses as recommended by ICH E14.
msec = milliseconds; NA = Not applicable.

Number and percentage of patients with QTcF, QTcB results in each of the following categories will be summarised:

- greater than AstraZeneca Cardiac SKG upper reference range at any time on treatment.
- absolute value [redacted].
- absolute value [redacted].
- absolute value [redacted].
- change from baseline [redacted].
- change from baseline [redacted].
- absolute value [redacted] and change from baseline [redacted].
- absolute value [redacted] and change from baseline [redacted].

Additional shift tables will also be presented using categorised results as specified below:

- Baseline heart rate to minimum value during treatment with categories: [redacted].
- Baseline [redacted] to maximum value during treatment with categories: [redacted].

4.11.8 [redacted]

[redacted]

4.12 Pharmacokinetic Evaluation

Plasma concentration-time data for AZD9833 will be presented using the pharmacokinetics analysis set (see Section 4.5). PK concentration data for AZD9833 will be summarised by Stage 1 and Stage 2 combined, Stage 3 alone and Stages 1, 2 and 3 combined by actual treatment, and PK concentration data will be listed for each patient. PK concentration data listings will be presented to the same number of significant decimal points as the data received from the bioanalytical laboratory (usually but not always to three significant decimal points) and against the same units as received. PK concentration descriptive statistics will all be presented to four significant decimal points with the exception of the min and max which will be presented to three significant decimal points; n and n<LLOQ which will be presented as integers.

Plasma concentration-time data for AZD9833 will not be analysed to determine the PK parameters. Plasma concentrations of AZD9833 will be summarised by means of descriptive statistics as follows:

- Geometric mean (gmean, calculated as exp[μ], where μ is the mean of the data on a logarithmic scale)
- Coefficient of variation (gCV%, calculated as 100 √ [exp(s2)-1], where s is the standard deviation of the data on a log scale)
- Gmean ± geometric standard deviation (gmean + gSD and gmean - gSD), calculated as exp [μ ± s])
- Mean
- Standard deviation
- Median
- Minimum (min)
- Maximum (max)

- Number of observations (n)
- n > LLoQ (Lower Limit of Quantification)

Plasma concentrations that are below the limit of quantification (BLQ) will be reported as follows:

Individual concentrations below the LLoQ of the bioanalytical assay will be reported as NQ (not quantifiable) in the listings with the LLoQ defined in the footnotes of the relevant tables, listings and figures (TLFs).

Individual plasma concentrations that are not reportable will be reported as NR and those that are missing will be reported as NS (no sample) in the listings. Plasma concentrations that are NQ, NR or NS will be handled as follows for the provision of descriptive statistics:

- Any values reported as NR or NS will be excluded from the summary tables and figures. At a time point where less than or equal to 50% of the concentration values are NQ, all NQ values will be substituted with the LLoQ concentration, and all descriptive statistics will be calculated accordingly.
- At a time point where more than half (but not all) of the values are NQ, the mean, gmean, gCV%, +gSD and SD will be set to Not Calculable (NC). The maximum value will be reported from the individual data and the minimum and median will be set to NQ.
- If all concentrations are NQ at a time point, the mean, gmean, min, median and max will be reported as NQ and the +gSD, gCV% and SD will be reported as NC.

The number of values above LLoQ (n >LLoQ) will be reported for each time point together with the total number of collected values.

Three observations > LLoQ will be required as a minimum for PK plasma concentrations to be summarised. Two values will be presented as minimum and maximum with the other summary statistics as NC. For consistency, the same plasma concentration values are used in the mean data graphs as those given in the descriptive statistics summary table for each time point.

The plasma PK concentration data for AZD9833 will be displayed graphically by nominal sample time.

Displays will include:

- Individual patient plasma concentration-time profiles of AZD9833 (on the linear scale).
- Gmean plasma concentration-time profiles (with and without gSD error bars) of AZD9833 (on the linear scale).
- Mean plasma concentration-time profiles (with and without SD error bars) of AZD9833 (on the linear scale).

4.13 Sample Size Considerations

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 2020b Robertson JF).

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).

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 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 ER.

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 2020b Robertson JF). 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]

4.14 SDMC Analysis and Reporting

Following the availability of the IHC data from the last evaluable patient in Stage 1, the SDMC will convene to review the Stage 1 data alone or potentially alongside 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 SDMC charter and, if proceeding, will select up to four treatment groups for post-menopausal patients and confirm whether a pre-menopausal treatment group should be included. Refer to the SDMC charter and Section 9.6 of the CSP for more details on the SDMC members, SDMC recommendations and rationale for SDMC recommendations. Based on the data review, the recommendations of the SDMC may include but are not limited to:

- Continue the study to Stage 2 with a focus on lower AZD9833 doses.
- Continue the study to Stage 2 with a focus on higher AZD9833 doses.
- Increase the number of patients in Stage 2 at the same dose levels from Stage 1 to provide more precision.
- Add more dose levels of AZD9833.
- Add a fulvestrant group in stage 2.
- Add a pre-menopausal women AZD9833 treatment arm.

Analysis of tumour samples will be batched, and the resulting data reviewed on an ongoing basis throughout the study. Raw data will be plotted to provide information for the ongoing development of the clinical program.

Stage 1 data will be analysed and summarised following the methodology outlined in the previous sections of this SAP in an unblinded fashion. For the SDMC, only the Stage 1 data analysis and summaries will be provided by PXL.

The patient disposition, demographic characteristics, baseline patient and disease characteristics, study drug exposure, baseline and post-baseline safety parameters (AEs, clinical laboratory evaluations, vital signs, ECG data etc.) will be summarised. The primary/secondary endpoints will

be analysed as specified in Section 4.10 of SAP. The list of tables, listings and figures required for the SDMC review will be prepared as described in the SDMC charter and as per AZ standards; and they will be flagged in the list of TLFs for the entire study.

Refer to Section 1 for the SDMC recommendations for stage 2, and Section 3 for the detailed investigational plan for stage 2.

4.15 Interim Analysis

There will be no formal interim statistical analyses during the conduct of Stage 1. At the end of Stage 1, the SDMC will review the data emerging from Stage 1 and provide the recommendations for the Stage 2 treatment groups (sample size, dose, number of treatment groups, inclusion of a possible pre-menopausal women group). Please refer to Section 4.14 for more details on SDMC reporting.

In Stage 2, there will be an interim analysis conducted on completion of recruitment and once all patients have completed treatment in GE/MX (and with provision to include any patients who have been recruited from the UK at the date of data cut off). This analysis will inform internal decision making and follow the analysis methods outlined in the main body of this SAP.

No formal interim analysis will be performed during Stage 3.

4.16 Other Analysis

At the end of all stages, data across countries and stages will be combined by treatment groups; and summarised following the methodology outlined in the previous sections of this SAP in an unblinded fashion.

A selected number of summaries will be produced splitting by country (GE/MX together and the UK).

5 REFERENCES

SAS Institute Inc. 2013. SAS® 9.4 Statements: Reference. Cary, NC: SAS Institute Inc.

The SAS System Requirements for SAS® 9.4 Foundation for Microsoft Windows: Copyright ©2020. SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

Nakonezny PA, Shull RD. Hettmansperger and Mckean linear model aligned rank test for the single covariate and one-way ANCOVA case (SAS). Journal of Modern Applied Statistical Methods. 2007; 6:336-340.

Robertson JF, Dixon JM, Sibbering DM, Jahan A, Ellis IO, Channon E, et al. A randomized trial to assess the biological activity of short-term (pre-surgical) fulvestrant 500 mg plus anastrozole versus fulvestrant 500 mg alone or anastrozole alone on primary breast cancer. Breast Cancer Res 20136; 15R18.

Robertson S, Acs B, Lippert M, Hartman J. Prognostic potential of automated Ki67 evaluation in breast cancer: different hot spot definitions versus true global score. Breast Cancer Res Treat. 2020;183(1):161-175.

Robertson et al 2020b Robertson JF, Evans A, Henschen S, Kirwan CC, Jahan A, Kenny LM, et al. A randomized, window of opportunity study comparing the effects of the novel oral SERD AZD9496 with fulvestrant in patients with ER+ HER2- primary breast cancer. Clin Cancer Res 2020; doi: 10.1158/1078-0432.CCR-19-3387

Robertson JF, Evans A, Henschen S, Kirwan CC, Jahan A, Kenny LM, et al. A randomized, window of opportunity study comparing the effects of the novel oral SERD AZD9496 with fulvestrant in patients with ER+ HER2- primary breast cancer. Clin Cancer Res 2020; doi: 10.1158/1078-0432.CCR-19-3387.

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d8530c00003-sap-ed-4		
Document Title:	Statistical Analysis Plan Edition 4	
Document ID:	Doc ID-004422454	
Version Label:	4.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
21-Jul-2023 14:31 UTC	PPD	Content Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.