



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 May 2026

[EMADOC-1829012207-55475](#)

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Etcamah

International non-proprietary name: camizestrant

Procedure No. EMEA/H/C/006494/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted. Additional information has been redacted in order to protect data integrity for the ongoing blinded pivotal trial SERENA-6; this information will be made publicly available once the SERENA-6 full results have been submitted to EMA.

Official address Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us

Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

An agency of the European Union



Table of contents

1. Administrative/regulatory information and recommendations on the procedure	12
1.1. Information on the product.....	12
1.2. Scientific advice	13
1.3. Eligibility to the centralised procedure.....	15
1.4. Legal basis and dossier content.....	15
1.5. Information on paediatrics.....	15
1.6. Information on orphan market exclusivity	16
1.6.1. Similarity with authorised orphan medicinal products	16
1.7. Applicant's request for consideration.....	16
1.7.1. New active substance status	16
1.8. Third party interventions.....	16
1.9. Patient experience data.....	16
1.10. Steps taken for the assessment of the product.....	17
1.11. CHMP outcome.....	17
1.11.1. Considerations related to paediatrics.....	17
1.11.2. Considerations related to orphan market exclusivity	17
1.11.3. Opinion	18
1.11.4. Conditions or restrictions regarding supply and use.....	18
1.11.5. Other conditions and requirements of the marketing authorisation.....	18
1.11.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product	18
2. Introduction	20
2.1. Therapeutic context.....	20
2.2. Aspects of development	20
2.3. Description of the product	22
2.4. Inspection issues.....	23
2.4.1. Good manufacturing practice (GMP) inspection(s).....	23
2.4.2. Good laboratory practice (GLP) inspection(s)	23
2.4.3. Good clinical practice (GCP) inspection(s)	23
3. Quality aspects.....	24
3.1. Introduction	24
3.2. Active substance	24
3.2.1. General information	24
3.2.2. Manufacture, characterisation, and process controls	25
3.2.3. Specification	25
3.2.4. Stability	26
3.3. Finished medicinal product	27
3.3.1. Description of the product and pharmaceutical development.....	27
3.3.2. Manufacture of the product and process controls	29
3.3.3. Product specification	30
3.3.4. Stability of the product.....	31
3.3.5. Post approval change management protocol(.....	32
3.3.6. Adventitious agents	32
3.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects	32
3.5. Recommendations for future quality development	32

4. Non-clinical aspects.....	32
4.1. Introduction	32
4.2. Analytical methods	33
4.3. Pharmacology	33
4.3.1. Pharmacodynamics.....	33
4.3.2. Pharmacokinetics	42
4.4. Toxicology	43
4.4.1. Single-dose toxicity	43
4.4.2. Repeat-dose toxicity	43
4.4.3. Genotoxicity	47
4.4.4. Carcinogenicity.....	48
4.4.5. Developmental and reproductive toxicity	48
4.4.6. Toxicokinetics and exposure margins	52
4.4.7. Local tolerance.....	54
4.4.8. Other toxicity studies	54
4.4.9. Ecotoxicity/environmental risk assessment	59
4.5. Overall discussion and conclusions on non-clinical aspects.....	62
4.5.1. Discussion	62
4.5.2. Conclusions	66
5. Clinical aspects.....	67
5.1. Introduction	67
5.1.1. Good Clinical Practice (GCP) aspects	67
5.1.2. Tabular overview of clinical trials	68
5.2. Clinical pharmacology	74
5.2.1. Methods	74
5.2.2. Pharmacokinetics	74
5.2.3. Pharmacodynamics	100
5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)	103
5.2.5. Relationship between plasma concentration and effect and safety.....	104
5.2.6. Dose selection and therapeutic window	109
5.2.7. Overall discussion and conclusions on clinical pharmacology	109
5.3. Clinical efficacy	113
5.3.1. Dose response study	113
5.3.2. Main study.....	113
5.3.3. Clinical studies in special populations	144
5.3.4. <i>In vitro</i> biomarker test for patient selection for efficacy	144
5.3.5. Supportive studies.....	147
5.3.6. Analysis performed across trials (pooled analyses and meta-analysis).....	152
5.3.7. Observational data/Data from registries	152
5.3.8. Patient experience data (PED).....	152
5.3.9. Healthcare professional engagement.....	153
5.3.10. Overall discussion and conclusions on clinical efficacy.....	153
5.4. Clinical safety	157
5.4.1. Safety data collection.....	158
5.4.2. Patient exposure	160
5.4.3. Adverse events	167
5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events.....	180
5.4.5. Discontinuation due to adverse events	185

5.4.6. Adverse events leading to discontinuation of treatment	185
5.4.7. Adverse events leading to dose modifications.....	186
5.4.8. Safety in special populations	188
5.4.9. Immunological events	188
5.4.10. Safety related to drug-drug interactions and other interactions	189
5.4.11. Vital signs and laboratory findings	189
5.4.12. Clinical laboratory evaluations	189
5.4.13. Vital signs and physical findings	190
5.4.14. Electrocardiogram data.....	191
5.4.15. Post-marketing experience.....	193
5.4.16. Overall discussion and conclusions on clinical safety.....	193
6. Risk management plan	195
6.1. Safety specification	195
6.1.1. Proposed safety specification	195
6.1.2. Discussion on proposed safety specification	195
6.2. Pharmacovigilance plan.....	196
6.2.1. Proposed pharmacovigilance plan.	196
6.2.2. Discussion on the pharmacovigilance plan	196
6.3. Plans for post-authorisation efficacy studies.....	196
6.4. Risk minimisation measures	197
6.4.1. Proposed risk minimisation measures.....	197
6.4.2. Discussion on the risk minimisation measures	197
6.5. RMP summary and RMP annexes overall conclusion	197
6.6. Overall conclusion on the Risk Management Plan.....	197
7. Pharmacovigilance	198
7.1. Pharmacovigilance system.....	198
7.2. Periodic safety update reports (PSURs) submission requirements	198
8. Product information	198
8.1. Summary of product characteristics (SmPC)	198
8.1.1. SmPC section 4.1 justification	198
8.1.2. SmPC section 4.3 justification	198
8.2. Labelling	198
8.2.1. User consultation.....	198
8.3. Additional monitoring.....	199
9. Benefit-risk assessment	199
9.1. Therapeutic context.....	199
9.1.1. Disease or condition, proposed therapeutic indication	199
9.1.2. Available therapies and unmet medical need.....	199
9.2. Main clinical studies.....	200
9.3. Favourable effects	200
9.3.1. Uncertainties and limitations about favourable effects	201
9.4. Unfavourable effects.....	201
9.4.1. Uncertainties and limitations about unfavourable effects.....	202
9.5. Effects table	202
9.6. Benefit-risk assessment and discussion	203
9.6.1. Importance of favourable and unfavourable effects.....	203
9.6.2. Balance of benefits and risks.....	204

9.6.3. Additional considerations on the benefit-risk balance	204
9.7. Benefit-risk conclusions.....	205
10. Appendices	206

List of abbreviations

1L	First-line
AAFE	Average fold error
ABC	Advanced breast cancer
ADC	Antibody-drug conjugate
ADME	Absorption, distribution, metabolism and excretion
ADP	Adenosine diphosphate
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AI	Aromatase inhibitor
AKTi	Protein kinase B inhibitor
ALT	Alanine aminotransferase
AMS	Accelerator mass spectrometry
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{(0-24)}$	Area under plasma concentration-time curve from time 0 to 24 hours
$AUC_{(0-t)}$	Area under plasma concentration-time curve from time 0 to time t
AUC_{inf}	Area under plasma concentration-time curve from time 0 to infinity
AUC_{last}	Area under the plasma concentration-time curve from time 0 to last quantifiable concentration
$AUC_{0-Tlast}$	Area under the plasma concentration time curve from zero to last timepoint
AUC_{ss}	Area under plasma concentration-time curve at steady state
AUC_{tau}	Area under plasma concentration-time curve during a dosing interval
$AUC_{tau/Dose}$	Dose normalised AUC_{tau}
BBW	Baseline body weight
BCRCL	Baseline creatinine clearance
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BCT	Blood collection tubes
BCVA	Best-corrected visual acuity
BICR	Blinded Independent Central Review
BID	Twice daily
BMI	Body mass index
B/R	Benefit/risk
CAT	Committee for Advanced Therapies
CBR	Clinical benefit rate
CDC	Continuous direct compression
CDK4/6i	Cyclin-dependent kinase 4/6 inhibitor
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval

CL	Total body clearance
CL/F	Apparent total body clearance
C _{max}	Maximum plasma concentration
C _{max} /Dose	Dose normalised C _{max}
C _{maxss}	C _{max} at steady state
CMH	Cochran–Mantel–Haenszel
C _{min}	Minimum plasma (trough) drug concentration after repetitive dosing before steady state is reached
C _{minss}	C _{min} at steady state
CNA	Copy number amplification
CrCL	Creatine clearance
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
ctDNA	Circulating tumour DNA
CV	Coefficient of variation
CYP450	Cytochrome P450
DC	Direct compression
DCO	Data cut-off
DDI	Drug drug interaction
DLT	Dose limiting toxicity
DMPK	Drug metabolism and pharmacokinetics
DMSO	Dimethyl sulfoxide
DoR	Duration of response
EAIR	Exposure-adjusted incidence rate
EC50	Concentration giving 50% of drug-induced effect
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDR	Early discrepancy rate
EFD	Embryofoetal development study
EMA	European Medicines Agency
EoT	End of treatment
ER	Estrogen receptor
ER(α/β)	Estrogen receptor (alpha/beta)
ERA	Environmental Risk Assessment
ERG	Electroretinography
ESMO	European Society for Medical Oncology
ESR1	Estrogen receptor alpha 1 gene
ET	Endocrine therapy
F	Female
FAS	Full Analysis Set
FIH	First-in-human

FEED	Fertility and early embryonic development study
FT-IR	Fourrier Transform Infrared Spectroscopy
GC	Gas Chromatography
GCP	Good Clinical Practice
GD	Gestation Day
Geomean	Geometric mean
GLDH	Glutamate dehydrogenase
GLP	Good Laboratory Practice
GMFE	Geometric mean fold error
GMR	Geometric mean ratio
GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
hCE1	Human carboxylesterase 1
HCN	Hyperpolarization-activated cyclic nucleotide-gated
HER2	Human epidermal growth factor receptor 2
hERG	Human ether-a-go-go-related gene
hESC	Human Embryonic Stem Cell
HPLC	High performance liquid chromatography
HR	Hazard Ratio
HR	Heart rate
I2	Intestinal concentration
IA	Interim analysis
IC ₅₀	50% inhibitory concentration also called potency
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IM	Intramuscular or intramuscularly
IMP	Investigational medicinal product
INV	Investigator
IP	Investigational product
IPC	In process control
IPCW	Inverse probability of censoring weights
IR	Immediate release
IR	Infrared
IRT	Interactive Response Technology
IS	Internal standard
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
IV	Intravenous
K _i	Inhibition constant
Ki67	Antigen Kiel 67
KI	Inhibitor concentration required to achieve half-maximal inactivation
Kinact	Maximal inactivation

KRASi	Kirsten rat sarcoma virus gene inhibitor
LAMP2	Lysosome-associated membrane protein 2
LBD	Ligand binding domain
LC	Liquid chromatography
LC MS/MS	Liquid chromatography coupled to tandem mass spectrometry
LD	Lactation Day
LDPE	Low Density Polyethylene
LDR	Late discrepancy rate
LHRH	Luteinizing hormone releasing hormone
LE	Long evans
LLOQ	Lower limit of quantification
LV	Left Ventricular
λ_z	Terminal elimination rate constant
M	Male
M	Metabolite
MAA	Marketing authorization application
MATE	Multi-antimicrobial extrusion protein
Max	Maximum
MCF7	Michigan Cancer Foundation-7 breast cancer cell line
MoA	Mode of action
mBC	Metastatic breast cancer
MBq	Megabecquerel
MedDRA	Medical Dictionary for Regulatory Activities
MF	Matrix factor
MIDD	Model informed drug development
Min	Minimum
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MS	Mass Spectrometry
mTORi	Mechanistic target of rapamycin
MTP	Multiple testing procedure
N	Number
NA	Not applicable
NC	Not calculated
NCA	Non-compartmental analysis
NC	Not calculable
NCCN	National Comprehensive Cancer Network
nd	Not determined
nM	Nanomolar
NIR	Near Infrared Spectroscopy
NMR	Nuclear Magnetic Resonance
NMT	Not more than

NOAEL	No observed adverse effect level
Nobs	Number of patients with at least one on-treatment post-baseline result
NOEL	No observed effect level
OATP	Organic anion transporter protein
OC	Other concern
OCT	Organic cation transporter
OECD	Organisation of Economic Co-operation and Development
ORR	Objective response rate
OS	Overall survival
OVAT	one variable at a time
PAR	Proven Acceptable Range
PARPi	Poly (ADP-ribose) polymerase inhibitor
PBT	Persistent, Bioaccumulative and Toxic
PBPK	Physiologically based pharmacokinetic
PD	Pharmacodynamics
PDX	Patient derived xenograft
PEC	Predicted Environmental Concentration
PFS	Progression free survival
PFS1	Progression-free survival from the time of switch from AI to camizestrant during first-line therapy
PFS2	Second progression-free survival
Ph. Eur.	European Pharmacopeia
PI3Ki	Phosphoinositide 3-kinase inhibitor
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PK	Pharmacokinetics
PK/PD	Pharmacokinetic/Pharmacodynamic
PgR	Progesteron receptor
PNEC	Predicted No Effect Concentration
PO	Oral
PopPK	Population PK
PPE	% prediction error
PR	Progesterone receptor
PR interval	ECG interval from the onset of the P wave (the onset of atrial depolarization) to the start of the QRS complex (the onset of ventricular depolarization)
PRAC	Pharmacovigilance Risk Assessment Committee
PROs	Patient reported outcomes
PT	Preferred term
QA	ECG interval between the Q wave and the onset of the systolic blood pressure signal. A surrogate marker for cardiac contractility
QC	Quality control
QD	Once a day dose
QoL	Quality of life
QT	ECG interval measured from the beginning of the QRS complex to the end of

	the T wave
QTc	Corrected QT interval
QTcF	QT interval corrected by Fridericia's formula
QTcI	Optimised heart rate-corrected QT interval
QWBA	Quantitative whole body autoradiography
Rac	Accumulation ratio (index)
Rac AUC	Accumulation rate for AUC
Rac Cmax	Accumulation ratio for Cmax
RC	Roller Compaction
RECIST 1.1	Response Evaluation Criteria in Solid Tumours version 1.1
R.H	Relative Humidity
RMP	Risk management plan
RMST	Restricted mean survival time
RTD	Residence time distribution
RTRT	Real time release testing
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SD	Standard deviation
SERD	Selective estrogen receptor degrader
SmPC	Summary of product characteristics
SNV	Single nucleotide variants
SOC	System organ class
T1/2	Half life
$t_{1/2\lambda z}$	Terminal elimination half-life
TAMC	Total Aerobic Microbial Count
TCP	Temporal change parameter
TEAE	Treatment-emergent adverse event
TFST	Time to first subsequent therapy or death
TGI	Tumor growth inhibition
TK	Toxicokinetic
tlag	Time delay between drug administration and the first observed concentration
tmax	Time to reach maximum concentration following drug administration
TR	Total radioactivity
TROP2	Trophoblast Cell Surface Antigen 2
TSST	Time to second subsequent therapy or death
TYMC	Total Combined Yeasts/Moulds Count
UDU	Uniformity of Dosage Units
UGT	Uridine diphosphate-glucuronosyltransferases
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
UPLC	Ultra performance liquid chromatography
UV	Ultraviolet

UVR	Ultraviolet radiation
VSAQ	Visual symptom assessment questionnaire
Vss	Steady state volume of distribution
Vss/F	Apparent volume of distribution at steady state after non-intravenous administration
Vz	Volume of distribution based on the terminal phase
Vz/F	Apparent volume of distribution during the terminal phase after non-intravenous administration
Y537S	Amino acid 537 in ERα mutated from tyrosine to serine
XRD	X-Ray Diffraction
µg	microgram
µM	micromolar
µMol	micromoles

1. Administrative/regulatory information and recommendations on the procedure

1.1. Information on the product

Product data	
Product name	Etcamah
Active substance	camizestrant
INN or common name	camizestrant
Applicant	AstraZeneca AB 151 85 Sodertalje SWEDEN
EMA product number	EMA/H/C/006494
ATC code and pharmacotherapeutic group	L02BA05 L2: I02endocrine therapy, L3: I02bhormone antagonists and related agents, L4: I02ba anti-estrogens
Pharmaceutical form(s) and strength (s)	Film-coated tablet 75 mg
Packaging	blister (alu/alu)
Package size(s)	28 x 1 tablets (unit dose)
Route of administration	Oral use
Device or diagnostic	Guardant360® CDx assay: companion diagnostic with CE Mark under IVDR. The Guardant360 CDx test provides tumour mutation profiling through detection of single nucleotide variants (SNVs), insertions and deletions (indels) in seventy-four (74) genes, copy number amplifications (NAs) in eighteen (18) genes, fusions in six (6) genes, and microsatellite instability (MSI)-High status. The test utilizes circulating cell-free DNA (cfDNA) from plasma of peripheral

Product data	
	whole blood. The test is intended to be used by qualified health care professionals as a companion diagnostic to identify patients who may benefit from treatment with the therapies approved accordingly. A negative result from a plasma specimen does not assure that the patient's tumour is negative for genomic findings. Patients who are negative for the biomarkers listed should be reflexed to tissue biopsy testing using a tumour tissue test, if feasible. Additionally, the test is intended to provide tumour mutation profiling to be used by qualified health care professionals in accordance with professional guidelines for cancer patients with any solid malignant neoplasm. The test is for use with patients previously diagnosed with cancer and in conjunction with other laboratory and clinical findings.
Orphan designation	N
Orphan indication status confirmed	Not applicable
PRIME scheme	Not applied for
Type of marketing authorisation granted at opinion	Standard
Legal basis	Article 8.3 of Directive 2001/83/EC
Final indication	Etcamah in combination with a CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib) is indicated for the treatment of adult patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer upon detection of <i>ESR1</i>-mutation and without disease progression during first-line endocrine therapy in combination with a CDK4/6 inhibitor (for biomarker based patient-selection, see section 4.2 and 5.1). In pre- or peri-menopausal women and in men, Etcamah plus a CDK4/6 inhibitor should be combined with a luteinizing hormone releasing hormone (LHRH) agonist or antagonist.
New active substance status	Applied for

1.2. Scientific advice

Table 1: Scientific advice and protocol assistance

Date	Topic (quality/ non-clinical/ clinical)	Reference number / Coordinator(s)	Brief summary of the advice
15 October 2020	Non-clinical and clinical	EMA/H/SA/4613 /1/2020/III	- Planned nonclinical programme and clinical pharmacology strategy to support registration of AZD9833 plus a CDK4/6 inhibitor in advanced breast cancer; - Adequacy of the proposed design aspects of the SERENA-4 study to support the

			benefit/risk assessment, in particular, the proposed patient population and stratification factors, the choice of control arm, the sample size, targeted magnitude of benefit, statistical analysis approach, and multiple testing procedure to control the overall Type 1 error rate, the proposed plan for the assessment of PROs
22 April 2021	Clinical	EMA/SA/0000051172	Design of the phase III study SERENA-6 to support authorisation of AZD9833 in combination with a CDK4/6i (palbociclib or abemaciclib) for the treatment of HR+ HER2-MBC in adult patients with detectable levels of ESR1 mutation, who are currently on 1L NSAI + CDK4/6i therapy and have not had clinical or radiological disease progression; in particular, the patient population selection, appropriateness of endpoints, and statistical analysis plan.
22 July 2021	Quality	EMA/SA/0000061972	- Manufacturing process; finished product control strategy and batch release procedure for Phase 3; proposed validation and batch extension; proposed changes to in-process controls. - Manufacturing process modelling; bridging strategy between tablet manufacturing procedures.
9 November 2023	Quality	EMA/SA/0000148250	Ensuring State of Control; Sampling strategy; In-Line NIR Model for Blend Uniformity IPC and Assay (Model Development and Validation); decision tree for RTRT versus reference method use; control of degradation products; use of disintegration.
19 September 2024	Clinical	EMA/SA/0000180143	Proposed PK, efficacy and safety evidence plan; overall clinical development plan to support the B/R assessment for a CDK4/6i agnostic indication

EMA and national scientific advice have been received on the camizestrant quality, pre-clinical and clinical development to support marketing authorisation in the EU.

The EMA SA from September 2024 included the following key CHMP recommendations:

- The CHMP was of the opinion that an early PFS benefit at an interim analysis (IA) (i.e., 135 events as per protocol, information fraction 69%, 43% maturity), is unlikely to be considered sufficient to declare superiority from a clinical perspective as the need for support from PFS2 and OS data will be considered key.
- The CHMP indicated that support by PFS2 of good quality will be important for contextualisation of PFS effect within the patient's treatment strategy.
- The CHMP raised concerns on the interchangeability between the different CDK4/6 inhibitors in the proposed indication. The study design was revised to include all 3 CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib), and the randomisation was stratified per CDK4/6 inhibitor.
- The CHMP recommended to justify the choice of 6 months on AI + CDK4/6 inhibitor treatment before screening patients at time of submission.

- The CHMP was of the opinion that *ESR1*m surveillance of 8 to 12 weeks could introduce additional variability and ideally should be more tightly defined to e.g., every 8 ($\pm$ 1) weeks within a prospective trial setting.
- The CHMP acknowledged that the effect of early change of ET cannot be disentangled from the effect associated with continuation with CDK4/6 inhibitor and no data are available yet comparing camizestrant with fulvestrant.
- In addition, specific CHMP scientific advice was sought on the proposed overall clinical development plan (PK, efficacy and safety) to support the benefit-risk assessment for a CDK4/6 inhibitor agnostic indication (EMA/SA/0000180143).

Confirmation of European Union Paediatric Investigation Plan class waiver applicability for camizestrant has been received from EMA as adopted by the Paediatric committee during the plenary meeting held from 21 to 24 June 2022 (EMA-01-2022). The Paediatric committee confirmed that camizestrant proposed for the 'treatment of hormone receptor positive breast cancer' falls under the scope of Agency Decision CW/0001/2015.

1.3. Eligibility to the centralised procedure

The applicant AstraZeneca AB submitted on 29 May 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for Etcamah (camizestrant), through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 January 2024.

The applicant applied for the following indication:

Etcamah (camizestrant) in combination with a CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib) is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer upon detection of ESR1-mutation during first-line endocrine-based therapy.

In pre- or peri-menopausal women and in men, Etcamah (camizestrant) plus a CDK4/6 inhibitor should be combined with a luteinizing hormone releasing hormone (LHRH) agonist, in accordance with current clinical practice standards.

1.4. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, and non-clinical and clinical data based on applicant's own tests and studies.

1.5. Information on paediatrics

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA decision CW/0001/2015 on the granting of a class waiver for the classes of androgen receptor modulator, of oestrogen receptor modulator, of growth and sex hormone as well as their releasing or inhibiting factors, and of sex hormone-metabolism modulator medicinal products for treatment of breast malignant neoplasms¹, prostate malignant neoplasms² and neuroendocrine malignant neoplasms.

¹ Previously listed: breast carcinoma

² Previously listed: prostate carcinoma

1.6. Information on orphan market exclusivity

1.6.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products from the start of the procedure because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.7. Applicant's request for consideration

1.7.1. New active substance status

The applicant requested the active substance camizestrant contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.7.1.1. CHMP recommendation on new active substance status

Based on the review of available data on the active substance, the CHMP considers that camizestrant is to be qualified as a new active substance in itself, as it is not a constituent of a medicinal product previously authorised within the European Union.

1.8. Third party interventions

A third party intervention was received during the procedure. Discussion on this is reflected as relevant in the scientific report below in efficacy/safety discussions and/or benefit/risk.

1.9. Patient experience data

Table 2: Patient experience data relevant to the application

Patient experience data submitted with this application			Section where discussed (if applicable)
☒	Patient experience data submitted by the applicant:		
	☒	Clinical outcome assessments (COAs) such as	
	☒	Patient-reported outcomes (PRO)	See section 5.3.2
	☐	Other	
	☐	Patient preference studies	
	☐	Observational studies/RWD designed to capture patient experience data	
	☒	Qualitative information or studies (Consultation of 3 groups for patient-impacting study design elements (eg, visit schedule, sample collection, study activities (eg, CT scans), storage and use of data, ICF process and wording, etc.).)	See section 5.3.8

1.10. Steps taken for the assessment of the product

The rapporteur and Co-rapporteur appointed by the CHMP were:

Rapporteur:	Thalia Marie Blicher
Co-rapporteur:	Martin Mengel

The application was received by the EMA on	29 May 2025
The procedure started on	19 June 2025
The CHMP rapporteur's first assessment report was received on	8 September 2025
The CHMP Co-rapporteur's first assessment report was added to the rapporteur's report on	10 September 2025
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC and CHMP members on	11 September 2025
The CHMP agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on	16 October 2025
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 January 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs joint assessment report on the applicant's responses to the list of questions (LoQ) to all CHMP and PRAC members on	02 March 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 March 2026
The CHMP agreed on a list of outstanding issues (LoOI) to be sent to the applicant on	26 March 2026
The applicant submitted the responses to the CHMP list of outstanding issues on	21 April 2026
The CHMP rapporteur circulated the CHMP and PRAC rapporteurs Joint assessment report on the applicant's responses to the list of outstanding issues to all CHMP and PRAC members on	08 May 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to ETCAMAH on	21 May 2026
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see appendix on NAS)	21 May 2026

1.11. CHMP outcome

1.11.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.5 of this report.

Relevant paediatric statement in Section 5.1 of the SmPC if the EMA has waived a paediatric development have also been included.

1.11.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.6 of this report.

1.11.3. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of ETCAMAH is favourable in the following indication(s):

Etcamah in combination with a CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib) is indicated for the treatment of adult patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer upon detection of *ESR1*-mutation and without disease progression during first-line endocrine therapy in combination with a CDK4/6 inhibitor (for biomarker based patient-selection, see section 4.2 and 5.1).

In pre- or peri-menopausal women and in men, Etcamah plus a CDK4/6 inhibitor should be combined with a luteinizing hormone releasing hormone (LHRH) agonist or antagonist.

The CHMP, therefore, recommends the granting of the marketing authorisation subject to the conditions described in the following sections.

1.11.3.1. Divergent position(s)

Divergent position(s) to the majority recommendation on benefit/risk – full CHMP opinion and is appended to this report.

1.11.4. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

1.11.5. Other conditions and requirements of the marketing authorisation

1.11.5.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

1.11.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.11.6.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being

reached.

1.11.6.2. Obligation to conduct post-authorisation measures

In accordance with the Commission Delegated Regulation (EU) No. 357/2014 criteria 2(a), the MAH shall complete, within the stated timeframe, the below measures:

Table 3: Post-authorisation measures

Description	Due date
Post-authorisation efficacy study (PAES): In order to further characterise the long term efficacy of camizestrant in combination with a CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib) for the treatment of adult patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer upon detection of <i>ESR1</i> -mutation and without disease progression during first-line endocrine therapy in combination with a CDK4/6 inhibitor, the MAH shall submit the results of the final OS analysis from the SERENA-6 study, a phase III, randomised, double-blind study.	31 December 2028

2. Introduction

2.1. Therapeutic context

Disease

Breast cancer ranks as the second most prevalent cancer globally, accounting for 11.6% of all cancer cases (Bray et al 2024). It is the most commonly diagnosed cancer in women, comprising 23.8% of all cancer diagnoses. In 2022, over 2.3 million new cases of breast cancer were identified worldwide (Bray et al 2024). Although many patients are cured of their early-stage disease due to advances in local/regional and systemic treatment, advanced breast cancer (ABC) remains incurable. Approximately 70% of patients present with HR-positive (ER-positive and/or PgR positive), HER2-negative disease (American Cancer Society 2024-2025), making it the most common subtype in both women and men. Over two-thirds of breast cancers express the oestrogen receptor (ER), which is a key driver of breast cancer initiation and progression (Bray et al. 2024). Various studies have reported that the frequency of *ESR1*m is low (approximately 4%) at the initial diagnosis of HR-positive, HER2 negative ABC (Bardia et al 2020, Goetz et al 2024, Hortobagyi et al 2018). However, approximately 40% of patients at the end of first-line (1L) treatment of aromatase inhibitor (AI) + cyclin-dependent kinase 4/6 (CDK4/6) inhibitor have detectable *ESR1*m in ctDNA, and the prevalence of *ESR1*m rises further to > 50% in patients who have been treated with AI + CDK4/6 inhibitor for more than one year (Bhave et al 2024, Bidard et al 2022, Cardoso et al 2023, Chaudhary et al 2024).

Current therapies and unmet medical need

The preferred standard 1L treatment for patients with locally advanced/metastatic HR positive, HER2 negative breast cancer is the combination of CDK4/6 inhibitors with endocrine therapy (ET) (fulvestrant or AI) based on the results of several Phase III trials and current clinical guidelines. However, most patients eventually experience disease progression on this regimen.

A common resistance mechanism to current ET is the emergence of *ESR1*m, the gene encoding ERα (Rinaldi et al 2020). Evidence suggests that detection of *ESR1*m is associated with poor treatment outcomes in terms of PFS and OS (Turner et al 2020, Turner et al 2023), mainly owing to the lack of effective treatment options to address this driver mutation.

There are currently no 1L therapies specifically approved for the treatment of patients with HR-positive, HER2 negative ABC with emergent *ESR1*m, ahead of disease progression. Progression beyond 1L is often associated with increased toxicities of therapy regimens and diminished treatment efficacy, likely due to the increased genetic complexity of disease and increased tumour burden. Currently, Orserdu (elacestrant) and Inluriyo (imlunestrant) are approved monotherapy options for patients with *ESR1*m who have progressed on ET + CDK4/6 inhibitor, and PFS increase has been shown ((median PFS 3.8 months with elacestrant vs 1.9 months for ET's (including AI and fulvestrant) and mPFS 5.5 months with imlunestrant vs 3.8 months for ET's (including AI and fulvestrant), (Orserdu EPAR, Inluriyo EPAR)).

2.2. Aspects of development

An overview of the clinical development in view of the proposed indication and posology is presented below (Table 4).

Table 4 Overview of Clinical Studies with Efficacy Data Supporting Camizestrant in this Application

Study (DCO)	Design and Patient Population	Study and Control Drugs (Dose, Route, and Regimen)	Key Outcome Measures	Patients by Treatment (Treated)
Pivotal study				

Table 4 Overview of Clinical Studies with Efficacy Data Supporting Camizestrant in this Application

Study (DCO)	Design and Patient Population	Study and Control Drugs (Dose, Route, and Regimen)	Key Outcome Measures	Patients by Treatment (Treated)
D8534C000 01 SERENA-6 (28 Nov 2024)	Phase III, parallel, randomised, double-blind with matching placebos, 2-arm, multicentre study Patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer with detectable <i>ESR1m</i> , without disease progression during first-line treatment with AI + CDK4/6 inhibitor	Camizestrant + CDK4/6 inhibitor arm: Camizestrant (75 mg oral, QD) + CDK4/6 inhibitor (continuing palbociclib, ribociclib, or abemaciclib, maintained at the same dose as when the <i>ESR1m</i> was detected) + placebo for AI AI + CDK4/6 inhibitor arm: AI (continuing anastrozole 1 mg oral, QD or letrozole 2.5 mg oral, QD) + CDK4/6 inhibitor (continuing palbociclib, ribociclib, or abemaciclib, maintained at the same dose as when the <i>ESR1m</i> was detected) + placebo for camizestrant Note: All pre- or peri-menopausal female or male patients (as medically applicable) received a concurrent monthly LHRH agonist (goserelin or leuprorelin) during Treatment Phase	Primary: PFS (Investigator) Secondary: PFS2, OS, ORR, CBR at 24 weeks, TFST, TSST, chemotherapy-free survival, TTD in PROs, PK, safety and tolerability including AEs, laboratory evaluations, ECGs, vital signs and ophthalmologic assessments	Randomised: 315 Treated: 310 Camizestrant + CDK4/6 inhibitor arm: 155 AI + CDK4/6 inhibitor arm: 155
Supportive Phase I/II studies				
D8530C000 01 SERENA-1 (Parts C and D 09 Sep 2021; Parts G and H, and Parts K and L: 16 Sep 2024)	FIH Phase I, open-label, multicentre, multi-cohort, dose-escalation and expansion study Women with ER-positive, HER2-negative advanced breast cancer, progressed on at least one line of endocrine-based therapy in advanced setting	Part C (dose-escalation): pre-and post-menopausal patients: 3 cohorts - camizestrant (75, 150, or 300 mg, oral, QD) + palbociclib (125 mg, oral QD; 21 days on, 7 days off) Part D (dose-expansion): pre-menopausal patients: camizestrant (300 mg oral, QD) + palbociclib (125 mg oral, QD; 21 days on, 7 days off); post-menopausal patients: camizestrant (75, 150, or 300 mg, oral, QD) + palbociclib (125 mg, oral, QD; 21 days on, 7 days off) Part G (dose-escalation): pre-and post-menopausal patients: 2 cohorts - camizestrant (75 and 150 mg, oral, QD) + abemaciclib (150 mg, oral, BID) Part H (dose-expansion): pre-and post-menopausal patients: 2	Primary: safety and tolerability including AEs, DLTs, laboratory evaluations, ECGs Secondary: efficacy (ORR, DoR, CBR at 24 weeks, change in tumour size, PFS), PK (single and multiple dose), biomarker changes	Part C: 36 Part D: 42 Part G: 28 Part H: 25 Part K: 30 Part L: 30

Table 4 Overview of Clinical Studies with Efficacy Data Supporting Camizestrant in this Application

Study (DCO)	Design and Patient Population	Study and Control Drugs (Dose, Route, and Regimen)	Key Outcome Measures	Patients by Treatment (Treated)
		cohorts - camizestrant (75 and 150 mg, oral, QD) + abemaciclib (150 mg, oral, BID) Part K (dose-escalation): pre- and post-menopausal patients: 2 cohorts - camizestrant (75 mg, oral, QD) + ribociclib (400 and 600 mg, oral, QD; 21 days on, 7 days off) Part L (dose-expansion): pre- and post- menopausal patients: 2 cohorts - camizestrant (75 mg, oral, QD) + ribociclib (400 and 600 mg, oral, QD; 21 days on, 7 days off)		
D8530C000 02 SERENA-2 (Primary PFS analysis: 30 Aug 2022; and 50% OS analysis: 30 Mar 2024)	Phase II, randomised, open-label, parallel-group, multicentre study Post-menopausal women with ER-positive, HER2-negative advanced breast cancer who were suitable for therapy with fulvestrant and had received no more than one previous ET and one previous chemotherapy in the advanced setting	Camizestrant (75 mg oral, QD) Camizestrant (150 mg oral, QD) Camizestrant (300 mg oral, QD) Fulvestrant (500 mg IM, Day 1, Day 15, Day 29, and 4-weekly thereafter)	Primary: PFS Secondary: ORR, DoR, percentage change in tumour size, OS, CBR at 24 weeks, PK, PD, HRQoL, safety and tolerability including AEs, ECGs, laboratory evaluations, vital signs	Total: 240 Camizestrant 75 mg: 74 Camizestrant 150 mg: 73 Camizestrant 300 mg: 20 ^a Fulvestrant 500 mg: 73

^a Enrolment to camizestrant 300 mg stopped as of December 2020 with ongoing patients in this arm continuing treatment.

2.3. Description of the product

Camizestrant is an oral selective SERD and estrogen receptor (ER) antagonist. Camizestrant binds to the ligand binding domain of ER α , antagonising the activity of ER α encoded by both wild-type *ESR1* and *ESR1m*, and inducing proteasome-dependent degradation of ER α , without agonising ER α .

The therapeutic indication applied for was:

Etcamah in combination with a CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib) is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer upon detection of *ESR1*-mutation during first-line endocrine-based therapy.

In pre- or peri-menopausal women and in men, Etcamah plus a CDK4/6 inhibitor should be combined with a luteinizing hormone releasing hormone (LHRH) agonist, in accordance with current clinical practice standards.

The final approved therapeutic indication is:

Etcamah in combination with a CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib) is indicated for the treatment of adult patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer upon detection of *ESR1*-mutation and without disease progression during first-line endocrine therapy in combination with a CDK4/6 inhibitor (for biomarker based patient-selection, see section 4.2 and 5.1).

In pre- or peri-menopausal women and in men, Etcamah plus a CDK4/6 inhibitor should be combined with a luteinizing hormone releasing hormone (LHRH) agonist or antagonist.

The recommended dose of Etcamah in combination with a CDK4/6 inhibitor is 75 mg once daily. The CDK4/6 inhibitor should be continued at the same dose at the time of initiation with Etcamah as when the *ESR1*m was detected. For the recommended dosing information reference is advised to the SmPC of the CDK4/6 inhibitor or LHRH agonist or antagonist. If the CDK4/6 inhibitor is permanently discontinued, Etcamah should also be discontinued.

Camizestrant is not currently approved for marketing in any country.

2.4. Inspection issues

2.4.1. Good manufacturing practice (GMP) inspection(s)

Proof of GMP compliance for all manufacturing and testing sites is available. No inspection was deemed required.

2.4.2. Good laboratory practice (GLP) inspection(s)

All pivotal non-clinical safety pharmacology and toxicology studies were conducted in Organisation of Economic Co-operation and Development (OECD) member countries under an extensive GLP audit program with the majority of studies being conducted at European located Laboratories. In general, the studies appeared to be GLP compliant.

No inspection was considered to be additionally required.

2.4.3. Good clinical practice (GCP) inspection(s)

No inspection was considered to be additionally required. GCP inspection information from the US FDA was also considered during this assessment.

3. Quality aspects

3.1. Introduction

The finished product is presented as film-coated tablets containing 75 mg of camizestrant as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose (type 102), calcium hydrogen phosphate, sodium starch glycolate (Type A) and magnesium stearate

Tablet coating: polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, iron oxide red (E172), iron oxide yellow (E172) and iron oxide black (E172).

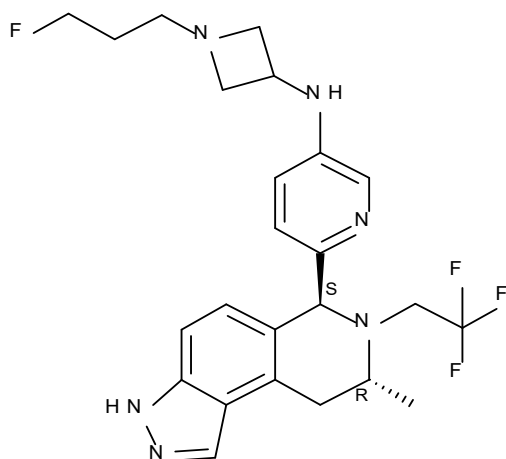
The product is available in aluminium/aluminium perforated unit dose blisters, as described in section 6.5 of the SmPC.

3.2. Active substance

3.2.1. General information

The applicant provided full details of the manufacturing and control of the active substance.

The chemical name of camizestrant is N-[1-(3-Fluoropropyl)-3-azetidiny]-6-[(6S,8R)- 8-methyl-7-(2,2,2-trifluoroethyl)-6,7,8,9- tetrahydro-3H-pyrazolo[4,3-f]isoquinolin-6-yl]-3-pyridinamine corresponding to the molecular formula $C_{24}H_{28}F_4N_6$. It has a relative molecular mass of 476.51 and the following structure, scheme 1:



Scheme 1. Camizestrant chemical structure

The chemical structure of the active substance was elucidated by a combination of mass spectrometry (MS), 1H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy, infrared spectroscopy (IR), elemental analysis and ultraviolet spectroscopy.

The absolute configuration and crystal status of camizestrant have been confirmed by single crystal X-ray diffraction (SXRD).

Camizestrant is a crystalline powder that is slightly soluble in water (0.14 mg/mL) and very soluble (> 1.2 mg/mL) below pH 4.5.

Camizestrant exhibits stereoisomerism due to the presence of two chiral centres, which are in the 6S,

8R configuration Chiral purity is controlled routinely by chiral Supercritical Fluid Chromatography (SFC) which is specific for all the four possible stereoisomers

Extensive polymorph screening has confirmed the existence of solvated and non-solvated crystal modifications of camizestrant. The manufacturing process from the applicant consistently produces camizestrant of a non-solvated crystalline form. Stability studies on camizestrant showed that there is no conversion to other forms under long-term, accelerated or stressed conditions (see stability section).

Camizestrant is a non-hygroscopic stable molecule and is only slowly degraded in basic, acidic or oxidative conditions.

3.2.2. Manufacture, characterisation, and process controls

Description of manufacturing process and process controls

Satisfactory GMP documentation for drug substance manufacturing sites has been provided.

The synthesis of camizestrant can be described as a 3-step convergent synthesis starting from well defined starting materials.

Proposed starting materials are acceptable

Starting materials and isolated intermediates, critical parameters are defined by the applicant.

A design space is not claimed. Proven acceptable ranges (PARs) have been defined for the manufacturing process from factorial experimental design (FED) or one variable at a time (OVAT) studies.

Manufacturing process development

Throughout development the conversion of the starting material to camizestrant has used the same bond-forming steps. Several minor adjustments have been incorporated over time. These have been adequately described. Briefly, the evolution of the synthetic process can be divided into five distinct 'generations'. Generation 1 and 2 are classed as early-phase development version of the process (generation 1 was used to manufacture pre-clinical batches of camizestrant). Generation 3 is classed as mid-development version of the process. Generations 4 and 5 are classed as late-development versions of the process. Generation 5 is the commercial manufacturing process. The other generations have provided some of the material used for batches for toxicology studies, etc.

3.2.3. Specification

Specifications

The active substance specification includes tests for description, identification (FT-IR), assay (LC), organic impurities (LC), polymorphic form (XRD), residual solvents (GC), particle size distribution (laser diffraction) and sulphated ash (Ph.Eur.).

The EU/ICH Q3A thresholds are applied (maximum daily dose is not defined. Daily dose is 75 mg):

Reporting level: 0.05%; ID threshold: 0.10%; Qualification threshold: 0.15 %.

During the review the applicant was requested to tighten the assay limit and several impurity limits in line with batch data from commercial generation 5 synthesis and not use historical batch data and to include a test for residue of ignition or sulphated ash. This was satisfactorily addressed.

Acceptable justifications for the omission of water content, stereoisomeric impurities, palladium, elemental impurities, other residual solvents, microbiological quality and mutagenic impurities have been provided.

A discussion of the present and potential impurities, including mutagenic impurities has been presented. The information is considered satisfactory.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

Analytical procedures and reference standards

The analytical methods for assay (LC), organic impurities (LC) and Residual solvents (GC) have been validated. Polymorphic form (by XRPD) has been validated for specificity and PSD (by laser diffraction) has been validated for Precision, accuracy and robustness. Satisfactory information regarding the reference standards has been presented.

Batch analysis

Batch analysis data from eleven commercial scale batches of the active substance manufactured using the proposed manufacturing process (Generation 5) are provided. The results are within the specifications and consistent from batch to batch.

Container closure

The active substance is stored in low-density polyethylene (LDPE) bags, which are placed in a sealed aluminium foil bag. The aluminium bag is placed within a rigid outer container.

The primary packaging material complies with regulation EU No. 10/2011 (and its amendments). Specification and a typical IR spectrum for LDPE is provided.

3.2.4. Stability

Stability data from three pilot scale batches of camizestrant from the mid development process (generation 3, from a development site) and supportive stability studies of three commercial scale batches of camizestrant from the late development process proposed for commercial use (generation 5) from the proposed commercial manufacturing site stored in the intended commercial package were presented. Changes between generation 3 and generation 5 were minor; they were intended to improve process robustness and efficiency. There were no significant changes in the final stages to form AZD9833 crude and camizestrant. The quality of AZD9833 crude and camizestrant batches manufactured during the mid development and the late development processes are comparable. As a result, the primary stability batches are deemed representative of the batches produced by the commercial process.

Samples were stored for up to 24 months under long term conditions (25 °C / 60% RH and intermediate conditions 30°C/75% RH), and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines. Photostability testing following the ICH guideline Q1B was performed on one batch.

The following parameters were tested: description, assay, organic impurities, stereoisomeric impurities, polymorphic form, particle size distribution, water content, microbial quality and water activity. The analytical methods used were the same as for release and were stability indicating

No significant changes were observed in any of the attributes tested under any of the storage conditions. The data confirms that camizestrant is stable when exposed to light.

With regards to the ongoing stability program any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Results on stress conditions were also provided. Thermal stability of camizestrant in solid state was assessed for camizestrant at 50°C for 3 months, hydrolytic stability was assessed by storing camizestrant at 40°C/75% RH for 6 months. No significant degradation was observed under any of the conditions studied, demonstrating that camizestrant is inherently stable in the solid state

In addition, forced degradation studies were performed to elucidate degradation pathways and to confirm the suitability of the analytical methods applied to the stability studies using camizestrant solutions in pH 1 (acidic), pH 7 (neutral), pH 13 (basic) under high temperature, oxidative conditions (hydrogen peroxide, 4,4'-azobis(4-cyanovaleric acid) (ACVA, copper (II) chloride and iron (III) chloride). Degradation of camizestrant was observed under strong acidic, basic and oxidative (hydrogen peroxide, ACVA, Cu(II)Cl₂ and Fe(III)Cl₃) when in solution.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months when stored at or below 30°C in the proposed container.

3.3. Finished medicinal product

3.3.1. Description of the product and pharmaceutical development

Description of the product

The finished product is an immediate release film-coated tablet for oral administration in the strength of 75 mg packed in blister packaging.

The finished product is a beige, round, biconvex, film-coated tablet, approximately 9 mm in diameter and debossed with 'CM' above '75' on one side and plain on the reverse.⁵

Pharmaceutical development

The aim of the pharmaceutical development was to develop a once daily immediate release oral dosage form of camizestrant. The early development program of camizestrant covered three tablet strengths, 25, 75 and 100 mg. The 75 mg strength was selected for commercialization.

As indicated in the active substance section, camizestrant is a non-hygroscopic highly soluble non-solvated crystalline solid. Its polymorphic form and particle size are controlled in the active substance specification.

Polymorphic form within the finished product was monitored throughout development confirming the presence of the proposed commercial polymorphic form of camizestrant.

The chosen excipients are conventional in pharmaceuticals and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. Given the continuous manufacturing (CM) process the applicant was requested to discuss the functionality related characteristics (FRC) of the excipients and update their specifications accordingly. The limits were sufficiently justified based on the excipient batches used to manufacture the DoE batches and process validation batches.

The formulation development has sufficiently shown that the chosen formulation is suitable for film-coated tablet that fulfill the quality target product profile for an immediate release tablet.

Process robustness to excipient variability include attributes that is potentially relevant to continuous direct compression (CDC) process robustness.

The formulation has been demonstrated to be robust towards minor changes in excipients amounts and coating weight gain.

In the original submission, the applicant proposed an in-silico model for disintegration (based on porosity of the core tablets and coating weight gain) as a surrogate for disintegration to support real time release testing. The justification was based on ICH Q6A and the criteria outlined in its decision tree 7(1). Disintegration testing in lieu of dissolution testing was not considered acceptable by CHMP as the dissolution method development was not considered sufficient and it could not be concluded

that the dissolution is rapid as per ICH Q6A or that disintegration testing is more discriminatory than dissolution (MO 1). To address this MO the applicant presented a more thorough discussion and further clarifications on the dissolution method development, and included dissolution testing in the specification in addition to disintegration testing. The early development work of camizestrant drug product included a formulation selection study focused on screening of chemical stability and manufacturability of various tablet prototypes. Prototype tablet formulations containing different diluents, disintegrants and lubricant were produced through a roller compaction (RC) process. The diluents were selected to obtain a combination of plastic and brittle compression properties of the prototype formulations and to provide robust mechanical properties for a dry manufacturing process. A specific drug load was chosen to enable production of relevant tablet strengths for the clinical program by using a common powder blend or granule. By comparing the results from chemical stability, processability and dissolution performance, the most suitable prototype composition to proceed with for the early clinical program was selected. This formulation was deemed suitable for continued clinical supply. Further development work was conducted during phase 3 to change the manufacturing process from RC to CDC process for commercial use. Camizestrant film-coated tablets produced through RC and CDC are of the same qualitative and quantitative composition.

Bridging between the RC and DC tablets (representative of the CDC tablets) was justified by comparative in vitro dissolution pH 1.2, 4.5 and 6.8 and comparative plasma exposures generated in a relative bioavailability study in conjunction with dosing of an oral solution (study D8530C00004). In vitro studies showed that dissolution was very rapid (85% or more dissolved within 15 minutes) in all media. The bioavailability study showed similarity in exposure between the RC and DC tablets and between RC and DC tablets and the oral solution. These data demonstrate there is no impact of manufacturing process technology on camizestrant plasma exposure and therefore the change to CDC during pivotal clinical studies has no impact on finished product in vivo performance.

The development of the CDC process started with a material characterisation study and proof of concept study to demonstrate the suitability of CDC as manufacturing technology for camizestrant tablets but also to identify suitable target parameter settings for production of clinical trial material.

Loss in weight feeders are used to add the active and excipients into a blender for mixing. After blending the blend is compressed into tablet cores. Up to and including tablet compression the process is in continuous manufacturing mode and coating of the tablet cores is performed in batch mode.

The applicant has not applied QbD principles in the development of the finished product and their manufacturing process. A factorial DoE experiment is performed that included 4 factors. Detailed results of these experiments are not provided and a short discussion and conclusion by the applicant is included.

The control strategy described in the original submission was insufficiently documented and critical information was missing from dossier sections P.2.3., P.3.3 and P.3.4. e.g, justification of the proposed process parameters ranges, description of the mechanism is in place to evaluate the consistency of the process (e.g. alert and action limits), residence time distribution (RTD) characteristics, information about the loss in weight feeders and the in-line blender, diversion and rejection mechanisms, characterisation of the process dynamics, description of the sampling strategy for the NIR method and equipment design and system integration. This led to MO2 and MO3.

In addition, the control strategy in the original submission also included real time release testing (RTRT) for identification of the active substance, assay, uniformity of dosage units and disintegration. RTRT had not been adequately supported by data in line with the CHMP guideline on RTRT (EMA/CHMP/QWP/811210/2009-Rev1), section 6.2 and a valid proof of GMP compliance including RTRT for the manufacturing site was missing (MO6).

The applicant acknowledged the concerns and updated the dossier providing further context to the control strategy. The applicant also reported issues with the NIR equipment and NIR model prior to Process Performance Qualification (PPQ) and the start of commercial manufacturing, and given the

failed attempts to re-establish the NIR model to support process validation activities decided to withdraw the NIR methods from the proposed control strategy. Consequently, at line liquid chromatography (LC) stratified testing to control the process was established.

The control strategy for the continuous manufacturing process includes active process controls and in process testing. The strategy for start-up, pause and shutdown mitigations to prevent material build-up and assessment of process robustness to variability of active substance and excipient characteristics has been defined.

3.3.2. Manufacture of the product and process controls

Manufacture

Satisfactory evidence of GMP compliance has been provided for all sites involved in the manufacturing, testing and batch release of the finished product.

The proposed batch size is defined by the input material.

The manufacturing process consists of four main steps: feeding/milling/mixing, compression, film-coating and packaging.

The manufacturing process is non-standard as it includes continuous manufacturing. , The core tablets are obtained by continuous manufacturing and the film-coated is performed in a batch-mode.

As requested by CHMP during the review the description of the manufacturing process was revised to include process parameters with defined and acceptable proven ranges, a summary of start-up, shutdown, pause and restart procedures, the equipment design and the sampling plan and detailed diversion strategy.

Proven acceptable ranges (PARs) have been defined for several steps of the manufacturing process. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

A holding time for the uncoated core tablets of up to 90 days at below 25°C has been proposed.

To support this hold time, two commercial scale batches of core camizestrant tablets, 75 mg, manufactured at the commercial site packed in double LDPE bags inside an aluminium foil bag with desiccants were placed on stability at long-term condition (25°C/60% RH) for 90 days. Samples were tested for the same parameters as in the finished product stability studies (see section below). No changes were observed in any of the attributes tested and therefore the proposed holding time is acceptable.

Process controls

The in-process controls are sufficiently described, as well as the active process controls. The sampling plan for the IPCs is described.

Process validation / verification

Satisfactory process validation data has been provided by the applicant as requested by CHMP in a scientific advice and during the MAA review (MO 4). Manufacturing process validation is shown regarding start-up, pauses, shutdown and the state control during manufacturing of validation batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

3.3.3. Product specification

Specifications

:

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: description (visual), identification (LC/UV), assay (LC), degradation products (LC), disintegration (Ph.Eur.), dissolution (in-house), uniformity of dosage units by weight variation (Ph.Eur.) and microbiological quality (TAMC, TYMC, E.coli) (Ph.Eur.).

T6

In the original submission the applicant proposed a NIR spectroscopy method (test done just before tablet compression) as the primary method for identification, assay and UDU. However, since critical documentation for real time release testing (RTRT) in line with the CHMP guideline on RTRT was missing (e.g. relationship between end-product testing, material attributes, process monitoring and acceptance criteria, suitable scoped MIA/GMP certificate for the site in question, minimum acceptable sample size for the RTRT, substantial comparative data at commercial scale -parallel testing-) CHMP raised a MO (MO 6). Due to performance issues with the NIR equipment/model, these were withdrawn by the applicant during the review.

In addition, as discussed above, disintegration as a surrogate for dissolution was originally proposed but was not considered sufficiently justified by CHMP (MO1). The applicant was requested to develop a suitable dissolution method and include dissolution in the finished product specification.

Description and identification acceptance criteria are acceptable. Assay limit at release and shelf-life (tightened during the review) is also acceptable. Disintegration limits at release and at shelf-life are sufficiently justified. The degradation product limits were tightened during the review and are considered acceptable. Uniformity of dosage units and microbiological acceptance criteria is acceptable.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three commercially representative batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

Following the request from CHMP (MO5), a risk assessment concerning the potential presence of nitrosamine impurities in the finished product was provided considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Since camizestrant is intended for the treatment of cancer patients with serious and life-threatening malignancies as defined by guidance ICH S9 'Non-clinical Evaluation for Anticancer Pharmaceuticals'. *N*-Nitrosamine impurities controlled according to ICH Q3B guidelines. The risk assessment considered the active substance, excipients, manufacturing process, packaging materials and stability of the tablets. In the active substance, two potential nitrosamines have been identified in addition to the nitrosamine of camizestrant, although it has been concluded there is no risk for formation of these above the permitted level of 0.10% in the active substance. Camizestrant is a secondary amine, and an evaluation of the formulation composition and manufacturing process

identified the potential presence of nitrites in the excipients at levels <10 ppm. A calculation has been performed to assess the theoretical amount of nitrosamines that could potentially form assuming the reaction goes to 100% completion using the daily dose of 75 mg. This calculated amount is significantly below (<10%) the ICH Q3B identification limits of 0.2%. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

Sufficient justification has also been provided for not including residual solvents, stereoisomeric impurities, water content and physical form in the finished product specification.

Analytical procedures and reference standards

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Stress studies of the finished product show that the analytical methods are stability indicating.

The only reference standard used for routine analysis of the finished product is the camizestrant reference standard and a reference is given to active substance module, where it is sufficiently detailed.

Batch analysis

Batch analysis data has been presented for multiple batches including the initial clinical batches and three commercial scale batches manufactured by CDC used for process validation. The batch analysis shows similar results confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Container closure

The finished product is packed in aluminium/aluminium perforated unit dose blisters. The material in direct contact with the drug product is confirmed to comply with EU 10/2011. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

3.3.4. Stability of the product

Stability data from three pilot and one commercial scale batches of finished product stored for up to 36 months at long-term (25 °C / 60% RH) and intermediate (30°C/75% RH) storage conditions and 6 months at accelerated storage conditions (40 °C / 75% RH) according to ICH guidelines were provided.

The batches were manufactured using commercial process, except for the debossing, which is not expected to impact any conclusions. The batches were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay, degradation products, disintegration, dissolution, water content and microbiological quality.

Stability data showed no significant change in description, assay, degradation products, dissolution, water content or microbiological quality under any of the conditions tested. A slight increase in disintegration time was observed. This trend was consistent across all batches in the primary stability studies. However, the change is not considered to have any impact on the quality or performance of the product.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The data confirm that the finished product is not photolabile.

Based on available stability data, the proposed shelf-life of 36 months with no storage conditions as stated in the SmPC (section 6.3) are acceptable.

In order to support bulk hold times between the end of manufacture and primary packaging, two pilot scale batches of camizestrant film-coated tablets manufactured at the commercial site were packed in aluminium foil bags and set down on stability in accordance with ICH Q1A at long-term condition (25 °C/60% RH) for up to 24 months and accelerated condition (40°C/75% RH) for 6 months . No change in description, assay, degradation products, dissolution, water content or microbiological quality was observed. A slight increase in disintegration time was observed. However, the changes were not significant and have demonstrated no impact on the quality or performance of the product. Therefore, the proposed bulk holding time of the film-coated tablets of 24 months is acceptable.

3.3.5. Post approval change management protocol(

Not applicable.

3.3.6. Adventitious agents

No excipients derived from animal or human origin have been used.

3.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The finished product is manufactured using a hybrid CM mode (i.e. some unit operations operate in a batch mode while others are integrated and operate in a continuous mode). Several MOs were raised during the procedure concerning: MO1 on the development of the dissolution method and the proposal for an in-silico model for disintegration as a surrogate for dissolution to support real time release testing; MO2 and MO3 on the lack of relevant information in P.2.3. to support the proposed control strategy and the insufficiently documented control strategy; MO4 on the missing process validation results on the finished product; MO5 on the incomplete risk assessment for potential nitrosamine impurities; and MO6. on the original proposal to use RTRT as part of the control strategy. Acceptable documentation was provided to address each MO. The NIR method and RTRT proposal was withdrawn. The proposed control strategy consists of material attributes of the input materials, set-points and/or PARs for process parameters, process monitoring and control, the strategy for diversion and collection of non-conforming material, the equipment design, system integration and end product testing. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

3.5. Recommendations for future quality development

Not applicable.

4. Non-clinical aspects

4.1. Introduction

Camizestrant is a next generation oral selective estrogen receptor degrader (nSERD) and complete estrogen receptor (ER) antagonist. Camizestrant has been tested in a range of ER-positive breast cancer PDX models that harbour either wild type or mutant *ESR1* and has been tested in combination with a CDK4/6i. ADME studies to describe the pharmacokinetic profile in rats and dogs were

performed. Camizestrant has also been tested in a panel of safety pharmacology GLP studies, and secondary pharmacology and cardiac ion channel screens. Camizestrant has been evaluated in repeat dose oral toxicology GLP studies of up to six months duration in rat, and up to 9-months duration in dog. In addition, *in vitro* and *in vivo* genotoxicity studies, reproductive toxicology studies (assessing male fertility on the 6-month rat toxicity study, embryofetal development with pre- and post-natal assessments in rats and female fertility and early embryonic development in rats) and an *in vitro* phototoxicity study have been conducted according to GLP. Mechanistic studies related to heart rate reduction and visual effects have been conducted. A 1-month rat GLP study has been conducted for the purpose of impurity qualification. Scientific advice was obtained EMA/CHMP/SAWP/528818/ 2020, Procedure No.: EMEA/H/SA/4613/1/2020/III regarding CHMP recommendations on cardiovascular safety, which have been adequately addressed in the MAA for camizestrant with the exception of mechanistic studies to explore potential mechanisms of non-hERG-related QT prolongation.

4.2. Analytical methods

Camizestrant was quantified in rat, dog and monkey serum using extraction via protein precipitation and then analysed by liquid chromatography with mass spectrometric detection (LC-MS/MS). Samples from the GLP rat (28-day and 6-month), GLP dog toxicology studies (28-day and 9-month), safety pharmacology studies and investigative dog cardiovascular studies were extracted via protein precipitation and subsequently analysed for camizestrant using a validated LC-MS/MS method. Bioanalytical methods developed for quantitation of serum camizestrant in rat and in dog GLP toxicity and safety pharmacology studies were considered sufficiently validated and fit for purpose.

4.3. Pharmacology

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

4.3.1.1.1. *In vitro* pharmacology

Several *in vitro* studies were conducted in support of the suggested mode of action (MoA) of camizestrant (AZD9833) to evaluate its estrogen receptor binding affinity, specificity and efficacy.

Estrogen receptor (ER) binding:

In an *in vitro* competitive binding assay using human wild-type (WT) ER α and ER β ligand-binding domains (LBDs) and a fluorescent marked ER ligand (fluormone ES2), camizestrant displaced the ER ligand with IC₅₀ values of 2.4 nM and 11.3 nM for WT ER α and ER β , respectively. Additionally, camizestrant also displaced the ER ligand from ER α LBDs containing clinically relevant *ESR1* mutations (Y537N, Y537C, S463P, D538G, Y537S and E380Q) with IC₅₀ values of 2.0, 2.2, 2.9, 6.7, 13.6 and 13.7 nM, respectively. Selectivity was shown by a >4000-fold difference in IC₅₀ values to closely related nuclear hormone receptors, androgen receptor (AR) and progesterone receptor (PR) with an IC₅₀ of > 100000 nM and 59790 nM, respectively.

ER α degradation:

Camizestrant downregulated ER α in a dose-dependent manner with an IC₅₀ of 0.2 nM in an *in vitro* plate-based immunofluorescence assay in ER+ MCF7 breast cancer cells. Reduction in ER α protein levels (100%) were shown by Western Blot to be comparable between camizestrant and fulvestrant at saturated concentrations of 100 nM in a panel of nine ER-positive cell lines (MCF7, CAMA-1, T47D, BT474, MDA-MB-134, MDA-MB-361, ZR-75-1, HCC1428 and an ER+ve human endometrial cell line

(Ishikawa)). No effect on ER β or androgen receptor (AR) was noted in MCF7 cells under the same condition, indicating that camizestrant is selective for ER α . Addition of a proteasome inhibitor (MG132) counteracted ER α reduction in MCF7 cells, indicating that the observed decrease in ER α protein was due to proteasome-dependent degradation mechanisms. Camizestrant dependent degradation was further confirmed in a SILAC assay, where heavy-labelled ER α peptide was tracked over time to measure ER α half-life in two independent experiments, and half-life was reduced from 2.54 and 3.86 hours in DMSO to 0.70 and 0.46 hours in the presence of camizestrant.

Antagonistic effect of camizestrant:

The ability of camizestrant to antagonize ER α activity was evaluated by reduction in progesterone receptor (PR) protein expression levels by using immunofluorescence in wild-type MCF7 cells in the presences of estradiol, or in engineered MCF7(Y537S) cells with a Y537S *ESR1* mutation. Camizestrant antagonized PR expression with an IC₅₀ concentration of 0.3 nM in MCF7 cells and 7.7 nM in MCF7(Y537S) cells. Maximal PR downregulation was equivalent to fulvestrant at 100nM.

RNA sequencing, presented as a heatmap, was used to determine the effect of camizestrant on a core set of common oestradiol-induced and oestradiol-repressed genes in MCF7 and CAMA1 cells. Camizestrant (100nM) downregulated the expression of all ER-regulated genes normally increased by oestradiol, such as PGR, TFF1 and GREB1, and likewise, camizestrant increased the expression of all genes whose expression was normally decreased by oestradiol. Comparable results were observed at whole transcriptome level, where camizestrant (100 nM) completely reversed all oestradiol-induced gene expression changes in three ER+ cell lines (MCF7, CAMA1 and BT474c) without modulating any genes that were not modulated by oestradiol. These data confirmed camizestrant as a selective ER antagonist.

ER antagonistic activity and selectivity was confirmed in a panel of cell lines expressing related nuclear hormone receptors (NHRs) sharing structural homology in core elements, including the LBD. Camizestrant showed a high level of antagonism against human ER α and ER β with 88 and 95% inhibition, respectively, and minimal activity (< 25% inhibition) against other receptors in the panel.

Lack of agonistic effect of camizestrant:

In order to show that camizestrant does not act as a full or partial agonist (like tamoxifen), levels of PR expression, a marker of transcriptional ER activity, were assessed by immunofluorescence in two ER-positive cell lines (MCF7 and Ishikawa, an endometrial cancer cell line) cultured in the absence of oestradiol. No PR expression was induced by camizestrant in concentrations of 300 nM or 100 nM in MCF7 or Ishikawa cells. Lack of response in the Ishikawa cell line furthermore indicated a reduced risk of uterotrophic agonism in vitro.

Furthermore, the lack of agonistic effect of camizestrant was also confirmed in the NHR panel assay, where no significant agonist activity was observed in the tested receptors (< 2% agonism relative to the control agonist).

Antiproliferative effect of camizestrant:

Camizestrant inhibited cell proliferation in the ER-positive breast cancer cell lines MCF7, CAMA1, T47D and HCC1428 at IC₅₀ values in the low nanomolar range of 0.3 to 0.8 nM in a 7-day cell proliferation study using a sytox green assay for determining the number of dead cells. It was noted that cells were not treated with oestradiol and hence only limited cell growth is expected. However, an IC₅₀ of 4.8 nM was seen in a 4-day sytox green proliferation assay using MCF7 WT cells in the presence of oestradiol (0.1 nM), whereas an IC₅₀ of 33.3 nM was noted in MCF7 Y537S mutated cells without oestradiol. Camizestrant was > 400-fold less potent at inhibiting proliferation in the ER-negative cells lines Calu-6 and A375 with IC₅₀ values of >14422.5 and >17367 nM, respectively.

An antiproliferative effect with a potency within the nanomolar range was supported in MCF7 models engineered by CRISPR to express the most prevalent *ESR1* mutations (D538G, Y537S, E380Q,

Y537N/C/D, L536H/P/R and S463P), all gain of function mutations that confer constitutive ER activity in the absence of oestradiol. Camizestrant inhibited proliferation with IC₅₀ values ranging from 0.15 to 8.71 nM in all these models.

Antiproliferative effect of camizestrant in combination with CDK4/6i:

Two *in vitro* studies were conducted exploring the effect of camizestrant in combination with CDK4/6i on anti-proliferative effect (#ONC9833-010) and expression of downstream pathway biomarkers (#ONC9833-011). In the first study, MCF7 and T47D cells were exposed to increasing concentrations of CDK4/6 inhibitors (i.e. abemaciclib, palbociclib or ribociclib) in the presence or absence of a fixed dose of camizestrant. Enhanced anti-proliferative activity was observed in the presence of camizestrant for all three CDK4/6 inhibitors across a range of concentrations.

The second study was conducted in MCF7 cells to evaluate the effect of camizestrant and CDK4/6i combination-treatment on modulation of ER and CDK4/6 pathway biomarkers by western blotting, as well as on cell cycle by EDU and DNA staining followed by flow cytometry. Results were not highly convincing but some trends could be seen. Camizestrant caused a dose-dependent reduction in ER and the ER-regulated gene for the TFF1 protein which was maintained in the presence of the CDK4/6i, indicating that CDK4/6i did not impact the ability of camizestrant to inhibit and degrade ER α .

Phosphorylated RB (pRB) S780 levels, a cell cycle marker for G1/S transition and hence cell proliferation, was dose-dependently reduced by each monotherapy but even more by the combination of camizestrant and the different CDK4/6 inhibitors. This correlated with cell cycles data indicating a dose-dependent arrest in G1, which increased with combination-treatment especially at the higher concentrations tested (>100 nM CDK4/6i and 30 nM camizestrant). Similar tendencies were seen in the mutated MCF7 *ESR1* Y537S cells.

In vitro cellular activity of the glucuronide metabolites of camizestrant:

The major drug-related circulating metabolites of camizestrant in human plasma were the N-glucuronide M4 (AZ14191353) (accounting for 20.1% in humans) and the N-glucuronide of an acid metabolite M14 (AZ14484678) (accounting for 11.2% in humans). Two *in vitro* studies were conducted in order to evaluate potency and extent of ER α degradation induced by M4 (AZ14191353) and M14 (AZ14484678) using a plate-based immunofluorescence assay or a HTRF assay in ER-positive MCF7 cells. N-glucuronide M4 (AZ14191353) degraded ER to the same extent as camizestrant but with a much lower potency (approximately 500-fold lower), as seen by pIC₅₀ values of 10 and 7.3 for camizestrant and M4, respectively. Conversely, M14 appeared to be inactive at ER α (pIC₅₀ >5). Potential metabolite off-target effects were not addressed in these studies.

4.3.1.1.2. *In vivo* pharmacology

Pharmacodynamic and -kinetic properties of camizestrant:

The pharmacodynamic and -kinetic properties were evaluated in human cell line xenograft and patient derived xenograft (PDX) mouse models expressing respectively mutant (CTC174 DG538G *ESR1*m) and wildtype (MCF7 *ESR1*wt) forms of the receptor in order to assess the effect of camizestrant on ER α protein levels or progesterone receptor (PR) levels, a protein whose expression is regulated by ER. In the PDX *ESR1* mutant model female NSG mice were administered a single oral dose of 0.1, 0.8 or 10 mg/kg camizestrant. Blood and tumour tissue were sampled at 2, 5, 8 and 24 h for PK analysis (plasma concentration) and immunoblotting. Likewise, in the wildtype xenograft model, male SCID mice supplemented oestrogen, were treated orally for 3 days with 0.5, 2 or 10 mg/kg camizestrant and samples were taken at 24, 72 and 120 h.

Generally, a time and dose-dependent effect of camizestrant on ER α degradation or PR protein levels in tumour tissue were shown in mice xenograft models expressing mutant and wildtype forms of the receptor, respectively. In the *ESR1* mutant PDX model, the highest dose of 10 mg/kg was required to achieve > 80% ER α degradation that was maintained for 24 h. Lowering the dose, reduced both the

extent and duration of ER α degradation. Likewise, in the wildtype model, an effect on PR protein levels was noted by a significant reduction in expression levels of 89% and 93% at doses of 2 mg and 10 mg/kg at 24h. The significant reduction was maintained for the 10 mg/kg dose group for 72 and 120 h (85% and 46% reduction, respectively), whereas PR levels were only significantly reduced up to 72 h for the 2 mg/kg group (47% reduction).

In vivo effect of camizestrant monotherapy:

In vivo anti-tumour efficacy of camizestrant was shown in a number of *ESR1* wild-type and *ESR1* mutant ER+ breast cancer cell line and patient derived xenograft (PDX) models in immuno-compromised mice (wt MCF7, MCF7 Y537S *ESR1*m, CTC174 D538G *ESR1*m, oestrogen independent HBXF079_LTED *ESR1*m, CTG1211 D538G *ESR1*m and ST941 Y537S *ESR1*m). The animals were orally dosed daily in up to 42 days (21 to 42 days). In initial models, a number of doses were tested (from 0.5 up to 50 mg/kg), whereas later models were conducted with doses of 10 mg/kg. The dose of 10 mg/kg was established as the most suitable dose, as it generally provided significant better anti-tumour efficacy compared to lower doses and higher doses did not prove marked superiority.

Across all models, *in vivo* anti-tumour efficacy was evident as significant tumour growth inhibition (TGI) compared to vehicle control and, in most models, also tumour regression. Anti-tumour activity was dose-dependent and generally most significant at doses of 10 mg/kg, and at this dose tumour regression also occurred in the majority of models. Additionally, ER α and/or PR protein levels was measured in the tumour tissue and reduction in levels appeared to correlate with anti-tumour efficacy. Mathematical PK/PD/efficacy modelling based on the CTC174 DG538G *ESR1*m data confirmed ER α as a biomarker for tumour growth and indicated that 60% ER α degradation leads to 50% tumour growth inhibition, while tumour stasis requires 90% ER degradation.

Additionally, camizestrant monotherapy was tested at oral doses of 10 mg/kg for up to 60 days across a panel of 28 ER-positive breast cancer patient derived xenograft (PDX) models in different strains of mice. The models were established from primary or metastatic biopsies, containing both *ESR1* wild-type and mutant forms of the receptor. Significant tumour growth inhibition (TGI>75%) compared to control were noted in 16/28 (57%) of the models, with tumour regression in 7 of those models. When overlaying the *ESR1*m status of the 16 sensitive models, 8 of them were *ESR1*wt and 8 contained an *ESR1* mutation. Activity was seen in models conducted from patients that had previously been exposed to endocrine therapies (ET) plus a CDK4/6i and from patients with acquired palbociclib resistance.

In vivo effect of camizestrant in combination with CDK4/6i therapy:

In initial studies, the combination of camizestrant (10 or 40 mg/kg) and the CDK4/6 inhibitors palbociclib or abemaciclib (50 mg/kg) were tested in a number of wildtype and mutant PDX mouse models (i.e. CTC174 D538G *ESR1*m, HBXF079-LTED *ESR1*wt and treatment naïve ST3632 *ESR1*wt). In all models, a significant increased anti-tumour efficacy compared to the individual monotherapies was noted for the combinations, and in some models also tumour regression.

Superiority of combination treatment with CDK4/6i's were furthermore confirmed across a panel of eight ER-positive breast cancer PDX models including both wildtype and *ESR1* mutants (CTC174, CTG-1211, CTG-3266, CTG-2432, ST2056, ST3164BPBR, ST1799PBR and ST941HIPBR) treated with camizestrant (10 mg/kg) and/or the CDK4/6i's abemaciclib (50 mg/kg), palbociclib (50 mg/kg) or ribociclib (75 mg/kg) either as monotherapies or in combination. Compared to camizestrant monotherapy, which showed anti-tumour efficacy in 6/8 PDX models, the combination of camizestrant with the three CDK4/6i significantly improved tumour growth inhibition in 4/8 for abemaciclib, 3/8 for palbociclib and 4/6 for ribociclib. In the 4 models where camizestrant monotherapy drove tumour stasis or regression, the combination treatment still drove equivalent or greater results. A mathematical Bayesian mixed-effect model confirmed superiority for the combination-treatments compared to monotherapies and indicated that efficacy was not affected by the choice of CDK4/6i.

A 21-day dose-response combination study in an ER-positive MCF7 xenograft male mouse model combining camizestrant doses of 1, 3 or 10 mg with ribociclib doses of 37.5 or 75 mg/kg, showed that camizestrant inhibited tumour growth in an exposure dependent manner, both as a monotherapy and in combination with ribociclib. Furthermore, a greater anti-tumour efficacy was noted for the combination, which was also associated with more pronounced inhibition of pRB1 (target of CDK4/6i) when measuring the cell cycle biomarker with western blot in tumour tissue. Whereas, PR levels in tumour tissue appeared to be more related to camizestrant alone with a dose-dependent relationship. 4.3.2.1. It was noted that the combination with ribociclib, noticeably increased camizestrant exposure in plasma from 2 to 5-fold at the highest and lowest dose, respectively. See also section 4.3.2.1. for more details. This was further addressed in the clinical part of the dossier, where data indicated the other CDK4/6i's (i.e. abemaciclib and palbociclib) did not cause similar increases in camizestrant exposure (see 5.2.). Additionally, an exposure/efficacy analysis confirmed that the increased camizestrant exposure was not sufficient to explain the improved efficacy seen for the combination treatment in the non-clinical dose-response study.

In vivo ER agonism:

The uterotrophic effect of camizestrant was explored *in vivo* to exclude a risk of endometrial cancer in patients as seen for the selective ER modulator tamoxifen due to partial ER agonism in uterine tissue (Fisher et al, 1995). Lack of uterotrophic agonistic effect of camizestrant was shown in a 3-day repeat-dose study in juvenile Han Wistar rats. Treatment with the known partial ER α agonist tamoxifen (10 mg/kg PO) caused a significant increase in uterine weight compared to vehicle control, whereas both camizestrant (50 mg/kg PO) and fulvestrant (5 mg/kg SC, negative control) significantly reduced uterine weight. This indicated a lack of ER α uterotrophic agonism for camizestrant under the current study conditions.

Common to all the conducted *in vivo* animal studies, no in-life signs of toxicity or significant reductions in body weight were observed.

4.3.1.2. Secondary pharmacodynamics

In order to explore secondary off-target pharmacology, camizestrant was screened in a panel of *in vitro* radioligand binding, enzyme and functional assays, covering 195 distinct molecular targets (receptors, ion channels, transporters and enzymes). Activity was detected for 31 targets as a defined K_i , IC_{50} or EC_{50} value. Apart from ER α and β , no targets had activity within 100-fold of the ER α primary target or within the clinically relevant maximum unbound plasma concentration of 0.037 μ M obtained at 75 mg. It was, however, noted, that only a 9-fold difference existed in binding K_i values for the H₃ histamine receptor and the clinically relevant maximum unbound plasma concentration. The H₃ histamine receptor primary regulates neurotransmitter release in the brain and CNS. However, no neurological issues were detected in the toxicity studies or in a modified Irwin screen in rats conducted as part of the safety pharmacology program. Hence, despite the relatively small fold change for antagonistic effect on the H₃ histamine receptor *in vitro*, no clear correlation was seen to relevant *in vivo* findings. Additionally, an *in vitro* agonistic effect on the μ opioid receptor were noted with a 116-fold change for binding K_i and 257-fold for IC_{50} compared the clinically relevant unbound C_{max} of 0.037 μ M.

Moreover, camizestrant was screened in an *in vitro* selective voltage-gated cardiac ion channel electrophysiological assay at concentrations up to 33.3 μ M (#4428SV) and no activity was noted at any of the channels tested, including the hHCN4 channel. Hence, $IC_{50} > 33.3 \mu$ M existed for all the tested channels (>892-fold to clinically relevant unbound C_{max}). Nevertheless, an effect of camizestrant on HCN-channels appeared relevant *in vivo* with respect to toxicity findings in the heart and eye (see Section 4.4.8 on mechanistic studies).

4.3.1.3. Safety pharmacology

A core battery of safety pharmacology studies was conducted to evaluate the effect of camizestrant on the central nervous, cardiovascular and respiratory system in accordance with ICH S7A and S7B guidelines. Additional non-GLP follow-up and supplementary studies were conducted to further evaluate the cardiovascular effects of camizestrant.

Table 7: Summary of safety pharmacology studies

Summary of safety pharmacology studies				
Study ID/ GLP	Study type	Test system	Concentration / dose/ route	Major results
614889 GLP	Nervous system (single dose)	Rat Crl:WI (Han) 6 M/group	0, 10, 25, 200 mg/kg Oral	NOAEL = 200 mg/kg No effect in modified Irwin parameters or pupil size. No statistically significant changes in temperature or body weight; slight non-significant decrease in body weight at 200 mg/kg. Unbound plasma concentration 1.14 μ M; 31-fold margin vs human unbound C_{max}
781812 GLP	Cardiovascular (hERG)	CHO cells expressing the hERG channel n=5 cells	0, 0.0290, 0.0969, 0.437, 1.89, 7.94, 27.6 μ M	Mean IC_{50} = 20.7 μ M for hERG tail current inhibition 95% confidence intervals = 13.8 to 31.1 μ M ~559-fold margin vs human unbound C_{max} (373–841-fold based on CI)
CBL0108 Non-GLP	Cardiovascular (Human cardiomyocytes)	Human IPS- CMs N=10 wells	0, 0.01, 0.1, 1, 10, μ M	No effect on action potential parameters ≤ 1 μ M (corresponds to ~27-fold clinical unbound C_{max}) <u>10 μM:</u> ↑action potential duration (ADP_{90}). Time-dependent increase (74% at 1 h post-dose, 149% at 72 h post-dose); corresponds to ~270-fold clinical unbound C_{max}
BE001764- 09 Non-GLP	Cardiovascular (Conscious telemetry, single dose)	Rat Crl:WI (Han) 8 M/group	0, 25, 200 mg/kg Oral	NOAEL = 25 mg/kg (corresponds to ~7-fold clinical unbound C_{max}) <u>200 mg/kg:</u> ↑blood pressure (both systolic and diastolic) (18%), ↑QT interval (up to 9ms or 15%) ↓heart rate (decrease by 64 bpm or -20%) QT prolongation persisted >24 h; blood pressure increase up to 24 mmHg within 5 h post-dose.
BE001764- 27 Non-GLP	Cardiovascular (Conscious)	Rat Crl:WI (Han) 8 M/group	0, 25, 75 mg/kg/day Oral	No cardiovascular NOAEL determined. <u>≥ 25 mg/kg:</u> ↑systolic blood pressure (12%), ↓diastolic blood pressure (day 5) (-8%) (transient increase followed by decrease from day 5) ↓ heart rate (not evaluated)

Summary of safety pharmacology studies				
Study ID/ GLP	Study type	Test system	Concentration / dose/ route	Major results
	telemetry; 7 day repeat)			<u>75 mg/kg:</u> ↓ heart rate (maximum decrease of 89 bpm or -23% on dosing day 5) Peak effects Day 5; NT-proBNP unchanged (marker of severity of cardiac failure); QT not assessed.
614522 GLP	Cardiovascular (Conscious telemetry; single and 7 day repeat)	Dog Beagle 4 M	Single dose: 0, 3, 30 mg/kg 7 day Repeat dose: 10 mg/kg/day	NOEL = 3 mg/kg (single dose) (corresponds to ~1.6-fold clinical unbound C_{max}). No NOAEL determined for repeat-dose. <u>30 mg/kg (single dose):</u> ↑LV dP/dt+ (1211 mmHg/s, 25%). ↑LV dP/dt- (450 mmHg/s, 12%). ↑Systolic blood pressure (11 mmHg, 7%). ↑Pulse pressure (12 mmHg, 17%). ↓ PR interval (5 ms, 6%). ↓ QA interval (7 ms, 6%). <u>10 mg/kg (repeat dose):</u> ↑LV systolic pressure (21 mmHg, 16%). ↑Corrected LV end diastolic pressure (7 mmHg, 54%). ↑LV dP/dt+ (index of LV contractility, 1951 mmHg/s, 41%). ↑LV dP/dt- (index of LV relaxation, 1137 mmHg/s, 28%). ↑Systolic blood pressure (32 mmHg, 21%). ↑Pulse pressure (21 mmHg, 32%). ↑QT (34 ms, 15%) ↑QTca interval (15 ms, 6%) ↓ Diastolic blood pressure (11 mmHg, 13%). ↓ Heart rate (40 bpm, 37%). ↓ QA interval (index inversely related to LV contractility, 9 ms, 8%). ↓ PR interval (6 ms, 7%). Atrial premature complex (APC) in 1 out of 4 Peak effects observed on Days 5–7 of repeat-dosing; findings reversible within 5 days post-treatment; exposure margins for the 10 mg/kg repeat-dose ~12-fold (C_{max}) and ~8-fold (AUC).
616053 Non-GLP	Cardiovascular (Conscious telemetry; combination of	Dog Beagle 4 M	Camizestrant: 0, 20 mg/kg/day Oral	Similar magnitude of exercise induced increase in heart rate in the absence and presence of camizestrant treatment. Lower magnitude of heart rate increases for chronotropic agents (i.e. isoprenaline and atropine) in dogs with camizestrant-induced heart rate reduction compared to vehicle administered dogs.

Summary of safety pharmacology studies				
Study ID/ GLP	Study type	Test system	Concentration / dose/ route	Major results
	camizestrant with atropine, isoprenaline or atenolol; effect of exercise)		Atropine: 0, 30, 100 µg/kg IV Isoprenaline: 0, 0.2, 0.4 µg/kg/min for 10 minutes IV Atenolol: 10 mg/kg Oral	Mild to severe clinical signs of anticholinergic nature when atropine (100 µg/kg) is administered in the presence of camizestrant. Atenolol (10 mg/kg) resulted in a decrease in heart rate and the magnitude of the effect was similar in the presence and absence of camizestrant (10 mg/kg/day). Atropine (100 µg/kg) produced anticholinergic clinical signs (e.g. tremor, ataxia, agitation); atropine exposure increased up to 2.7-fold (plasma) and 3.5-fold (brain); recovery of full chronotropic response >24 h
510439 Non-GLP	Cardiovascular (conscious telemetry; combination of camizestrant with atropine, glycopyrrolate, atenolol)	Dog Beagle 3 M/group	Camizestrant:0, 10, 20_mg/kg/day Oral Glycopyrrolate: 0, 10, 30 µg/kg IV Atropine:0, 60, 100 µg/kg IV Atenolol: 10 mg/kg Oral	Confirmed major findings from study 616053. Lower magnitude of heart rate increases for glycopyrrolate in dogs with camizestrant-induced heart rate reduction compared to vehicle administered dogs. The magnitude of change in heart rate following administration of glycopyrrolate were lower with increasing dose of camizestrant. Increased plasma exposure of glycopyrrolate (up to 4.3-fold) and atropine (up to 2.7-fold) <i>in the presence of camizestrant</i> . Brain exposure increased up to 3.5-fold for atropine in the presence of camizestrant. Recovery of full chronotropic effectiveness after last camizestrant dose: >24 h for atropine and > 4 days for glycopyrrolate.
614894 GLP	Respiratory (single-dose)	Rat Crl:WI (Han) 8 M	0, 10, 25, 200 mg/kg Oral	NOEL = 200 mg/kg No effect on respiratory parameters in a whole-body plethysmography study. Parameters assessed included respiratory rate, tidal volume, minute volume, inspiratory and expiratory time, and flow rates; unbound plasma concentration 2.0 µM corresponding to ~54-fold margin vs clinical exposure.

4.3.1.4. . Pharmacodynamic drug interactions

Pharmacodynamic drug interactions were assessed in the clinical efficacy section, see 5.2.3. .

4.3.2. Pharmacokinetics

4.3.2.1. Absorption

Similar to humans, exposure in rats and dogs increased greater than dose-proportional after repeated dosing based on AUC, and a high volume of distribution is observed indicating high distribution to tissues. Non-linear kinetics are observed in both humans and dogs as increasing dose levels led to a decrease in plasma clearance and volume of distribution. Oral bioavailability in rats, dogs and humans were 22%, 39% and 43%, respectively. While a large difference in plasma exposure was observed between male and female rats with up to 4.5-fold higher exposure in females, no sex difference was observed in dogs. Additionally, an exposure/efficacy analysis confirmed that the increased camizestrant exposure was not sufficient to explain the improved efficacy seen for the combination treatment in the non-clinical dose-response study. No dedicated PK studies with co-administration of CDK4/6 inhibitors were conducted, but a PD study showed increased plasma concentrations when camizestrant is co-administered with ribociclib. It was noted that the combination with ribociclib, noticeably increased camizestrant exposure in plasma from 2 to 5-fold at the highest and lowest dose, respectively. This was further addressed in the clinical part of the dossier, where data indicated the other CDK4/6i's (i.e. abemaciclib and palbociclib) did not cause similar increases in camizestrant exposure (see section 5.2.).

4.3.2.2. Distribution

The free percentage of camizestrant in plasma *in vitro* was determined at 24.7% in humans compared to 15.8% in dogs and 29.3% in rats. Rapid and widespread distribution was observed to all tissues in albino rats with the highest distribution to uveal tract, liver, adrenals, pancreas, spleen, lung and glandular tissues. Tissue levels were overall reversible, however, with higher retention in thyroid, pituitary and uveal tract at the end of the study. Very high amounts were still present in the uveal tract at the end of the study in pigmented rats, indicating an affinity of camizestrant to melanin-containing tissue, which may correlate with observed ocular toxicity. A very low distribution across the blood-brain barrier was observed. While placental transfer was not specifically investigated, developmental toxicity findings suggest that foetuses are exposed to camizestrant via the placenta (see Section 4.4.5).

4.3.2.3. Metabolism

Identified metabolites of camizestrant were either oxidative metabolites or glucuronides of oxidative metabolites. Large variation was observed in metabolism pattern between male and female rats and between rats and dogs, where the metabolism profile in dogs seems to be more comparable to humans. Two major metabolites (i.e. above 10%) were observed in human plasma which were not found in rat and dog plasma; M4 (AZ14191353, an N-glucuronide conjugate of camizestrant) and M14 (an N-glucuronide of an acid metabolite). Oxidative metabolism products in human plasma were also observed in animals and glucuronide metabolism products are of low concern due to high polarity. It was documented *in vitro* that the human glucuronides M4 and M14 are considered stable at pH 7.4 and thus pose no risk of chemical reactivity.

4.3.2.4. Excretion

Excretion studies showed that fecal elimination was the main route of excretion of camizestrant and its metabolites in all species after oral and IV administration, with renal excretion only constituting a minor route. Human excretion data suggested that biliary excretion of camizestrant and its metabolites occurs prior to fecal excretion and data from BDC rats and dogs supports this. Excretion in milk in non-clinical species was not investigated.

4.3.2.5. Pharmacokinetic drug interactions

Pharmacokinetic drug interactions are assessed in the clinical safety (see Section 5.4.10).

4.3.2.6. Other pharmacokinetic studies

In dogs, camizestrant inhibited the metabolism of atropine, which resulted in higher atropine plasma concentrations.

4.4. Toxicology

4.4.1. Single-dose toxicity

Dedicated single dose toxicity studies have not been conducted for camizestrant, in line with ICH M3(R2) 2009 and ICH S9 2010 guidance, but information on acute oral toxicity is available from other studies that have defined the maximum tolerated dose (MTD) following short term dosing in mice (20377186), rats (BE001738-15 and 505104) and dogs (505120). Acute oral toxicity of camizestrant in mice, rats and dogs was dose-dependent, with reduced tolerability at high doses leading to premature termination in rodents (150 mg/kg/day in rats and 300 mg/kg/day in mice) and dogs (≥ 40 –50 mg/kg/day), associated with decreased activity, body weight loss and neurological or other adverse clinical signs. At lower dose levels, toxicity was limited, with no mortality in rodents and generally good tolerability in dogs at 10–20 mg/kg/day. In dogs, the maximum tolerated dose was 20 mg/kg/day for 14 days, with higher exposures resulting in CNS-related toxicity and early euthanasia. Treatment-related findings in dogs included cardiovascular effects (decreased heart rate with QT/QTc prolongation) and reproductive organ changes consistent with oestrogen receptor antagonism.

4.4.2. Repeat-dose toxicity

An overview of repeat dose toxicity studies is provided in Table 9.

Table 8. Overview of repeat-dose toxicity studies of camizestrant in mouse, rat and dog.

Type of study	Species and strain	Method of administration	Duration of dosing	Doses (mg/kg/day)	Exposure	No: Sex / Group		GLP compliance
					C _{max} (nmol/L)	AUC (nmol.h/L)		
14-day DRF	Mouse / CByB6F1 non-transgenic littermates	Oral (gavage)	14 days	0, 50, 100, 300	-, 5540, 8360, 15400 (Day1)	-, 51800, 107000, 217000 (Day1)	Main: 3M/3F TK satellites: 12M/12F	No
6-week			42 days	0, 25, 75, 150	-, 3.84, 11.7, 16.8	-, 31.9, 117, 191	Main: 10M/10F TK satellites: 12/12F	Yes
MTD/DRF	Rat / Han Wistar	Oral (gavage)	14 days	0, 15, 75, 150	-, 0.793/1.46, 3.59/8.95, 6.18/15.4 (Day 7)	-, 4.56/11.8, 54.8/167, 100/332 (Day 7)	3M/3F	No
1-month (+ 1-month recovery)			28 days	0, 10, 25, 75 (NOAEL M only)	-, 0.635/1.35, 1.78/3.21, 5.27/10.4	-, 4.95/10.3, 15.9/37.8, 67.7/182	Main: 10M/10F Recovery: 5M/5F (control and high dose)	Yes
3-month			12 weeks	0, 0.1, 0.25, 1, 5	-, 0.689/0.760, 1.58/2.02, 10.7/15.0, 113/174	-, 4.01/3.81, 8.04/11.9, 79.1/94.8, 858/1140	Main: 10M/10F	Yes
6-month (+ male fertility)			26 weeks	0, 10, 25, 75	-, 0.611/0.802, 1.59/2.12, 4.21/7.35	-, 4.51/5.02, 14.9/24.2, 59.1/133	Main: 15M/15F	Yes

Type of study	Species and strain	Method of administration	Duration of dosing	Doses (mg/kg/day)	Exposure	No: Sex / Group		GLP compliance
					C _{max} (nmol/L)	AUC (nmol.h/L)		
MTD/DRF	Dog / Beagle	Oral (gavage)	MTD phase: dosed on Days 1, 15-17, 22-24 and 29-31 DRF phase: 4 days, 14 days	50; 15; 30; 40 40 10, 20	10mg/kg: 2.44, 20mg/kg: 6.90, 40mg/kg: 11.9 (Day 1)	23.8, 84.9, 129 (Day 1)	MTD: 1M/1F 14 D: 1M/1F	No
1-month (+ 1-month recovery)			4 weeks	0, 5, 10, 20	-, 1.17, 2.78, 7.8	-, 8.49, 30.4, 97.2	Main: 3M/3F Recovery: 2M/2F (control and high dose)	Yes
9-month			39 weeks	0, 5, 10, 20	-, 0.973, 2.50, 9.31	-, 7.72, 29.7, 115	Main: 4M/4F	Yes

MOUSE

In mice, repeat dose toxicity was characterised by dose dependent effects from ≥ 25 mg/kg/day, with a non-tolerated dose of 300 mg/kg/day. No NOAEL was established. The most sensitive targets were the reproductive organs, immune system, and liver, often occurring at exposures with limited margins to clinical exposure.

Marked reproductive tract changes were observed in females from ≥ 25 mg/kg/day, including ovarian haemorrhagic follicles, reduced corpora lutea, follicular cysts, and epithelial atrophy of uterus, oviduct, and vagina. These findings were associated with adrenal cortical atrophy and pituitary hypertrophy. In males, Leydig cell hypertrophy was observed.

Liver findings included hepatocellular vacuolation and hypertrophy, supported by increases in liver enzymes and alterations in protein and lipid parameters, indicative of functional hepatic effects.

Immunosuppressive effects were evident from ≥ 25 mg/kg/day, with lymphopenia, reduced white blood cell counts at higher doses, thymic atrophy, reduced spleen weight, and lymphoid depletion. Other findings included increased heart and kidney weights, alveolar macrophage accumulation in lungs, and renal epithelial changes. At non tolerated doses, multi organ degenerative changes were observed, consistent with systemic toxicity.

RAT

In rats, toxicity was evaluated in studies up to 26 weeks, with a non-tolerated dose of 150 mg/kg/day. The heart and reproductive systems were the principal targets, with a consistent profile across studies. Females had higher systemic exposure than males (up to 4.5-fold), contributing to greater sensitivity.

Reproductive toxicity was a prominent finding. In females, adverse effects occurred from ≥ 0.1 mg/kg/day (no NOAEL), and in males from ≥ 10 mg/kg/day (NOAEL 5 mg/kg/day). Females showed widespread changes in reproductive tissues including ovarian cysts and tumours, adrenal cortical atrophy, mammary hyperplasia, and uterine/vaginal epithelial atrophy, with necrosis and inflammation at higher doses. In males, there was degeneration and atrophy of testes and accessory glands, reduced sperm counts and motility, and impaired fertility, with marked effects at higher doses.

Hepatobiliary toxicity consistent with cholestasis was observed, particularly in females, with biochemical changes from ≥ 10 mg/kg/day and histopathological findings at higher doses. These effects were largely reversible after treatment cessation.

Phospholipidosis and macrophage aggregation were observed in lungs and lymphoid tissues from ≥ 10 mg/kg/day, confirmed ultrastructurally and considered treatment-related.

Cardiovascular findings included progressive cardiomyopathy in females at ≥ 25 mg/kg/day. Additional effects included altered body weight and food consumption, with sex-dependent patterns over long-term dosing.

DOG

In dogs, repeat-dose toxicity was assessed up to 39 weeks, with a non-tolerated dose of 40 mg/kg/day and a maximum tolerated dose of 20 mg/kg/day (14 days). The cardiovascular and reproductive systems were the primary targets, with no NOAEL established.

Cardiovascular toxicity was a key finding, occurring from ≥ 5 mg/kg/day (~ 3.5 – 4 fold human exposure). Effects included bradycardia, QT/QTc prolongation, PR interval shortening, and blood pressure changes, with delayed onset and partial reversibility. QT prolongation was independent of heart rate changes, suggesting a direct electrophysiological effect. These findings are consistent with nonclinical pharmacology indicating HCN channel inhibition and are considered of potential clinical relevance.

Reproductive toxicity affected both sexes from ≥ 5 mg/kg/day. In females, findings included uterine and vaginal atrophy, cystic endometrial hyperplasia, inflammation, and ovarian cysts and neoplastic changes (granulosa cell tumours and stromal hyperplasia). In males, testicular and epididymal degeneration, Leydig cell changes, impaired spermatogenesis, and pituitary cysts were observed. These findings indicate disruption of the hypothalamic–pituitary–gonadal axis and are considered adverse. Additional observations included transient visual effects (linked to retinal ion channels), hormonal changes consistent with central endocrine modulation (TSH suppression with unchanged T4), and limited CNS findings at high exposures.

Cross-species findings

Across all species, reproductive and endocrine findings (including adrenal and pituitary changes) were consistent with pharmacological ER antagonism.

Cardiovascular effects (heart rate reduction and QT prolongation) were observed in rats and dogs and supported by mechanistic studies demonstrating HCN4 channel involvement.

Phospholipidosis and macrophage accumulation were identified in rats and mice, primarily at high exposures, and were generally reversible.

Overall, repeatdose toxicity of camizestrant is characterised by dose-dependent, pharmacologically driven effects on reproductive, cardiovascular, and endocrine systems, with additional multiorgan effects at higher exposures.

4.4.3. Genotoxicity

Camizestrant was negative in a standard battery of genotoxic tests and thus appears to be without genotoxic potential (Table 10).

Table 9. Overview of genotoxicity studies.

Type of test/GLP/ study ID	Test system	Concentrations/ Concentration range/ Metabolising system	Results positive/negative/equivocal
Gene mutations in <i>vitro</i> bacterial reverse mutation (AMES) GLP (8379660)	Salmonella Strains (TA98, TA100, TA1535 and TA1537) and E-coli (WP2 uvrA pKM101)	5-5000 ug/plate +/- S9	Negative in all strains tested with and without S9 Toxic concentration in Salmonella strains: ≥ 1600 $\mu\text{g}/\text{plate}$
Micronuclei <i>in vitro</i> GLP (8379661)	L5178Y mouse lymphoma cells	Tested up to 51 $\mu\text{g}/\text{ml}$ – limited by cytotoxicity +/- S9	Negative: micronuclei cell frequency within the normal ranges and not significantly higher than controls (at the $p \leq 0.05$ level)
Micronuclei <i>in vivo</i> GLP (8379662)	Rat (female), bone marrow	40, 200 and 400* mg/kg/day*	Negative: no micronucleated immature erythrocytes up to MTD <u>Clinical observations:</u> at MTD (400 mg/kg/day): piloerection, hunched posture, noisy respiration, reduced activity, and swollen abdomens with concurrent body weight loss of 7.2%

*Maximum tolerated dose: MTD

4.4.4. Carcinogenicity

No carcinogenicity studies have been performed for the current procedure in accordance with ICH S9. Findings in the ovaries in chronic repeat-dose studies included hyperplasia at total plasma exposures (AUC) $\geq$ 2-fold (rat granulosa cell) and 52-fold (dog sex cord stromal) relative to human exposure at MRHD and benign granulosa cell tumours at total plasma exposures (AUC) of approximately 60-fold (rats) and 3.5-fold (dogs) relative to human exposure at MRHD. An interstitial (Leydig) cell adenoma was observed in the testis of a single dog at 13-fold human exposure at MRHD. Findings are considered hormone-driven, based on the pharmacological action of camizestrant and therefore not relevant for post-menopausal women or in pre- or peri menopausal women or men administered an LHRH agonist.

4.4.5. Developmental and reproductive toxicity

Male fertility was assessed as part of the 6-month study in rats (Study 509329) and female fertility was assessed in a stand-alone fertility study (Study 490021). A modified rat embryofoetal development study (Study 490005) was conducted which included a littering phase in which dams received camizestrant from Day 6 of gestation until Day 6 of lactation. Assessment of embryofoetal development was not assessed in a second species.

4.4.5.1. Fertility and early embryonic development

In a dedicated fertility and early embryonic development (FEED) study evaluating fertility in female rats (Study 490021), 14 days dosing with camizestrant was associated with alterations in oestrous cycles, mating behaviour, and fertility. At the mid-dose of 0.075 mg/kg/day and higher, mating signs were increased while marked reductions in fertility were observed, primarily due to a reduction in oestrous cycles followed by decreased pregnancy rates. From the lowest dose of 0.001 mg/kg/day, fewer implantations and live embryos were detected, accompanied by increased rates of both pre-implantation and post-implantation losses. All effects on fertility were fully reversible following a 4-week recovery period. No female fertility NOAEL was determined from the study, but effects are likely to have occurred at clinically relevant exposure levels based on extrapolations of exposures values with an estimated safety margin <1 for all findings and far below clinical exposure for pre- and post-implantation losses specifically (>400 -fold). Study results are summarised in Table 11.

Effects of camizestrant on male fertility was assessed as part of the GLP 6month repeat-dose study in rats (Study 509329). Relevant histopathology findings were observed in a dose-dependent manner at ≥ 10 mg/kg/day encompassing atrophy in the prostate gland and seminal vesicle, tubular dilation, degeneration/atrophy of the seminiferous tubules in the testis and reduced sperm cellularity in the epididymis. Sperm evaluation revealed decreased testis spermatid and epididymal sperm counts at ≥ 10 mg/kg/day, increased abnormal sperm at ≥ 25 mg/kg/day, and reduced sperm motility at 75 mg/kg/day. Reproductive performance was also affected with a reduction in mating rate (≥ 25 mg/kg/day) and non-dosed females experiencing a decreased number of live foetuses accompanied by higher implantation loss (75 mg/kg/day) reflecting transferred toxicity from dosed males. No male NOAEL was determined. Effects occurred at the lowest administered dose at exposures corresponding to 2x human exposure with an estimated safety margin <1 . Study results are summarised in Table 12.

Table 10. Female fertility study in rats.

Study details Species	No:Sex/ Group	Dose (mg/kg/ day)	Exposure – not assessed		Major (alt salient) findings & NOAEL
			Cmax	AUC (nmol.h/L)	

treatment period			(nmol/L)		
Route					
GLP status					
(Study ID)					
Fertility and early embryonic development studies					
Rat (Han Wistar) Main: 2 weeks prior to/during pairing, up to GD 6 Recovery: 3 weeks + 4 weeks wash-out prior to mating PO GLP (490021)	16 F Recovery: 16 F	0	-	-	<u>Female fertility</u>
		0.001	-	-	↓ oestrous cycle (↓ oestrus smears ↑ dioestrus smears, ≥0.075 mg/kg/day)
		0.075	0.76*	3.81*	
		0.75	15.0#	94.8#	Changes mating behaviour (↑ mating signs, ↑ No. animals with multiple mating signs, ≥0.075 mg/kg/day)
		*Extrapolated from 0.1 mg/kg/day repeat-dose study 521854			
		# Extrapolated from 1 mg/kg/day repeat-dose study 521854			↓ fertility rate (↓ pregnancies (≥0.075 mg/kg/day)
		10	0.611	4.51	
		25	1.59	14.9	↓ numbers of corpora lutea, implants and live embryos, with an associated lower gravid uterus weight (≥0.001 mg/kg/day)
		75	4.21	59.1	
					↑ pre- and post-implantation losses (≥ 0.001 mg/kg/day)

<u>Recovery</u> No related findings
NOAEL not established in females

Table 11. Male fertility study in rats (integrated in repeat-dose study)

Study details Species treatment period Route GLP status (Study ID)	No:Sex/ Group	Dose (mg/kg/ day)	Exposure		Major (alt salient) findings & NOAEL
			Cmax (nmol/L)	AUC (nmol.h/L)	
Repeat dose toxicity study, independent assessment of male fertility					
Rat (Han Wistar)	10 M	0	-	-	<u>Male fertility /reproductive performance</u> ↓ mating rate (≥25 mg/kg/day) ↓ number of live foetuses accompanied by higher implantation loss (75 mg/kg/day)
		10	0.611	4.51	
		25	1.59	14.9	
		75	4.21	59.1	

Prior to mating until GD 6					↓ testis spermatid and epididymal sperm counts (≥ 10 mg/kg/day)
PO					↑ number of abnormal sperm (≥ 25 mg/kg/day)
26-weeks					↓ motile sperm (75 mg/kg/day)
Animals not dosed during pairing or gestation					<u>Microscopic</u> ≥ 10 mg/kg/day: atrophy of the prostate gland, seminal vesicle, seminiferous tubules; tubular dilation of testis, and; reduced epididymis sperm cellularity
GLP					NOAEL not established in males
(509329)					

4.4.5.2. Embryo-fœtal development

In a non-standard rat embryofoetal development study (EFD, Study 490005), dosing of 0.1 mg/kg/day to female rats during fallopian transport and implantation led to a full lack of implantation in all females in spite of unaffected mating behaviour. This resulted in a fertility index of 0% and indicates that camizestrant has early pre-implantation effects. Dosing in the range of 0.001 and 0.075 mg/kg/day from the time of implantation GD6, had no notable effects on implantation sites, embryofoetal survival, growth and development. However, when dams were dosed 0.075 and 0.75 mg/kg/day from the point of implantation through lactation on LD 6, camizestrant appeared to have detrimental effects on parturition in the form of difficulties birthing and/or prolonged gestation and parturition with example of remaining pups in utero after completed labour. Importantly, camizestrant led to increased pup mortality and overall deterioration in the well-being of dams, which resulted in unscheduled euthanasia GD 22/23 of all dams/pups at the high dose 0.75 mg/kg/day. Female fertility and pup survival were negatively affected at an estimated safety margin <1 .

Table 12. Embryofoetal development study in rats.

Study details Species treatment period Route GLP status (Study ID)	No:Sex / Group	Dose (mg/kg/day)	Exposure		Major (alt salient) findings & NOAEL
			Cmax nmol/L	AUC (nmol·h/L)	
Rat (Han Wistar)					
From Day 6 of gestation until Day 6 of lactation					
PO					

GLP (49005)					
Phase 1: GD 2-20 Fallopian transport and embryofoetal development phase	6F	0.1	2 hours post-dose 0.767 nmol/L		No evidence of implantation in any female (0.1 mg/kg/day): fertility index of 0% No effect on mating rate
Phase 2: GD 6-16 Embryofoetal development phase	6F	0	-	-	No treatment related findings
		0.001	BLQ	BLQ	
		0.01	0.113	ND	
		0.025 (0.024/0.030*)	0.293	1.65	
		0.075 (0.073/0.091)	0.858	5.17	
Phase 3: GD 6-LD6 Pre- and post-natal phase	6F	0.075 and 0.75	No blood samples at 0.75 mg/kg/day due to unscheduled euthanasia of all dams/offspring 0.075 mg/kg/day - quantifiable concentrations in dams at 2 hours post dose (similar to corresponding timepoint/dose in Phase 2): 5.17 nmol·h/L. Not quantifiable from pups on LD 6.		<u>Mortality</u> Unscheduled euthanasia GD 22/23 of all dams/pups at 0.75 mg/kg/day. Difficulties giving birth along with dead pups in cage and in utero and adverse clinical observations resulted in all females at 0.75 mg/kg/day and 1 female at 0.075 mg/kg/day being prematurely euthanised GD 23/LD0. Necropsy findings: 1 incidence of spongy lungs at 0.075 mg/kg/day and 1 incidence of enlarged spleen at 0.75 mg/kg/day. Dams ↓ maternal body weight and body weight gain (≥0.075 mg/kg/day) ↓ maternal food consumption (≥0.075 mg/kg/day) Delayed and prolonged parturition (≥ 0.075 mg/kg/day) ↑ number of dams with a lack of prominent teats. <u>Clinical observations</u> ≥0.075, laboured, breathing, hunched posture, abnormal gait, subdued, erect fur, red staining vulva, pale eyes and ears, reduced food consumption Pups High pup mortality (≥0.075 mg/kg/day) In surviving litters at 0.075 mg/kg/day, ↓ pup survival, ↓ pup weights NOAEL not established in dams nor pups

* animals were dosed GD 6-12 at 0.024 or 0.073 mg/kg/day and GD 13-16 at 0.030 mg/kg/day or 0.091 mg/kg/day, respectively

4.4.5.3. Prenatal and postnatal development, including maternal function

In accordance with ICH S9 (2010), a dedicated pre-natal and post-natal development study is not required for the patient population. However, the modified rat embryofoetal development study included a littering phase in which dams received camizestrant from Day 6 of gestation until Day 6 of

lactation (Study 490005), see Table 14.

4.4.5.4. Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

Juvenile studies have not been conducted as the proposed indication is for adult patients.

4.4.6. Toxicokinetics and exposure margins

Details on pharmacokinetics are provided in the section on *Absorption*, see 4.3.2.1.

In repeat dose toxicity studies, systemic exposure to camizestrant was generally dose-proportional in mice, slightly greater than dose-proportional in rats (particularly in females also increasing disproportionately to males ≥ 10 mg/kg/day), and greater than dose-proportional in dogs at higher doses. In humans, for comparison, exposure to camizestrant increased in a greater than dose proportional manner after single and multiple dosing across the 25 to 450 mg dose range (SERENA-1 study).

In rats, systemic exposure increased from low levels at ≤ 0.01 mg/kg/day to approximately AUC(0-24) ~ 0.005 $\mu\text{mol}\cdot\text{h/L}$ at 0.073/0.091 mg/kg/day and further to ~ 0.08 – 0.09 $\mu\text{mol}\cdot\text{h/L}$ at 1 mg/kg/day, reaching ~ 0.86 – 1.14 $\mu\text{mol}\cdot\text{h/L}$ at 5 mg/kg/day, with higher exposures consistently observed in females. At higher dose levels in rats, exposure increased disproportionately, with AUC values up to ~ 67 – 182 $\mu\text{mol}\cdot\text{h/L}$ at 75 mg/kg/day and up to ~ 332 – 535 $\mu\text{mol}\cdot\text{h/L}$ in females at ≥ 150 – 200 mg/kg/day, together with corresponding increases in C_{max} (e.g. up to ~ 10.4 $\mu\text{mol/L}$ at 75 mg/kg/day in females).

In mice, exposure was generally dose-proportional across the tested range, with AUC values of ~ 32 – 52 $\mu\text{mol}\cdot\text{h/L}$ at 25–50 mg/kg/day and up to ~ 182 – 225 $\mu\text{mol}\cdot\text{h/L}$ at 150–300 mg/kg/day, without consistent sex differences.

In dogs, exposure also increased more than dose-proportionally at higher doses, with AUC values of ~ 8 – 9 $\mu\text{mol}\cdot\text{h/L}$ at 5 mg/kg/day, increasing to ~ 38 $\mu\text{mol}\cdot\text{h/L}$ at 10 mg/kg/day and up to ~ 110 – 120 $\mu\text{mol}\cdot\text{h/L}$ at 20 mg/kg/day, with corresponding C_{max} values up to ~ 8 – 12 $\mu\text{mol/L}$.

Following repeated dosing, no accumulation was observed in mice and dogs, whereas in rats exposure increased with repeated administration, particularly at higher doses. No consistent sex differences were observed in mice or dogs, whereas female rats showed higher exposure than males.

Across species, there was no evidence of marked accumulation over time. Tissue distribution studies in dogs showed higher concentrations in the heart compared with brain and plasma, consistent with cardiac tissue as a potential site of accumulation.

4.4.6.1.1. Interspecies comparison and exposure margins to clinical exposure

Exposure margins (animal:human) are calculated by comparing exposure parameters (C_{max} and AUC) at the No-Observed-Adverse-Effect Level (NOAEL) from toxicology studies with those at a clinical dose of 75 mg once daily (as monotherapy or in combination) and presented in Table 14. When a NOAEL is not available, the Lowest-Observed-Adverse-Effect Level (LOAEL) is used instead, signifying that adverse effects likely occurred below the lowest dose administered.

Table 13. Interspecies comparison and exposure margins. When exposure margins are based on the lowest dose administered and findings were reported at this dose, the values are presented in bold and italics.

Species GLP	Study type Duration	Study No	Dose level (mg/kg/day) NOAEL/ LOAEL	Total C _{max} (μmol/L)	Total AUC ₀₋₂₄ (μmol.h/L)	Exposure margin 75 mg QD (M/F)		
						+/- abemaciclib or palbociclib		+ribociclib (600 mg)
						C _{maxss} 0.150 μmol/L	AUC _{ss} 2.206 μmol.h/L	AUC _{tau} * 5.777 μmol.h/L
Mouse GLP	Repeat-dose 6 W	20377187	10/25/75 M+F: LOAEL	3.84	31.9	25.6	14.5	5.5
Rat GLP	Repeat-dose 4 W	506480	10/25/75 M: NOAEL 75 F: LOAEL	M: 5.27 F: 1.35	M: 67.7 F: 10.3	35.1 9.0	30.7 4.7	11.7 1.8
	Repeat-dose 13 W	521854	0.1/0.25/1/5 M=NOAEL 5 F: LOAEL	M: 0.113 F: 0.000760	M: 0.858 F: 0.00381	0.8 0.01	0.4 0.002	0.2 0.001
	Repeat-dose 26 W	509329	10/25/75 M+F: LOAEL	M: 0.611 F: 0.802	M: 4.51 F: 5.02	4.1 5.3	2.0 2.3	0.8 0.9
	EFD Phase I-III: D6 of gestation til D6 of lactation	490005	I:0.1 II:0.001/0.0 1/0.025/0.0 75 III:0.075/0. 75 F:< LOAEL Pups: < LOAEL Lowest quantifiable plasma level at 0.025 mg/kg	0.025: F:0.0002 93 Pups: -	0.025: F:0.0016 5 Pups: -	0.002 -	0.001 -	0.0003 -
	FEED 2 W	490021	0.001/0.075 /0.75 F: LOAEL	Extrapolated from 521854		Not assessable at LOAEL but likely tight/non-existing		
Dog GLP	Repeat-dose 4 W	506464	5/10/20 M+F: LOAEL	1.17	8.49	7.8	3.8	1.5
	Repeat-dose 39 W	509313	5/10/20 M+F: LOAEL	0.973	7.72	6.5	3.5	1.3

Data presented are total plasma exposure AUC at steady state. Animal:human exposure margins were calculated to at clinical dose of 75 mg QD. When camizestrant was combined with ribociclib, median AUC_{tau} corresponded to 2749 ng.h/mL or 5.777 μmol.h/L. When camizestrant was used as monotherapy or combined with abemaciclib or palbociclib, median AUC_{ss} and C_{maxss} corresponded to 1050.9 ng•hr/mL and 71.5 ng/mL or 2.206 μmol.h/L and 0.150 μmol/L, respectively. Human exposure values were based on a pop-PK model. When camizestrant was administered in combination with 400 mg ribociclib, the camizestrant C_{maxss} and AUC_{tau} were 2.4-fold and 2.6-fold higher than achieved with monotherapy and, when administered in combination with 600 mg ribociclib, the C_{maxss} and AUC_{tau} were 2.8-fold and 3.2-fold higher and comparable with 150 mg monotherapy.

*AUC_{tau} achieved with monotherapy+600 mg ribociclib was chosen for calculations as a worst-case scenario.

Interspecies comparisons were conducted across pivotal repeat-dose toxicity studies in mice, rats, and dogs, as well as in stand-alone EFD and FEED studies in rats. Among these, NOAELs were established only for male rats in the 2- and 4-week studies of shorter duration. For most animals, no safety threshold could be defined, and no NOAELs were identified for females in any species across the pivotal studies, indicating that drug-induced toxicity occurred at all dose levels and at clinically relevant exposures in all species evaluated.

Systemic exposure to camizestrant differed across species, with female rats showing higher sensitivity, consistent with pharmacokinetic differences. In rats, systemic exposure (AUC) increased more than dose-proportionally at doses ≥ 10 mg/kg/day, reaching up to approximately 4.3-fold higher levels in females compared with males, which may have contributed to the greater sensitivity observed in this species.

Findings related to phospholipidosis and macrophage aggregation were observed at high exposure multiples relative to humans, including approximately 30.7-fold and 82.5-fold human exposure in male and female rats, respectively, and ~ 53 -fold in mice. In dogs, similar findings were observed at approximately 58.5-fold human exposure.

Cardiovascular findings in dogs occurred at comparatively lower exposure margins, with a cardiac LOAEL at 5 mg/kg/day corresponding to approximately 3.5-fold human exposure, while ocular findings in dogs were identified at 10 mg/kg/day (approximately 13.8-fold human exposure).

4.4.7. Local tolerance

Camizestrant is orally administered and gastrointestinal tract toxicity has been assessed as part of repeat dose toxicity studies, see 4.4.2. No relevant gastrointestinal changes were noted.

4.4.8. Other toxicity studies

4.4.8.1. Antigenicity

No dedicated antigenicity studies have been conducted for camizestrant.

4.4.8.2. Immunotoxicity

No dedicated immunotoxicity studies have been conducted for camizestrant, see 4.4.2. . This aspect is covered by repeat dose toxicity studies in rodents and dog.

4.4.8.3. Dependence

Dependence studies have not been conducted in accordance with ICH S9.

4.4.8.4. Studies on metabolites

No separate evaluation has been performed with disproportional metabolites. Metabolites have been described under the dedicated section on Metabolism, see 4.3.2.3.

4.4.8.5. Studies on impurities

Specified levels of impurities are considered toxicologically qualified.

4.4.8.6. Phototoxicity studies

The phototoxic potential of camizestrant was investigated using 3T3 Neutral Red Uptake (NRU) assay and measured by the relative reduction in viability of Balb/c 3T3 mouse fibroblasts (GLP Study 20136267) following exposure to camizestrant and ultraviolet radiation (UVR). Promethazine was used as a positive control in the definitive assay. The $IC_{50}(\text{light})$ of camizestrant was comparable to $IC_{50}(\text{dark})$, indicating no phototoxic potential. No reduction was observed in viability of fibroblasts after +UVR. Camizestrant was not phototoxic when tested up to 100 $\mu\text{g/mL}$.

4.4.8.7. Excipient studies

No studies have been conducted on excipients.

4.4.8.8. Other (toxicity) studies (including mechanistic studies)

4.4.8.8.1. Mechanistic studies on heart rate reduction

A reduction in heart rate has been observed in nonclinical species and in clinical trials with camizestrant. *In vitro* and *in vivo* mechanistic studies related to these findings were conducted to assess the hypothesis that camizestrant-related heart rate reduction is via an HCN channel-mediated mechanism. Studies and their results are described below in Table 15.

Table 14. Overview of mechanistic studies on heart reduction.

Study purpose	Dose/route/duration/ test system	Results	Study
Effect of vagotomy on heart rate (HR) <i>in vivo</i>	75 mg/kg, PO, 4 days, Han Wistar rats	Camizestrant-induced ↓HR unaffected by vagotomy demonstrating that the heart rate reduction is independent of parasympathetic nervous system involvement, supporting a direct cardiac mechanism.	BE00176 4-30
Effect on recombinant hHCN4 <i>in vitro</i>	CHO cells expressing hHCN4. IonWorks platform. 0.1 – 10 µM, 1-72h exposure	Conc. and time-dependent inhibition of hHCN4 current. IC ₅₀ 2.5 ≤ µM after 72h demonstrating direct HCN4 channel inhibition with increasing potency upon prolonged exposure, consistent with a cumulative effect.	BE00362 4-95
Effect on recombinant hHCN4 <i>in vitro</i> (QPatch®)	CHO cells expressing hHCN4. QPatch® platform. 0.17 – 50 µM, 3 min to 72h exposure	Acute IC ₅₀ = 14.2 µM (when hyper-polarized at -90mV) with voltage-dependent block, more pronounced at physiologically relevant membrane potentials (~-60 mV). Time-dependent ↓ in functional expression: Chronic exposure reduced functional expression (-54% at 10 µM, 72 h), indicating long-term down-regulation of HCN4 activity.	BE00362 4-96
Effect on sinoatrial node (SAN) cell beat rate <i>in vitro</i>	hESC-derived SAN cells, 0.1-30 µM for 7 days	Time- and concentration-dependent ↓beat rate, peaking at 48h. IC ₅₀ = 11 µM on D7. The delayed onset and plateau support progressive suppression of pacemaker activity with sustained exposure.	BE00238 5-25
Effect on action potential (AP) of SAN cell <i>in vitro</i>	hESC-derived SAN cells. 0.1-10 µM, 10 min-48h exposure	↓ diastolic depolarization rate (DDR) of the AP after 48h, 44.3/86.9% at 1/10 µM, indicating direct HCN-mediated slowing of pacemaker depolarisation; at higher concentrations, prolongation of APD ₉₀ suggests additional off-target ion channel effects at supra-therapeutic exposure.	BE00362 4-97
Effect on the pacemaker current in SAN cells <i>in vitro</i>	hESC-derived SAN cells 0.01-10 µM, 72h exposure; 1 µM: 24 h exposure	Time- and concentration-dependent ↓ in functional expression of pacemaker current. -24% at 0.01 µM, 72h. Higher concentrations produced faster onset of inhibition, while lower concentrations required longer exposure, indicating cumulative potency and delayed SAN response	BE00362 4-98

Effect on ion channels (HCN1, HCN2, HCN4) expressed in mammalian cells	hHCN1 and hHCN4 in HEK293 cells, and hHCN2 in CHO cells;10 and 50 μ M for 5 min, 1 and 10 μ M for 48h exposure	μ M	hHCN1	hHCN2	hHCN4	211108. BAQ_01 and _02
		Short exposure, % inhibition				
		10	4.3	12.4	7.7	
		50	9.4	31.9	37.5	
		48 h exposure, % inhibition				
		1	76-81	<10	44	
		10	90-96	<50	71	
Preferential inhibition of HCN1 and HCN4 over HCN2, with limited acute effects but marked inhibition after 48 h (e.g. HCN1 up to 96%, HCN4 up to 71%). This demonstrates isoform selectivity and strong time-dependent functional down-regulation, consistent with tissue expression in heart and CNS						
Effect on cardiac pacemaker current (I_f) in sinoatrial node myocytes (<i>ex vivo</i>)	Myocytes isolated from Han Wistar rats given 75 mg/kg/day for 7 days	Camizestrant reversibly inhibited the I_f current with an IC_{50} of 10.3 μ M. Chronic dosing reduced pacemaker current (g_{max} –37.7%) with altered activation properties, supporting both acute and sustained inhibition of native pacemaker activity, consistent with <i>in vivo</i> bradycardia.				4577SR
All studies non-GLP						

Collectively, these results indicate that camizestrant produces both acute bradycardia via direct HCN4 inhibition and cumulative chronotropic suppression with chronic exposure/repeated dosing. At high exposures, abnormal APD90 lengthening at a high concentration indicates additional uncharacterised ion channel involvement.

4.4.8.8.2. Mechanistic studies on visual effects

Visual effects have been reported in clinical trials with camizestrant. Three *in vivo* mechanistic rat studies were conducted to determine if there was a functional effect on the retina (Table 16).

No histological changes were observed as evaluated by light microscopy, supporting a functional effect rather than structural damage to the retina, which is in line with the lack of ophthalmic findings in repeat-dose toxicity studies. Retinal changes occurred at 12 mg/kg/day (5 $\times$ human exposure) and displayed a delayed onset.

Table 15. Overview on mechanistic studies on visual effects.

Study purpose	Dose/route/test system	Results	Study
Retinal exposure and distribution after single- and 7-days dosing	Rat: Long Evans, 3M/dose, PO 0, 6.8 mg/kg, 1 or 7 days 3F/dose: 0, 75, 100 mg/kg, 7 days	Camizestrant distributes mainly in pigmented areas; eye exposure higher on D7. Higher relative abundance in the RPE/ choroid region than the OS/IS. Conc. in neural layers of the retina comparable to extra-ocular tissue (75 or 100 mg/kg). LE rats suitable for ERG study.	BE003082-27
Effect on ERG after 7 days of dose, and 7 days recovery	Rat: LE, 5-6/group 0, 25, 75 mg/kg/day, PO, 7 days @	Dose-dependent $\downarrow$ in dark-adapted b-wave and oscillatory potential amplitudes. $\uparrow$ in light adapted b-wave amplitudes and latency times in response to flicker stimuli and $\uparrow$ in amplitudes following sinusoidal stimuli. Similar magnitude on D1 and 7 and reversible. Data suggest reversible functional effect on rod bipolar cells, rather than structural effect.	8498695
Effect on ERG after 7 days of dose, and 7 days recovery	Rat, LE, 6F/dose 0, 5, 12, 25 mg/kg/day, PO, 7 days	Similar effects as previous ERG study plus on D7 at 25 mg/kg/day marked reduction of the photopic B-wave during the early stages of light adaptation that recovered to control levels by the end of the 10-minute adaptation period. Thus, effects evident in the photopic response immediately after transitioning to a lighted background and diminished after light adaptation. All ERG changes recovered to control levels. NOEL = 5 mg/kg. Day 1 plasma levels: 1, 5 and 12-fold above clinical 75 mg dose	8518228

Study purpose	Dose/route/test system	Results	Study
Histopathology (rats) from 8498695	Eyes from all groups 0, 25, 75 mg/kg/day	No treatment related changes	6977DV
Histopathology (rats) from 8518228	Eyes from all group 0, 5, 12, 25 mg/kg/day	No treatment related changes	7181DV
RPE: Retinal pigmented epithelium. OS/IS: outer segment/inner segment. Ivabradine (12 mg/kg, IV, single dose) included in ERG study 8498695 (results not shown). All studies non-GLP.			

4.4.8.9. Investigative Toxicity Study in Female Han Wistar Rats

An investigative toxicity study (non-GLP Study BE001738-15) was conducted to assess tolerability and safety margins over 7 days dosing and to assess the effect of an extended dosing period (28 days) on tolerance and potential toxicities. Doses 0, 50, 200 or 400 mg/kg/day for 7 days; 0 or 50 mg/kg/day for 28 days (Table 17)

Table 16. Investigative repeat-dose toxicity study in female rats.

Study details	No:Sex/ Group	Dose (mg/kg/day)	Exposure (Day 7 unless stated otherwise)		Major findings & NOAEL
			C _{max} (µmol/L)	AUC (µmol.h/L)	
RAT (Han Wistar) 7 D or 28 D PO Non-GLP BE001738-15	3F	0	-	-	<u>Mortality</u> All in group 400 mg/kg euthanised Day 4. <u>Haematology</u> ↑ neutrophils (≥50 mg/kg/day), ↑ monocytes (≥50 mg/kg/day), ↓ eosinophils (≥200 mg/kg/day), ↓ lymphocytes (400 mg/kg/day) <u>Clinical chemistry</u> : ↑ AST, ALT and GLDH (≥50 mg/kg/day), ↑ ALP (50 and 200 mg/kg/day), ↑ creatinine (50 and 200 mg/kg/day), ↑ phosphate (50 and 400 mg/kg/day), ↓ albumin (≥50 mg/kg/day), ↑ cholesterol (200 mg/kg/day), ↓ triglycerides (400 mg/kg/day) <u>Histopathology</u> Ovary (cysts, ≥50 mg/kg/day), uterus (atrophy, ≥50 mg/kg/day), vagina (atrophy, epithelial degeneration, ≥50 mg/kg/day) lung (↑ alveolar macrophages, ≥50 mg/kg/day; vacuolation of the alveolar septum, ≥200 mg/kg/day, and at 50 mg/kg/day for 28 days; increase in severity of alveolar macrophages (↑ number and ↑ size) with increased duration of dosing when comparing animals dosed at 50 mg/kg/day camizestrant for 7 or 28 days); mesenteric lymph node and spleen (macrophage vacuolation, ≥200 mg/kg/day); liver (hepatocellular vacuolation and single cell degeneration, ≥200 mg/kg/day); non-glandular stomach (hyperkeratosis, ulceration (squamous) and inflammation of the submucosa, 200 mg/kg/day). All vacuoles present in H&E sections were positive for Lysosome-associated membrane protein 2 (LAMP2) indicating that they are lysosomal in nature. Electron microscopy of the lung, liver and mesenteric lymph node confirmed the presence of membranous whorls in cells which were identified as being vacuolated in H&E sections, an ultrastructural change consistent with the accumulation of phospholipid.
		50	4.59	65.0	
		200	33.3	535	
		400	9.31 (Day 1)	175 (Day 1)	
		50	4.00 (Day 28)	57.2 (Day 28)	

4.4.8.10. Determination of Parathyroid Hormone (PTH) in Dog Serum

Parathyroid hormone levels were measured in serum samples (Study 3801030) collected from surviving animals in Week 39 of the 9-month dog study (Study 509313). No significant differences in parathyroid hormone levels were noted between the control and treated groups.

4.4.9. Ecotoxicity/environmental risk assessment

Table 17: Summary of main study results: Phase I

Substance (INN/Invented Name):		camizestrant	
CAS-number (if available):		2222844-89-3	
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential-log Kow	OECD107	1.01 at pH 5	Potential PBT: N
		2.60 at pH 7	
		3.71 at pH 9	
PBT/vPvB assessment			
Property	Parameter	Result	Conclusion
Bioaccumulation	Log Dow	1.01 at pH 5	Not B
		2.60 at pH 7	
		3.71 at pH 9	
	BCF _{kg} l	11 L/kgww	Not B
Persistence	Ready biodegradability	N/A	N/A
	DT _{50, total system} at 12°C	476 d	vP
Toxicity	NOEC _{aquatic} C, M, R	13 µg/L Reproductive toxicity Category 1B	T
PBT/vPvB statement:	Camizestrant is considered to be not PBT, nor vPvB. Camizestrant is considered to be vP.		

Phase I			
Parameter	Value	Unit	Conclusion
PEC _{sw} , refined (revalence)	0.0276	µg/L	≥ 0.01 threshold: Y
Other concerns (e.g. chemical class)	Endocrine active substance		Y

Table 18: Summary of main study results: Phase II

Phase II Physical-chemical properties and fate			
Study type	Test protocol	Result	Remarks
Water solubility	OECD 105	102000 mg/L at pH 4 876 mg/L at pH 7 62.6 mg/L at pH 9	shake flask

Phase II Physical-chemical properties and fate			
Study type	Test protocol	Result	Remarks
		at 20 °C	
Dissociation in Water	OECD 112	pK _{a, 1} = 4.59 pK _{a, 2} = 8.26	
Adsorption-Desorption	OECD 106		
Soil 1 = Silty Clay Loam soil (TB-L-PF)		K _{OC, soil 1} = 43300 L/kg _{oc}	
Soil 2 = Loamy Sand soil (RMN-LS)		K _{OC, soil 2} = 947000 L/kg _{oc}	
Soil 3 = Loam soil (MSL-PF)		K _{OC, soil 3} = 116000 L/kg _{oc}	
Soil 4 = Clay Loam soil (DU-L)		K _{OC, soil 4} = 555000 L/kg _{oc}	
Sludge 1 = Denton WWTP (DAS-060822)		K _{OC, sludge 1} = 637L/kg _{oc}	
Sludge 2 = Easton WWTP (EAS-053122)		K _{OC, sludge 2} = 828 L/kg _{oc}	
Ready Biodegradability Test	OECD 314B	DT _{50,parent} = 5.9 d (12 °C) k = 0.2502 d ⁻¹ CO ₂ formation = 1.7 %	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT _{50, water 1} = 2.82 d DT _{50, sediment 1} = 314 d DT _{50, whole system 1} = 478 d CO ₂ = 1 % NER _{total} = 40.4 %	12 °C CO ₂ and NER values at test end
Sediment 1 = loam (High Organic Carbon, Brandywine Creek)			
Sediment 2 = sand (Low Organic Carbon, Choptank River)		DT _{50, water 2} = 13.1 d DT _{50, sediment 2} = 141 d DT _{50, whole system 2} = 101 d	12 °C CO ₂ and NER values at test end

Phase II Physical-chemical properties and fate					
Study type	Test protocol	Result		Remarks	
		CO ₂ = 1 % NER _{total} = 36.6 %			
Transformation products		>10% = Y TP1:ROI1(max) = 10.6 % TP2:ROI8 (max) = 10.9 % TP3:ROI10 (max) = 11.4 % TP3:ROI11 (max) = 12.2 %		at day 28, sed 2 at day 28, sed 2 at day 28 sed 1 at day 28 sed 2 no identification and DT ₅₀ , since TPs observed in one replicate, ≤12.2 %, no increase over time	
Phase II Aquatic effect studies					
Study type	Test protocol	Endpoint	Value	Unit	Remarks
Algae, Growth Inhibition Test/ <i>Raphidocellus subcapitata</i>	OECD 201	EC10	130	µg/L	growth rate
Daphnia sp. Reproduction Test/ <i>Daphnia magna</i>	OECD 211	NOEC	4000	µg/L	reproduction
Fish, FFLC/ <i>Pimpephales promelas</i>	OECD 95/210229/234	NOEC	13	µg/L	spawning frequency & female wet weight
Activated Sludge, Respiration Inhibition Test	OECD 209	EC10	60.8	mg/L	total respiration
Phase II Sediment effect studies					
Sediment Dwelling Organism Test/ <i>Chironomus riparius</i>	OECD 218	NOEC	756	mg/kg _{dw}	Development rate, emergence Normalised to 10% OC
Phase II Secondary poisoning					
Bioaccumulation Test/ <i>Lepomis macrochirus</i> Test 1 = 420 µg/L* *Time-weighted mean measured radioactivity	OECD 305 (minimised design)	BCF _{KgL, 1}	11	L/kg	
Risk characterisation					
Compartment	PEC	PNEC	RQ		Conclusion
STP	0.276 µg/L	6080 µg/L	0.000045		No risk
Surface water	0.0276 µg/L	1.3 µg/L	0.0212		No risk

Phase II Physical-chemical properties and fate				
Study type	Test protocol	Result		Remarks
Groundwater	0.0069 µg/L	0.13 µg/L	0.053	No risk
Sediment	626.6 µg/kg _{dw}	7562.5 µg/kg _{dw}	0.083	No risk

Considering the above data of the definitive hazard assessment, camizestrant is not considered a PBT nor vPvB substance. Camizestrant fulfils the vP criterion. A bioaccumulation potential is not indicated based on the $\log K_{OW} < 4.5$. A definitive PBT/vPvB assessment is not required.

Risk mitigation including statements in relevant sections of the Product information (SmPC and Patient Leaflet) have been included as appropriate.

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

Pharmacodynamics

Several *in vitro* and *in vivo* studies were conducted in support of the suggested mode of action (MoA) of camizestrant (AZD9833) showing evidence of estrogen receptor (ER α) binding affinity, specificity and efficacy. Furthermore, literature was presented to demonstrate that human ER α has high sequence homology with the animal species used in the non-clinical program, particularly in the ligand binding domain.

Primary pharmacology

Camizestrant is a potent and selective oestrogen receptor (ER) antagonist and degrader, targeting both wild-type and *ESR1*-mutated ER α with IC₅₀'s in the low nanomolar range. *In vitro*, camizestrant inhibited oestradiol-induced signalling and demonstrated antiproliferative activity in ER-positive breast cancer cell lines, including models harbouring ESR1 mutations. The compound showed no evidence of agonistic activity. While camizestrant does not degrade ER β , it binds to ER β with high potency. The two camizestrant metabolites M4 and M14 showed respectively low potency or inactivity in terms of ER α degradation *in vitro*.

In vivo, camizestrant demonstrated dose-dependent antitumour activity in ER-positive xenograft and patient-derived models, including tumour regression. Reduction of ER α levels in tumour tissue correlated with antitumour efficacy and supports the proposed mechanism of action.

Combination with CDK4/6 inhibitors (i.e. abemaciclib, palbociclib or ribociclib) resulted in increased antitumour activity compared with monotherapy, consistent across different inhibitors. While camizestrant markedly improved efficacy of CDK4/6i, camizestrant activity appeared only to be minimally influenced by CDK4/6 inhibitors. However, it should be noted that the combination with ribociclib, noticeably increased camizestrant exposure in plasma.

No evidence of uterotrophic or agonistic ER activity was observed.

Secondary pharmacology

No clinically relevant off-target activity was identified at relevant exposure in a broad receptor screening panel or an *in vitro* selective voltage-gated cardiac ion channel electrophysiological assay. Binding to histamine H3 and μ -opioid receptors was observed at high margins without associated functional effects. Given the high affinity for ER β , pharmacological activity in non-target tissues cannot be excluded but this is included in the observed safety profile.

Safety pharmacology

Safety pharmacology studies identified a **cardiovascular safety concern**. In rats and dogs, camizestrant induced effects on cardiac electrophysiology, including QT/QTc prolongation, decreased heart rate (bradycardia), and haemodynamic changes. These findings were more pronounced following repeated dosing and occurred at exposure levels with limited safety margins in dogs.

In dogs, repeated administration resulted in consistent electrophysiological effects, including QTc prolongation, reduced heart rate, and occasional arrhythmias (atrial premature complexes), with no clear no observed adverse effect level (NOAEL). These findings were partially reversible but showed delayed onset and persistence after treatment cessation for at least 3 days up to 22 days.

Mechanistic investigations indicated that bradycardia is likely mediated via inhibition of HCN4 ion channels. However, QT prolongation was not associated with hERG inhibition, and its underlying mechanism remains insufficiently characterised.

Overall, the non-clinical data indicate a treatment-related effect on cardiac repolarisation and conduction with potential clinical relevance, particularly under conditions of prolonged exposure or combination therapy.

No adverse effects of relevance were identified for the central nervous or respiratory system.

Pharmacokinetics

Camizestrant exhibits moderate oral bioavailability (22–43% across species) and a high volume of distribution, indicating extensive tissue penetration. Systemic exposure increased non-linearly, particularly after repeated dosing.

Distribution studies in animals showed widespread tissue exposure, including preferential accumulation in pigmented tissues (notably the uveal tract), while central nervous system exposure was low. Placental transfer is assumed based on developmental toxicity findings.

Camizestrant is primarily metabolised through CYP3A4/5-mediated oxidation and UGT1A4-mediated glucuronidation. Significant human-specific metabolites (M4 and M14) were identified but, in accordance with ICH S9, further non-clinical qualification was not considered necessary.

Excretion occurs mainly via the faecal route following biliary elimination.

In vitro data indicated that camizestrant inhibits several CYP enzymes (including CYP2C9, CYP2C19, and CYP3A4/5), supporting a potential for drug–drug interactions. Increased exposure with co-administration of ribociclib was observed in non-clinical studies.

Toxicology

Repeat-dose toxicity studies

Repeat-dose studies identified as target organs across species the reproductive organs and hypothalamic–pituitary–gonadal axis, liver and endocrine glands, heart and eye and finally lung (phospholipidosis-related findings).

Reproductive toxicity was observed in both sexes at clinically relevant exposures and is consistent with the pharmacological mechanism of ER inhibition. Findings included gonadal atrophy, altered fertility parameters, and hormone-related tissue changes. In general, these effects were reversible, although some ovarian findings persisted.

In rats, hepatobiliary changes and pulmonary phospholipidosis were observed at high exposure multiples and were considered of limited clinical relevance. Isolated cases of rat cardiomyopathy related to treatment were reported with unclear mechanism and may support overall treatment-related cardiac disturbances given the general lack of hERG involvement by camizestrant.

In dogs, cardiovascular findings were consistently observed, including bradycardia, QT/QTc

prolongation (confirming safety pharmacology findings of delayed onset and persistence off dose), and effects on cardiac conduction. These occurred at exposure levels close to clinical exposure and no clear NOAEL was established. Additional cases of atrial premature complex (APC) episodes were observed at slightly higher exposures. The totality of findings is considered of potential clinical relevance.

Genotoxicity

Camizestrant was negative in a standard battery of genotoxic tests (*in vitro* Ames, *in vitro* micronucleus assay and *in vivo* micronucleus test in rats). In pivotal repeat-dose studies, proliferative changes in dogs and rats occurred at 2x human exposure with the exception of an interstitial (Leydig) cell adenoma in a single dog at 13.5x human exposure. The observed abnormal proliferative changes in reproductive tissue are likely to be hormone-driven and are expected counterbalanced in the clinic with concomitant antihormonal treatment or by decreased hormonal status in postmenopausal women. Moreover, the majority of findings were fully reversible. Exceptions included benign granulosa cell tumours in the ovaries of rats and dogs, and a single interstitial (Leydig) cell adenoma in one dog, which were observed only in longer-duration studies (26-week study in rat and 39-week study in dog) not including recovery groups for assessment of reversibility. These could be progression stages of initial proliferative changes observed in the 4-week study. These findings have been appropriately described in the SmPC. No formal carcinogenicity testing was performed in accordance with ICH S9, which has been considered as acceptable.

Carcinogenicity

No carcinogenicity studies have been submitted, which is accepted given the sought indication in accordance with ICH S9.

Developmental and reproductive toxicology

Female fertility was evaluated in a dedicated fertility and early embryonic development (FEED) study in rats following 14 days dosing with camizestrant, which showed that treatment was associated with alterations in oestrous cycles, mating behaviour, reduced fertility (primarily due to a reduction in oestrous cycles) and impaired implantation (fewer implantations and live embryos were detected, accompanied by increased pre- and post-implantation losses). All effects on fertility were fully reversible following a 4-week recovery period. No female fertility NOAEL was determined from the study, and thus effects are likely to have occurred at clinically relevant exposure levels based on extrapolations of exposure values.

Effects on male fertility was assessed as part of the GLP 26-week repeat-dose study in rats where related histopathology findings were observed in a dose-dependent manner at ≥ 10 mg/kg/day. Decreased sperm quality (decreased testis spermatid and epididymal sperm counts, increased abnormal sperm, and reduced sperm motility). Reproductive performance was also affected (mating rate and fertility) with a suggestion to be noted of transmitted reproductive toxicity to undosed female rats at 27x the human exposure. No male fertility NOAEL was determined. Low dose effects occurred at the lowest tested dose at 2x human exposure. Fertility findings observed in the 26-week rat study are adequately reported in the SmPC and a statement was included that reversibility of effects on male fertility was not investigated.

Embryo-foetal development was assessed in a three-phase modified dose range finding embryofoetal development (EFD) study in rats which included a pre- and postnatal assessment spanning a dose range of 0.001- 0.75 mg/kg/day. Developmental studies did not show major direct embryofoetal toxicity at tested exposures; however, pre- and postnatal development was adversely affected, including parturition difficulties and increased pup mortality. No NOAEL was determined and dam fertility, gestation and parturition alongside pup survival were negatively affected at $< < 2.3$ x human exposure (AUC exposure at the highest dose for embryo-foetal development was far

below human exposure).

Based on its mechanism of action, camizestrant is expected to adversely affect reproductive function and is contraindicated in pregnancy and during breastfeeding. Camizestrant carries risk to impair milk production (Rusidze et al., 2021; Jin et al., 2024; Hannan et al., 2023; Kansra et al., 2005; Saji et al., 2000), therefore in line with CHMP Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation (EMA/CHMP/203927/2005) and with the SERDs approved for treatment of pre-, peri- and postmenopausal women, camizestrant contraindication for breastfeeding is considered adequate.

Considering camizestrant's therapeutic indication and the intended patient population as well as the concurrent treatment with a LHRH agonist or antagonist in pre- and perimenopausal women, the wording in section 4.6 of the SmPC is acceptable for use/exposure in women of childbearing potential and during pregnancy as well as the recommended contraceptive measures in women and men.

Although adverse clinical observations related to the central nervous system were observed in a male dog following a single dose of 50 mg/kg and in one male and one female dog following 4 daily repeat doses at 40 mg/kg/day these findings were observed at a total maximum plasma concentration above 50x human exposure. Therefore, it was considered acceptable not to have conducted dependence related studies. In addition, nonclinical studies of abuse liability are generally not warranted under ICH S9 guidance (ICH S9 2010).

Phototoxicity

No phototoxic potential was identified.

Mechanistical studies

Mechanistic investigations for heart and eye confirmed:

- **HCN4 channel inhibition** as a key driver of bradycardia;
- Likely involvement of HCN channels in ocular effects (functional retinal changes without structural damage).

Mechanistic studies also revealed that camizestrant has *in vitro* preference for both HCN1 and HCN4 over HCN2, supporting some functional effects in retina and heart. Given that camizestrant engages multiple members of the HCN ion channel family, which show distinct tissue distribution, it cannot be excluded that other toxicities are mediated by off-target HCN inhibition.

Heart

While it is acknowledged that the mechanistic studies have demonstrated how camizestrant may act, at least in part, through HCN4 ion channels to reduce heart rate, other key cardiovascular findings in safety PD studies and in three repeat-dose studies in dog have not been mechanistically characterised, namely the lengthening of QTc interval. The main non-clinical concern is that the totality of evidence indicates sustained disturbances in cardiac electrophysiological balance across species that may worsen over time and with repeated dosing. This risk may be further amplified in the clinical setting, where co-medications are expected, including agents that independently increase the risk of arrhythmias or QTc prolongation. Of particular concern is the absence of clear mechanistic understanding for several findings. This uncertainty is compounded by the lack of precedent for similar findings among marketed SERDs (to current knowledge), suggesting that the observed cardiac profile may represent a compound-specific risk rather than a class effect. From a non-clinical perspective, a cumulative cardiac risk cannot be ruled out and therefore cardiac findings have been reflected in the SmPC section 5.3. The risk of bradycardia in humans has been acknowledged and implemented in the SmPC as well as will be followed up by routine pharmacovigilance measures.

Eye

The functional electroretinography (ERG) changes observed in rats in the mechanistic studies on visual effects are consistent with temporary visual disturbances observed in the clinical trials—such as photopsia, blurred vision, and impaired vision—arising from rod bipolar cell dysfunction, as demonstrated by the Applicant. Rod bipolar cell dysfunction could be mediated in part by camizestrant's inhibition of HCN1 ion channels expressed by photoreceptors in the inner segments of the retina. However, the ERG pattern observed is not strongly consistent with classic HCN1 inhibition alone as reduced oscillatory potentials in rats suggest additional inner retinal mechanisms contribute to the mixed ERG response. Ocular effects in rats displayed a delayed onset. In humans, the median time to onset of the first visual effect was 8 days, supporting delayed effects as mirrored in the cardiac changes. The ocular toxicity risk in humans has been reflected in the SmPC.

Impurities

Despite the exemption according to the ICHS9, the classification and control of the potential genotoxic impurities have been carried out in accordance with ICH M7. Specified levels of impurities are considered toxicologically qualified. Dedicated studies on single-dose toxicity, carcinogenicity, local tolerance, antigenicity, immunotoxicity, dependence, metabolites and excipients have not been performed which has been considered acceptable.

Environmental risk assessment (ERA)

Camizestrant is not PBT nor vPvB, but vP. Camizestrant is not expected to pose a risk to the STP, surface water, groundwater and sediment compartment based on the prescribed use of camizestrant. Camizestrant is not expected to pose a risk to the environment via secondary poisoning. Camizestrant should be used according to the precautions stated in the SmPC in order to minimize any potential risks to the environment

4.5.2. Conclusions

The PD findings support the potential benefit of camizestrant for patients with *ESR1* mutations in the therapeutic indication.

The non-clinical data package evaluating the pharmacology and toxicity of camizestrant is considered acceptable to support the marketing authorisation.

In general, the findings in toxicology studies are related to the pharmacological action. Relevant information has been reflected in section 5.3 of the SmPC.

The overall toxicity profile of camizestrant is largely consistent with that of two marketed SERDs (elacestrant and fulvestrant)), however, cardiovascular and ocular toxicities appear unique to camizestrant, and some events are demonstrated to be mediated through the HCN ion channel family. Cardiovascular toxicity remains the non-clinical key area of concern and associated risks have been reflected in Section 5.3 of the SmPC.

5. Clinical aspects

5.1. Introduction

5.1.1. Good Clinical Practice (GCP) aspects

The clinical trials were performed in accordance with GCP as claimed by the Applicant.

The Applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier (see section 2.4.3.).

5.1.2. Tabular overview of clinical trials

Table 19 Tabular overview of main clinical studies

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
Supportive Phase I/II studies (contributed to the clinical pharmacology analysis)					
D8532C00002 Hepatic impairment study (LSLV 22Feb2024/ Completed)	Phase I, open-label, non-randomised, multicentre, parallel-group.	Group 1: normal hepatic function. Group 2: moderate hepatic impairment (CP Class B, score of 7 to 9). Group 3: severe hepatic impairment (CP Class C, score of 10 to 15). Dose: camizestrant oral 75 mg on Day 1	Post-menopausal female patients with moderate or severe hepatic impairment and post-menopausal female patients with normal hepatic function	Primary: comparison of PK of single oral dose of camizestrant in post-menopausal patients with moderate and several hepatic impairment with patients with normal hepatic post-menopausal patients Secondary: safety and tolerability including AEs, ECGs, laboratory evaluations, vital signs	Group 1: 8 Group 2: 8 Group 3: 6
D8530C00003 SERENA-3 (19Jun2023/ Completed)	Phase II, 3 stage, randomised, open-label, parallel-group, pre-surgical to investigate the biological effects of different doses of camizestrant oral QD.	Stage 1: (1:1): Camizestrant (75 or 150 mg, oral QD, 5 to 7 days) Stage 2 (1:1 UK or 1:1:1 [Mexico and Georgia] based on geographical stratification factor): Camizestrant (75 or 150 mg [all	Post-menopausal women with ER+/HER2-negative invasive breast cancer	Primary: ER PD effects of camizestrant between pre- and on-treatment tumour samples Secondary: PgR and Ki67 PD effects of camizestrant between pre- and on treatment tumour samples, safety and tolerability including AEs, vital signs, ECGs, and PK	Stage 1 and 2 (combined): 79 Stage 3: 59

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
		countries] or 300 mg [Mexico and Georgia only] oral QD, 5 to 7 days) Stage 3: (1:1): Camizestrant (75 or 150 mg, oral QD, 12 to 15 days)			
D8532C00003 Itraconazole DDI Study (LSLV 28Dec2022/ Completed)	Phase I, open-label, 3 period, fixed sequence study	All participants received the following treatments: Period 1: camizestrant (75 mg oral QD) on Day 1 Washout period between Periods 1 and 2: 7 to 10 days Period 2: itraconazole (oral) for 3 days (200 mg BID on Day 1, 200 mg QD on Days 2 and 3) No washout between Periods 2 and 3 Period 3: camizestrant 75 mg, oral and 200 mg itraconazole on Day 1 with itraconazole 200 mg QD only dosing continued on Days 2 and 3	Healthy post-menopausal female participants	Primary: effect of itraconazole on the PK of camizestrant Secondary: safety and tolerability including AEs, ECGs, laboratory evaluations, vital signs	14
D8532C00006 (midazolam and carbamazepine DDI Study)/ Part A Completed Part B Completed (DCO: 9-Sept-25)	Phase I, open-label, fixed sequence, 2-part, (Part A [midazolam] and Part B [carbamazepine])	Part A: single oral dose of midazolam: Day 1 of Period 1; camizestrant (oral 75 mg QD): Day 2 to Day 6 of Period 2;	Healthy post-menopausal female participants, conducted at a single study centre.	Primary: Part A: effect of repeated oral doses of camizestrant on	Part A: 22 Part B: Approximately 28 (enrolled: 23, completed: 18)

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
		single oral dose of midazolam and camizestrant (oral 75 mg): Day 7 of Period 3. Part B: single oral dose of camizestrant 75 mg: Day 1 of Period 1; carbamazepine BID oral doses at different dose levels: Day 4 to Day 15 of Period 2; single oral dose of camizestrant 75 mg: Day 13 of Period 2.		PK of single dose of midazolam Part B: effect of repeated titrated doses of carbamazepine on PK of single dose of camizestrant Secondary: safety and tolerability including AEs, ECGs, laboratory evaluations, vital signs	
D8530C00004 Relative bioavailability/ food effect/absolute bioavailability study (10Feb2021/ Completed)	A Phase I, single-centre, open-label, randomised, single-dose study to determine the relative bioavailability of different oral camizestrant tablet formulations and a camizestrant oral solution, the effect of food on the PK of an oral camizestrant tablet formulation, and the absolute bioavailability of camizestrant following co administration of an oral camizestrant tablet formulation with a single radiolabelled IV microdose of [¹⁴C] camizestrant, in healthy post-menopausal female participants	Cohorts 1 and 2: 4 administrations of the camizestrant 75 mg oral dose level Cohorts 3 and 4: 3 administrations of the camizestrant 300 mg oral dose level Participants received a single oral dose of camizestrant on up to 4 separate occasions, in either the fed or fasted state. It was planned that for half the participants, on 1 fasted dosing occasion, the oral dose would be co-administered with a radiolabelled IV microdose of [¹⁴C] camizestrant 100 µg	healthy post-menopausal female participants	Primary: Relative bioavailability of camizestrant following single dose oral administration of camizestrant tablet formulations at 2 different dose levels and an oral solution formulation at 1 dose level, in the fasted state. Relative bioavailability of camizestrant following single dose oral administration of a camizestrant late phase studies tablet administered in the fed and fasted state at 2 different dose levels. Secondary: Absolute bioavailability of	Total: 32/32 camizestrant 75 mg: 16/16 camizestrant 300 mg: 16/16

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
				camizestrant following single dose oral administration of a camizestrant late phase studies tablet co-administered with a single radiolabelled intravenous (IV) microdose of [¹⁴ C] camizestrant. Safety and tolerability information for oral camizestrant formulations	
D8532C00005 ADME Study/ (Study completion date 20Jun2022)	Phase I, single centre, single period, non-randomised, open-label study.	camizestrant oral 75 mg on Day 1	Healthy post-menopausal female participants	Primary: mass balance recovery following single oral dose of [¹⁴ C]camizestrant Secondary: routes and rates of elimination of camizestrant, safety and tolerability	6
Supportive Phase I/II studies (contributed to the efficacy, pooled safety and clinical pharmacology analysis)					
D8530C00001 SERENA-1 (Parts A, B, C, D G, H, K, L)	FIH Phase I, randomised, open-label, multicentre, multi-cohort, dose escalation and expansion Patients could continue to receive study treatment as long as they continued to show clinical benefit, as judged by the Investigator	Part A: camizestrant 25, 75, 150, 300, or 450 mg QD oral Part B: camizestrant 75, 150, or 300 mg QD oral Part C: camizestrant 75, 150, or 300 mg QD oral + palbociclib 125 mg QD oral Part D: camizestrant 75, 150, or 300 mg QD oral + palbociclib 125 mg QD oral Part G: camizestrant 75 or 150 mg QD oral +	Women with ER-positive HER2-negative ABC, progressed on at least one line of ET-based therapy in advanced setting	Safety and tolerability, efficacy, PK, biomarker changes Primary endpoint: safety and tolerability including AEs, DLTs, laboratory evaluations, ECGs	Part A: 62/38 Part B: 46/24 Part C: 36/19 Part D: 42/14 Part G: 28/16 Part H: 25/14 Part K: 30/17 Part L: 30/12

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
		abemaciclib 150 mg BID oral Part H: camizestrant 75 or 150 mg QD oral + abemaciclib 150 mg, BID oral Part K: camizestrant 75 mg QD oral + ribociclib 400 or 600 mg QD oral Part L: camizestrant 75 mg QD oral + ribociclib 400 or 600 mg QD oral			
D8530C00002 SERENA-2	Phase II, randomised, open-label, parallel-group, multicentre study Patients could continue to receive study treatment as long as they continued to show clinical benefit, as judged by the Investigator	camizestrant 75 mg QD oral camizestrant 150 mg QD oral Camizestrant 300 mg QD oral fulvestrant 500 mg IM	Post-menopausal women with ER positive, HER2 negative ABC who were suitable for therapy with fulvestrant and had received no more than one previous ET and one previous chemotherapy in the advanced setting	Efficacy, PROs, safety and tolerability Primary endpoint: PFS by investigator assessment as defined by RECIST v1.1	Total: 240/18 ongoing (DCO: 30-Mar-25) camizestrant 75 mg: 74/21 ongoing camizestrant 150 mg: 73/26 ongoing camizestrant 300 mg: 20 ^b /9 ongoing fulvestrant 500 mg: 73/19 ongoing
Pivotal efficacy and safety study					
D8534C00001 SERENA-6 (DCO1: 28 Nov 2024/ongoing)	Phase III, parallel, randomised, double-blind with matching placebos, 2-arm, multicentre, international study Patients continued study treatment until objective radiological disease progression as defined by RECIST v1.1, unacceptable toxicity occurred, treatment	camizestrant + CDK4/6 inhibitor arm: camizestrant (75 mg QD oral) + CDK4/6 inhibitor (continuing palbociclib, ribociclib, or abemaciclib, maintained at the same dose as when the <i>ESR1m</i> was detected) + placebo for AI AI + CDK4/6 inhibitor	Patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer with detectable <i>ESR1m</i> , without disease progression during 1L treatment with AI + CDK4/6 inhibitor	Efficacy, safety and tolerability, PK, PROs Primary endpoint: PFS by investigator assessment as defined by RECIST v1.1	Total: Randomised: 315 Treated: 310 Ongoing: 244 camizestrant + CDK4/6 inhibitor arm: Randomised: 157 Treated: 155 Ongoing: 125 AI + CDK4/6 inhibitor arm:

Study	Design, control type, duration	Treatment	Subject population	Study objectives and primary endpoint	Number of subjects total and per group randomised (treated)/completed study
	discontinuation criterion was met, the patient withdrew consent, or death	arm: AI (continuing anastrozole 1 mg QD oral or letrozole 2.5 mg QD oral) + CDK4/6 inhibitor (continuing palbociclib, ribociclib, or abemaciclib, maintained at the same dose as when the <i>ESR1</i> m was detected) + placebo for camizestrant			Randomised: 158 Treated: 155 Ongoing: 119

5.2. Clinical pharmacology

5.2.1. Methods

Bioanalytical methods for the determination of camizestrant in human plasma and urine were developed and validated (data not shown).

Other analytes

Full validation reports and amendments were provided for for bioanalytical methods of compounds co-administered with camizestrant including abemaciclib, ribociclib, palbociclib and midazolam.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

The pharmacokinetics of camizestrant were investigated in 8 Phase 1 studies in patients (SERENA 1, D8530C00006, D8530C00007) as well as in healthy post menopausal female participants (D8532C00002, D8532C00003, D8530C00004, D8532C00006), including an ADME study (D8532C00005) also in healthy post menopausal female participants. Camizestrant PK parameters were also investigated in 2 phase II studies (SERENA-2, SERENA-3) and 1 phase III study (SERENA-6).

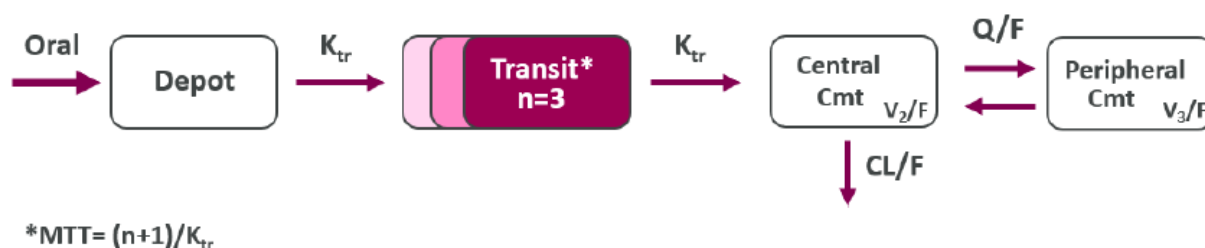
5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population pharmacokinetics

A PopPK model for camizestrant was developed based on data from 7 clinical studies, SERENA-1 (D8530C00001), SERENA-2 (D8530C00002), SERENA-3 (D8530C00003), Japan PK study (D8530C00006), China PK study (D8530C00007) and SERENA-6 (D8534C00001).

The final PopPK model for camizestrant was a 2-compartment model with three transit compartments and first-order elimination. The model was based on data from camizestrant monotherapy and in combination with CDK4/6 inhibitors. Baseline body weight (BBW), ethnicity, concomitant use of ribociclib, and dose were identified as significant covariates of V_2/F , and baseline creatinine clearance (BCRCL), concomitant use of ribociclib, and dose on CL/F (Clearance/bioavailability). Figure 1 shows the structure of the camizestrant PopPK model.

Figure 1: Structure of Camizestrant PopPK Model



The parameter estimates for the selected camizestrant final model are reported in Table 21. RSE for typical parameters and random effect was below 30%. Eta-shrinkage for CL/F , V_2/F (peripheral compartment/bioavailability) and MTT (mean transit time) were 7.98%, 22.27% and 31.5% respectively. Epsilon-shrinkage was 11.54%. No trends were observed in the presented goodness-of-fit (GoF) plots.

Table 20: Final Model Parameter Estimates

			Final Model			Non-parametric Bootstrap	
			Estimate	Shrinkage (%)	RSE (%)	Median	95% CI
Structural model parameters							
MTT (hr)	θ_1	Mean Transit Time	1.41	-	4.08	1.41	[1.30, 1.52]
V2/F (L)	θ_2	Apparent central volume	1280	-	2.96	1290	[1200, 1370]
CL/F (L/h)	θ_3	Apparent clearance	69.1	-	2.01	69.5	[66.9, 72.7]
V3/F (L)	θ_4	Apparent peripheral volume	608	-	5.4	613	[500, 715]
Q/F (L/h)	θ_5	Apparent intercompartmental clearance	44.1	-	5.8	43.8	[38.0, 50.4]
Covariate effect parameters							
Dose ~ V2/F	θ_7	Dose effect on V2/F	-0.261	-	12.7	-0.271	[-0.352, -0.192]
BBW ~ V2/F	θ_8	Baseline Weight on V2/F	0.619	-	13.7	0.617	[0.456, 0.794]
BCRCL ~ CL/F	θ_9	Baseline CrCL on CL/F	0.245	-	16.5	0.244	[0.166, 0.322]
RIBOS ~ CL/F	θ_{10}	Ribociclib effect on CL/F	-0.518	-	5.42	-0.532	[-0.575, -0.472]
RIBOS ~ V2/F	θ_{11}	Ribociclib effect on V2/F	-0.54	-	6.54	-0.547	[-0.607, -0.473]
HISPNC ~ V2/F	θ_{12}	Hispanic effect on V2/F	-0.187	-	27.2	-0.188	[-0.295, -0.0939]
Dose ~ CL/F	θ_{13}	Dose effect on CL/F	-0.127	-	20.2	-0.133	[-0.192, -0.0728]
Interindividual variance parameters							
IIV-MTT	$\Omega_{(1,1)}$	Variance of MTT	0.517 [CV%=82.2]	31.5	11.7	0.509	[0.357, 0.647]
IIV-V2/F	$\Omega_{(2,2)}$	Variance of apparent central volume	0.171 [CV%=43.2]	22.3	9.72	0.169	[0.135, 0.204]
IIV-CL/F	$\Omega_{(3,3)}$	Variance of apparent clearance	0.153 [CV%=40.6]	7.98	6.27	0.152	[0.134, 0.171]
Interindividual covariance parameters							
CL/F-V2/F	$\Omega_{(3,2)}$	Covariance of CL/F - V2/F	0.119 [Corr=0.735]	--		0.119	[0.0931, 0.143]
Residual variance							
Proportional Error	θ_6	Standard Deviation	0.29	--		0.29	[0.279, 0.301]

Abbreviations: BBW: baseline body weight; BCRCL: baseline creatinine clearance; CI: confidence intervals; Corr: correlation coefficient; CV: coefficient of variation; RSE: relative standard error; MTT: mean transit time; RIBOS: Use of ribociclib; SE: standard error.

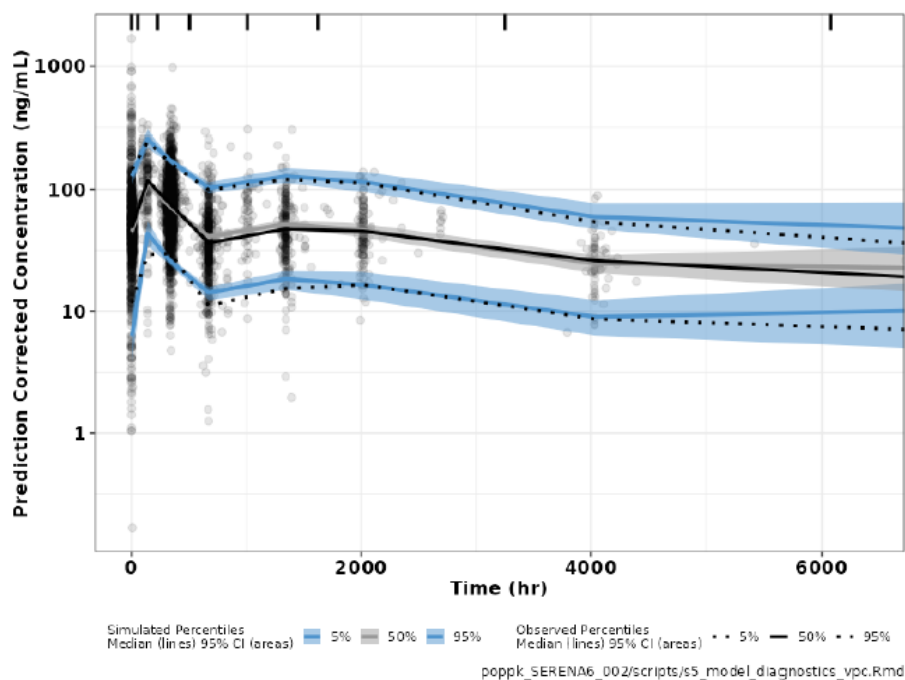
Bootstrap converged 100% of the time

The CI was determined from the 2.5th and 97.5th percentiles of the non-parametric bootstrap (n = 300) estimates. CIs = estimate $\pm$ 1.96 SE.

CV% of log-normal omegas = $\sqrt{\exp[\text{estimate}] - 1} \times 100$

Figure 2 shows a pcVPC of the final model.

Figure 2: Predicted Corrected VPC (pcVPC) of Camizestrant Final Population PK Model



5.2.2.2.2. Physiology based pharmacokinetic model

A PBPK model for camizestrant was developed using a combination of in vitro data, human ADME data and clinical pharmacokinetic data following a single 75 mg dose in healthy subjects. The model applied a “middle-out” approach and incorporated first-order absorption and mechanistic clearance pathways.

The model was qualified against observed clinical data, showing agreement between simulated and observed plasma concentration–time profiles, as well as key pharmacokinetic parameters (C_{max} and AUC) after both single and repeated dosing. Simulations in cancer patients receiving 75 mg once daily reproduced the observed accumulation and exposure profiles described in clinical studies.

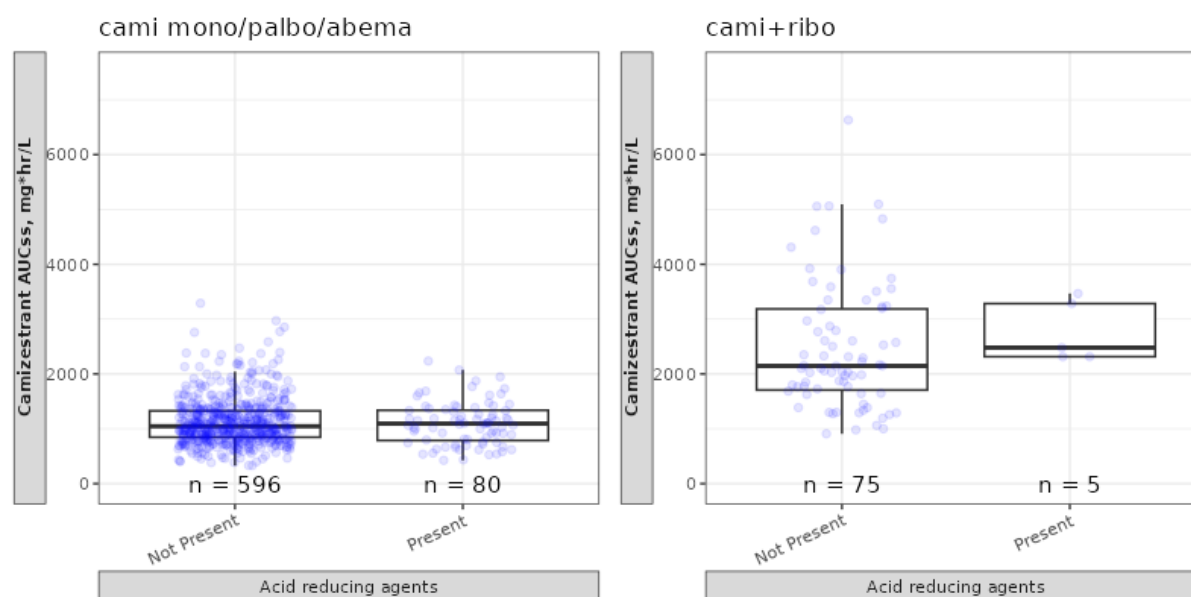
The PBPK model further described the impact of CYP3A4 modulation, reproducing the observed increase in camizestrant exposure with strong CYP3A4 inhibition (e.g. itraconazole) and the interaction with CYP3A4 substrates (e.g. midazolam). The camizestrant PBPK model was used to predict DDI potential for camizestrant as a victim when co-administered with CYP3A4/5 inhibitors.

5.2.2.3. Absorption

BCS classification

Camizestrant is a di-basic molecule with pK_a of 4.8 and 8.4 and logD of 2.3 at pH 7.4. Camizestrant showed high aqueous solubility at pH ranges below neutral (≥ 1.2 mg/mL in simulated gastric fluid pH 1.2 or acetate buffer pH 4.5 and 1.1 mg/mL in phosphate buffer pH 6.8). Dissolution is fastest at pH 1.2 and decrease with increasing pH. However, dissolution was still $>95\%$ after 30 minutes at pH 6.8. Hence, co-administration with PPIs is not expected to impact the degree of absorption. This was confirmed by PopPK modelling where 85 patients (11%) of the population included in the model were using acid reducing agents.

Figure 3 Effect of Acid-reducing Agents on Camizestrant AUC_{ss} for Participants on Camizestrant Monotherapy or Camizestrant in Combination with Abemaciclib or Palbociclib, or Camizestrant in Combination with Ribociclib



In vitro, camizestrant was shown to be a substrate of P-gp, but not BCRP, OATP1B1 or OATP1B3.

Table 21 Summary of camizestrant substrate identification studies with selected efflux and SLC transporters

Transporter	Efflux or Uptake ratio determined at 1 μ M*		Result
	Without Inhibitor	With Inhibitor	
P-gp	66	1.0	Is a substrate
BCRP	12	11	Not a substrate
OATP1B1	1.0	1.5	Not a substrate
OATP1B3	0.5	1.2	Not a substrate

*Data presented from 0.5 min incubation time for SLC transporters

Permeability of camizestrant was evaluated in a Caco-2 cell monolayer permeability assay. The conclusion of the study was that camizestrant has a permeability higher than, or equal to, the high permeability marker minoxidil, but camizestrant permeability is concentration-dependent and subject to efflux at lower concentrations.

Hence, camizestrant may be classified as BCS class 1 compound, although the solubility decreases with higher pH.

Time for maximal plasma concentration

Camizestrant was administered to both healthy volunteers and patients in single dose Phase 1 studies. In healthy volunteer's full PK profiles are available for doses 75 and 300 mg. Time to maximal plasma concentration was typically between 2 and 6 hours but the range was 1 to 10 hours. There were no obvious differences between the different tablet formulations and the oral solution or whether subjects were fasted or fed. In cancer patients, camizestrant was administered at 25, 75, 150, 300 and 450 mg as a single dose. Here the full range for T_{max} was 1 to 24 hours. Following oral administration, camizestrant is absorbed with median peak plasma concentrations achieved between approximately 2 to 4 hours after dosing.

Table 22: Summary of Single Oral Dose Camizestrant Pharmacokinetics in Healthy Participants

Abbreviated Study Code	D853 04	D853 04	D853 04	D853 04	D853 04	D853 04	D853 04	D853 04	D853 05	D853 03	D853 02
Formulation	DC	DC	DC	DC	RC	Oral solution	DC	RC	Oral Solution	Tablet	Tablet
Feeding Status	Fasted	Fed	Fasted	Fed	Fasted	Fasted	Fasted	Fasted	Fasted	Fasted	Fasted
Dose (mg)	75	75	300	300	75	75	75	300	75	75	75
N	15	16	16	15	15	15	15	15	6	14	8
t _{max} (h)	4.00 (2.00–6.04)	4.00 (1.00–10.0)	4.00 (2.02–6.00)	3.02 (2.00–6.00)	6.00 (2.00–6.20)	6.00 (2.00–6.22)	4.00 (2.00–6.04)	2.01 (2.00–8.00)	4.51 (2.00–6.17)	3.83 (1.85–7.90)	5.00 (1.93–8.00)
C _{max} (ng/mL)	30.6 (44.1)	33.7 (39.6)	182 (18.4)	208 (19.0)	32.2 (34.2)	34.3 (39.6)	30.6 (44.1)	184 (22.8)	34.9 (44.4)	45.1 (46.9)	34.4 (19.4)
AUC (ng·h/mL)	636 (35.1)	699 (35.1)	3190 (19.2)	3280 (19.8)	671 (40.4)	688 (36.9)	636 (35.1)	3180 (22.2)	826 (30.3)	821 (36.1)	709 (31.5)
CL/F (L/h)	118 (35.1)	107 (35.1)	94.1 (19.2)	91.6 (19.8)	112 (40.4)	109 (36.9)	118 (35.1)	94.3 (22.2)	88.8 (30.3)	91.3 (36.1)	106 (31.5)
V _z /F (L)	3970 (34.5)	3430 (36.4)	2870 (21.1)	2590 (24.3)	3460 (35.0)	3500 (31.6)	3970 (34.5)	2650 (22.0)	3470 (18.2)	3050 (44.7)	3420 (21.3)
t _{1/2} (h)	23.3 (18.3)	23.2 (25.1)	21.1 (17.6)	19.6 (17.9)	21.4 (15.0)	22.2 (32.6)	23.3 (18.3)	19.5 (12.2)	27.1 (21.4)	23.1 (19.5)	22.4 (29.8)

Geometric mean (geometric CV%) presented. t_{max} median (range).

Abbreviated study numbers: D85304=D8530C00004, D85305=D8532C00005, D85303=D8532C00003, D85302=D8532C00002.

Source: Relative Bioavailability, Food Effect and Absolute Bioavailability Study: D8530C00004 CSR, ADME Study D8532C00005 CSR, Itraconazole DDI Study D8532C00003 CSR, Hepatic Impairment Study D8532C00002 CSR.

Figure 4: Geomean (±SD) plasma concentrations (ng/mL) of camizestrant versus time following a single dose of camizestrant monotherapy in cancer patients in SERENA-1 Part A, cycle 1, Day 1

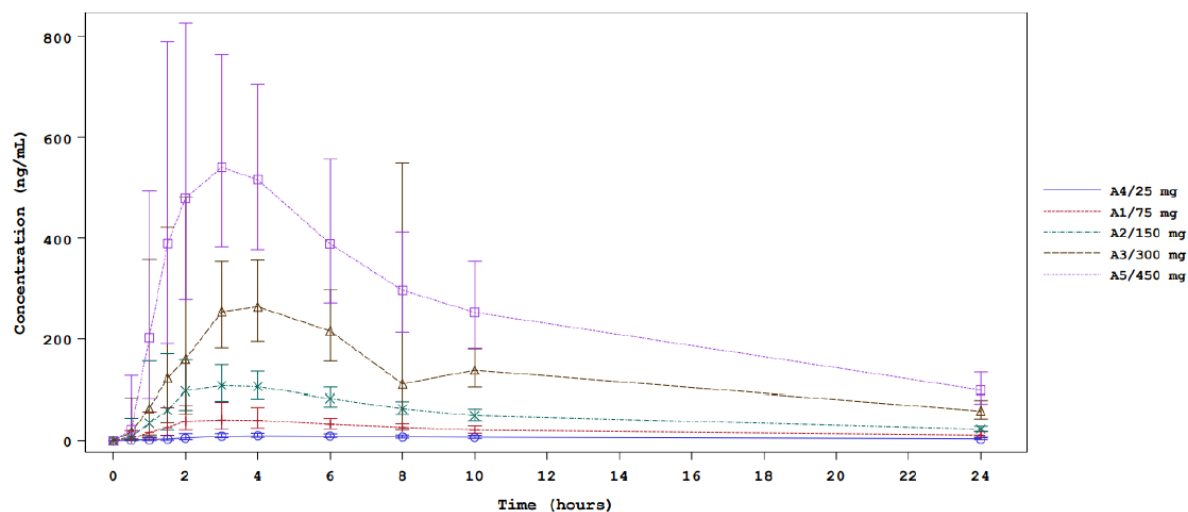


Figure 5: Geomean ($\pm$ SD) plasma concentrations (ng/mL) of camizestrant versus time following a single dose of camizestrant monotherapy in cancer patients in SERENA-1 Part A, cycle 1, Day 15

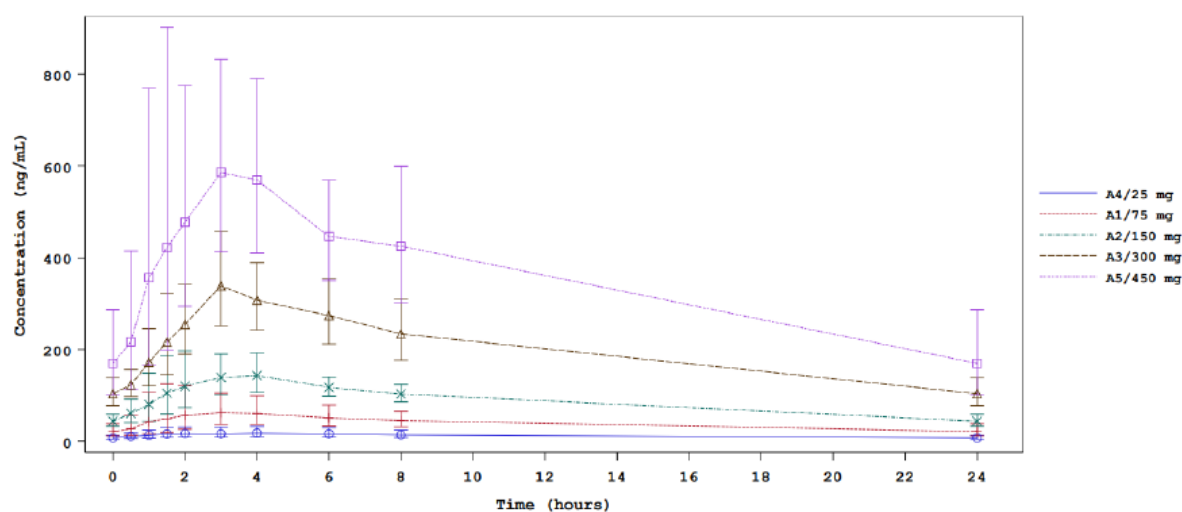


Table 23: Summary of Single Dose Camizestrant Monotherapy PK Parameters in Participants with Cancer

Study	Dose (mg)	AUC _{inf} (ng.h/mL)	AUC _{last} (ng.h/mL)	C _{max} (ng/mL)	T _{max} (h)	t _{1/2} (h)	CL/F (L/h)	V _z /F (L)	V _{ss} /F (L)
SERENA-1 Phase I (D8530C00001)	25	210 (52.3)	139 (46.3)	10.8 (46.3)	3.89 (1.50–7.37)	13.8 (24.4)	119 (52.3)	2370 (46.2)	2560 (46.2)
	[N]	[12]	[12]	[12]	[12]	[12]	[12]	[12]	[12]
	75	729 (57.2)	487 (41.7)	51.7 (49.4)	3.00 (1.00–6.13)	11.9 (56.5)	103 (57.2)	1760 (34.6)	1850 (38.1)
	[N]	[12]	[12]	[12]	[12]	[12]	[12]	[12]	[12]
	150	1560 (24.2)	1190 (27.2)	125 (31.9)	2.32 (1.13–6.35)	10.2 (24.6)	96.2 (24.2)	1410 (25.3)	1450 (25.5)
	[N]	[13]	[13]	[13]	[13]	[13]	[13]	[13]	[13]
	300	4160 (22.0)	2890 (31.3)	306 (28.3)	3.00 (1.50–4.23)	10.0 (39.6)	72.2 (22.0)	1040 (35.4)	1120 (28.5)
	[N]	[13]	[13]	[13]	[13]	[12]	[12]	[12]	[12]
	450	7380 (31.6)	5900 (32.6)	645 (40.9)	2.50 (1.50–6.27)	9.82 (19.9)	61.0 (31.6)	864 (36.8)	882 (35.8)
	[N]	[12]	[12]	[12]	[12]	[12]	[12]	[12]	[12]

Table 24: Summary of Camizestrant Monotherapy PK after Multiple Doses on Cycle 1 Day 15 in SERENA-1 Parts A + B (DC8530C00001)

Camizestrant Dose (mg)	C _{maxss} (ng/mL)	t _{max} (h)	AUC _{tau} (ng.h/mL)	C _{min} (ng/mL)	CL/F (L/h)	t _{1/2} (h)	TCP	Rac (C _{max})	Rac (AUC)
25 [N]	19.9 (65.5) [11]	3.00 (1.50–5.97) [11]	291 (60.6) [11]	7.28 (63.1) [11]	85.9 (60.6) [11]	14.9 (21.5) [10]	1.35 (27.8) [11]	1.81 (39.4) [11]	2.04 (31.0) [11]
75 [N]	64.7 (49.2) [22]	3.72 (1.08–8.00) [22]	862 (46.5) [22]	20.4 (57.9) [22]	87.0 (46.5) [22]	14.4 (28.5) [18]	1.25 (15.3) [12]	1.42 (23.3) [12]	1.75 (16.6) [12]
150 [N]	166 (36.0) [23]	2.17 (1.00–24.0) [23]	2160 (33.9) [23]	50.6 (64.2) [23]	69.4 (38.9) [23]	13.2 (26.7) [19]	1.31 (25.1) [12]	1.30 (30.3) [12]	1.65 (22.5) [12]
300 [N]	376 (40.6) [28]	3.03 (1.70–7.10) [28]	4780 (37.7) [26]	97.8 (49.5) [27]	62.7 (37.7) [26]	12.0 (19.1) [22]	1.23 (18.5) [9]	1.27 (31.8) [10]	1.61 (17.9) [10]
450 [N]	723 (37.9) [11]	3.02 (1.00–6.13) [11]	8420 (31.1) [11]	170 (56.0) [11]	53.5 (31.1) [11]	13.1 (35.1) [9]	1.15 (22.4) [11]	1.15 (26.8) [11]	1.43 (23.9) [11]

5.2.2.4. Bioavailability

The absolute bioavailability of camizestrant was investigated in post-menopausal healthy participants following a single 75 or 300 mg oral dose of camizestrant, administered as the direct compression (DC) tablet, co-administered with a microdose IV administration of [¹⁴C]-camizestrant. Camizestrant was rapidly absorbed following administration of the 75 mg tablet, with C_{max} observed at approximately 2 to 6 h post-dose. The absolute bioavailability was estimated to be 43% (90% confidence interval [CI]: 36.8%, 49.0%) and 55% (90% CI: 48.5%, 62.5%), respectively, following dosing with 75 and 300 mg camizestrant. Simulations in cancer patients receiving 75 mg once daily reproduced the observed accumulation and exposure profiles described in clinical studies, consistent with the steady state reached by approximately Day 5 once daily dosing and a terminal half-life of ~23 hours.

5.2.2.5. Bioequivalence

Table 25: Camizestrant Relative Bioavailability Study D8530C00004 Formulations

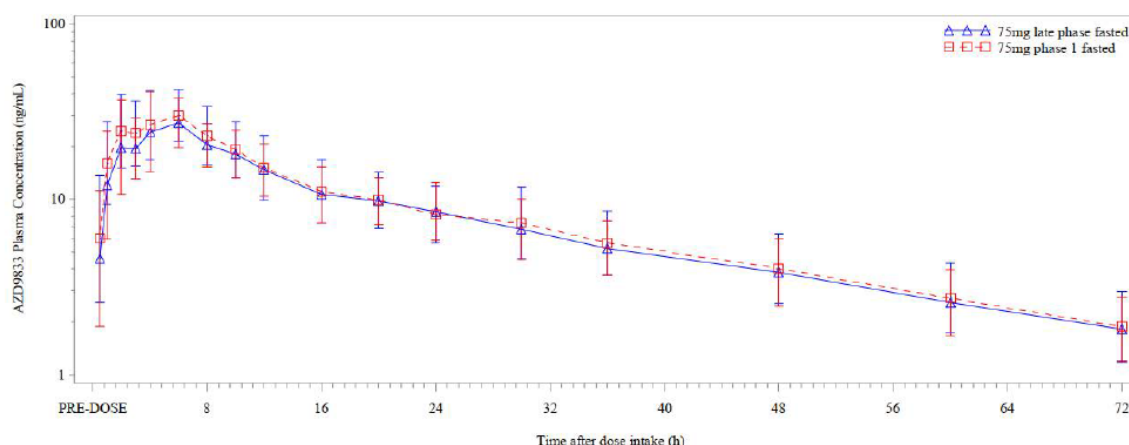
Formulation description	Strength	Tablet size and shape
Film-coated IR tablet produced through RC	25 mg	5 mm round, biconvex
Film-coated IR tablet produced through RC	100 mg	13.0 x 7.5 mm, oval

Formulation description	Strength	Tablet size and shape
Film-coated IR tablet produced through DC representing CDC	25 mg	5 mm round, biconvex
Film-coated IR tablet produced through DC representing CDC	150 mg	14.5 x 7.25 mm, oval
Oral solution	1.5 mg/ml	NA

The relative bioavailability of camizestrant following single dose oral administration of camizestrant tablet formulations at 2 different dose levels (75 and 300 mg) and an oral solution formulation at 75 mg only, in the fasted state in post-menopausal healthy participants was conducted in study D8530C00004.

Exposure was similar when comparing the DC tablet with the RC tablet as well as the oral solution.

Figure 6: Geometric mean ($\pm$ SD) plasma concentrations vs time profiles of camizestrant following single oral doses of 75 mg camizestrant: Late phase fasted vs Phase 1 fasted



Note: Data in the above graph are presented in table 14.2.1.3

All subjects received a single oral dose of AZD9833 on up to 4 separate occasions, in a randomised manner, in either the fed or fasted state. For half the subjects, on 1 fasted dosing occasion, the oral dose will be co administered with a radiolabelled IV microdose of $[^{14}C]$ AZD9833. If at a given time point, 50% or less of the plasma concentrations are NQ, the geometric mean is calculated by substituting the lower limit of quantification (LLOQ) for values which are NQ (LLOQ = 0.500 ng/mL). If more than 50% of the plasma concentrations are NQ then geometric mean is not calculated and presented as missing.

Figure 7: Geometric mean ($\pm$ SD) plasma concentrations vs time profiles of camizestrant following single oral doses of 300 mg camizestrant: Late phase fasted vs Phase 1 fasted

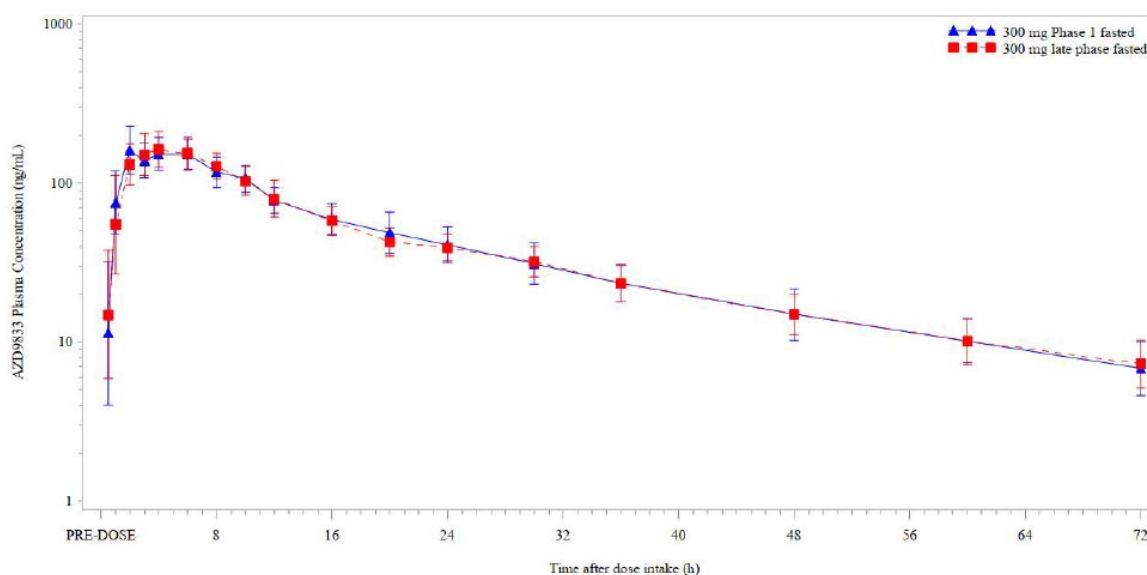
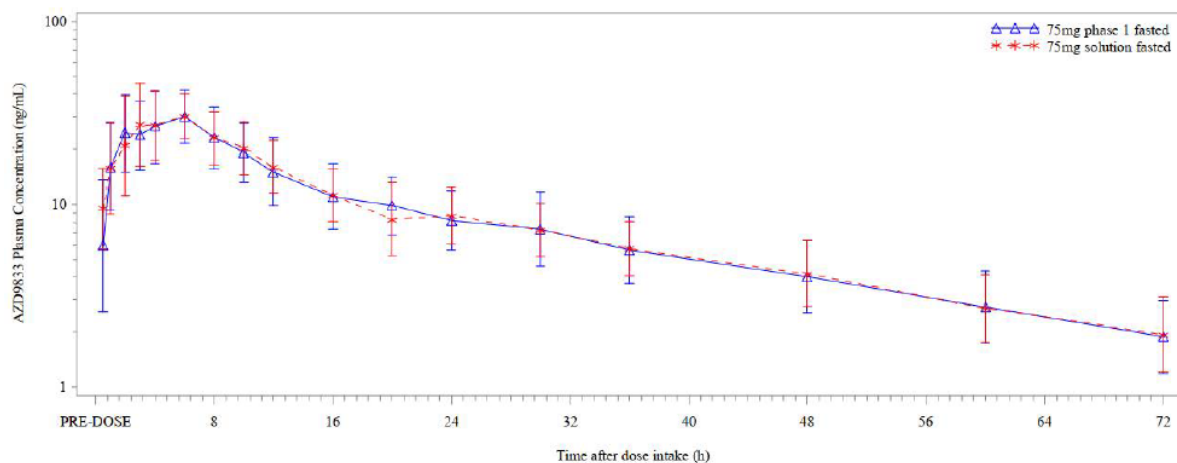


Figure 8: Geometric mean ($\pm$ SD) plasma concentrations vs time profiles of camizestrant following single oral doses of 75 mg camizestrant: Phase 1 fasted vs oral solution fasted



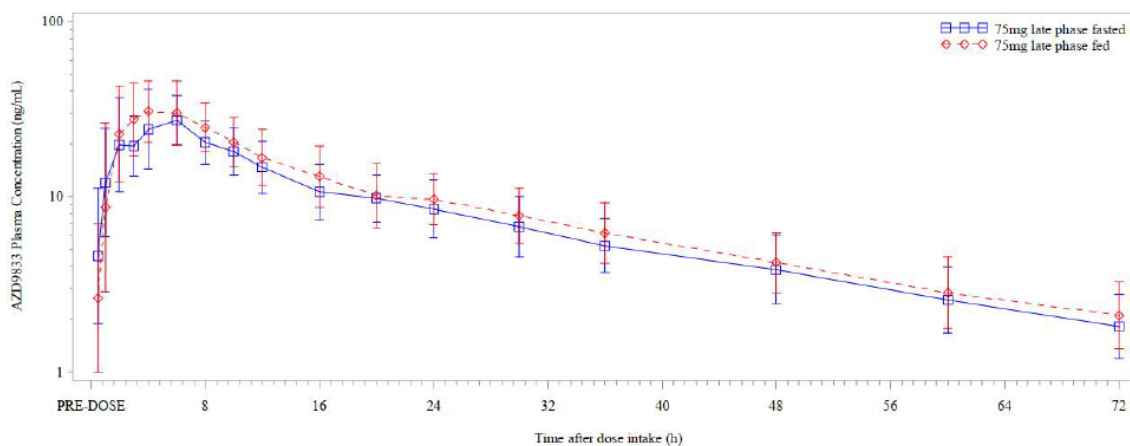
Note: Data in the above graph are presented in table 14.2.1.3

All subjects received a single oral dose of AZD9833 on up to 4 separate occasions, in a randomised manner, in either the fed or fasted state. For half the subjects, on 1 fasted dosing occasion, the oral dose will be co administered with a radiolabelled IV microdose of [14 C]AZD9833. If, at a given time point, 50% or less of the plasma concentrations are NQ, the geometric mean is calculated by substituting the lower limit of quantification (LLOQ) for values which are NQ. (LLOQ = 0.500 ng/mL). If more than 50% of the plasma concentrations are NQ then geometric mean is not calculated and presented as missing

5.2.2.6. Influence of food

At both 75 mg ($n = 16$) and 300 mg ($n = 15$), the exposures were similar between the fed and fasted treatments. Following a 75mg dose, the fed to fasted C_{max} and AUC geometric mean ratios (90% CI) were 106.2% (90% CI: 94.3%, 119.7%) and 109.8% (90% CI: 104.4%, 115.5%), respectively.

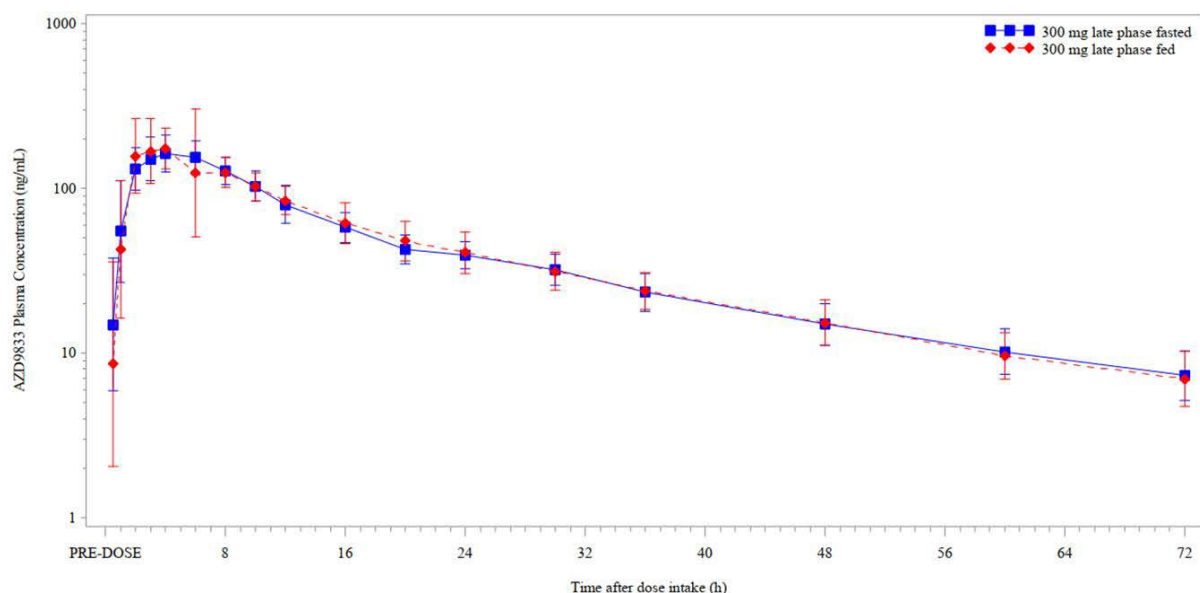
Figure 9 Geometric mean ($\pm$ SD) plasma concentrations vs time profiles of camizestrant following single oral doses of 75 mg camizestrant: Late phase fed vs fasted



Note: Data in the above graph are presented in table 14.2.1.3

All subjects received a single oral dose of AZD9833 on up to 4 separate occasions, in a randomised manner, in either the fed or fasted state. For half the subjects, on 1 fasted dosing occasion, the oral dose will be co administered with a radiolabelled IV microdose of [14 C]AZD9833. If, at a given time point, 50% or less of the plasma concentrations are NQ, the geometric mean is calculated by substituting the lower limit of quantification (LLOQ) for values which are NQ. (LLOQ = 0.500 ng/mL). If more than 50% of the plasma concentrations are NQ then geometric mean is not calculated and presented as missing

Figure 10: Geometric mean ($\pm$ SD) plasma concentrations vs time profiles of camizestrant following single oral doses of 300 mg camizestrant: Late phase fed vs fasted



5.2.2.7. Distribution

Volume of distribution

In the relative bioavailability, food effect, and absolute bioavailability study in post-menopausal healthy participants (D8530C00004), the geomean (CV%) V_z for camizestrant was estimated to be 1430 L (15.6%) and 1240 L (40.2%) following a single IV infusion of 100 μ g [14 C]-camizestrant after a single oral dose of the late phase tablet at 75 or 300 mg, respectively.

Across the dose range 25 to 450 mg administered to cancer patients in SERENA-1, V_{ss}/F decreased from 2563 L to 882 L with dose. At 75 mg, the V_{ss}/F was 1849 L and was similar to the PopPK value of 1888 L (26.97 L/kg).

Protein binding

Table 26: Summary of plasma protein binding (% free) camizestrant in mouse, rat, rabbit, dog, mini-pig, monkey and human (mean $\pm$ SD)

AZ14066724 concentration (μ mol/L)	% Free						
	Mouse	Rat	Rabbit	Dog	Mini-pig	Monkey	Human
0.03	< 23.1*	30.3 $\pm$ 2.89	29.7 $\pm$ 4.33	< 20.9*	38.3 $\pm$ 1.43	29.5 $\pm$ 1.72	25.9 $\pm$ 0.192
0.3	19.9 $\pm$ 0.380	26.7 $\pm$ 0.118	28.3 $\pm$ 0.325	15.7 $\pm$ 0.440	37.3 $\pm$ 0.704	27.6 $\pm$ 0.220	25.2 $\pm$ 0.464
3	20.0 $\pm$ 0.770	29.4 $\pm$ 0.559	25.3 $\pm$ 0.0592	14.6 $\pm$ 0.112	34.0 $\pm$ 0.420	26.6 $\pm$ 0.123	23.5 $\pm$ 0.785
30	23.1 $\pm$ 0.582	30.6 $\pm$ 0.848	27.5 $\pm$ 0.754	17.0 $\pm$ 1.15	35.1 $\pm$ 0.435	28.9 $\pm$ 0.994	24.2 $\pm$ 0.478
0.03-30 (Mean)	21.0 $\pm$ 1.81	29.3 $\pm$ 1.76	27.7 $\pm$ 1.85	15.8 $\pm$ 1.22	36.2 $\pm$ 1.97	28.2 $\pm$ 1.30	24.7 $\pm$ 1.08

* The free concentrations were BLOQ (below the lower limit of quantitation). The cutoff value was calculated by using LLOQ (5 nmol/L) as the free concentration.

Distribution in plasma and whole blood

Table 27: Summary of whole blood to plasma ratio of camizestrant and references in the human whole blood (mean $\pm$ SD)

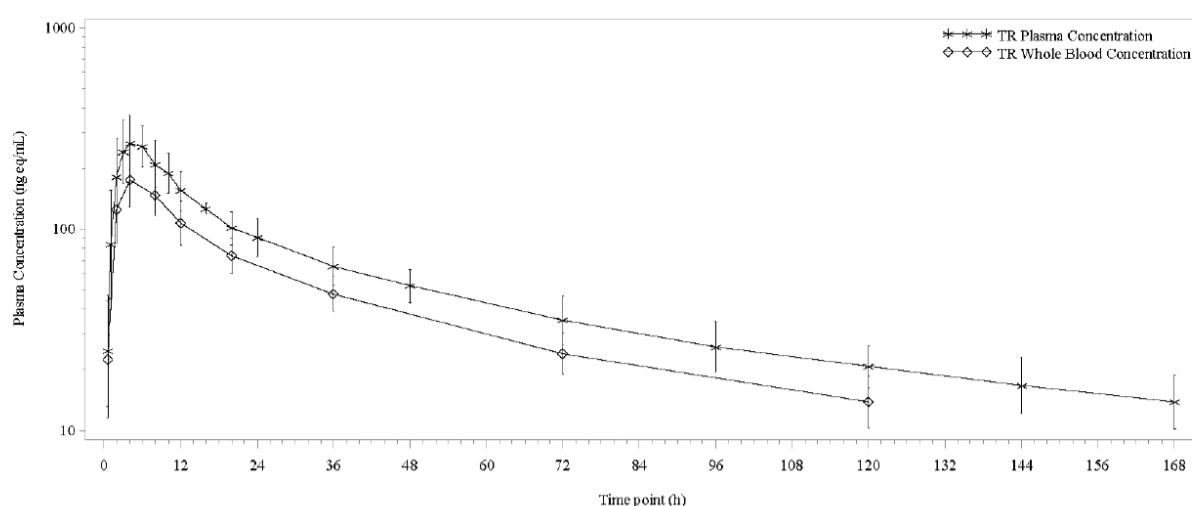
Species	Test item	Blood to Plasma ratio			
		Experiment 1	Experiment 2	Experiment 3	Mean $\pm$ SD
Human	Test compound				
	AZD9833	0.976	1.08	0.915	0.991 $\pm$ 0.0846
	Reference				
	AZ10003646-025	0.534	0.607	0.673	0.605 $\pm$ 0.0697
	AZ11657055-002	28.5	26.6	25.6	26.9 $\pm$ 1.47

Table 28: Geometric mean (CV%) plasma and whole blood pharmacokinetic parameters following a single oral dose of 75 mg ¹⁴C-camizestrant

Analyte Matrix Parameter	AZD9833 Plasma N=6	Total Radioactivity Plasma N=6	Total Radioactivity Whole Blood N=6
T _{lag} ^a (h)	0.000 (0.00-0.00)	0.000 (0.00-0.00)	0.000 (0.00-0.00)
T _{max} ^a (h)	4.508 (2.00-6.17)	4.008 (4.00-6.17)	4.000 (4.00-4.02)
C _{max} (ng/mL ^b)	34.9 (44.4)	271 (29.4)	175 (31.6)
AUC ₀₋₉₆ (ng.h/mL ^b)	767 (28.6)	N/A	N/A
AUC _{0-t} (ng.h/mL ^b)	798 (30.8)	8530 (23.9)	5380 (23.5)
AUC (ng.h/mL ^b)	826 (30.3)	9820 (26.2)	6240 (28.2) [n=5]
t _{1/2} (h)	27.063 (21.4)	63.909 (13.2)	47.504 (16.9)
CL/F (mL/min)	1480 (30.3)	N/A	N/A
CL _R (mL/min)	66.8 (29.0)	N/A	N/A
V _z /F (L)	3470 (18.2)	N/A	N/A
MRT _{0-t}	28.631 (9.5)	N/A	N/A
MRT	33.205 (9.9)	N/A	N/A

^aMedian (range), ^bUnits for total radioactivity are 'ng equivalent'.

Table 29: Geometric mean (± SD) concentration vs time profiles of total radioactivity in plasma and whole blood following a single oral dose of 75 mg ¹⁴C-camizestrant



5.2.2.8. Metabolism

In vitro

Table 30: Summary of UHPLC-UV-MS analysis of mouse, rat, dog and human hepatocytes following incubation of camizestrant at 5 μ M for 240 minutes ()

Peak ID	Proposed structure	Proportion of UV (330-345 nm)			
		Mouse	Rat	Dog	Human
M1	Oxidative defluorination (+O, -F)	t	t	t	m
M2	N-dalkylation (-C ₃ H ₆ F)	m	M	t	t
M3	Glucuronide (+Gluc)	-	-	-	t
M4	Glucuronide (+Gluc)	-	-	-	m
M5	Oxidation (+O)	M	M	t	t

M = 10 - 5%

m = 1-5%

t trace, $\leq$ 1%,

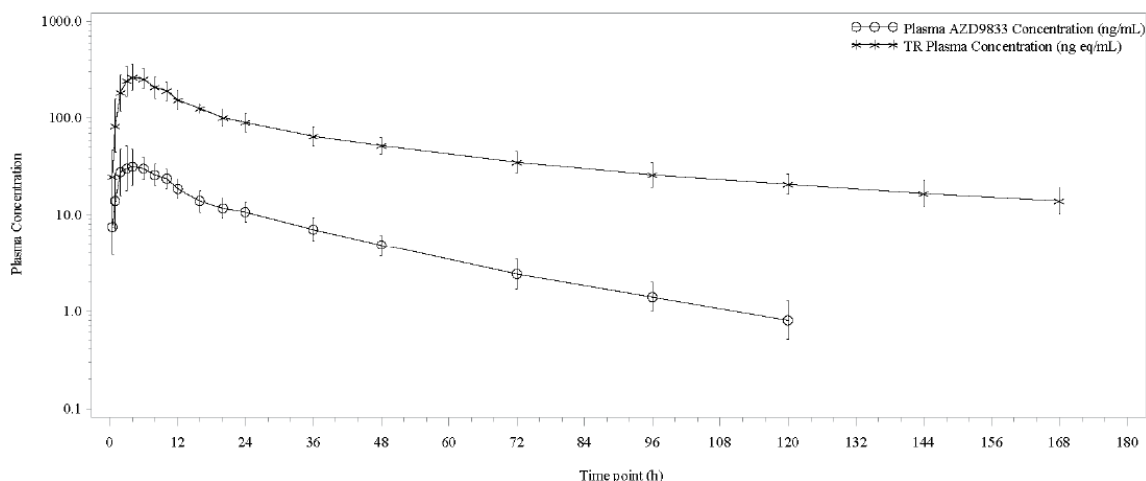
- for not detected

M* > 10%

Characterisation of metabolites in plasma from the mass balance study (*in vivo* study D853200005)

Metabolites of camizestrant were detected and quantified in healthy female volunteers (D853200005) receiving a single oral dose of 75 mg [¹⁴C]-camizestrant (0.67 MBq). Exposure to camizestrant accounted for 8.4% of circulating plasma TR based on AUC. The geometric mean (CV%) terminal plasma half-life for camizestrant and the TR half-life were 27.06 h (21.4%) and 63.9 h (13.2 %), respectively. The half-life for TR was longer than for camizestrant suggesting any metabolites may have longer terminal elimination.

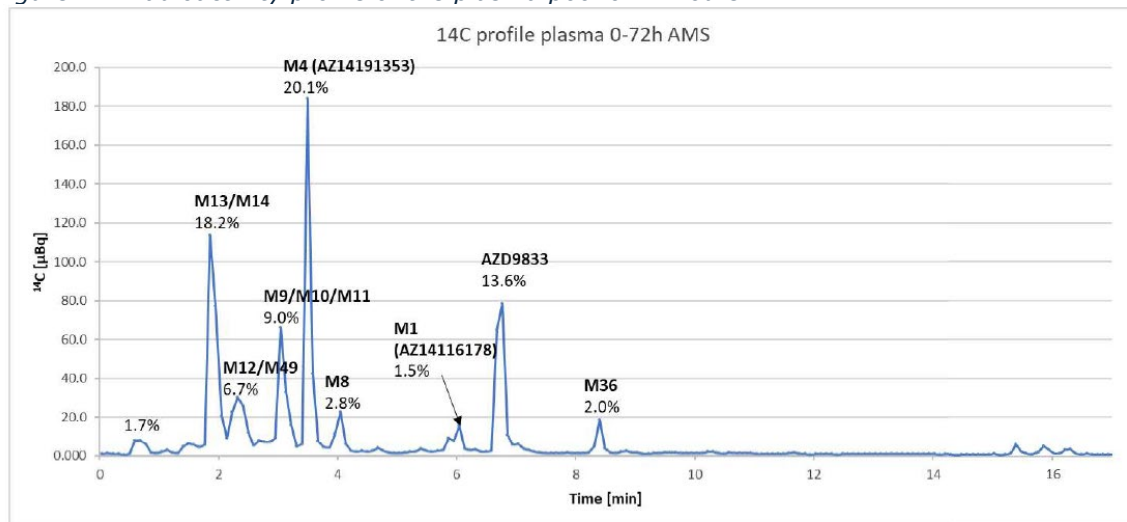
Figure 11: Concentration versus Time Profiles of Camizestrant and Total Radioactivity in Plasma Following a Single Oral Dose of 75 mg ¹⁴C-Camizestrant in Human ADME Study(D853200005)



Vertical lines represent the geomean $\pm$ geometric SD.

In the plasma unchanged camizestrant represented 13.6% of the drug related AUC (area under the curve). The main circulating metabolites were M4 (AZ14191353, an N-glucuronide conjugate of AZD9833) and M14 (an N-glucuronide of an acid metabolite) which represented 20.1% and 11.2% of the drug related AUC, respectively. The other nine minor metabolites, each of which had a relative abundance lower than 10% of the total drug-related materials in plasma, were either oxidative metabolites or glucuronides of oxidative metabolites.

Figure 12: Radioactivity profile of the plasma pool 0-72 hours



31

Figure 13: Radioactivity profile of the urine pool 0-96 hours

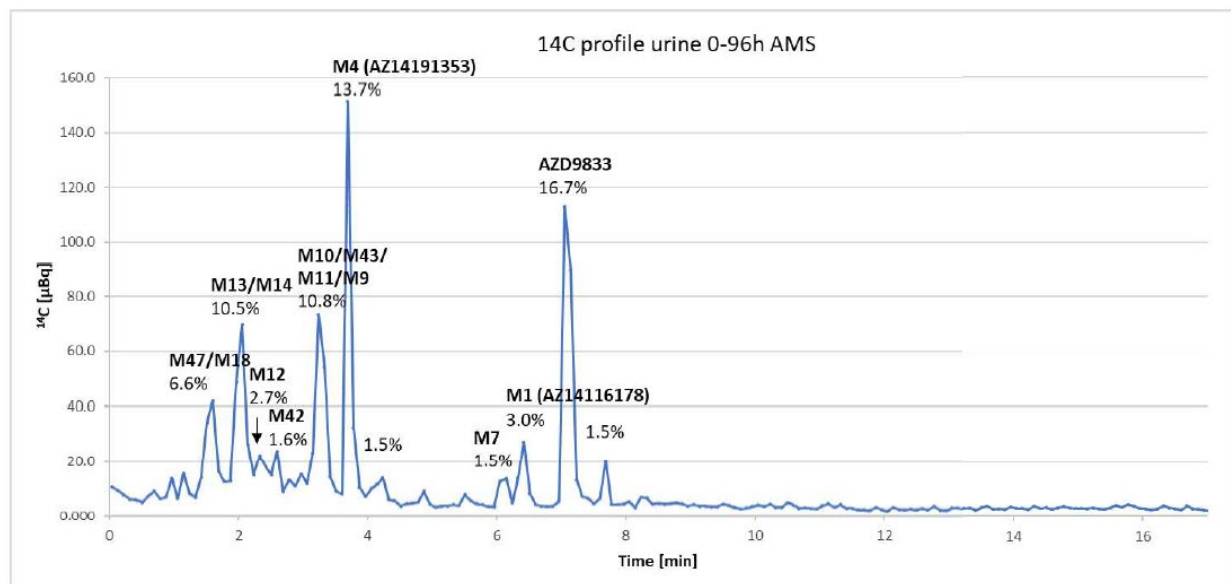
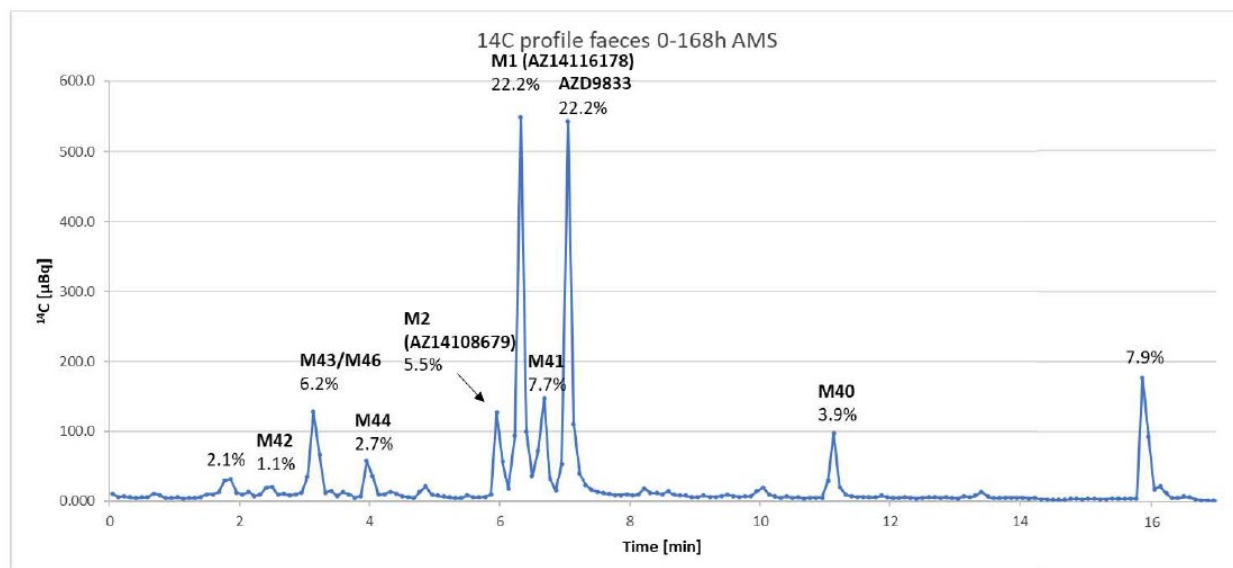


Figure 14: Radioactivity profile of the faeces pool 0-168 hours



In the ^{14}C -camizestrant hADME study, camizestrant N-glucuronide (M4) and an N-glucuronide of an acid metabolite (M14) showed >10% of drug-related exposure. M4 N-glucuronide metabolite was not detected in rat and dog *in vitro* hepatocyte experiments or in plasma samples collected from rat and dog toxicology studies or following dosing of ^{14}C -camizestrant from studies in rats and dogs. M14 was not detected in hepatocytes of human, rat and dog, and was not detected in plasma collected from rat and dog dosed with ^{14}C -camizestrant. No additional safety studies on M4 or M14 have been conducted.

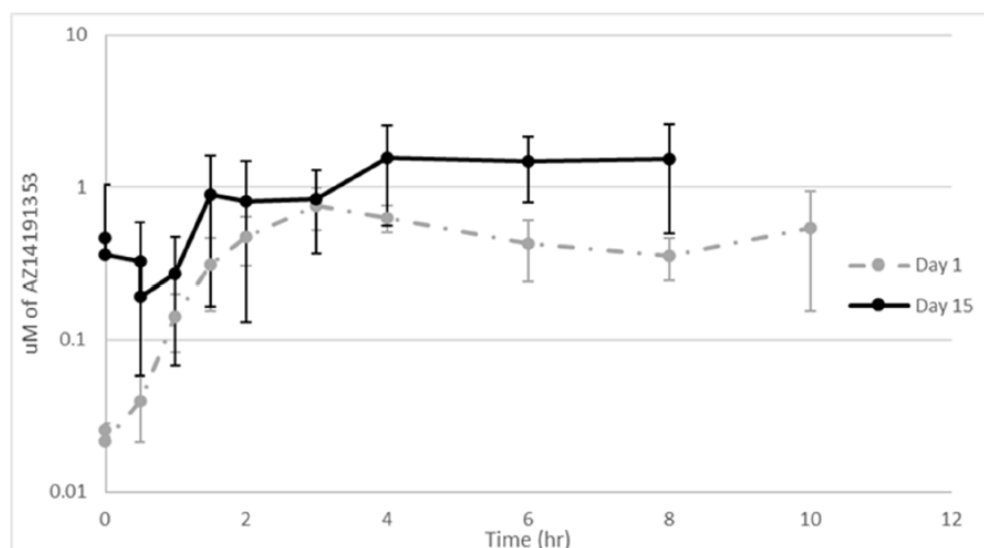
Identification of enzymes responsible for the metabolism of camizestrant

By the use of bacosomes prepared from *E. coli* bacteria which heterologously express individual human CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP3A5 isoforms, CYP3A4 and CYP3A5 were found to be the predominant CYP isoforms involved in the metabolism of AZD9833. UGT1A4 was the only UGT showing any significant activity when incubated with camizestrant.

None of the metabolites have had their pharmacokinetics formally characterised.

However, plasma samples from SERENA-1 were analysed for M4. The mean concentration for camizestrant metabolite AZ14191353 (M4) across 4 patients on Day 1 and Day 15 is shown below in Figure 15 M4 represented 20.1% of total radioactivity in plasma.

Figure 15: Mean plasma concentration of M4 for Day 1 and Day 15



5.2.2.9. Elimination

Across the 25 to 450 mg dose range in SERENA-1, geometric mean (CV%) CL/F decreased with dose from 119.1 L/h (52.28%) to 60.99 L/h (31.63%). At 75 mg across SERENA-1 Parts A+B, Japan Phase I and China Phase I, the CL/F ranged from 70.56 L/h to 102.9 L/h, which was similar to that seen in healthy volunteers (88.8 L/h to 118 L/h) and with the PopPK value (69.1 L/h).

Based on PopPK analysis and data from healthy participants, the terminal half-life is estimated to be approximately 23 h.

Mass balance study

Following single oral administration of 75 mg [14 C]-camizestrant to healthy female participants, an average of 82% of the radioactivity administered was recovered in excreta. The majority of total radioactivity (65.1%) was recovered in faeces indicating faecal excretion was the main route of elimination following oral dosing. In total approximately 17% of camizestrant-related radioactivity was excreted via urine. Approximately 14.5% of camizestrant was excreted unchanged in faeces indicating biliary excretion rather than unabsorbed drug.

Figure 16: Arithmetic mean ($\pm$ SD) cumulative amount of total radioactivity excreted in urine, faeces and total (urine + faeces) expressed as percentage of dose following a single dose of 75 mg 14 C-camizestrant.

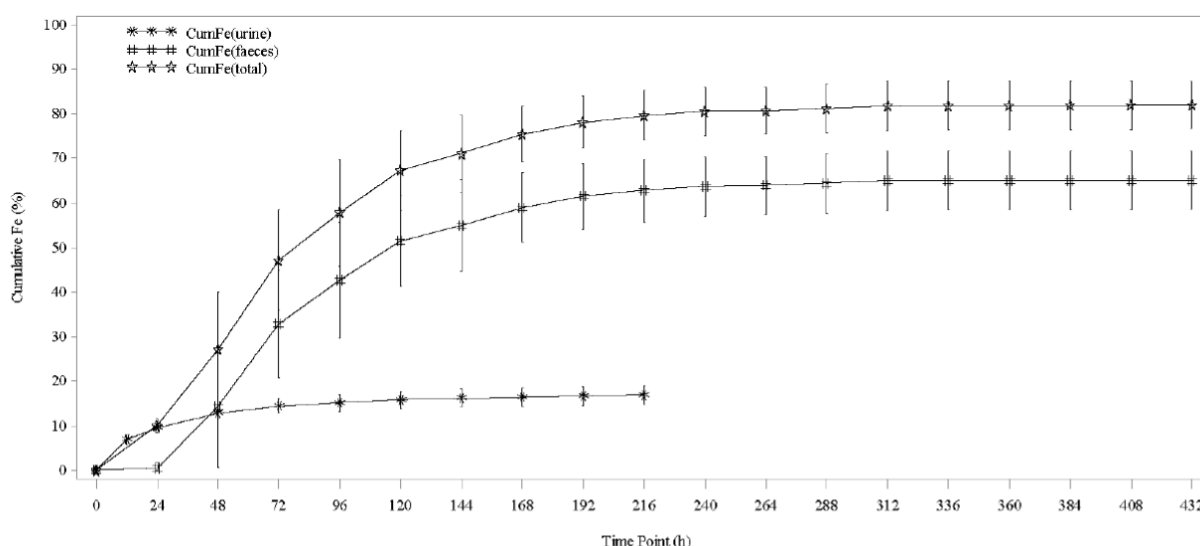
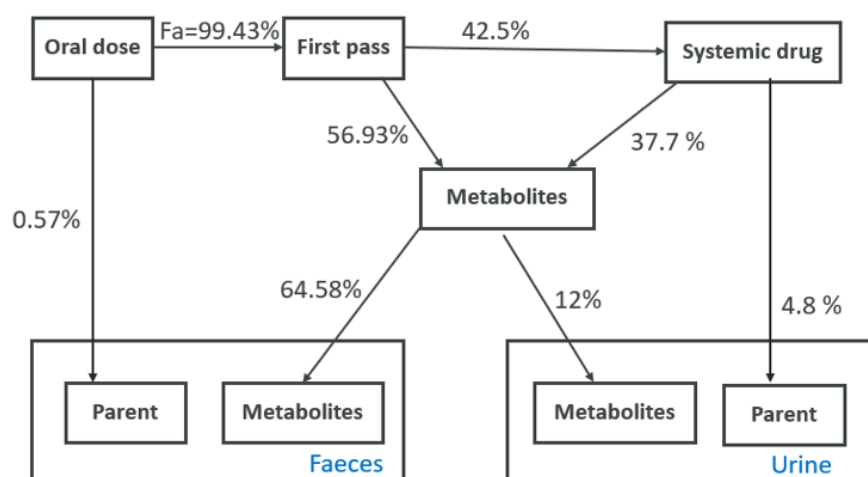
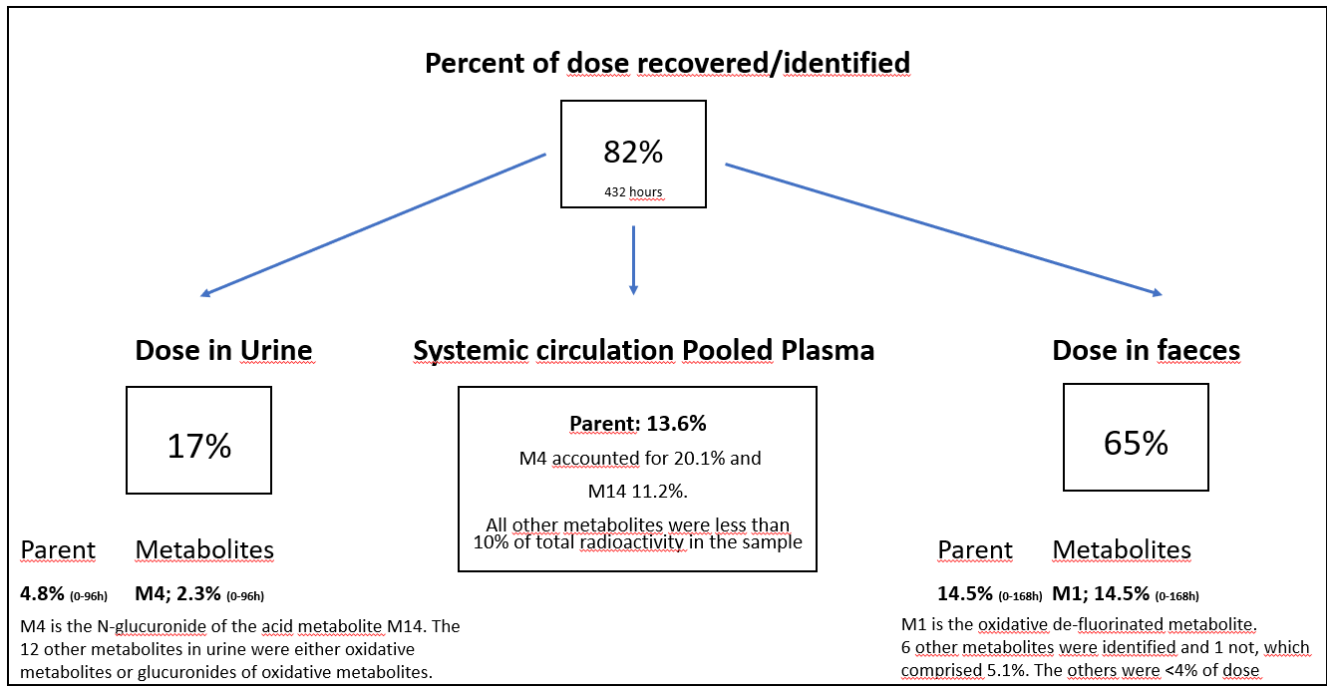


Figure 17: Mass Balance of Camizestrant from Human ADME Study D8532C00005 Following Single Administration of 75mg [14 C]-Camizestrant(provided by Applicant)



Metabolism was predominantly mediated by **CYP3A4/5 (~51%)**, with a secondary contribution from **UGT1A4 (~22%)**, and minor involvement of other pathways.

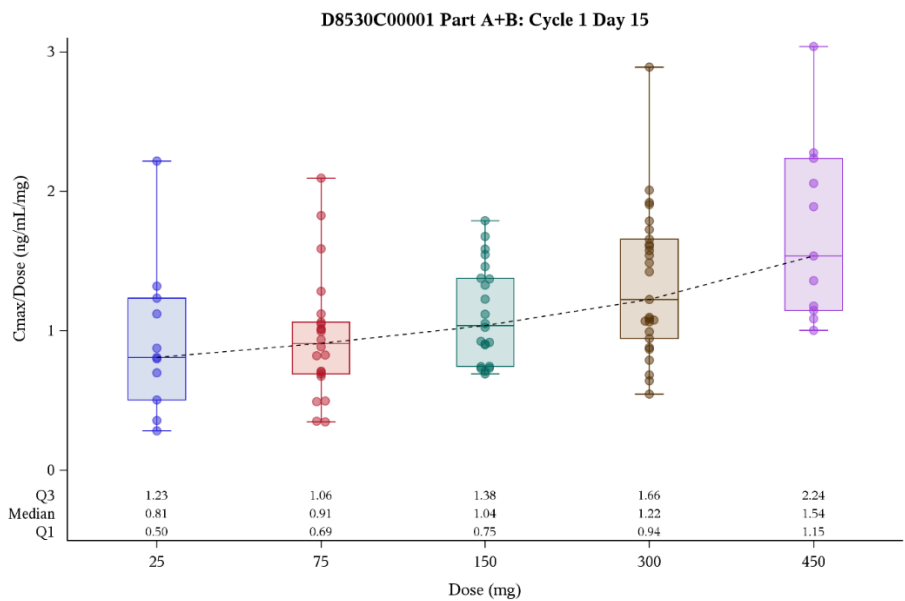
Figure 18: Percent of dose recovered/identified

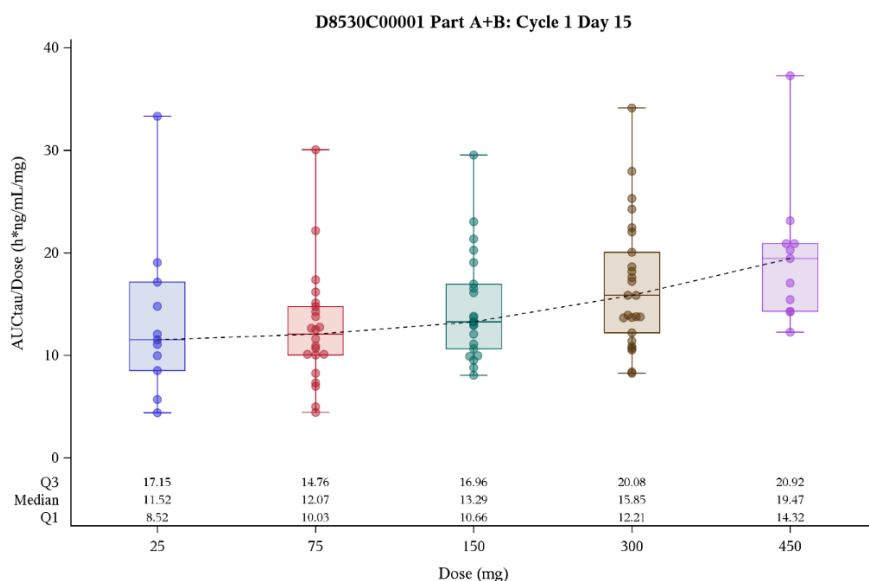


5.2.2.10. Dose proportionality and time dependency

Figure 19: Scatter Plot of Dose Normalised Camizestrant Individual Plasma C_{max} and AUC Parameters Following a Single Dose of Camizestrant Monotherapy: SERENA-1 Part A, Cycle 1 Day 15 (PK Analysis Set)

C_{max}/Dose





Boxes are interquartile range (IQR, Q1-Q3), with the median represented by the straight line within the box and the whiskers representing the median $\pm 1.5 \times$ IQR, with the open circles representing individual values.

Assessment of dose-proportionality was made using a power model. In Part A of SERENA-1, slope of 1.38 (90% CI: 1.30, 1.46) for C_{max} and 1.28 (90% CI: 1.21, 1.35) for $AUC_{(0-24)}$ (estimated following single oral doses) indicated greater than proportional increase in exposures with increasing dose. This was consistent with dose proportionality assessment from the combined data in Part A + B of SERENA-1, (after multiple doses) with slope estimates of 1.24 (90% CI: 1.15, 1.32) for C_{max} and 1.18 (90% CI: 1.10, 1.26) for AUC_{tau} (see Figure 19).

Camizestrant is accumulating from single dose to steady state in cancer patients within the range of 1.4 to 2 (SERENA-1). This is according to the dosing interval and the terminal elimination half-life of approximately 23 hours, which would anticipate an accumulation index of 2.

Otherwise, no time dependencies were noted.

5.2.2.11. Pharmacokinetics in the target population

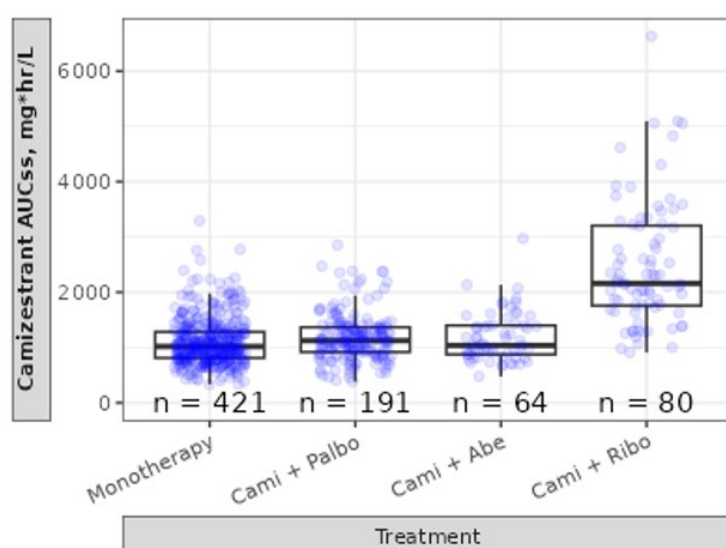
Table 32: Camizestrant Cycle 1 Day 15 PK Parameters for Camizestrant Monotherapy and in Combination with Palbociclib, Ribociclib or Abemaciclib

	Camizestrant Dose (mg)	C_{maxss} (ng/mL)	t_{max} (h)	AUC_{tau} (ng.h/mL)	C_{min} (ng/mL)
Camizestrant monotherapy	25	19.9 (65.5) [11]	3.00 (1.5-5.97) [11]	291 (60.63) [11]	7.28 (63.12) [11]
	75	64.7 (49.2) [22]	3.72 (1.08-8.00) [22]	862 (46.5) [22]	20.38 (57.86) [22]
	150	166 (36.1) [23]	2.17 (1.00-24.00) [23]	2162 (38.9) [23]	50.57 (64.16) [23]
	300	376 (40.6) [28]	3.03 (1.70-7.10) [28]	4784 (37.7) [26]	97.84 (49.52) [27]

	Camizestrant Dose (mg)	C_{maxss} (ng/mL)	t_{max} (h)	AUC_{tau} (ng.h/mL)	C_{min} (ng/mL)
	450	723.4 (37.86) [11]	3.02 (1.00-6.13) [11]	8416 (31.09) [11]	169.8 (56.03) [11]
Camizestrant +125mg palbociclib (21-days on-7- days off)	75	93.9 (55.7) [24]	3.91 (1.07-4.32) [24]	1197 (48.7) [24]	27.23 (57.76) [24]
	150	189 (39.5) [21]	3.92 (1.00-8.00) [21]	2419 (45.4) [21]	51.20 (60.56) [21]
	300	386 (63.4) [25]	3.97 (1.00-8.00) [25]	4936 (64.6) [25]	97.92 (74.05) [25]
Camizestrant + ribociclib (21-days on-7- days off)	75 + 400 mg ribociclib	153 (38.3) [23]	3.57 (0.98-6.00) [23]	2277 (42.7) [22]	55.10 (65.87) [22]
	75 + 600 mg ribociclib	179 (50.9) [22]	4.00 (1.00-8.00) [22]	2749 (54.9) [22]	72.79 (67.21) [22]
Camizestrant +150 mg BID abemaciclib	75	85.4 (41.2) [16]	4 (1.00-6.05) [16]	1124 (41.23) [15]	21.97 (57.55) [16]
	150	158.8 (33.3) [18]	4 (1.00-24.00) [18]	2050 (24.94) [18]	41.32 (47.68) [18]

Geomean (% geometric CV%) [n] presented with the exception of: t_{max} where median (min-max) [n]

Figure 20: Comparison of Camizestrant AUCss as a Monotherapy or in Combination with Palbociclib, Ribociclib or Abemaciclib AUCss



The corresponding Cycle 1 Day 15 combination plasma concentrations for abemaciclib, palbociclib, and ribociclib from SERENA-1 were overlaid on published PopPK simulations for the 3 CDK4/6 inhibitors. The steady state abemaciclib, palbociclib, and ribociclib exposures in combination with camizestrant are comparable to the expected PK for each of the CDK4/6 inhibitors, demonstrating that camizestrant did not affect the exposures of abemaciclib, palbociclib, or ribociclib.

Inter-individual variability

Across the studies reporting PK parameters in patients and healthy participants dosed with camizestrant, inter-individual ranged from low (10-20%) to high (>60%). There is no apparent trend of single v. multidose schemes. Intra-individual variability was not studied.

Therapeutic window

In the SERENA-1 study no MTD or MFD were identified. DLTs were infrequent (3 patients) and occurred only at higher dose levels (≥ 300 mg). Adverse events related to camizestrant exposure showed a dose-dependent increase from 300 mg onwards, with Grade ≥ 3 adverse events, serious adverse events, dose reductions, interruptions and discontinuations more frequently observed at 300 mg and 450 mg, resulting in reduced relative dose intensity at these dose levels. With regards to the safety profile at doses ≤ 150 mg, no Grade ≥ 3 treatment-related adverse events were reported. The most common treatment-related adverse events were visual disturbances and bradycardia, which were generally Grade 1–2. Bradycardia was observed across all dose levels with a clear dose-dependent trend in heart rate reduction, while visual adverse events increased with dose up to a plateau at higher exposures.

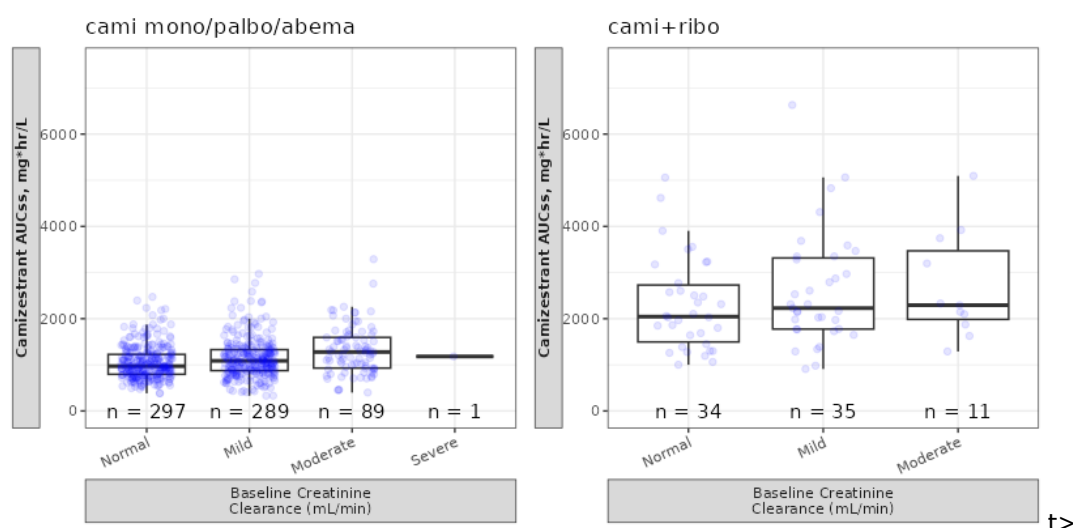
5.2.2.12. Special populations

Renal impairment

No formal study of the PK of camizestrant in subjects with renal impairment was performed based on the mass balance study results. Instead, the PopPK analysis evaluated renal impairment as a covariate. Baseline creatinine clearance was a covariate on CL/F. Patients with mild renal impairment had an exposure increase of 4%-5%, whereas patients with moderate renal impairment had exposure increase of 17-20% compared to a reference baseline of 86.2 mL/min, which was the median of the study. Patients with baseline creatine clearance > 90 mL/min had a reduction in exposure of 9% compared to the reference value of 86.2 mL/min.

The impact of renal impairment on AUCss for cancer patients with impaired renal function is shown in Figure 21. The analysis indicated no clinically meaningful effect of mild and moderate renal impairment at baseline on camizestrant PK, therefore, no dose adjustment is required for participants with mild and moderate renal impairment.

Figure 21: Impact of Renal Impairment on Camizestrant AUCss for Participants on Camizestrant Monotherapy or Camizestrant in Combination with Abemaciclib or Palbociclib, or Camizestrant in Combination with Ribociclib



There was a single patient with severe renal impairment and no patients on dialysis included in the clinical studies of camizestrant.

Hepatic impairment

The liver is the main organ responsible for clearing camizestrant from the body. Hence a dedicated clinical study (D8532C00002, see Table 20) in subjects with normal (N=8), moderate (N=8) and severe (N=6) hepatic impairment was conducted comparing exposure to 75 mg camizestrant as a single dose.

A dedicated single-dose study was performed in patients with normal, moderate, and severe, hepatic impairment and found that moderate and severe hepatic impairment increased camizestrant C_{max} (geometric mean) with 2.7-fold and 2.4-fold and AUC_{inf} (geometric mean) with 3.1-fold and 3.8-fold, respectively, while the half-life (geometric mean) increased from 22.43 hours to 28.61 hours and 36.14 hours and CL/F (geometric mean) decreased from 105.8 to 43.72 and 27.98 L/hours, respectively. However, the 90% CI is up to 6.28 for AUC_{inf} , 5.43 for AUC_{last} and 4.71 for C_{max} in severe hepatic impairment while the 90% CI is up to 3.87 for AUC_{inf} , 3.57 for AUC_{last} and 4.00 for C_{max} in moderate hepatic impairment.

Subjects with mild hepatic impairment were not included in this study as patients in this category were included in the pivotal clinical studies of safety and efficacy feeding into the PopPK model. Hence, mild hepatic impairment was evaluated as a covariate in the PopPK model.

The impact of hepatic impairment on the PK of camizestrant was assessed in post-menopausal female participants with normal, moderate, and severely impaired hepatic function as classified using the Child-Pugh method. Camizestrant exposure was higher in participants with moderate and severe hepatic impairment (Child-Pugh Class B and Class C, respectively), compared with participants with normal hepatic function. Figure 22 shows the concentration – time curve for camizestrant in subjects with normal hepatic function, moderate hepatic impairment and severe hepatic impairment. The statistical comparison is presented in Table 34.

Figure 22: Geometric mean ($\pm$ SD) plasma concentration (ng/mL) of camizestrant over time for each hepatic function group

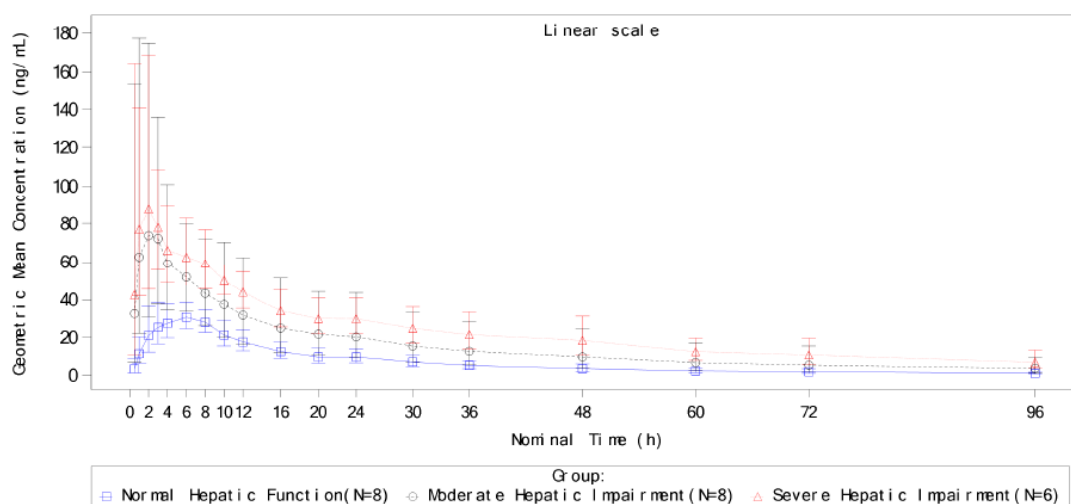


Table 33: Statistical comparison of key camizestrant pharmacokinetic parameters

	Comparison	n	Geometric LS mean	90% CI	Comparison of hepatic impairment groups	
					Ratio	90% CI
AUCinf (h*ng/mL)	Moderate hepatic impairment vs Normal hepatic function	8 vs 8	1715 vs 709.0	(1230, 2392) vs (508.4, 988.5)	2.42	(1.51, 3.87)
	Severe hepatic impairment vs Normal hepatic function	6 vs 8	2680 vs 709.0	(1826, 3934) vs (508.4, 988.5)	3.78	(2.28, 6.28)
AUClast (h*ng/mL)	Moderate hepatic impairment vs Normal hepatic function	8 vs 8	1539 vs 667.4	(1131, 2095) vs (490.3, 908.5)	2.31	(1.49, 3.57)
	Severe hepatic impairment vs Normal hepatic function	6 vs 8	2262 vs 667.4	(1585, 3230) vs (490.3, 908.5)	3.39	(2.12, 5.43)
Cmax (ng/mL)	Moderate hepatic impairment vs Normal hepatic function	8 vs 8	93.41 vs 34.40	(70.99, 122.9) vs (26.14, 45.26)	2.72	(1.84, 4.00)
	Severe hepatic impairment vs Normal hepatic function	6 vs 8	106.6 vs 34.40	(77.63, 146.3) vs (26.14, 45.26)	3.10	(2.04, 4.71)

Result based on analysis of variance (ANOVA) of log transformed PK parameter with hepatic impairment category as fixed effect.

Geometric LS mean and corresponding 90% CI are back-transformed. Geometric mean ratio and corresponding CI are back-transformed.

Ratio is the ratio of geometric LS mean of Moderate (Severe) hepatic impairment / Normal hepatic function for corresponding comparison of Moderate (Severe) hepatic impairment vs Normal hepatic function.

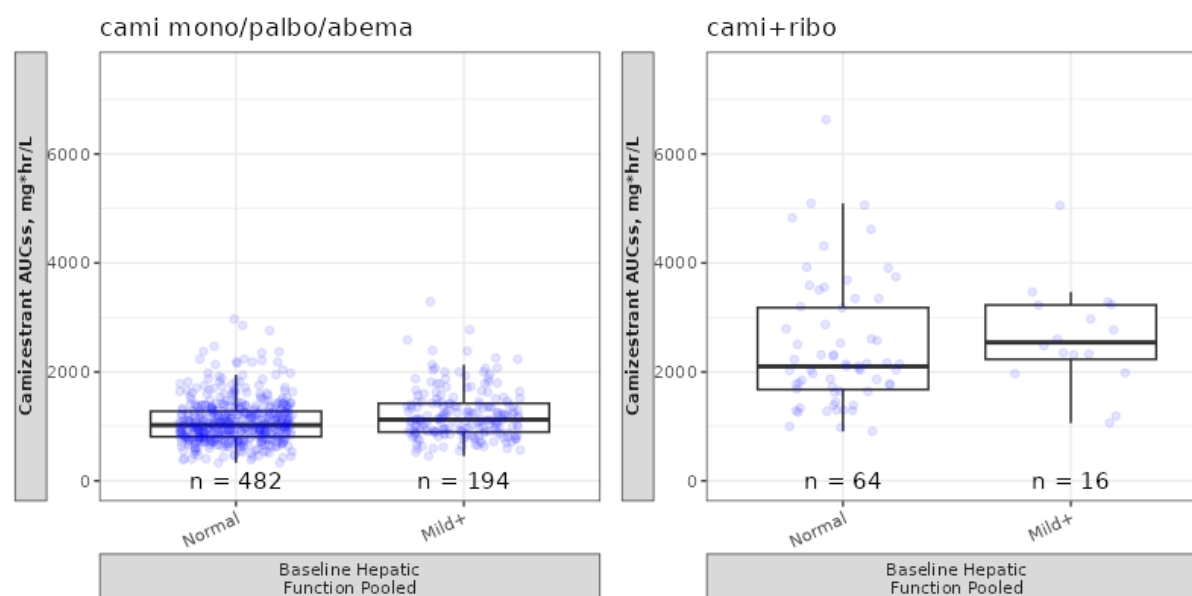
CI Confidence interval; LS Least-squares; n Number of subjects in analysis.

T:\latephase\programs\000000241703\prod\tfl\tables\t_pk_param_stats.sas T_14_02_01.rtf 10JUN2024 23:04

Given that the hepatic impairment dedicated study was not performed at steady state despite camizestrant showing higher than dose-proportional exposure, three different approaches were used to simulate exposure to camizestrant in the three categories at steady state, which were not accepted.

The pooled PopPK analysis included participants with normal hepatic function at baseline (546 participants [72.2%]), mild hepatic impairment (209 participants [27.6%]), and moderate hepatic impairment (1 participant [0.1%]), as defined using the NCI criteria for hepatic impairment. The analysis indicated that there was no statistically significant effect of mild hepatic impairment at baseline on the PK of camizestrant compared to participants with normal hepatic function.

Figure 23: Effect of Baseline Hepatic Function on Camizestrant AUCss for Participants on Camizestrant Monotherapy or Camizestrant in Combination with Abemaciclib or Palbociclib, or Camizestrant in Combination with Ribociclib



Gender

The effect of gender on PK has not been formally investigated during the clinical development of camizestrant as the available and unblinded data to date has been derived only from female participants.

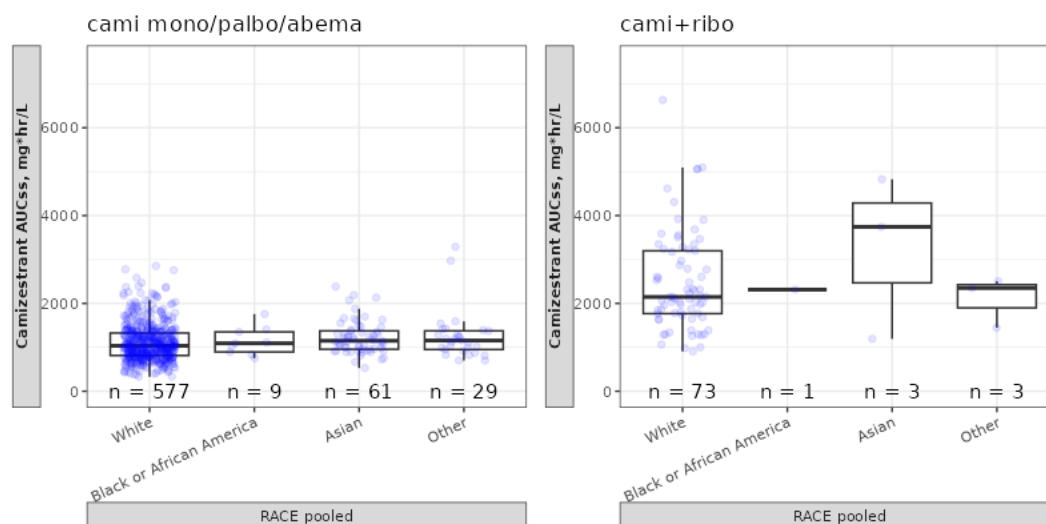
Ethnic factors

The PopPK model was used for evaluating if race or ethnicity had any impact on the exposure (AUCss)

to camizestrant.

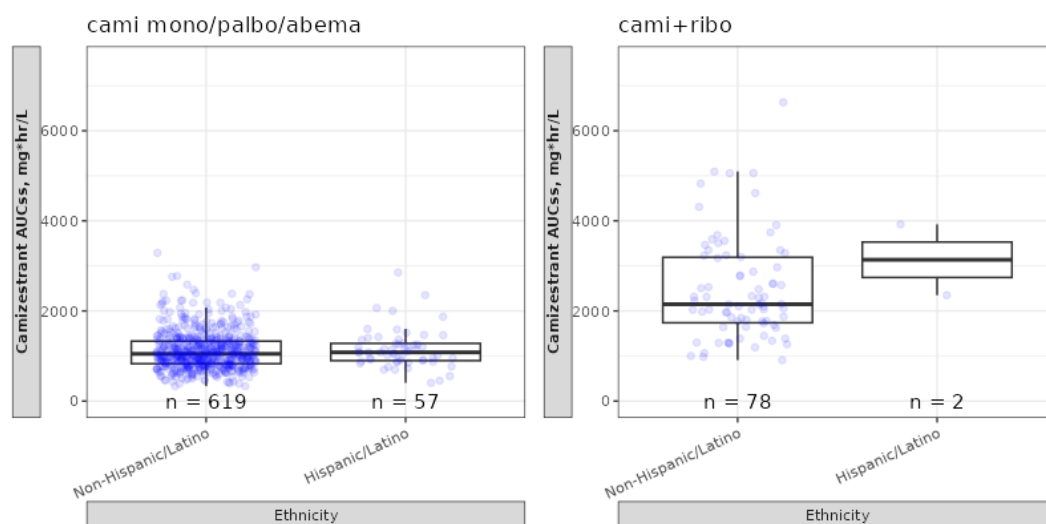
The PopPK analysis (n = 756) included data from participants in the White (n = 650, 86%), Asian (n = 64, 8.5%), Black or African American (n = 10, 1.3%) and Other (n = 32, 4.2%) racial groups. In addition, the impact of ethnicity on camizestrant AUC_{ss} was evaluated.

Figure 24: Impact of Race on Camizestrant AUC_{ss} for Participants on Camizestrant Monotherapy or Camizestrant in Combination with Abemaciclib or Palbociclib, or Camizestrant in Combination with Ribociclib



Abbreviation: abema, abemaciclib; cami, camizestrant; mono, monotherapy; palbo, palbociclib; ribo, ribociclib.

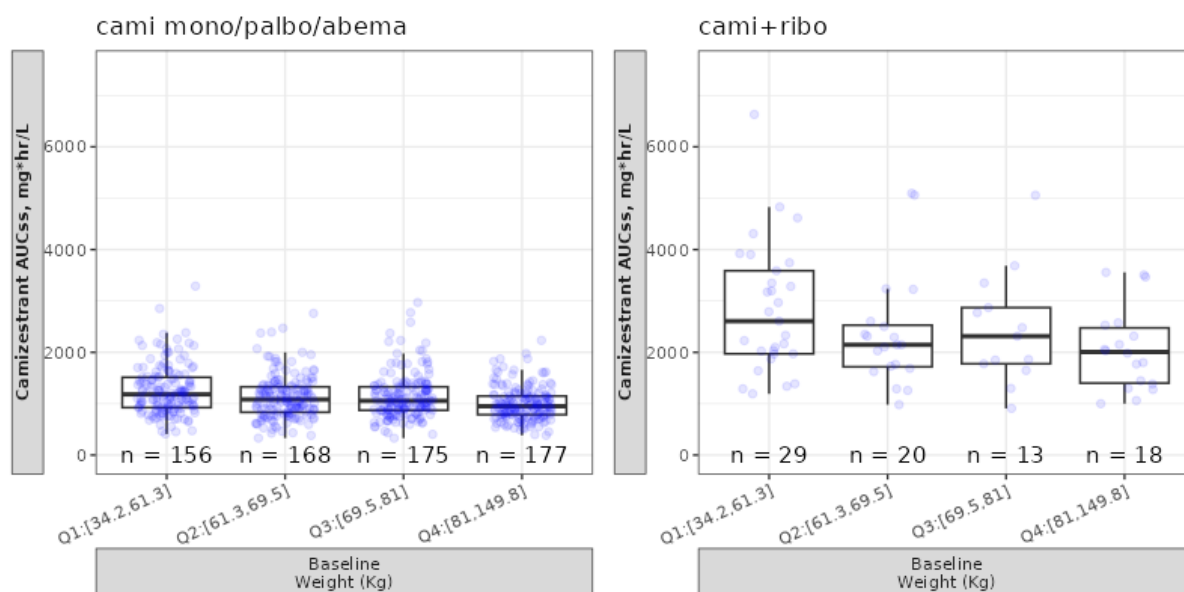
Figure 25: Impact of Ethnicity on Camizestrant AUC_{ss} for Participants on Camizestrant Monotherapy or Camizestrant in Combination with Abemaciclib or Palbociclib, or Camizestrant in Combination with Ribociclib



Weight

Baseline body weight was a statistically significant covariate impacting Vz/F; however, this was not clinically meaningful. As baseline body weight was not a significant covariate on CL/F, it did not impact AUC_{ss} (Figure 26).

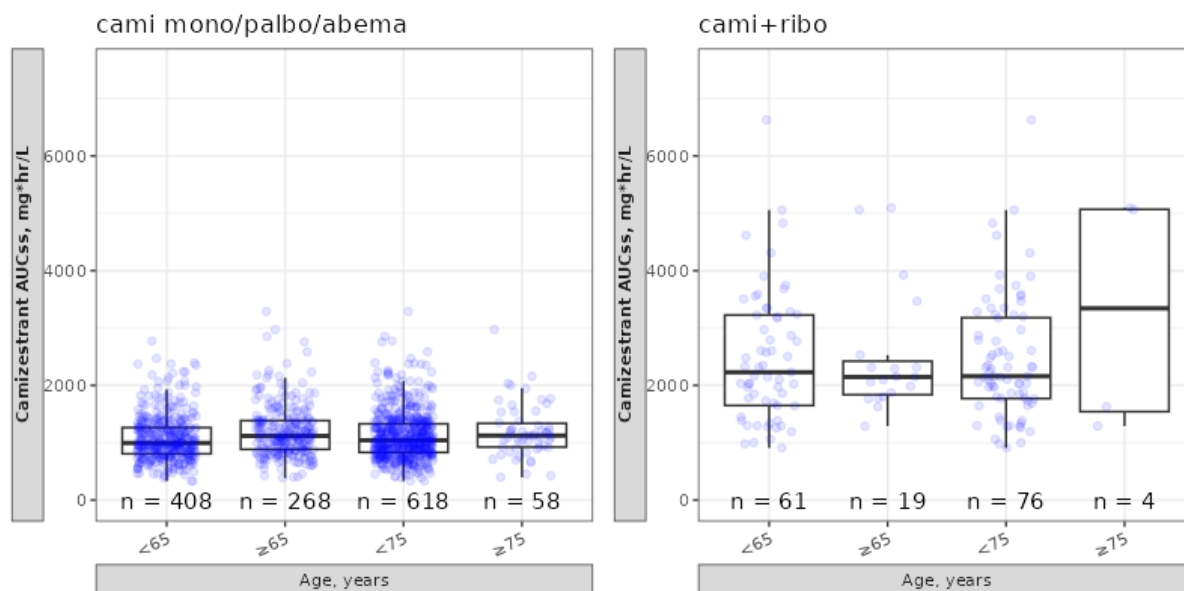
Figure 26: Effect of body weight on camizestrant AUCss for participants on camizestrant monotherapy or camizestrant in combination with abemaciclib or palbociclip, or camizestrant in combination with ribociclip



Elderly

No dose adjustment for camizestrant is required based on age or for geriatric patients.

Figure 27: Impact of Age on Camizestrant AUCss for Participants on Camizestrant Monotherapy or Camizestrant in Combination with Abemaciclib or Palbociclib, or Camizestrant in Combination with Ribociclib



Paediatric population

Camizestrant is not intended for the paediatric population.

5.2.2.13. Pharmacokinetic interaction studies

In vitro

The outcome of the *in vitro* drug interaction studies is summarised in Table 35

Table 34: Assessment of the Clinical DDI Potential of Camizestrant Based on In Vitro Studies and Static Equations

System	Substrate ^a (Camizestrant as victim)		Inhibition ^b (Camizestrant as perpetrator)		Induction ^c (Camizestrant as perpetrator)	
	Yes	No	DDI potential	No DDI potential	DDI potential	No DDI potential
CYP	3A4, 3A5	1A2, 2A6, 2B6 2C8, 2C9, 2C19 2D6 2E1	3A4/5 2B6 2C9, 2C19 2D6	1A2, 2A6 2C8 2E1		2B6 1A2, 3A4/5
Phase II Metabolism	UGT1A4	UGT1A1, UGT1A6, UGT1A9		UGT1A1, UGT2B7	-	-
		UGT2B7, UGT2B15				
		UGT1A3				
Transporters	P-gp	BCRP	P-gp BCRP OATP1B1	OCT2 MATE1, MATE2K OATP1B3, OAT1, OAT3	-	-

In silico

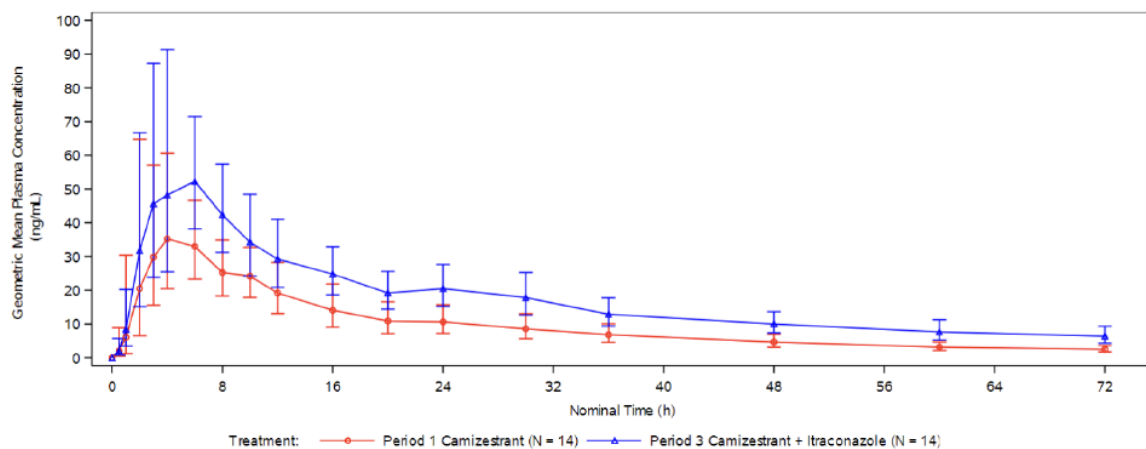
PBPK was used to predict DDIs of camizestrant (data not shown).

Clinical DDI studies

Table 35: Summary of clinical DDI studies

Comparison	Substance Geomean Ratio(90% CI)		Dosing Recommendation
	C _{max}	AUC _{inf}	
Victim			
Effect of co-administration with itraconazole on single dose 75 mg camizestrant	1.37 (1.05, 1.79)	1.90 (1.54, 2.36)	No adjustment
Effect of pretreatment with carbamazepine on a single 75 mg dose of camizestrant	0.41 (0.37, 0.46)	0.29 (0,28, 0.32)	Avoidance of strong and moderate CYP3A4/5 inducers. Moderate inducers in patients taking ribociclib in combination with camizestrant are allowed.
Perpetrator			
Effect 75 mg camizestrant on a single dose of 1 mg oral midazolam	1.50 (1.31, 1.71)	1.99 (1.74, 2.27)	Co-administration of sensitive CYP3A4/5 substrates can be allowed with caution. The co-administration of CYP3A4/5 substrates with a narrow therapeutic index may require dose adjustment and should be closely monitored

Figure 28: Geometric mean ($\pm$ gSD) Plasma concentration (ng/mL) of camizestrant alone and in the presence of itraconazole over time



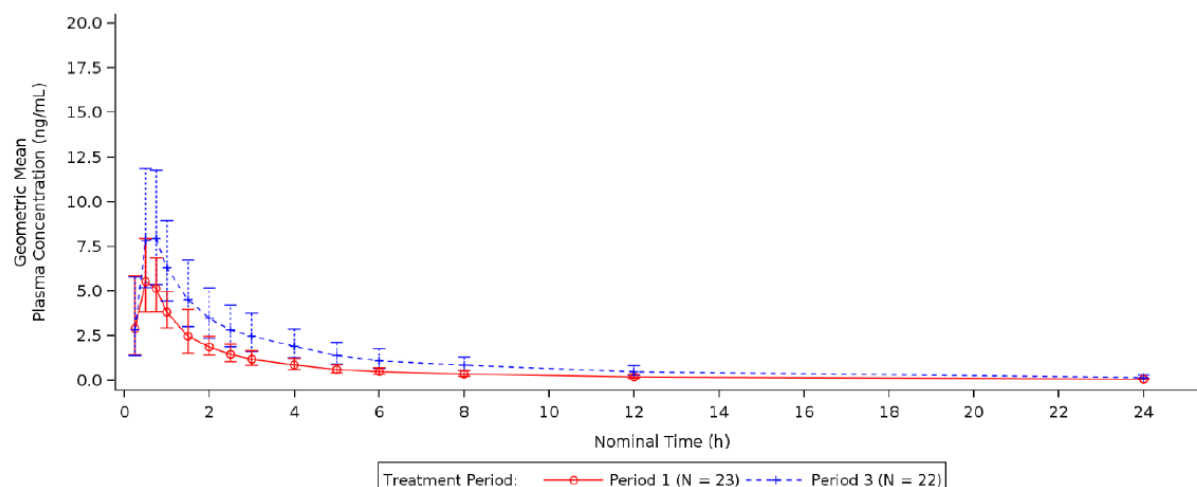
Vertical lines represent the geometric mean $\pm$ SD.

Geometric Mean - gSD: $\exp(\text{mean}(\log(\text{PK Conc})) - \text{SD}(\log(\text{PK Conc})))$.

Geometric Mean + gSD: $\exp(\text{mean}(\log(\text{PK Conc})) + \text{SD}(\log(\text{PK Conc})))$.

Abbreviations: gSD= geometric standard deviation; N= number of subjects.

Figure 29: Geometric mean ($\pm$ gSD) Plasma concentration (ng/mL) of midazolam alone and in the presence of camizestrant over time



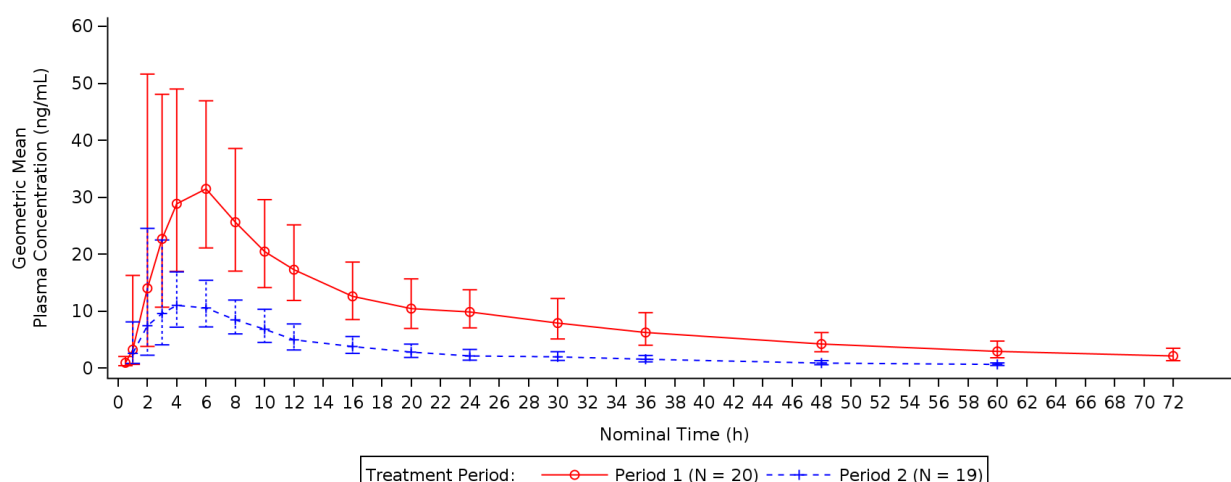
Treatment Period 1: Midazolam alone.

Treatment Period 2: Camizestrant alone.

Treatment Period 3: Midazolam with Camizestrant.

Vertical lines represent the geometric mean $\pm$ gSD.

Figure 30: Geometric mean ($\pm$ gSD) plasma concentration (ng/mL) of camizestrant alone and in the presence of carbamazepine over time (Linear scale) - Part B (PK Analysis Set)



Period 1, camizestrant alone.

Period 2, camizestrant with carbamazepine.

Vertical lines represent the geometric mean $\pm$ gSD.

5.2.2.13.1. Special populations

See 5.2.2.12.

5.2.2.13.2. PK drug-drug interactions

NA/See above

5.2.2.13.3. Dose proportionality/time independence/accumulation

NA/See above

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Camizestrant is an oral SERD and complete ER antagonist. It binds to the ligand binding domain of ER α , antagonising the activity of ER α encoded by both wild-type *ESR1* and *ESR1m* which cause constitutive ER α activation, and inducing proteasome-dependent degradation of ER α , without agonising ER α .

5.2.3.2. Primary and secondary pharmacology

Table 36: Percentage Change in Oestrogen Receptor H-score from Baseline to Biopsy Day, Analysis of Covariance: Stage 1 And Stage 2 Combined (PD Analysis Set)

Group	Percentage change from baseline ^a			
	n	Unadjusted mean	LS mean (SE)	80% CI
AZD9833 75 mg (N = 26)	26	-63.8	-62.7 (3.68)	-67.46, -57.93
AZD9833 150 mg (N = 31)	31	-62.1	-62.8 (3.36)	-67.13, -58.43
AZD9833 300 mg (N = 11)	11	-66.4	-67.1 (5.69)	-74.49, -59.74

^a ANCOVA model fitted with on-treatment percentage change in biomarker expression score from baseline as a dependent variable, baseline expression score as a covariate, and biopsy day and treatment group as fixed effects.

Table 37: Percentage Change in Oestrogen Receptor H-score from Baseline to Biopsy Day, Analysis of Covariance: Stage 3 (PD Analysis Set)

Group	Percentage change from baseline ^a			
	n	Unadjusted mean	LS mean (SE)	80% CI
AZD9833 75 mg (N = 24)	24	-67.4	-66.9 (4.19)	-72.34, -61.46
AZD9833 150 mg (N = 26)	26	-64.6	-65.0 (4.02)	-70.27, -59.81

^a ANCOVA model fitted with on-treatment percentage change in biomarker expression score from baseline as a dependent variable, baseline expression score as a covariate, and biopsy day and treatment group as fixed effects.

Table 38: Percentage Change in Progesterone Receptor H-score from Baseline to Biopsy Day, Analysis of Covariance: Stage 1 and Stage 2 Combined (PD Analysis Set) – Sensitivity#

Group	Percentage change from baseline ^a			
	n	Unadjusted mean	LS mean (SE)	80% CI
AZD9833 75 mg (N = 26)	19	-40.0	-35.2 (8.19)	-45.86, -24.57
AZD9833 150 mg (N = 31)	26	-40.5	-44.0 (7.00)	-53.09, -34.90
AZD9833 300 mg (N = 11)	8	-36.7	-36.7 (12.48)	-52.96, -20.52

^a ANCOVA model fitted with on-treatment percentage change in biomarker expression score from baseline as a dependent variable, baseline expression score as a covariate, and biopsy day and treatment group as fixed effects.

Excluded one HER2-positive patient by central assessment as well as patients with baseline H-score < 10. Number of patients excluded per treatment group: AZD9833 75 mg = 7; AZD9833 150 mg = 5; AZD9833 300 mg = 3.

Table 39: Percentage Change in Progesterone Receptor H-score From Baseline To Biopsy Day, Analysis of Covariance: Stage 3 (PD Analysis Set) – Sensitivity#

Group	Percentage change from baseline ^a			
	n	Unadjusted mean	LS mean (SE)	80% CI
AZD9833 75 mg (N = 24)	23	-61.6	-61.8 (11.63)	-76.93, -46.62

AZD9833 150 mg (N = 26)	20	-55.2	-55.0 (12.47)	-71.29, -38.78
-------------------------	----	-------	---------------	----------------

^a ANCOVA model fitted with on-treatment percentage change in biomarker expression score from baseline as a dependent variable, baseline expression score as a covariate, and biopsy day and treatment group as fixed effects.

Excluded patients with baseline H-score < 10. Number of patients excluded per treatment group: AZD9833 75 mg = 1; AZD9833 150 mg = 6.

Table 40: Log-Transformed Ki67 Labelling Index, Analysis of Covariance: Stage 1 and Stage 2 Combined (PD Analysis Set) – Sensitivity#

Group	n	Percentage change from baseline ^a		
		Unadjusted Geometric mean	Geometric LS mean (SE)	80% CI
AZD9833 75 mg (N = 26)	17	-48.8	-49.3 (11.47)	-62.18, -31.96
AZD9833 150 mg (N = 31)	28	-80.8	-81.3 (3.30)	-85.14, -76.49
AZD9833 300 mg (N = 11)	11	-80.6	-78.9 (5.99)	-85.37, -69.46

^a ANCOVA model fitted with change in log-transformed on-treatment biomarker expression score from log-transformed baseline as a dependent variable, log-transformed baseline expression score as a covariate, and biopsy day and treatment group as fixed effects.

There was 1 patient with biopsy day score = 0, where 1 was added to both baseline and biopsy day scores before log transformation of data.

Excluded one HER2-positive patient by central assessment as well as patients with baseline Ki67 labelling index < 5%. Number of patients excluded per treatment group: AZD9833 75 mg = 9; AZD9833 150 mg = 3; AZD9833 300 mg = 0.

Table 41: Log-Transformed Ki67 Labelling Index, Analysis of Covariance: Stage 3 (PD Analysis Set) – Sensitivity#

Group	n	Percentage change from baseline ^a		
		Unadjusted geometric mean	Geometric LS mean (SE)	80% CI
AZD9833 75 mg (N = 24)	18	-82.2	-81.7 (4.23)	-86.45, -75.24
AZD9833 150 mg (N = 26)	20	-81.4	-81.9 (3.97)	-86.38, -75.88

^a ANCOVA model fitted with change in log-transformed on-treatment biomarker expression score from log-transformed baseline as a dependent variable, log-transformed baseline expression score as a covariate, and biopsy day and treatment group as fixed effects.

There was 1 patient with biopsy day score=0, where 1 was added to both baseline and biopsy day scores before log transformation of data.

Excluded patients with baseline Ki67 labelling index < 5%. Number of patients excluded per treatment group: AZD9833 75 mg = 6. AZD9833 150 mg = 6.

Camizestrant was screened in a diverse set of *in vitro* radioligand binding, enzyme and functional assays, covering 195 distinct molecular targets (receptors, ion channels, transporters and enzymes; Study 4110SV). Apart from estrogen receptors α and β , no targets had activity within 100-fold of the estrogen receptor α primary target. Results of profiling (*in vitro* and *in vivo*) of camizestrant against hyperpolarization-activated cyclic nucleotide-gated (HCN) are consistent with the hypothesis that camizestrant-related heart rate reduction is via a HCN channel-mediated mechanism.

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

Pharmacodynamic interactions with other medicinal products or substances have not been investigated.

5.2.3.4. Genetic differences in PD response

Genetic differences in PD response have not been investigated.

5.2.3.5. Immunological events

Not applicable.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Evaluation and qualification of models

Exposure-Response modelling

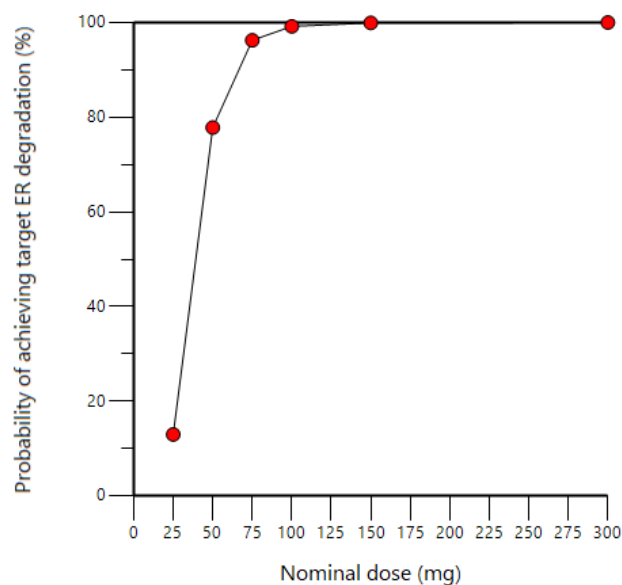
Cox proportional hazard analysis using SERENA-6 study data indicated no exposure-efficacy relationship at the 75 mg camizestrant dosing level. Exposure-safety relationship was explored graphically using boxplots, and unpaired two-sample t-test was performed for comparison. Exposure-safety analyses were performed independently for SERENA-6 and SERENA-1. Linear logistic regression modelling was performed for analyses, yielding a significant result ($p < 0.05$). No exposure-safety relationship was indicated for the pivotal study SERENA-6 (camizestrant 75 mg qd). Significant covariates were identified for SERENA-1 study (camizestrant 75 to 300 mg qd). Stepwise covariate analysis indicated that treatment effect from palbociclib had a significant impact on Grade ≥ 1 neutropenia, and treatment effect from palbociclib and baseline neutrophils had a significant impact on Grade ≥ 2 neutropenia and Grade ≥ 3 Neutropenia.

Concentration-QTc modelling

C-QTc relations of camizestrant was described by a linear mixed-effects model. The estimated population slope (0.019 ms per ng/mL [90% CI: -0.0076 to 0.0456]) and intercept (1.73 ms [90% CI: -2.102 to 5.565]) was not statistically significant. No time delay was indicated between camizestrant concentration and $\Delta QTcI$ for 75 mg dose. A slight increase in $\Delta QTcI$ was observed between 2 and 8 h post-dose for the 300 mg dose most pronounced in the pre-menopausal patients.

5.2.5. Relationship between plasma concentration and effect and safety

Figure 31: Probability of Success versus Camizestrant Dose



The probability of success defined as the number of virtual patients whose steady state average degradation is $\geq 45.5\%$ over the total number of virtual patients (5000).

Variability in the model simulations is due to population distribution of PK parameters from the clinical PopPK model.

Exposure-response analysis of efficacy:

Figure 32: Kaplan-Meier plot of PFS by quartiles of camizestrant AUCss in SERENA-2:

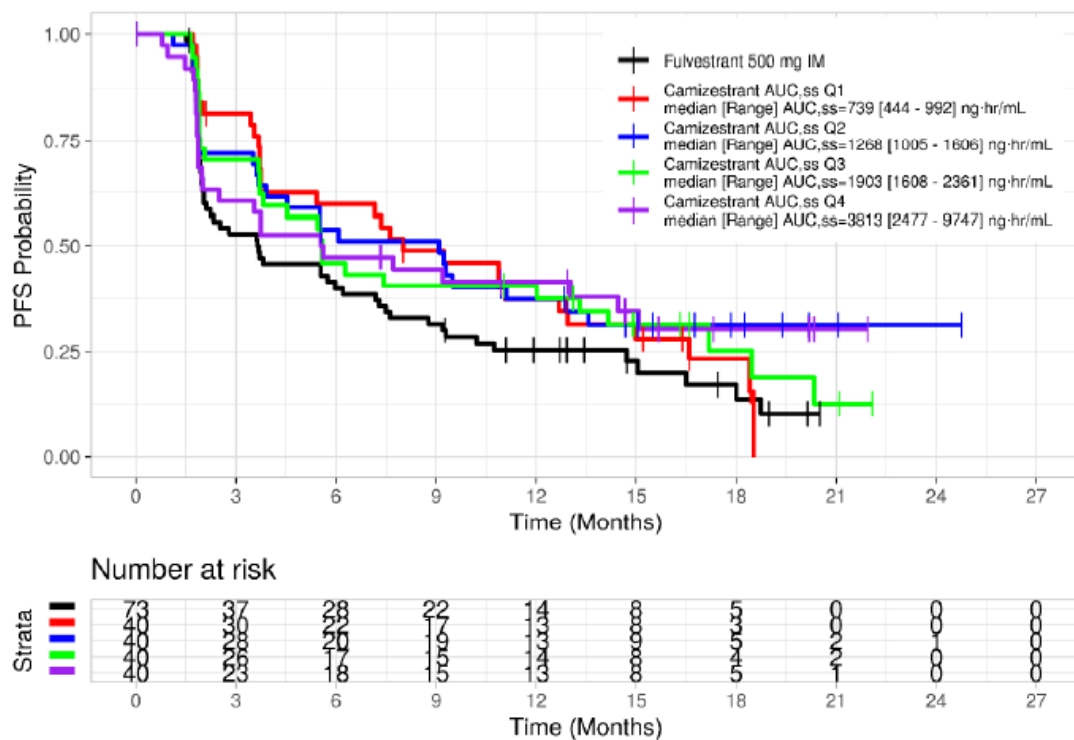
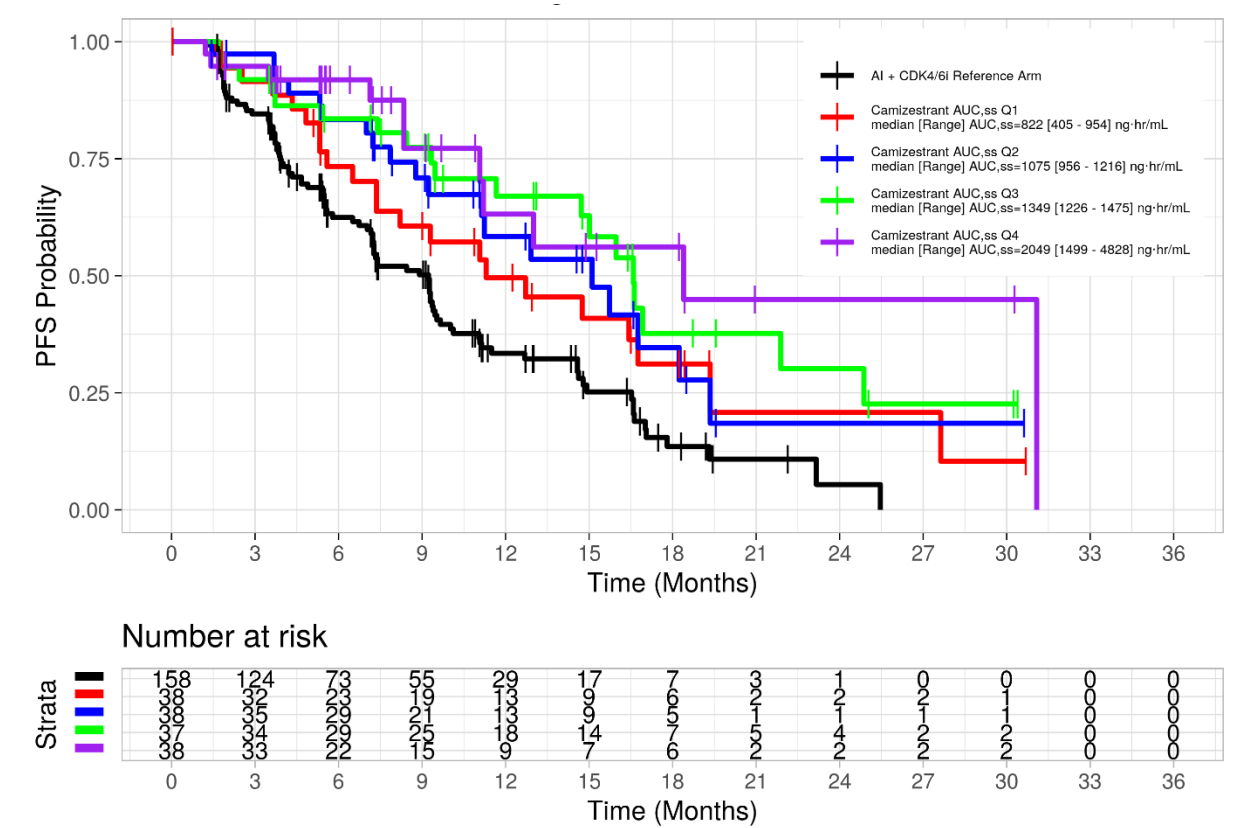


Figure 33: Kaplan-Meier Plots of PFS in SERENA-6 Following Camizestrant Administration Stratified by AUCss Quartiles



The number of patients at risk, indicated as a tabulated summary is shown below the plot.
AUCss represented as quartiles with Q1 (red), Q2 (blue), Q3 (green), Q4 (purple)

SERENA-6 clinical safety and exposure-safety analysis:

Figure 34: Distribution of Cmaxss of Camizestrant with (Yes) or Without (No) Grade ≥1 Bradycardia (Grouped Term) and Grade≥1 Visual Effect (Grouped Term) in SERENA-6

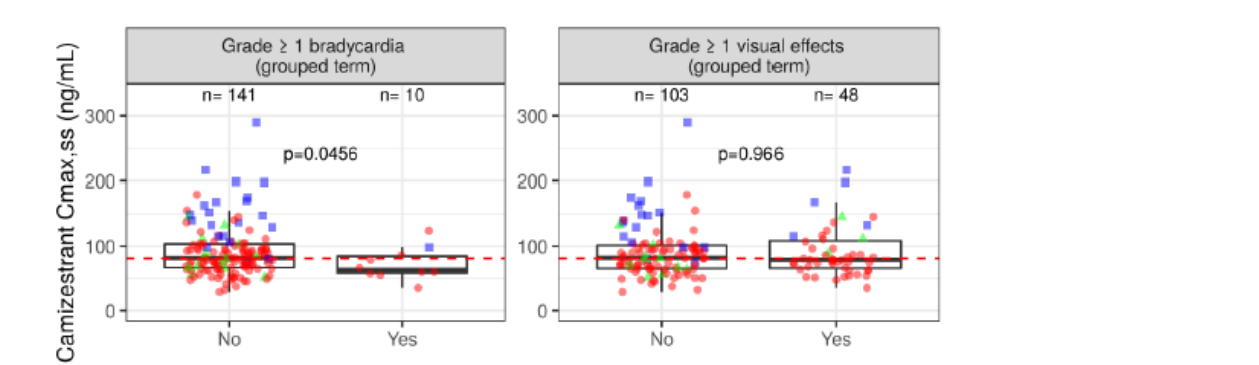
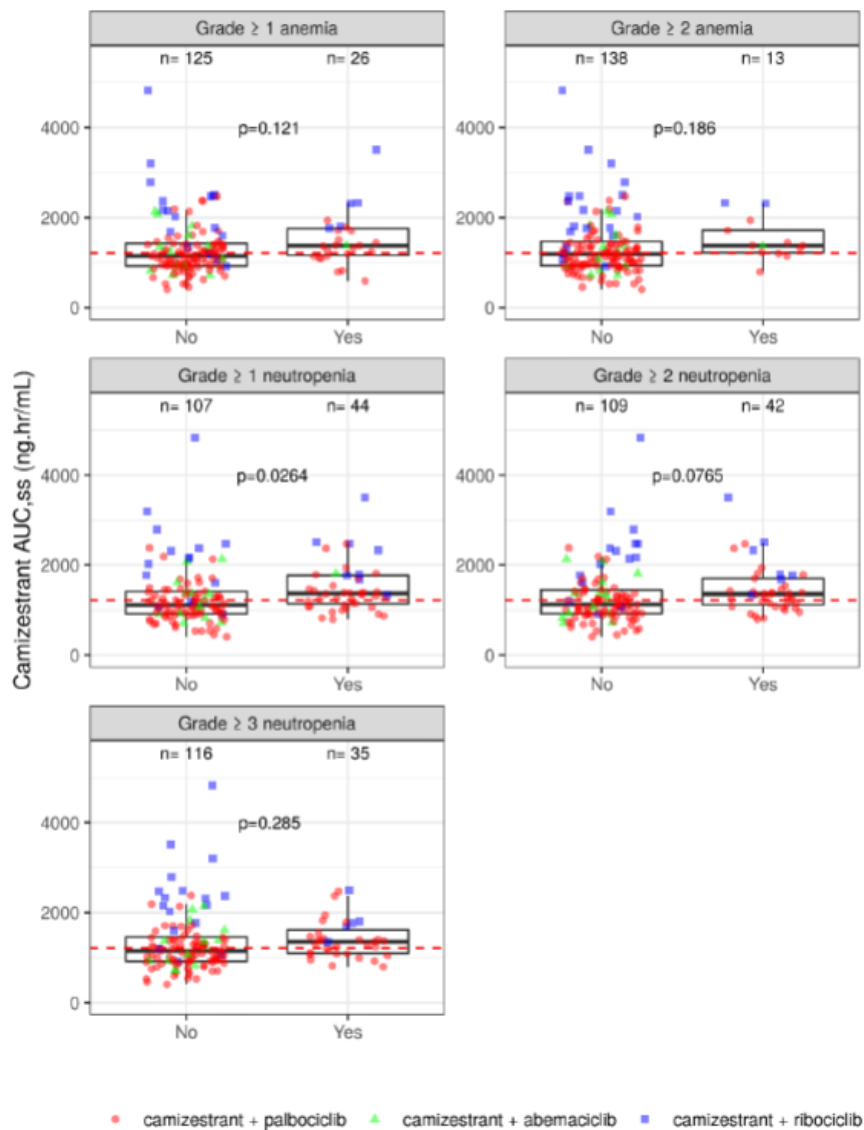


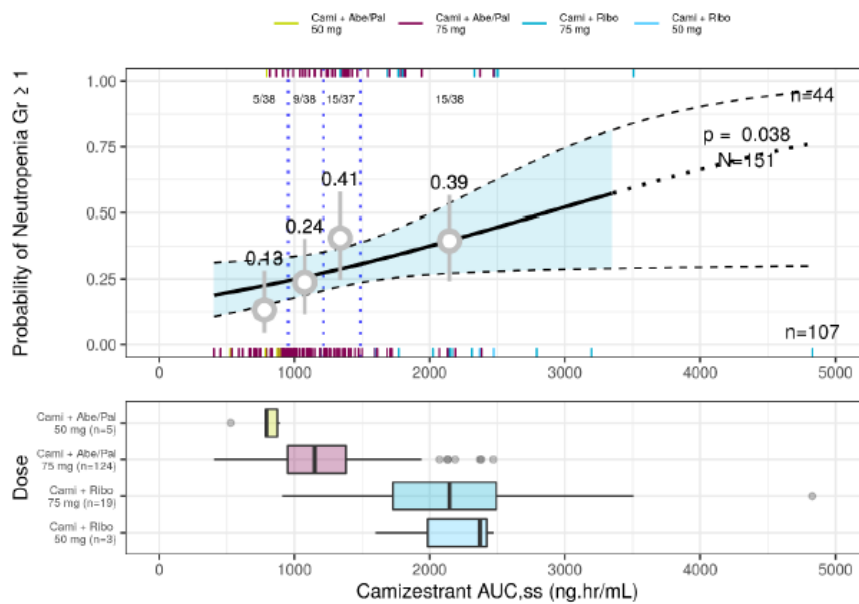
Figure 35: Distribution of AUCss of Camizestrant with (Yes) or Without (No) any Grade $\geq 1/\geq 2$ Anaemia, Grade $\geq 1/\geq 2/\geq 3$ Neutropenia in SERENA-6



P-value = unpaired two-samples t-test (parametric) was used for comparison

Dots = the values observed in participant; red line = the median; lower and upper part of the box = 25% and 75% percentile of the distribution; lower and upper whiskers = the median-1.5x IQR and median+1.5x IQR

Figure 36: Relationship Between Probability of Grade ≥ 1 Neutropenia and Camizestrant AUCss in SERENA-6

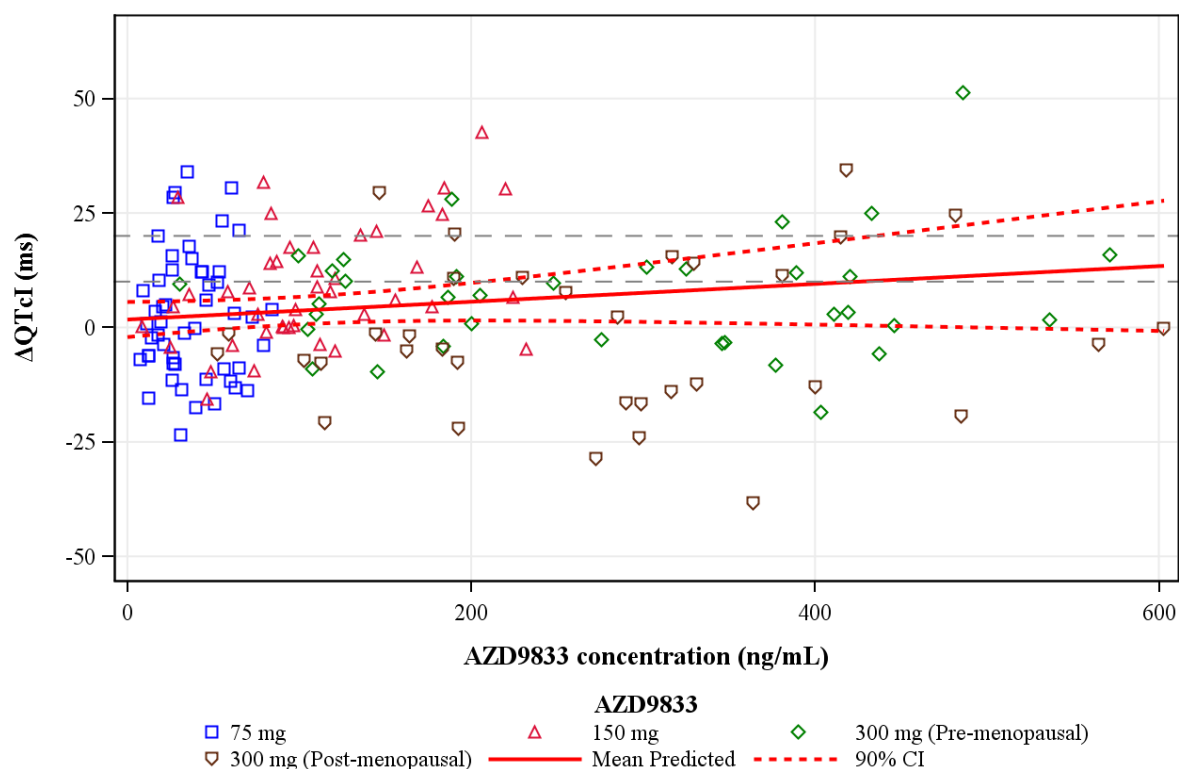


Colored ticks = the observed AE at various dose levels; open circle with error bars (95% CI) = the observed probability of response at each exposure quartile; black lines = the logistic regression between two variables; light blue area = the associated confidence interval; blue dotted lines = 1st quartile, median and 3rd quartile

Effect of camizestrant exposures on QTcI

An evaluation of the effect of 75, 150, and 300 mg steady state camizestrant monotherapy on the QTc interval was performed in Part B of SERENA-1. Continuous 24-h 12-lead ECGs recordings were performed both pre-dose and after repeat camizestrant doses on Cycle 1 Day 15 for the purpose of arrhythmia analysis (including evaluation of mean hourly heart rate), and to allow extraction of replicate 12-lead ECGs at predefined time points. Blood samples were also collected for determining plasma concentrations of camizestrant. Due to camizestrant causing a pronounced effect on HR, data collected during the baseline day (prior to camizestrant dosing) and on-treatment were used to derive individual corrected QTc data (QTcI).

Figure 37: Relationship between Camizestrant Plasma Concentration and Δ QTcI after 75, 150 and 300 mg QD Multiple Monotherapy Doses of Camizestrant



The solid red line with dashed red lines denotes the model predicted mean Δ QTcI with 90% CI, which is calculated from the equation Δ QTcI (ms) = 1.73 (ms) + 0.019 (ms per ng/mL) $\times$ camizestrant plasma concentration (ng/mL). The plotted points denote the pairs of observed drug plasma concentrations and observed Δ QTcI by subjects. The grey dashed line shows the 10 ms threshold.

Camizestrant geomean C_{maxss} calculated using non compartmental analysis (NCA) from SERENA-1 data for monotherapy and in combination with CDK4/6 inhibitors are presented in Table 43 along with the predicted Δ QTcI. All of the concentrations are below the upper 90% CI predicted concentration ($\sim$ 207 ng/mL) to cause a 10 ms change in QTcI.

Table 42: Camizestrant Geomean C_{maxss} and Predicted Upper 90% CI Δ QTcI using C-QTcI analysis

Study	Camizestrant C_{maxss} Geomean (CV%) ng/mL [n]	Mean (90% CI) Δ QTcI (ms)
SERENA-1 Parts A+B 75 mg camizestrant monotherapy	64.73 (49.19) [22]	2.99 (-0.11, 6.09)
SERENA-1 Parts C+D 75 mg camizestrant + palbociclib	93.94 (55.67) [24]	3.56 (0.55, 6.57) ^a
SERENA-1 Parts G+H 75 mg camizestrant + abemaciclib	85.43 (41.17) [16]	3.39 (0.37, 6.41) ^a
SERENA-1 Parts K+L 75 mg camizestrant + 400mg ribociclib	153 (38.29) [23]	4.73 (1.35, 8.011) ^a

Study	Camizestrant C _{maxss} Geomean (CV%) ng/mL [n]	Mean (90% CI) ΔQTcI (ms)
SERENA-1 Parts K+L 75 mg camizestrant + 600mg ribociclib	179 (50.88) [22]	5.21 (1.47, 8.95) ^a
PBPK simulation: 75 mg camizestrant + 400 mg ribociclib + Severe hepatic impairment (Child-Pugh)	214	5.89 (1.51, 10.28) ^a

^a. ΔQTcI predicted from camizestrant monotherapy-Δ selected method for QTcI linear model

As a 600 mg dose of ribociclib is predicted to impact camizestrant PK via a strong, time-dependent inhibition of CYP3A4/5, the upper 90% CI ΔQTcI was calculated using the geomean C_{maxss} for camizestrant in combination with 600 mg ribociclib as an additional extrinsic factor to evaluate a high-risk clinical scenario. In this scenario, the plasma concentration of camizestrant remained below the threshold concentration of ~207 ng/mL which would result in a 10 ms change in QTcI.

5.2.6. Dose selection and therapeutic window

- Non-clinical PK/PD indicated minimal increase in probability of achieving target ER degradation for monotherapy doses greater than 75 mg QD; doses < 75 mg were associated with a substantially lower probability of achieving target ER degradation.
- Comparable inhibition in the biomarkers ER, PgR and Ki-67 for doses from 75 to 300 mg was observed in SERENA-3 in primary breast cancer.
- No statistically significant relationship between camizestrant PK and PFS over the exposure range 75 and 150 mg in the Phase II randomised trial SERENA-2 was observed.
- PopPK analysis indicates no dose adjustment of camizestrant is required on the basis of age, body weight, menopausal status, obesity, albumin, creatinine clearance, or acid reducing agents.
- Ribociclib increases the exposure of camizestrant ~2-fold, consistent with ribociclib being an inhibitor of CYP3A4/5 and camizestrant being a substrate of CYP3A4/5 (itraconazole, a strong CYP3A4/5 inhibitor, increased camizestrant exposure ~2-fold). This ~2-fold increase in camizestrant exposure is comparable with the 2.6 to 3.2-fold increase seen with the observed PK data from the NCA. The C_{maxss} and AUC_{ss} ratios for 150 mg vs 75 mg camizestrant QD monotherapy in SERENA-1 Parts A and B are 2.6 and 2.5-fold respectively, and therefore greater than 2-fold for a doubling of dose. This reflects the greater than dose proportional increase in exposure with dose. The exposures associated with this increase are comparable to those achieved following 150 mg camizestrant monotherapy.

5.2.7. Overall discussion and conclusions on clinical pharmacology

5.2.7.1. Discussion

Bioanalytical methods

The bioanalytical method for camizestrant in plasma and urine appear acceptable.

PK modelling

The final PopPK model was considered fit for purpose to characterise the PK of camizestrant in the patient population, to estimate covariate effects and derive exposure metrics for PK/PD purposes. Statistically significant covariates identified were: baseline body weight (BBW), ethnicity, concomitant

use of ribociclib, dose, and BCRCL. GoF and pcVPC plots indicated that the PopPK model was able to capture the central tendency of the observations.

Absorption

Camizestrant can be considered a BCS Class 1 drug. Camizestrant is moderately absorbed and exhibit a bioavailability of 43% at the recommended dose of 75 mg and 55% for a 300 mg dose. This illustrates the magnitude of the non-dose proportional exposure to camizestrant. Despite the relatively good bioavailability, the interindividual variability in exposure was moderate to high. T_{max} was highly variable across individuals and independent of dose.

Camizestrant was co-administered with palbociclip and albociclip at dose levels up to 300 mg/day but with ribociclib only at 75 mg due to the irreversible inhibitory effect on CYP3A4 by ribociclib which in general doubled the exposure to camizestrant as compared to monotherapy and co-administered with palbociclip or albociclip.

Formulation differences did not affect bioavailability.

The food effects study showed similar exposures between the fed and fasted states. Therefore, this is reflected in section 4.2 of the SmPC allowing intake with or without food.

Distribution

The apparent volume of distribution based on PopPK analysis is noted as 26.97 L/kg. In SERENA 1 V_{ss}/F decreased from 2563 L to 882 L with increasing dose.

Camizestrant showed moderate binding to plasma proteins. The unbound fraction of camizestrant in human plasma was 24.7%. No impact of concentration range was observed.

No preferential distribution into blood cells was observed.

Metabolism

Identification of metabolites in plasma, urine and faeces was performed in a dedicated ADME-study.

In plasma, unchanged AZD9833 represented 13.6% of the drug-related AUC. The main circulating metabolites were M4 (AZ14191353, an N-glucuronide conjugate of AZD9833) and M14 (an N-glucuronide of an acid metabolite) which represented 20.1% and 11.2% of the drug related AUC, respectively. The other nine minor metabolites, each of which had a relative abundance lower than 10% of the total drug-related materials in plasma, were either oxidative metabolites or glucuronides of oxidative metabolites. No active metabolites were identified.

CYP3A4, CYP3A5 and UGT1A4 were identified as responsible for the majority of the metabolism of camizestrant. Thus, the exposure to camizestrant will be impacted by inhibitors and inducers of CYP3A4. The no-effect boundaries of camizestrant are not yet established. However, a conservative proposal could be that -50% to 200% of the exposure observed at the recommended dose of 75 mg is acceptable.

Camizestrant is a reversible inhibitor of CYP3A4, CYP2B6 and an irreversible inhibitor of CYP2C9 and CYP2C19 *in vitro*. The interaction with CYP3A4 was confirmed in clinical DDI studies.

CYP3A4/5 is not known for clinically relevant genetic polymorphism and is estimated to be responsible for a major part of clearance pathways (51%). UGT1A4 is polymorphic but is estimated to account for only 22% of clearance of camizestrant, therefore no investigations on genetic polymorphism were performed.

Moreover, camizestrant is a substrate of P-gp and an inhibitor of P-gp, BCRP and OATP1B1.

The information concerning biotransformation in section 5.2 of the SmPC is considered acceptable.

Elimination

Camizestrant clearance is primarily metabolic and liver-dependent.

Clearance estimated using the PopPK model (69.1 L/h) is referred to in the SmPC.

The terminal half-life of approximately 23 hours is calculated, which was increased with co-administration of ribociclib based on PopPK analysis. The main clearance pathway is through the liver with CYP3A4 being responsible for the majority of the metabolism correlating with the increase in exposure observed when coadministered with ribociclib.

The results of mass balance study indicate that faecal excretion is the major route of elimination, while urinary excretion is the minor elimination pathway: The mean cumulative recovery over the whole collection period (0-432 h) was 82.0 %, with 16.8% being excreted in urine (collected for 216 h) and 65.1% in faeces (collected for 432 h). A somewhat longer sampling time might have been preferable, as the total recovery of radioactivity in urine and faeces should exceed 90% of the dose. Fecally excreted, unchanged camizestrant accounted for 14.5% of the dose. The identified radioactivity was 71.5% in faeces. The majority of faecal recovery seems to be due to biliary elimination and not unabsorbed drug. Active secretion of camizestrant is indicated from the renal clearance which is above blood flow to the kidneys. The identified radioactivity was 67.1% in urine. In plasma, the identified radioactivity was 73.9%. Overall, the percentage identified in the three different matrices is considered sufficient. Camizestrant was present in plasma at 13.6% of the radioactivity. Two glucuronidated metabolites were present in higher amounts (20.1 and 18.2%). All other metabolites were present at levels lower than 10%.

Dose proportionality and time-dependency

Camizestrant exposure increased in a greater than dose proportional manner over the dose range of 25 to 450 mg, when administered alone (single and multiple dose slope estimates range: 1.18 to 1.38.)

The deviation from dose proportionality is considered modest and not clinically relevant at the recommended dose. Accumulation was limited.

Pharmacokinetics in the target population

Camizestrant PK was characterised in combination with CDK4/6 inhibitors. Exposure was comparable to monotherapy when combined with palbociclib or abemaciclib, while exposure increased with ribociclib. Overall variability was moderate to high. The exposure–efficacy analyses support that 75 mg provides adequate exposure across patients, without evidence of benefit from higher exposures.

Special populations

No formal study of the pharmacokinetics of camizestrant was performed in subjects with renal impairment, as only a mean of 4.8% of the dose administered in the mass balance study was excreted as unchanged camizestrant in the urine. Renal impairment is not expected to significantly affect PK. This is adequately reflected in the SmPC. Camizestrant is not recommended for participants with severe renal impairment, as safety and PK have not been studied in these participants.

For hepatic impairment, increased exposure and accumulation are expected due to hepatic clearance dependence. Therefore, as a precautionary measure, camizestrant should be avoided in patients with moderate and severe hepatic impairment. Patients with mild hepatic impairment are allowed to take camizestrant. When a small molecule medicinal product shows higher than dose-proportional exposure, it is recommended that the dedicated study in subjects with hepatic impairment is performed at steady state. In order to mitigate this deficiency, three different approaches were used to simulate exposure to camizestrant in the three categories at steady state which were not accepted. Based on PopPK analyses (n=756), no clinically significant relationships were identified between model predicted steady-state exposure, area under the curve at steady state (AUC_{ss}) and the following covariates: baseline median age 61 years (29 to 89 years) and racial groups. PopPK analysis showed baseline median body weight was 69.9 kg (34.2 to 150 kg) and it affected apparent volume of distribution (V_{2/F}), but this was not clinically relevant; it did not significantly impact apparent total

body clearance (CL/F) or AUC_{ss}. No dose adjustments for camizestrant are required based on age, gender, race, or body weight.

Pharmacokinetic interaction studies

In vitro

CYP2B6 and CYP2D6 were reversibly inhibited by camizestrant with CYP2B6 having the potential for *in vivo* inhibition. As there are no *in vivo* clinical data the SmPC includes the avoidance of sensitive substrates of CYP2B6. Camizestrant also inhibits CYP2C9 and CYP2C19, supporting precautionary measures in the SmPC. Transporter inhibition (P-gp, BCRP, OATP1B1) suggests potential interaction risk further supporting precautionary measures in the SmPC.

In vivo

An increase in midazolam exposure was observed when co-administered with camizestrant indicating that camizestrant is a weak inhibitor of CYP3A4/5.

Pretreatment with carbamazepine reduced the exposure to camizestrant. Thus, treatment with a strong CYP3A4/5 inducer decreases camizestrant exposure in a clinically significant manner and the avoidance of strong and moderate inducers is reflected in the SmPC. In patients taking camizestrant in combination with ribociclib moderate inducers are allowed.

As *in vitro* and mass balance data indicated that approximately 50% of the clearance of camizestrant is through CYP3A4/5, a clinical DDI study with the strong inhibitor itraconazole was conducted. With point estimates below 2 and relatively narrow 90% CIs, the itraconazole study did not indicate that the exposure of camizestrant was clinically significantly increased by co-administration with strong CYP3A4 inhibitors. However, based on the increase in camizestrant exposure when combined with ribociclib, this combination should be avoided in patients taking additional strong CYP3A4/5 inhibitors. Furthermore, appropriate caution should be exercised with concomitant use of additional weak/moderate CYP3A inhibitors in patients taking camizestrant in combination with ribociclib.

Pharmacodynamics

Camizestrant showed consistent ER target engagement across dose levels, with similar reductions in ER and proliferation markers.

Apart from the expected activity against estrogen receptors, camizestrant also inhibits HCN ion channels. This is considered to be the likely mechanism behind the AESIs bradycardia and visual effects.

Exposure-response

No clear exposure–efficacy relationship was identified within the clinical dose range. The available evidence supports that 75 mg achieves sufficient efficacy across exposure ranges. Exposure–safety analyses did not show strong relationships; however, dose-dependent trends for bradycardia and visual effects were observed across studies. QTc analyses did not indicate clinically relevant prolongation at the recommended dose.

5.2.7.2. Conclusions

The pharmacokinetics and pharmacodynamics of camizestrant alone and in combination with CDK4/6 inhibitors have been sufficiently characterised and reflected in the SmPC.

5.3. Clinical efficacy

5.3.1. Dose response study

The dose-response of camizestrant was investigated in **SERENA-2**, a Phase II study in post-menopausal women with advanced ER-positive/HER2-negative breast cancer, which investigated camizestrant as a monotherapy dose daily at 75, 150, and 300 mg. Based on review of the SERENA-1 Phase I camizestrant monotherapy data which revealed no increase in activity with doses above 150 mg, in terms of ORR, CBR24 or PFS, the 300 mg cohort in SERENA-2 was discontinued after enrolment of 20 participants.

Camizestrant produced a statistically significant and clinically meaningful improvement in PFS over fulvestrant at both 75 mg (HR [90% CI]: 0.59 [0.43 – 0.82]; p-value = 0.0177) and 150 mg (HR [90% CI]: 0.70 [0.51 – 0.95]; p-value = 0.0200) camizestrant doses. An increase in both ORR and CBR24 was observed in both the 75 mg and 150 mg camizestrant treatment arms when compared to fulvestrant, demonstrating that a 75 mg dose of camizestrant provided a clinical benefit.

5.3.2. Main study

5.3.2.1. Study D8534C0001 – Serena-6

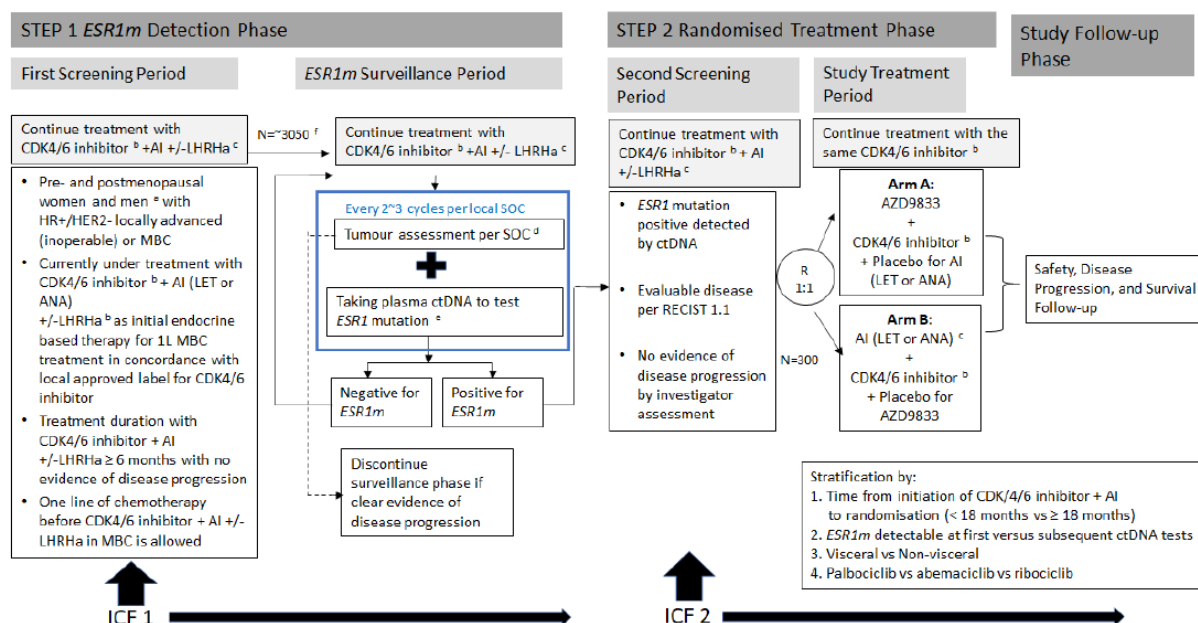
5.3.2.1.1. Study title

SERENA-6: A Phase III, Double-blind, Randomised Study to Assess Switching to AZD9833 (a Next Generation, Oral SERD) + CDK4/6 Inhibitor vs Continuing Aromatase Inhibitor (Letrozole or Anastrozole) + CDK4/6 Inhibitor in HR+/HER2- mBC Patients with Detectable ESR1 Mutation Without Disease Progression During 1L Treatment with Aromatase Inhibitor + CDK4/6 Inhibitor.

5.3.2.1.2. Study design

Phase III, randomised, double-blind, placebo-controlled study assessing the efficacy and safety of switching to camizestrant + CDK4/6 inhibitor compared with continuing AI + CDK4/6 inhibitor in patients with HR-positive, HER2-negative ABC who develop *ESR1* mutations detected in ctDNA using Guardant360 CDx assay during 1L treatment without disease progression.

Figure 38: Study Schema



- Pre/peri-menopausal females or males (if medically indicated) continued to receive concurrent LHRH agonist/antagonist during STEP 1 (ESR1m Detection Phase). During the STEP 2 (Treatment Phase), they received concurrent monthly LHRH (goserelin or leuporelin). Dose per local guideline or label.
- Patients received the same CDK4/6 inhibitor at the same dose level in STEP 1 and STEP 2.
- Patients received the same AI in the STEP 1 and STEP 2.
- If routine tumour assessment was performed within 28 days before STEP 2 randomisation and was consistent with RECIST v1.1 standard, no repeat baseline tumour assessment scan was needed. Therefore, it was preferable that tumour assessment during STEP 1 was performed to RECIST v1.1 standards (CT [preferred] or MRI, with IV contrast, of the chest, abdomen and pelvis).
- If the patient was followed in the clinic every 2 or 3 months for tumour assessment scans, it was recommended that the ctDNA blood sample collection was taken up to 14 days prior to (or on the same day as) the routine tumour imaging assessment, and ideally in time to allow for the result to be reported to the site in time for the patient's tumour assessment visit.
- Once the randomisation cap of about 300 patients was reached and recruitment was closed, patients under surveillance period had the option of providing a ctDNA blood sample for testing at the time of disease progression. Patients who progressed during the surveillance phase were allowed a last ctDNA test at the time of disease progression for detecting the mutation landscape of the tumour.

LET, letrozole; ANA, anastrozole

Treatment

Table 43: Study treatments

Arm Name	Arm A: camizestrant + CDK4/6 inhibitor + placebo for AI	Arm B: AI + CDK4/6 inhibitor + placebo for camizestrant
Treatment Name	camizestrant + CDK4/6 inhibitor + placebo for AI	AI (anastrozole or letrozole) + CDK4/6 inhibitor + placebo for camizestrant
Type	drug	drug
Dose Formulation	camizestrant (tablet) palbociclib (tablet or capsules) abemaciclib (tablet) ribociclib (tablet) placebo for anastrozole (tablet) placebo for letrozole (over-encapsulated tablet)	anastrozole (tablet) letrozole (over-encapsulated tablet) palbociclib (tablet or capsules) abemaciclib (tablet) ribociclib (tablet) placebo for camizestrant (tablet)

Unit Dose Strength(s)	camizestrant (25 and 75 mg) palbociclib (75, 100, and 125 mg) abemaciclib (50, 100, and 150 mg) ribociclib (200 mg) placebo for anastrozole (1 mg) placebo for letrozole (2.5 mg)	anastrozole (1 mg) letrozole (2.5 mg) palbociclib (75, 100, and 125 mg) abemaciclib (50, 100, and 150 mg) ribociclib (200 mg) placebo for camizestrant (25 and 75 mg)
Dosage Level(s)	camizestrant (75 mg, once daily, consecutively for 28 days per cycle) + CDK4/6 inhibitor (continuing palbociclib, abemaciclib, or ribociclib, maintained at the same dose as when the <i>ESR1m</i> was detected; palbociclib or ribociclib were administered once daily for 21 consecutive days per cycle followed by a 7-day off and abemaciclib was administered twice daily for 28 consecutive days per cycle) + placebo for AI (continuing anastrozole or letrozole)	AI (continuing anastrozole 1 mg, once daily or letrozole 2.5 mg, once daily consecutively for 28 days per cycle) + CDK4/6 inhibitor (continuing palbociclib, abemaciclib, or ribociclib, maintained at the same dose as when the <i>ESR1m</i> was detected; palbociclib or ribociclib were administered once daily for 21 consecutive days per cycle followed by 7 days off and abemaciclib was administered twice daily for 28 consecutive days per cycle) + placebo for camizestrant
Route of Administration	oral	oral
Use	camizestrant (experimental) palbociclib (background intervention) abemaciclib (background intervention) ribociclib (background intervention) placebo for anastrozole (placebo) placebo for letrozole (placebo)	anastrozole (active-comparator) letrozole (active-comparator) palbociclib (background intervention) abemaciclib (background intervention) ribociclib (background intervention) placebo for camizestrant (placebo)

Randomisation and blinding

Approximately 3050 patients were planned to be screened for *ESR1m* status (STEP 1: *ESR1m* detection phase) to allow approximately 300 (in reality 315) patients to be randomised in a 1:1 ratio to one of the following treatment arms (STEP 2: treatment phase):

- Arm A: camizestrant (75 mg oral, OD) + CDK4/6 inhibitor + placebo for AI.
- Arm B: AI (OD) + CDK4/6 inhibitor + placebo for camizestrant.

Randomisation was stratified by:

- Disease site (visceral disease versus non-visceral disease).
- *ESR1m* detectable at first versus subsequent ctDNA tests.
- Time from initiation of CDK4/6 inhibitor + AI to randomisation (< 18 months versus ≥ 18 months (< 78 weeks versus ≥ 78 weeks)).
- CDK4/6 inhibitor (palbociclib versus abemaciclib versus ribociclib).

All patients were centrally assigned to randomised study treatment using an IRT/RTSM. The kit identification number allocated to the patient at the treatment visit were provided by the IRT/RTSM to the investigator(s) or pharmacists.

The randomisation code was not to be broken except in medical emergencies when the appropriate management of the patient required knowledge of the treatment randomisation. The investigator had to document and report the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

Patient population

The study enrolled adult female (pre/peri-menopausal or post-menopausal) and male patients with advanced ER-positive, HER2-negative breast cancer and who are currently on AI + CDK4/6 inhibitor treatment in the first-line advanced setting. During STEP 1, at the *ESR1m* Detection Phase, if patients were confirmed to have *ESR1m* disease, meeting additional screening criteria and, upon confirming no disease progression they were then deemed eligible for STEP 2 phase of the study, where they were randomised to receive study treatment.

Key STEP 1 Inclusion criteria

Inclusion Criteria Assessed During Screening for the STEP 1 (ESR1m Detection Phase)

These criteria were to be checked to confirm eligibility prior to a patient signing ICF1 and entering into the study (ie, prior to entry into the *ESR1m* Surveillance Period), and patients were considered eligible to be included only if all the following criteria apply:

(a) Documentation of ER+ tumour irrespective of PgR status, based on most recent available tumour specimen prior to the screening period utilising an assay consistent with ASCO CAP 2020 guidelines (Allison et al, 2020).

(b) Documented HER2- tumour based on local testing on most recent available tumour specimen prior to the screening period, consistent with ASCO CAP 2018 guidelines (ASCO CAP 2018). Patient must be ≥ 18 years at the time of screening, or ≥ 20 years if in Japan.

- Proven diagnosis of adenocarcinoma of the breast with evidence of locoregionally recurrent or metastatic disease not amenable to resection or radiation therapy with curative intent.
- Documentation of histologically confirmed diagnosis of ER+/HER2- breast cancer based on local laboratory results.
- Currently on treatment and have received ≥ 6 months of AI (letrozole or anastrozole) + CDK4/6 inhibitor treatment as their initial endocrine based treatment for their metastatic disease in concordance with local CDK4/6 inhibitor label or treatment guideline.
- Could have received one prior line of chemotherapy for their locoregionally recurrent or metastatic ER+/HER2- disease before CDK4/6 inhibitor + AI treatment.
- No evidence of clinical³ or radiological⁴ disease progression per investigator assessment.
- Patients must be willing to provide archival radiological images used for tumour assessment at the initiation and/or during CDK4/6 inhibitor + AI for their metastatic disease treatment that support the non-PD assessment, if available, in the event that they have been identified to be *ESR1m* positive.
- Eastern Cooperative Oncology Group performance status of 0 or 1.
- Minimum life expectancy of at least 6 months
- Minimum body weight of 35 kg
- For those female or male patients who are not abstinent (in line with their preferred and usual lifestyle choice), and intend to be heterosexually active with a partner: female patients must be using highly effective non-hormonal contraceptive measures⁵ from the time of screening until 4 weeks after exiting from the *ESR1m* Detection Phase of the study. Male patients who intend to be sexually active

³ Clinical progression defined as unequivocal evidence of disease progression on clinical grounds in the absence of radiological progression

⁴ Radiological progression defined as unequivocal progression compared to previous imaging obtained during or prior to initiation of CDK4/6 inhibitor + AI

⁵ a highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly should follow local guidelines

with a female partner of childbearing potential must be surgically sterile or using an acceptable method of contraception.

- Pre-/peri-menopausal women and male patients who are currently receiving CDK4/6 inhibitor + AI treatment with concomitant LHRH agonist or antagonist must agree to continue to receive concurrent LHRH agonist or antagonist treatment during the entire *ESR1m* Detection Phase of the study.

Key STEP 1 Exclusion Criteria

- Patients who are currently treated with endocrine therapy (AI, tamoxifen or fulvestrant) alone.
- No evidence of disease, or bone only disease with sclerotic/osteoblastic bone lesions only (ie, no lytic or mixed lytic + sclerotic lesions) per standard of care imaging.
- Have advanced, symptomatic, visceral spread, that are at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal]), and/or pulmonary lymphangitis.
- Known active uncontrolled or symptomatic central nervous system (CNS) metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral oedema, and/or progressive growth. Patients with a history of brain or other CNS metastases or cord compression are eligible if they have been definitively treated with local therapy (e.g., radiotherapy, stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before screening phase of the study.
- Any evidence of severe or uncontrolled systemic diseases which, in the investigator's opinion, makes it undesirable for the patient to participate in the study or that would jeopardise compliance with the protocol.
- Chronic gastrointestinal disease, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption, distribution, metabolism, or excretion of CDK4/6 inhibitor + AI treatment.
- History of another primary malignancy except for the following:
 - (a) Malignancy treated with curative intent with no known active disease ≥ 3 years before STEP 1 (*ESR1m* detection phase), and of very low potential risk for recurrence.
 - (b) Adequately treated non-melanoma skin cancer or lentigo malignancy without evidence of disease.
 - (c) Other exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has undergone potentially curative therapy.
- Experience of any of the following procedures or conditions in the preceding 6 months: coronary artery bypass graft, angioplasty, vascular stent, any other structural heart disease interventions (eg, cardiac valve repairmen or replacement surgery or transcatheter valve intervention), severe aortic regurgitation (Grade 3/4), myocardial infarction, unstable angina pectoris, cerebrovascular accident, or, transient ischaemic attack.
- Congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives.
- Patients with CDK4/6 inhibitor treatment-induced symptomatic interstitial lung disease (Grade ≥ 2).
- Patient with known or family history of severe heart disease, including
 - (a) Experience of any of the following procedures or conditions in the preceding 6 months: coronary artery bypass graft, angioplasty, vascular stent, any other structural heart disease interventions (eg, cardiac valve repairmen or replacement surgery or transcatheter valve intervention), severe aortic

regurgitation (Grade 3/4), myocardial infarction, unstable angina pectoris, cerebrovascular accident, or, transient ischaemic attack.

(b) Congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives.

- Prior exposure to AZD9833 (camizestrant), other investigational SERDs/endocrine agents or fulvestrant.

Key STEP 2 inclusion criteria

- Minimum body weight of 35 kg
- Patients who have ESR1m positive disease irrespective of concurrent mutation(s) detected by ctDNA during screening or surveillance. Qualifying ESR1m status will be assessed by a prespecified Sponsor-selected assay at a central laboratory.
- Confirmation that the patients are currently on treatment and have received ≥ 6 months of AI (letrozole or anastrozole) + CDK4/6 inhibitor (palbociclib, abemaciclib, or ribociclib) $\pm$ LHRH agonist treatment as their initial endocrine based treatment for their advanced disease in accordance with local CDK4/6 inhibitor label or treatment guidelines
- Documented absence of disease progression⁶ (by investigator assessment) prior to randomisation.
- Whenever feasible and available, patients must be willing to provide archival radiological images (CT, MRI or bone scan, if not available, then available PET-CT scan is acceptable) used for tumour assessment at the initiation and/or during CDK4/6 inhibitor + AI for their metastatic disease treatment that support the non-PD assessment.
- Eastern Cooperative Oncology Group performance status of 0 to 1.
- Patients must have at least one evaluable lesion (defined as one lesion non previously irradiated, measurable and/or non-measurable, that can be accurately assessed at baseline by CT or MRI and is suitable for repeated assessment). Patients with bone disease only must have at least one non previously irradiated lytic or mixed (lytic + sclerotic) bone lesion that can be assessed by CT or MRI; patients with sclerotic/osteoblastic bone lesions only in the absence of evaluable disease are not eligible. Bone scan at baseline is required.
- Adequate organ and marrow function
- Willingness and ability to provide an archived tissue tumour sample, if available, (FFPE blocks [preferred] or unstained slides) to assess the correlation between genes, proteins, and RNAs relevant to the ER pathways and sensitivity/resistance to the investigational agents' status/expression prior to enrolment. Tissue from the most recent biopsy in the metastatic setting is preferred. If not available (for example bone only disease patients), then archival samples from the primary breast cancer could be used.

Key STEP 2 Exclusion criteria

- No evidence of disease, or bone only disease with sclerotic/osteoblastic bone lesions only at the screening for STEP 2.

⁶ (a) Clinical progression defined as unequivocal evidence of disease progression on clinical grounds in the absence of radiological progression. OR (b) Radiological progression defined as unequivocal progression compared to previous imaging obtained during or prior to initiation of CDK4/6 inhibitor + AI.

- Have advanced, symptomatic, visceral spread, that are at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal]), and/or pulmonary lymphangitis.
- Known active uncontrolled or symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral oedema, and/or progressive growth. Patients with a history of brain or other CNS metastases or cord compression are eligible if they have been definitively treated with local therapy (eg, radiotherapy, stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before the screening phase of the study.
- Any evidence of severe or uncontrolled systemic diseases which, in the investigator's opinion, makes it undesirable for the patient to participate in the study or that would jeopardise compliance with the protocol.
- Chronic gastrointestinal disease, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption, distribution, metabolism, or excretion of CDK4/6 inhibitor and/or study (AI or AZD9833 (camizestrant)) treatment.
- Persistent non-haematological toxicities (CTCAE Grade > 2) caused by CDK4/6 inhibitor and/or AI treatment. Patients with irreversible toxicity that is not reasonably expected to be exacerbated by study treatment in the opinion of the investigator may be included (eg, hearing loss).
- Patients with CDK4/6 inhibitor treatment-induced symptomatic interstitial lung disease (Grade ≥ 2).
- Known active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), HBV (known positive HBsAg result), and HCV.
- Known to have tested positive for HIV. Patients with HIV may be enrolled if they fulfil the criteria recommended by FDA and ASCO guidelines.
- Second- and third-degree heart block, or clinically significant sinus pause or sinoatrial block. Patients with pacemakers or medically controlled atrial fibrillation are not excluded.
- Left ventricular ejection fraction < 50% with heart failure NYHA Grade ≥ 2 .
- Experience of any of the following procedures or conditions in the preceding 6 months: coronary artery bypass graft, angioplasty, vascular stent, any other structural heart disease interventions (eg, cardiac valve repair or replacement surgery or transcatheter valve intervention), severe aortic regurgitation (Grade 3 and 4), myocardial infarction, unstable angina pectoris, cerebrovascular accident, or transient ischaemic attack.
- Untreated electrolyte abnormalities with potential QT-prolonging effect including serum/plasma potassium*, magnesium* and calcium* below the LLN. *Correction of electrolyte abnormalities to within normal ranges can be performed during screening.
- Mean resting QTcF interval > 480 ms (≥ 450 ms for the ribociclib combination), obtained from triplicate ECGs performed at screening.
- Resting heart rate < 55 beats per minute. Repeat measurements are permitted during the screening period.
- Uncontrolled hypertension. Blood pressure systolic > 160 and diastolic > 90 mmHg. Hypertensive patients may be eligible, but blood pressure must be adequately controlled at baseline. Patients may be rescreened regarding blood pressure requirement.

- Any concurrent anticancer treatment not specified in the protocol. Concurrent use of non-topical hormonal therapy for non cancer-related conditions (eg, hormone replacement therapy) is not allowed.
- Palliative radiotherapy with a limited field of radiation within 2 weeks or with wide field of radiation or to more than 30% of the bone marrow within 4 weeks before the first dose of study treatment.
- Major surgical procedure (excluding placement of vascular access) or significant traumatic injury within 14 days of the first dose of study treatment or an anticipated need for major surgery and/or any surgery requiring general anaesthesia during the study.

5.3.2.1.3. Objectives and estimands

Primary objective

The primary objective of the study was to demonstrate the superiority of camizestrant plus CDK4/6 inhibitor over AI (anastrozole or letrozole) plus CDK4/6 inhibitor by assessment of progression-free survival (PFS). The null hypothesis for the primary time to event endpoint (PFS) was that there is no difference between camizestrant plus CDK4/6 inhibitor and AI (anastrozole or letrozole) plus CDK4/6 inhibitor in the probability of a progression event in the FAS (full analysis set) at any time point.

Estimand for the primary objective

Estimand in plain words: *Whether first progression (based on **RECIST v1.1**) or death, estimated by the population summary measure HR, is prolonged in patients with ESR1 mutation receiving **camizestrant** plus CDK4/6 inhibitor versus AI (anastrozole or letrozole) + CDK4/6 inhibitor in patients with ESR1 mutation regardless of discontinuation or changes in received treatment prior to progression.*

Objectives	Estimand description/Endpoints
Primary	
To demonstrate superiority of camizestrant plus CDK4/6 inhibitor relative to AI plus CDK4/6 inhibitor by assessment of PFS in the FAS (patients randomised after entering STEP 2 due to detection of ESR1m positivity without concurrent PD).	PFS is defined as the time from randomisation until progression per RECIST 1.1 as assessed by the investigator at the local site, or death due to any cause. The analysis will include all randomised patients, as randomised, regardless of whether the patient withdraws from randomised therapy, receives another anti-cancer therapy, or clinically progresses prior to RECIST 1.1 progression. The measure of interest is the hazard ratio of PFS.

Statistical methods for estimation and sensitivity analysis on primary estimands

Analysis sets were defined as Enrolled Set (all patients for whom it was recorded on the eCRF that they met all eligibility criteria for STEP 1 [ESR1m Detection Phase]), FAS (all patients who were randomised in the study [after entering STEP 2 due to ESR1m positivity without concurrent progressive disease]). The FAS was used for all the efficacy analyses. Treatment arms were compared on the basis of randomised study treatment, regardless of the study treatment actually received. Patients who were randomised but did not subsequently receive study treatment were included in the analysis in the treatment arm to which they were randomised. The analysis of data using the FAS followed the principles of ITT.

Standard survival analysis methods (stratified Cox, Kaplan Meier) were used for analysing PFS.

Null hypothesis was tested by a stratified log-rank test.

Sensitivity and supplemental analyses: evaluation-time bias, deviation bias, censoring subjects after new anti-cancer therapy in absence of progression or death [for both primary analyses and blinded central review (BICR)], accounting for COVID-19 deaths) and sensitivity (stratification according to eCRF and confounding bias) analyses were also performed to assess the robustness of the primary endpoint.

Secondary objectives

To demonstrate superiority of camizestrant plus CDK4/6 inhibitor relative to AI plus CDK4/6 inhibitor by assessment of PFS2 and overall survival (OS). These are the key-secondary endpoints.

Estimands for the key-secondary objectives

Estimand in plain words (PFS2):

Whether second progression (PFS2, investigator based) following subsequent therapy is prolonged (measured by HR) in patients with ESR1 mutation receiving camizestrant plus CDK4/6 inhibitor versus AI (anastrozole or letrozole) + CDK4/6 inhibitor, regardless of missed visits, discontinuation or changes in received treatment prior to first or second progression.

Estimand in plain words (OS):

Whether overall survival (OS) is prolonged (measured by HR) in patients with ESR1 mutation receiving camizestrant plus CDK4/6 inhibitor versus AI (anastrozole or letrozole) + CDK4/6 inhibitor, regardless treatment withdrawal or change of anti-cancer therapy.

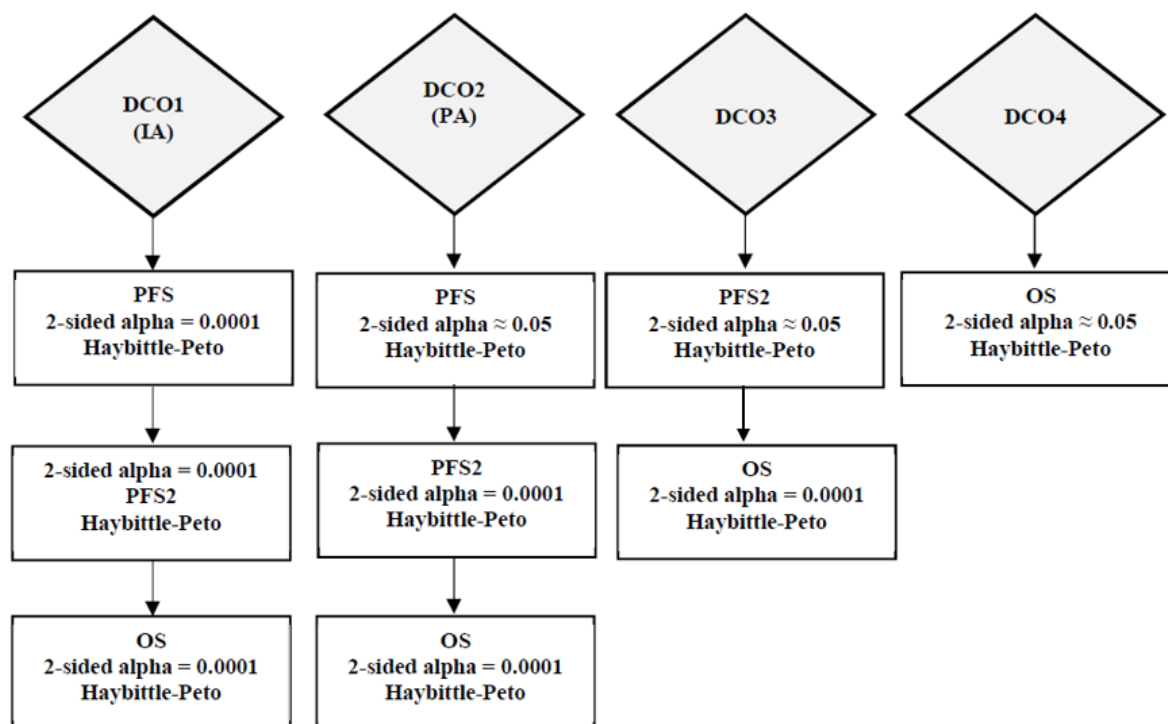
Secondary	
To demonstrate superiority of camizestrant plus CDK4/6 inhibitor relative to AI plus CDK4/6 inhibitor by assessment of PFS2 in the FAS.	PFS2 is defined as the time from the randomisation to the earliest of the progression event (following the initial progression), subsequent to first subsequent therapy or death. The investigator's assessment of the date of second progression will be defined according to local standard clinical practice (which may be clinical or radiological progression). This is the primary measure of PFS2. The comparison will include all randomised patients, as randomised, regardless of whether the patient withdraws from subsequent therapy and regardless of missed visits. In a supplementary analysis, PFS2 will be assessed using RECIST 1.1-defined progression as assessed by the investigator at the local site. The measure of interest is the hazard ratio of PFS2.
To demonstrate superiority of camizestrant plus CDK4/6 inhibitor relative to AI plus CDK4/6 inhibitor by assessment of OS in the FAS.	OS defined as the time from randomisation until the date of death due to any cause. The comparison will include all randomised patients, as randomised, regardless of whether the patient withdraws from therapy or receives another anti-cancer therapy. The measure of interest is the hazard ratio of OS; difference in OS probabilities at 2 years and 3 years will be presented.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

PFS2 and OS are analysed the same way as primary endpoint, PFS, i.e. by standard methods of survival analysis.

Sensitivity and supplemental analyses for PFS2: evaluation-time bias, Covid-19 and investigator assessment based on RECIST v 1.1.

Interim analyses (IA): (This application is based on results from data cut-off 1 (DCO1) where PFS was significant meeting the two-sided significance level at 0.0001 whereas PFS2 failed and OS was not formally tested due to the testing hierarchy. Subsequent planned analyses provided data regarding the investigated superiority of camizestrant with respect to PFS2 and OS, see figure below).



IA for PFS (DCO1): The study was designed to have one IA for PFS after approximately 135 events were observed (45% maturity). The DCO date was determined once the target number of PFS events was reached, but enrolment, follow-up time after last patient randomised, and time between IA and final analysis were also considered, and the DCO date was scheduled after sufficient data were collected for all patients.

Primary analysis for PFS (DCO2): The DCO for the primary analysis of PFS (DCO2) is expected to occur when approximately 195 events (65% maturity) have been observed.

Primary analysis for PFS2 (DCO3): The DCO for the primary PFS2 analysis (DCO3) will occur at 158 PFS2 events.

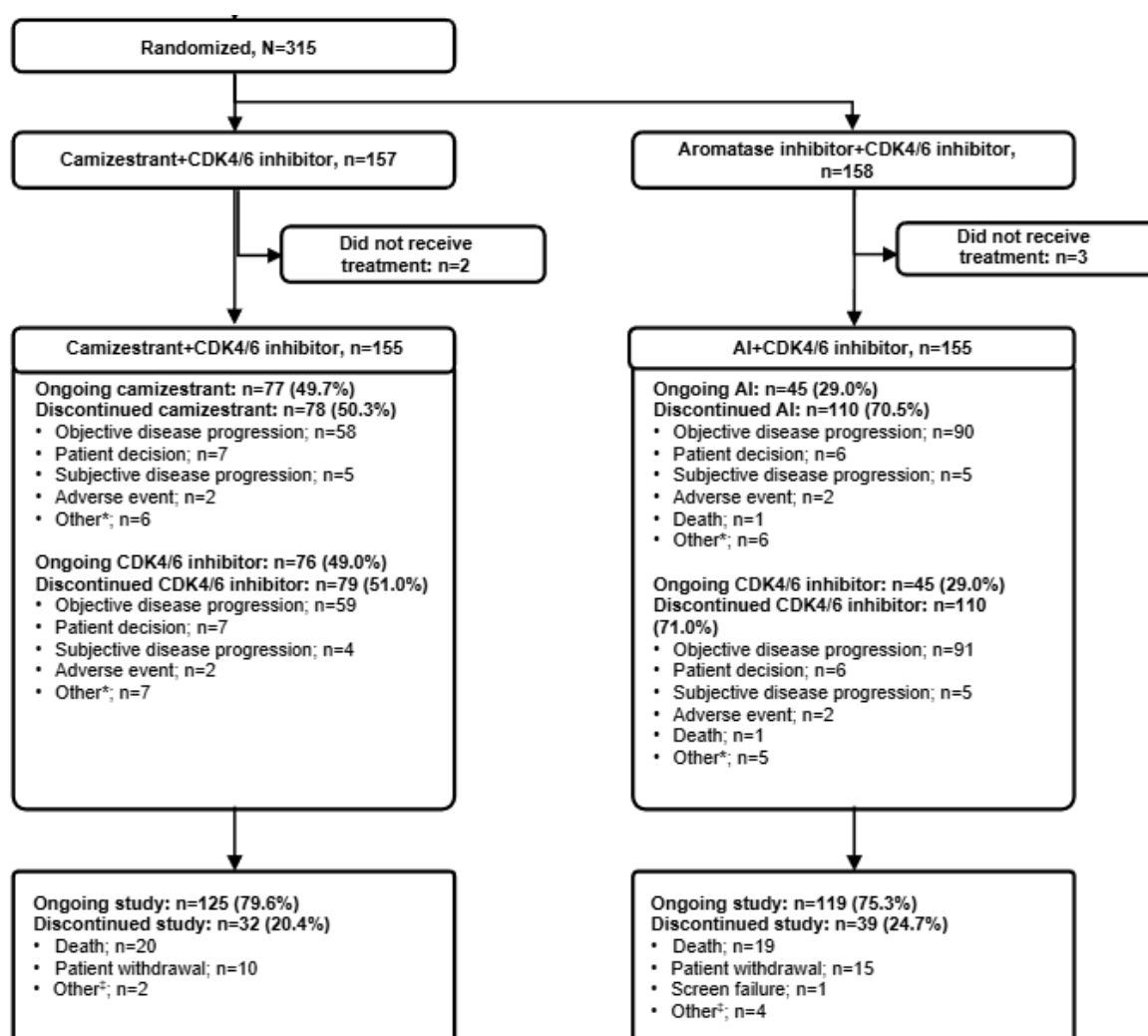
Primary analysis for OS (DCO4): The DCO for the OS final analysis (DCO4) will occur at 165 OS events (55% maturity).

5.3.2.1.4. Results

Participant flow and numbers analysed

SERENA-6 is a global study in which 3325 patients were screened in 264 centres in 23 countries worldwide. A total of 406 patients entered STEP 2, of whom 315 patients were randomised in a 1:1 ratio to receive the study treatment of either camizestrant + CDK4/6 inhibitor (N = 157) or AI + CDK4/6 inhibitor (N = 158). At the time of DCO1, treatment was ongoing for 49.3% of patients in the camizestrant + CDK4/6 inhibitor arm and 28.9% of patients in the AI + CDK4/6 inhibitor arm.

Figure 39: Study Schema



* 'Other' includes treatment discontinuation due to severe non-compliance to protocol, a development in study-specific discontinuation criteria, investigator decision, consent withdrawal, and other (reason not stated).

‡ Reason for study discontinuation not stated.

Note: One patient who discontinued study due to screen failure in AI + CDK4/6 inhibitor arm was randomised but found to have not met eligibility criteria prior to dosing and was miscategorised as a screen failure.

Source: see Table 14.1.1, SERENA-6 CSR, Module 5.3.5.1.

Deviations from study plan

The original study protocol (version 1.0 dated 25 March 2021) has been amended four times. Substantial changes in the conduct of the study that were implemented by protocol amendment(s) are shown and briefly described in Table 45. Protocol amendment 3, version 4.0 dated 05 April 2024 did not have any substantial changes, hence, it is not included in the table.

Table 44: Protocol Amendments Related to Changes in Study Conduct

Amendments made <i>after</i> the start of patient recruitment	
Amendment number and date	Key details of amendment
Protocol Amendment 4.0 dated 06 November 2024	Target number of PFS2 events at DCO3 updated.

Amendments made <i>after</i> the start of patient recruitment	
Amendment number and date	Key details of amendment
Protocol Amendment 2.0 dated 23 March 2023	- Text was updated in all occurrences of CDK4/6 inhibitor to include ribociclib. - An inclusion criterion was updated to state that patients must be willing to provide archival radiological images "<u>whenever feasible or available</u>". - An exclusion criterion was updated to allow patients with controlled stable HBV infection to be eligible. HBsAg and HBV DNA were added to the table of laboratory safety variables. - Text updated in all Sections applicable to clarify that archived tissue tumour sample (either "FFPE blocks [preferred] or unstained slides") was to be provided <u>if available</u>. - Removal of the censoring rule for patients who receive another anti-cancer therapy prior to RECIST v1.1 progression from PFS analysis. - Inclusion criterion was updated to change organ and marrow function thresholds. - Exclusion criterion updated to state TdP is as defined by CredibleMeds. - Removal of text recommending an alternative to atropine eye drops.
Protocol Amendment 1.0 dated 17 May 2022	- Objective revised as the investigator's assessment of the date of second progression according to local standard clinical practice was to be the primary measure of PFS2, with RECIST v1.1 as a supplementary measure. - Added that after first progression, tumour assessments were to be performed every 8-12 week until RECIST v1.1-defined second radiological disease progression and PFS2/survival -followup- window changed from ± 14 to $+ 28$ days. - Updated text to specify the requirement of RECIST scan prior to start of subsequent anti-cancer therapy if > 4 weeks had elapsed since the previous RECIST scan. - Amended eGFR criteria to include additional method and assessment for patients receiving abemaciclib. - Opening of the abemaciclib combination cohort in this study was agreed based on latest available data on abemaciclib. - Reduced resting heart rate from < 60 bpm to < 55 bpm. - Added patients who were screen failures for STEP 1 could be rescreened; screen failures from STEP 2 could be rescreened after consultation with the Global Study Team. - Addition of option for one dose level reduction of 2 weeks on and 2 weeks off for palbociclib treatment. - Included visual effects as an adverse event of special interest (AESI) and added guidance on CRF completion. - Concomitant medication section for drugs that are sensitive to P-gp inhibition and inhibitors or inducers of CYP3A4 was revised based on additional data. - Text updated to confirm that drugs with a known risk of TdP were not to be co-administered with camizestrant during study and for a period of 2 weeks after discontinuing study.

Baseline data

Table 45: Demographic Characteristics (FAS)

Demographic characteristic	Statistic	camizestrant + CDK4/6 inhibitor	AI + CDK4/6 inhibitor	Total
		N = 157	N = 158	N= 315
Age (years) ^a				
	N	157	158	315
	Mean (SD)	58.7 (11.2)	59.6 (11.4)	59.2 (11.3)
	Median (Min, Max)	61.0 (29, 81)	60.5 (35, 89)	61.0 (29, 89)
Age group (years)				
< 45	n (%)	21 (13.4)	20 (12.7)	41 (13.0)
≥ 45 to < 55	n (%)	41 (26.1)	35 (22.2)	76 (24.1)
≥ 55 to < 65	n (%)	33 (21.0)	49 (31.0)	82 (26.0)
≥ 65 to < 75	n (%)	57 (36.3)	37 (23.4)	94 (29.8)
≥ 75	n (%)	5 (3.2)	17 (10.8)	22 (7.0)
Sex				
Male	n (%)	0	3 (1.9)	3 (1.0)
Female	n (%)	157 (100)	155 (98.1)	312 (99.0)
Race				
Black or African American	n (%)	4 (2.5)	2 (1.3)	6 (1.9)
Asian	n (%)	39 (24.8)	34 (21.5)	73 (23.2)
White	n (%)	97 (61.8)	102 (64.6)	199 (63.2)
Other and Missing ^b	n (%)	3 (1.9)	1 (0.6)	4 (1.3)
Not reported	n (%)	14 (8.9)	19 (12.0)	33 (10.5)
Ethnicity				
Hispanic or Latino	n (%)	8 (5.1)	2 (1.3)	10 (3.2)
Not Hispanic or Latino	n (%)	146 (93.0)	152 (96.2)	298 (94.6)
Missing	n (%)	3 (1.9)	4 (2.5)	7 (2.2)

a. Age is calculated at the time of randomisation from date of birth.

This table includes all subjects from STEP 2 (Randomisation, Treatment Phase and Follow-up) phase.

b. Other and Missing have been aggregated for the purpose of the EPAR to protect SERENA-6 data integrity (blinding)

Table 46: Baseline Characteristics (FAS)

Baseline characteristic	Statistic	camizestrant + CDK4/6 inhibitor	AI + CDK4/6 inhibitor	Total
		N = 157	N = 158	N= 315
Height (cm)				
	N	152	154	306
	Mean (SD)	160.26 (6.47)	161.13 (7.79)	160.70 (7.16)
	Median (Min, Max)	160.35	160.70	160.50 (140.8, 180.0)
Weight (kg)				
	N	157	157	314
	Mean (SD)	69.70 (14.70)	72.16 (18.00)	70.93 (16.45)

Baseline characteristic	Statistic	camizestrant + CDK4/6 inhibitor	AI + CDK4/6 inhibitor	Total
		N = 157	N = 158	N = 315
	Median (Min, Max)	68.00	68.55	68.28 (38.9, 135.2)
Weight group (kg)				
< 50	n (%)	13	8	21 (6.7)
≥ 50 to < 70	n (%)	75	76	151 (47.9)
≥ 70 to ≤ 90	n (%)	56	45	101 (32.1)
> 90	n (%)			41 (13.0)
Missing	n (%)			1 (0.3)
BMI (kg/m²)				
	N	152	154	306
	Mean (SD)	27.01 (5.40)	27.69 (6.37)	27.35 (5.91)
	Median (Min, Max)	26.13	26.25	26.17 (15.8, 47.4)
Menopausal status				
Male or pre- or peri- menopausal female	n (%)	34 (21.7)	31 (19.6)	65 (20.6)
Post-menopausal female	n (%)	123 (78.3)	127 (80.4)	250 (79.4)
ECOG performance status at baseline				
(0) Fully active	n (%)	107	98	205 (65.1)
(1) Restricted in physically strenuous activity	n (%)	48	56	104 (33.0)
(2) Ambulatory and capable of self-care	n (%)			1 (0.3)
Missing	n (%)			5 (1.6)
Disease site				
Visceral	n (%)	66 (42.0)	71 (44.9)	137 (43.5)
Non-visceral	n (%)	91 (58.0)	87 (55.1)	178 (56.5)
Stratification factors according to IRT				
ESR1m detectable				
First ctDNA test	n (%)	84 (53.5)	84 (53.2)	168 (53.3)
Subsequent ctDNA test	n (%)	73 (46.5)	74 (46.8)	147 (46.7)
Time from initiation of CDK4/6 inhibitor + AI to randomisation				
< 18 months	n (%)	60 (38.2)	58 (36.7)	118 (37.5)
≥ 18 months	n (%)	97 (61.8)	100 (63.3)	197 (62.5)
CDK4/6 inhibitor				
Abemaciclib	n (%)	14 (8.9)	16 (10.1)	30 (9.5)
Palbociclib	n (%)	119 (75.8)	119 (75.3)	238 (75.6)
Ribociclib	n (%)	24 (15.3)	23 (14.6)	47 (14.9)

Outcomes and estimation

1. Progression free survival (PFS)

Primary efficacy endpoint: PFS by investigator assessment

Table 47: Progression-free Survival (FAS) by investigator assessment at DCO1, DCO2 and DCO3

	DCO1 28 November 2024		DCO2 30 June 2025		DCO3 02 January 2026	
	Camizestrant + CDK4/6i N = 157	AI + CDK4/6i N = 158	Camizestrant + CDK4/6i N = 157	AI + CDK4/6i N = 158	Camizestrant + CDK4/6i N = 157	AI + CDK4/6i N = 158
	Based on investigator assessment					
Total number of patients with events, n (%) ^a	71 (45.2)	100 (63.3)	90 (57.3)	115 (72.8)	99 (63.1)	124 (78.5)
Median, months ^b	15.97	9.23	16.59	9.23	16.76	9.23
95% CI ^c	12.71, 18.23	7.23, 9.53	14.72, 19.35	7.23, 9.66	14.72, 19.35	7.23, 9.66
HR (95% CI) ^d	0.44 (0.31, 0.60)		0.46 (0.34, 0.62)		0.45 (0.34, 0.59)	
2-sided p-value	p < 0.00001		nominal p < 0.00001		nominal p < 0.00001	
PFS rate at 6 months (%) (95% CI)	83.2 (75.9, 88.4)	62.4 (53.8, 69.9)	84.1 (77.2, 89.0)	62.0 (53.7, 69.2)	84.1 (77.2, 89.0)	62.0 (53.7, 69.2)
PFS rate at 12 months (%) (95% CI)	60.7 (51.1, 69.0)	33.4 (24.9, 42.2)	62.2 (53.7, 69.5)	35.3 (27.5, 43.2)	62.2 (53.8, 69.4)	35.3 (27.5, 43.0)
PFS rate at 24 months (%) (95% CI)	29.7 (19.0, 41.2)	5.4 (0.7, 18.2)	32.2 (23.1, 41.6)	14.3 (7.0, 23.9)	34.9 (26.8, 43.0)	14.2 (8.4, 21.4)
PFS rate at 30 months (%) (95% CI)	22.6 (11.8, 35.6)	0 (NC, NC)	23.5 (13.6, 35.1)	3.6 (0.3, 14.3)	30.4 (22.2, 39.1)	2.7 (0.3, 10.6)

[a] Includes progression events that occurred within 2 visits of last evaluable assessment.

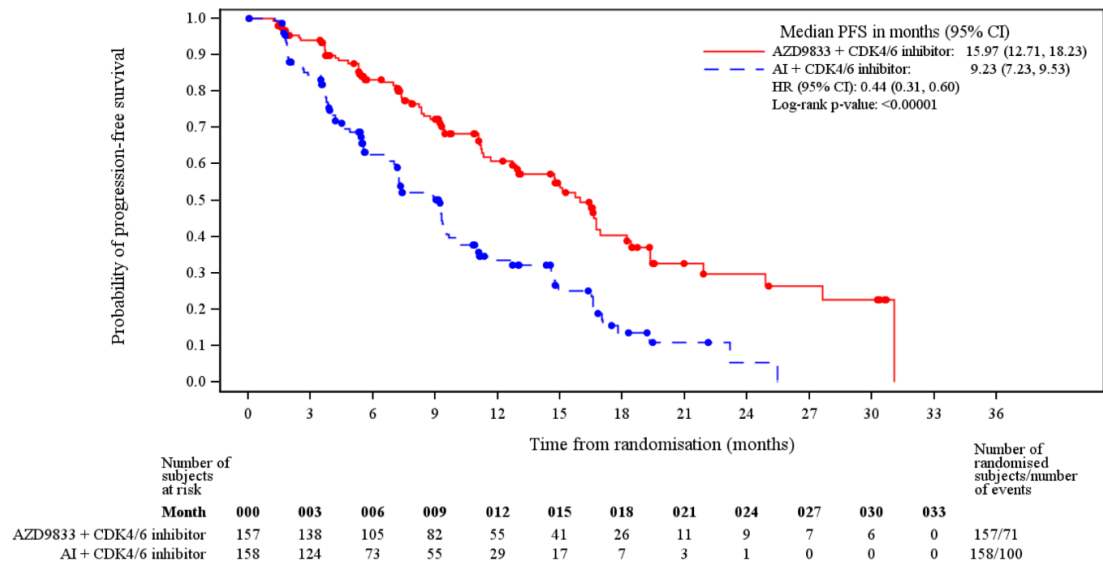
[b] The calculation is based on the Kaplan-Meier method.

[c] The CI for PFS is derived based on the Brookmeyer-Crowley method.

[d] The HR and its CI are estimated using a Cox proportional hazards model stratified by disease site, *ESR1m* status detectable at first vs subsequent ctDNA tests and time from initiation of AI + CDK4/6 inhibitor to randomisation.

A HR < 1 favours camizestrant + CDK4/6 inhibitor. The p-value is based on the stratified log-rank test, stratified by the same stratification factors used for the HR.

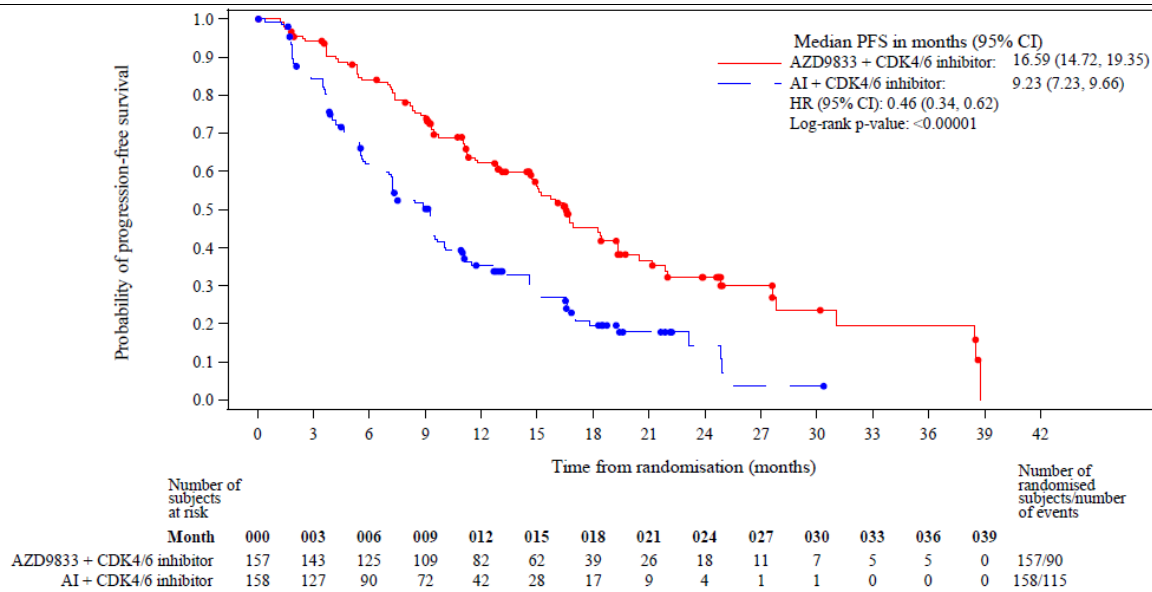
Figure 40: Progression-Free Survival based on Investigator Assessments according to RECIST v1.1, Kaplan-Meier Plot (FAS)– DCO1



Dots represents censored observations. 2-sided p-value.

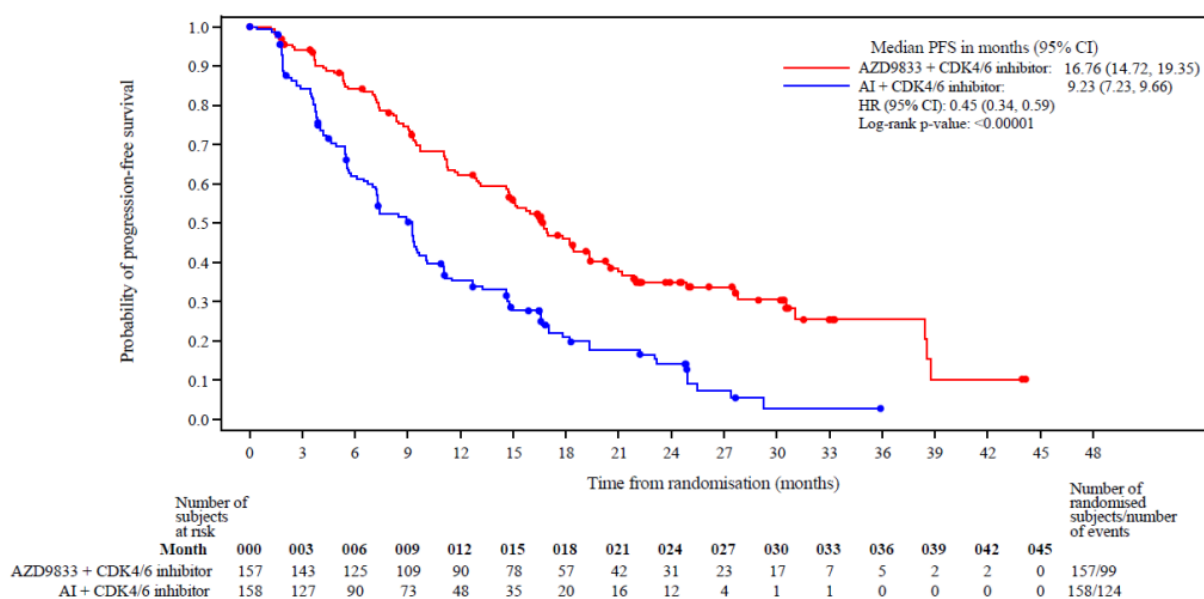
DCO1: 28 November 2024.

Figure 41: PFS Based on Investigator Assessments According to RECIST 1.1, Kaplan-Meier plot (FAS) – DCO2



Dots represent censored observations. 2-sided p-value.

Figure 42: Progression-free Survival Based on Investigator Assessments According to RECIST 1.1, Kaplan-Meier Plot (FAS) – DCO3



Dots represent censored observations. 2-sided p-value. The p-value is based on the stratified log-rank test, stratified by disease site, *ESR1m* status detectable at first vs subsequent ctDNA tests and time from initiation of AI + CDK4/6 inhibitor to randomisation.

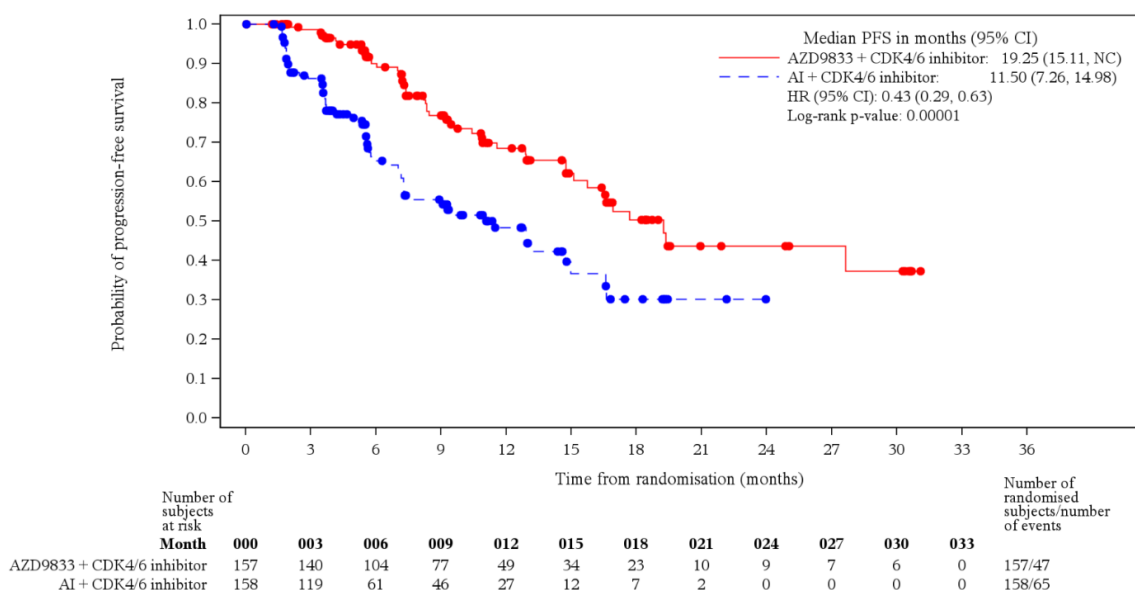
PFS by BICR

Table 48: Progression-free Survival (FAS) by BICR at DCO1, DCO2 and DCO3

	DCO1 28 November 2024		DCO2 30 June 2025		DCO3 02 January 2026	
	Camizestrant + CDK4/6i N = 157	AI + CDK4/6i N = 158	Camizestrant + CDK4/6i N = 157	AI + CDK4/6i N = 158	Camizestrant + CDK4/6i N = 157	AI + CDK4/6i N = 158
Based on BICR assessment						
Total number of patients with events, n (%)	47 (29.9)	65 (41.1)	60 (38.2)	75 (47.5)	60	76
Median, months (95% CI)	19.25 (15.11, NC)	11.50 (7.26, 14.98)	18.43 (15.74, NC)	12.68 (7.43, 14.72)	18.43 (15.74, NC)	12.68 (7.43, 14.69)
HR (95% CI); p-value ^a	0.43 (0.29, 0.63); nominal p=0.00001		0.46 (0.32, 0.66); nominal p= 0.00002		0.46 (0.32, 0.65) nominal p= 0.00001	

[e] The analysis is performed using BICR data. The p-value (nominal) is based on the stratified log-rank test, stratified by *ESR1m* status detectable at first vs subsequent ctDNA tests and time from initiation of AI + CDK4/6 inhibitor to randomisation.

Figure 43: Progression-free survival based on BICR assessments according to RECIST v1.1, Kaplan-Meier Plot (FAS)- DCO1



Dots represents censored observations. 2-sided p-value (nominal).

DCO1: 28 November 2024.

Concordance of investigator and central review of RECIST progression, including deaths

Table 49: Concordance of Investigator and Central Review of RECIST Progression Including Deaths, at the Same Timepoint (Full Analysis Set) -DCO2

	Statistic	Camizestrant + CDK4/6 inhibitor (N = 157)	AI + CDK4/6 inhibitor (N = 158)
RECIST progression declared by investigator and central review ^a	n (%)	56 (35.7)	67 (42.4)
No progression date difference between central review and investigator	n (%)	20 (12.7)	29 (18.4)
Progression date earlier by central review than by investigator	n (%)	27 (17.2)	31 (19.6)
Progression date earlier by investigator than by central review	n (%)	9 (5.7)	7 (4.4)
RECIST progression disagreements	n (%)	38 (24.2)	56 (35.4)
Investigator but not central review	n (%)	34 (21.7)	48 (30.4)
Central review but not investigator	n (%)	4 (2.5)	8 (5.1)
No progression by both	n (%)	63 (40.1)	35 (22.2)
EDR ^b	Rate	0.48	0.48
LDR ^c	Rate	0.42	0.41
EDR comparison between (camizestrant + CDK4/6 inhibitor) and (AI + CDK4/6 inhibitor)	Difference	0.00	
LDR comparison between (camizestrant + CDK4/6 inhibitor) and (AI + CDK4/6 inhibitor)	Difference	0.00	

[a] Progression events that do not occur within 26 weeks of the last evaluable assessment (or 25 weeks from randomisation) are censored. 1 day or more is considered a difference between the date of progression declared by central review and investigator.

[b] EDR is the frequency of investigator declared progressions before central review as a proportion of all investigator progressions.

[c] LDR is the frequency of investigator declared progressions after central review as a proportion of all discrepancies.

Secondary Endpoints

2. PFS2

PFS2 – DCO1, DCO2 (30 June 2025) and DCO3 (02 January 2026)

Table 50: Time from Randomisation to Second Progression or Death (PFS2) (FAS)

	DCO1 28 November 2024		DCO2 30 June 2025		DCO3 02 January 2026	
	Camizestrant + CDK4/6i N = 157	AI + CDK4/6i N = 158	Camizestrant + CDK4/6i N = 157	AI + CDK4/6i N = 158	Camizestrant + CDK4/6i N = 157	AI + CDK4/6i N = 158
Total number of patients with events, n (%)	38 (24.2)	47 (29.7)	62 (39.5)	71 (44.9)	80 (51.0)	90 (57.0)
Median, months (95% CI) ^{a, b}	22.31 (20.30, NC)	19.06 (16.82, 24.34)	25.72 (20.34, 28.85)	19.35 (17.77, 21.39)	25.72 (20.40, 30.32)	19.06 (16.82, 21.03)
HR	0.52		0.56		0.63	
2-sided p-value	p = 0.00376		p = 0.00153		p = 0.00373	
95% CI	0.33, 0.81		0.39, 0.80		0.46, 0.86	

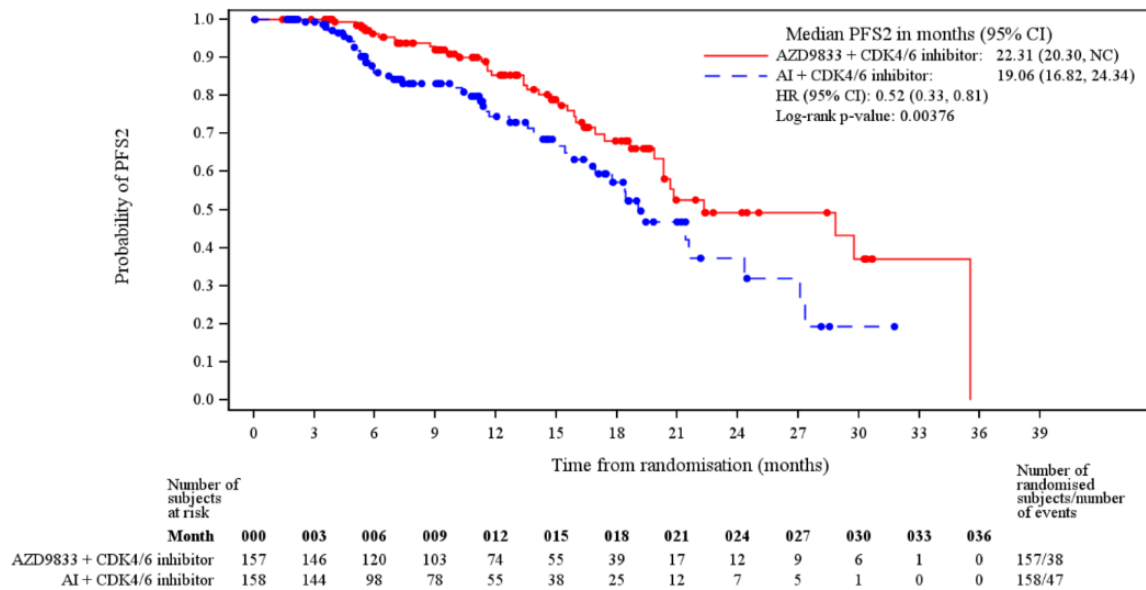
[a] The calculation is based on the Kaplan-Meier method.

[b] The CI for PFS2 is derived based on Brookmeyer-Crowley method.

[c] The HR and its CI are estimated using a stratified Cox proportional hazards model stratified by ESR1m detectable at first versus subsequent ctDNA tests and time from initiation of AI + CDK4/6 inhibitor to randomisation. The same patient may have more than one type of progression event. A HR < 1 favours camizestrant + CDK4/6 inhibitor. The p-value is based on the stratified log-rank test, stratified by disease site, ESR1m detectable at first vs subsequent ctDNA tests and time from initiation of AI + CDK4/6 inhibitor to randomisation.

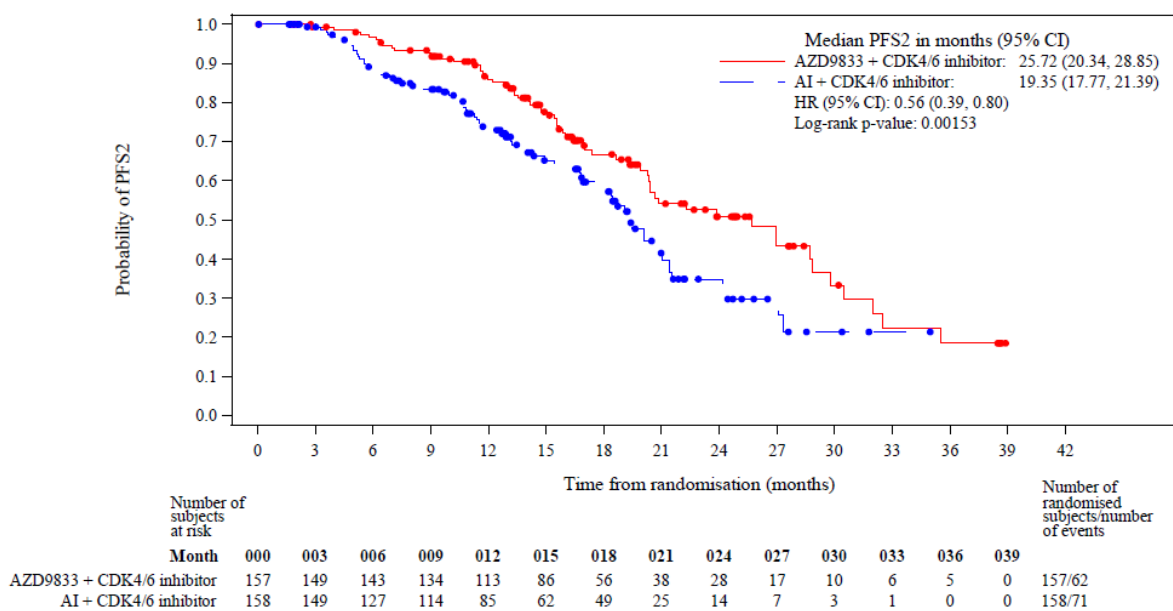
[d] The analysis is a repeat of the primary PFS2 analysis but the determination of second progression is assessed by investigator based on RECIST 1.1 (considering objective radiological progression only). A HR < 1 favours camizestrant + CDK4/6 inhibitor. The p-value is based on the stratified log-rank test, stratified by ESR1m status detectable at first vs subsequent ctDNA tests and time from initiation of AI + CDK4/6 inhibitor to randomisation.

Figure 44: Time from Randomisation to PFS2, Kaplan-Meier Plot (FAS)DCO1



Dots represent censored observations. The p-value is based on the stratified log-rank test, stratified by *ESR1m* detectable at first versus subsequent ctDNA tests and time from initiation of AI + CDK4/6 inhibitor to randomisation. At DCO1, PFS2 did not cross the MTP specified boundary of $p = 0.0001$ and is not statistically significant.

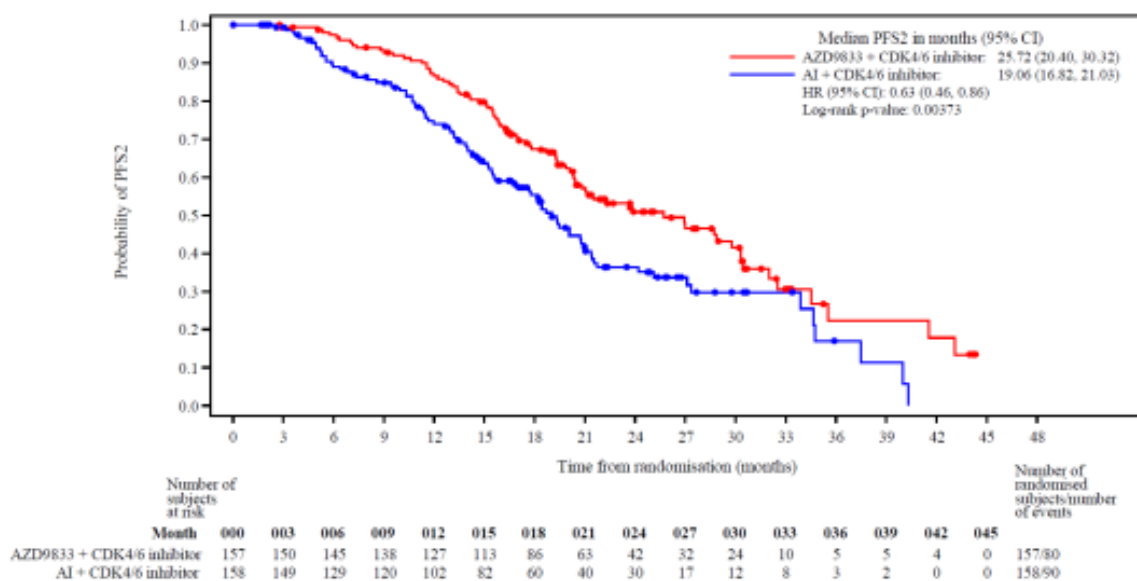
Figure 45: PFS2, KaplanMeier Plot (FAS) – DCO2



Dots represent censored observations. The p-value is based on the stratified log-rank test, stratified by disease site, by *ESR1m* detectable at first versus subsequent ctDNA tests and time from initiation of AI + CDK4/6 inhibitor to randomisation.

At DCO2, PFS2 did not cross the MTP specified boundary of $p = 0.0001$ and is not statistically significant.

Figure 46: Time from Randomisation to Second Progression or Death (PFS2), Kaplan-Meier Plot (FAS) – DCO3



Dots represent censored observations. The p-value is based on the stratified log-rank test, stratified by disease site, *ESR1m* detectable at first vs subsequent ctDNA tests and time from initiation of AI + CDK4/6 inhibitor to randomisation.

SERENA-6 protocol did not mandate RECIST assessments and defined an assessment interval of 8-12 weeks. Different types of progression contributed to the PFS2 analyses and only a subset of patients who received subsequent treatment were followed with RECIST methods (58/87 in the camizestrant arm and 60/117 in the control arm). Of note, only in 15 patients in each arm the assessment interval of 8-12 weeks was followed with RECIST methods.

Table 51: Time from Randomisation to second progression or death, at DCO3 (FAS)

		Statistic	Camizestrant + CDK4/6 inhibitor N = 157	AI + CDK4/6 inhibitor N = 158
Event	Any	n (%)	80 (51.0)	90 (57.0)
	Progression	n (%)	58 (36.9)	63 (39.9)
	Clinical progression	n (%)	17 (10.8)	15 (9.5)
	Objective radiological progression RECIST 1.1	n (%)	33 (21.0)	38 (24.1)
	Unequivocal radiological progression	n (%)	23 (14.6)	23 (14.6)
	Death without progression	n (%)	22 (14.0)	27 (17.1)
Censored observations	Any	n (%)	77 (49.0)	68 (43.0)

Table 52: Interval Characterization of the RECIST 1.1 Assessments for All Subjects Receiving Subsequent Therapy after First PD with at least 1 RECIST 1.1 PFS2 Assessment

	Camizestrant + CDK4/6i N=58	AI + CDK4/6i N=60
Time between PFS2 assessments [a]		
4-13 weeks, n(%)	37 (63.8)	37 (61.7)
8-12 weeks, n(%)	15 (25.9)	15 (25.0)

7-9 weeks, n(%)	7 (12.1)	12 (20.0)
-----------------	----------	-----------

[a] Number of subjects where all patient scans were within the window.

3. Overall survival (OS)

Table 53: Overall Survival (FAS) Updated Data – DCO1, DCO2 and DCO3

	DCO1 28 November 2024		DCO2 30 June 2025		DCO3 02 January 2026	
	Camizestrant + CDK4/6i	AI + CDK4/6i	Camizestrant + CDK4/6i	AI + CDK4/6i	Camizestrant + CDK4/6i N = 157	AI + CDK4/6i N = 158
	N = 157	N = 158	N = 157	N = 158	N = 157	N = 158
Event, Death n (%)	20 (12.7)	19 (12.0)	34 (21.7)	35 (22.2)	46 (29.3)	49 (31.0)
Censored observations						
Any n (%)	137 (87.3)	139 (88.0)	123 (78.3)	123 (77.8)	111 (70.7)	109 (69.0)
Still in survival follow-up ^a n (%)	125 (79.6)	119 (75.3)	112 (71.3)	104 (65.8)	100 (63.7)	88 (55.7)
Terminated prior to death ^b n (%)	12 (7.6)	20 (12.7)	11 (7.0)	19 (12.0)	11 (7.0)	21 (13.3)
Lost to follow-up n (%)	0	0	0	0	0	0
Withdrawn consent n (%)	10 (6.4)	15 (9.5)				
Other n (%)	2 (1.3)	4 (2.5)				
Screen failure n (%)	0	1 (0.6)	-	-	-	-
OS (months) ^{c, d}						
Median (95% CI)	37.49 (34.40, NC)	NC (NC, NC)	NC (33.28, NC)	40.21 (35.42, NC)	41.20 (35.48, NC)	40.21 (36.50, 43.27)
Comparison of treatment groups ^e						
HR (95% CI)	0.91 (0.48, 1.73)		0.92 (0.57, 1.48)		0.87 (0.57, 1.30); p = 0.48777 ^f	

	DCO1 28 November 2024		DCO2 30 June 2025		DCO3 02 January 2026	
	Camizestrant + CDK4/6i	AI + CDK4/6i	Camizestrant + CDK4/6i	AI + CDK4/6i	Camizestrant + CDK4/6i N = 157	AI + CDK4/6i N = 158
	N = 157	N = 158	N = 157	N = 158	N = 157	N = 158
OS rate ^{c, d}						
At 12 months (%) (95% CI)	92.3 (85.7, 96.0)	89.0 (81.9, 93.4)	94.0 (88.8, 96.9)	87.4 (80.9, 91.8)	94.1 (89.0,96.9)	87.4 (81.0, 91.8)
At 24 months (%) (95% CI)	78.0 (65.8, 86.3)	83.6 (74.5, 89.6)	76.7 (67.3, 83.7)	78.7 (70.3, 85.0)	76.6 (68.6, 82.9)	77.0 (69.1, 83.1)

[a] Includes subjects not known to have died on or before DCO date.

[b] Includes subjects with unknown survival status or subjects who were lost to follow-up.

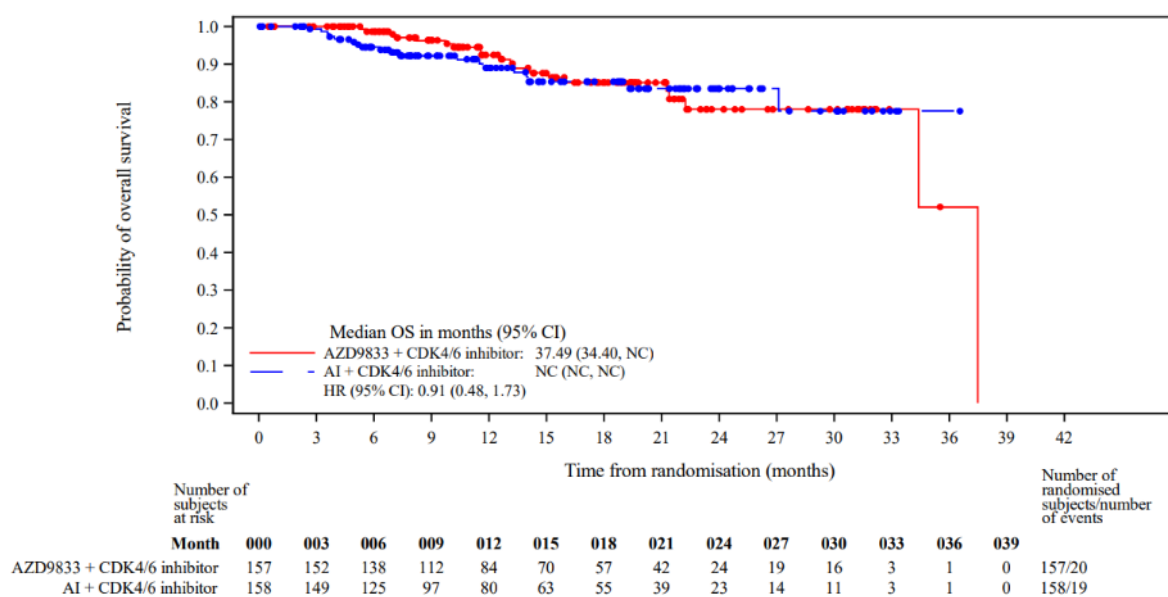
[c] The calculation is based on the Kaplan-Meier technique.

[d] The CI for OS is derived based on Brookmeyer-Crowley method.

[e] The hazard ratio and its CI are estimated using a Cox proportional hazards model, stratified by ESR1m status detectable at first versus subsequent ctDNA tests and time from initiation of CDK4/6 inhibitor + AI to randomisation. A hazard ratio < 1 favours AZD9833 + CDK4/6 inhibitor. The p-value is based on the stratified log-rank test, stratified by the same stratification factors used for the hazard ratio. As per the multiple testing procedure specified in the statistical analysis plan, since the PFS2 analysis is not significant, the p-value is not presented.

[f] The HR and its CI are estimated using a Cox proportional hazards model, stratified by ESR1m status detectable at first vs subsequent ctDNA tests and time from initiation of AI + CDK4/6 inhibitor to randomisation. A HR < 1 favours camizestrant + CDK4/6 inhibitor. The p-value is based on the stratified log-rank test, stratified by the same stratification factors used for the HR.

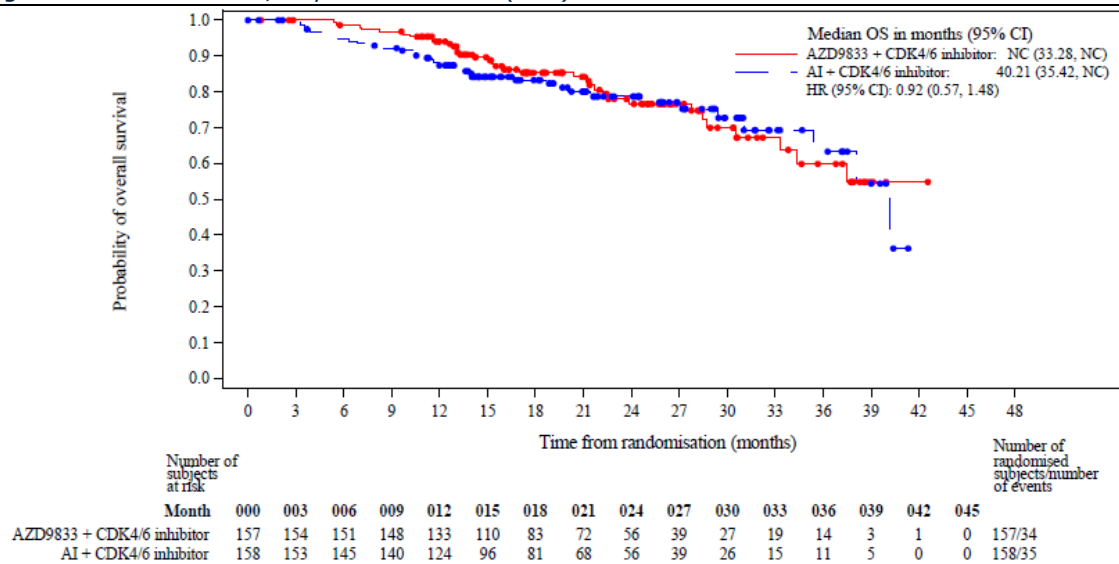
Figure 47: OS, Kaplan-Meier Plot (FAS), DCO1



Dots represent censored observations.

As per the MTP specified in the SAP, since the PFS2 analysis is not significant, the p-value is not presented.

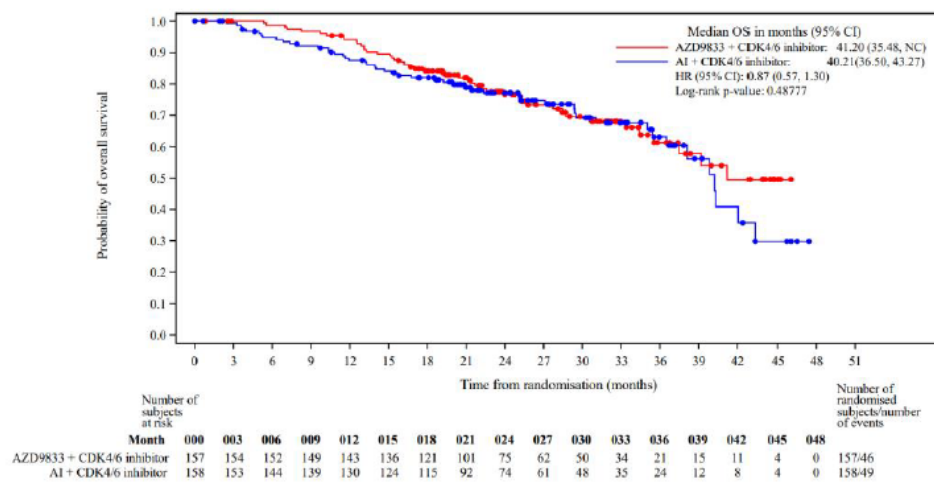
Figure 48: OS at DCO2, Kaplan-Meier Plot (FAS)



Dots represent censored observations.

As per the multiple testing procedure specified in the statistical analysis plan, since the PFS2 analysis is not significant, the p-value is not presented.

Figure 49: Overall survival at DCO3, Kaplan-Meier plot (FAS)



Dots represent censored observations.

The p-value is based on the stratified log-rank test, stratified by *ESR1m* status detectable at first vs subsequent ctDNA tests and time from initiation of CDK4/6 inhibitor + AI to randomisation.

DCO3: 02 January 2026

4. Other secondary endpoints

Time to First Subsequent Therapy (TFST), Time to Second Subsequent Therapy (TSST), and chemotherapy-free survival – updated at DCO2

Table 54: Summary of First Subsequent Anti-cancer Regimen - **summary of patients receiving subsequent therapies contributing to PFS2, presented by subsequent regimen and regimen sequence**

Subsequent regimen ^a	Camizestrant + CDK4/6i N = 87 n (%)	AI + CDK4/6i N = 117 n (%)
Cytotoxic therapy	30 (34.5)	29 (24.8)
Antibody-drug conjugate	2 (2.3)	7 (6.0)
DB1303		
Sacituzumab tirumotecan	1 (1.1)	1 (0.9)
Datopotomab deruxtecan		
Trastuzumab deruxtecan		
Chemotherapy	28 (32.2)	22 (18.8)
Pyrimidine based regimen	19 (21.8)	11 (9.4)
Taxanes	8 (9.2)	6 (5.1)
Other antineoplastic agent		
Anthracycline		
Endocrine-based therapy	43 (49.4)	69 (59.0)
Endocrine + targeted therapy	30 (34.5)	48 (41.0)
ET + mTORi	11 (12.6)	16 (13.7)
AI + CDK4/6i	7 (8.0)	4 (3.4)
Fulvestrant + CDK4/6i	6 (6.9)	8 (6.8)
Fulvestrant + PI3Ki or AKTi	4 (4.6)	13 (11.1)
Fulvestrant + CDK4/6i + KRASi		
Novel ET + PARPi	1 (1.1)	1 (0.9)
Fulvestrant + PI3Ki or AKTi + CDK4/6i		
Novel ET + CDK4/6i		
Endocrine monotherapy	13 (14.9)	21 (17.9)
Fulvestrant	8 (9.2)	11 (9.4)
AI		
Novel ET		
Tamoxifen		
Others ^b	0	3 (2.6)
Regimen sequences for patients who have multiple regimens	14 (16.1)	16 (13.7)
GROUP 1: Cytotoxic --> Cytotoxic	7 (8.0)	5 (4.3)
Taxanes → pyrimidine based regimen		
Pyrimidine based regimen → anthracycline		
Anthracycline → pyrimidine based regimen		
Pyrimidine based regimen → taxanes	1 (1.1)	1 (0.9)
Taxanes → anthracycline		

Subsequent regimen ^a	Camizestrant + CDK4/6i N = 87 n (%)	AI + CDK4/6i N = 117 n (%)
Taxanes → anthracycline → other antineoplastic agent → pyrimidine based regimen		
Taxanes → trastuzumab deruxtecan		
Pyrimidine based regimen → taxanes → trastuzumab deruxtecan		
Sacituzumab govitecan → anthracycline → other antineoplastic agent		
GROUP 2: ET based regimen	3 (3.4)	4 (3.4)
AI + CDK4/6i → fulvestrant		
ET + mTORi → fulvestrant		
Androgen receptor modulator → fulvestrant		
AI + CDK4/6i → novel ET		
ET + mTORi → novel ET		
Fulvestrant → ET + mTORi		
Fulvestrant → novel ET		
GROUP 3: ET based regimen --> Chemotherapy	3 (3.4)	5 (4.3)
ET + mTORi → pyrimidine based regimen → taxanes		
ET + mTORi → taxanes		
Fulvestrant + PI3Ki or AKTi → pyrimidine based regimen		
AI + CDK4/6i → novel ET → pyrimidine based regimen		
AI + CDK4/6i → taxanes → fulvestrant		
ET + mTORi → pyrimidine based regimen		
Fulvestrant → pyrimidine based regimen		
Fulvestrant + CDK4/6i → pyrimidine based regimen		
GROUP 4: Cytotoxic --> ET based regimen	1 (1.1)	2 (1.7)
Anthracycline → tamoxifen		
Trastuzumab deruxtecan → fulvestrant		
Trastuzumab deruxtecan → fulvestrant + PI3Ki or AKTi		

[a] Patients are only counted once in each regimen that contributes to PFS2. Those patients who received more than one regimen before PFS2 are described in the "regimen sequence" category reflecting the sequence.

[b] Others include poly (ADP-ribose) polymerase inhibitors/PARPi (olaparib, talazoparib), antiangiogenic (bevacizumab) or androgen receptor modulator (enobosarm). (Update according to DCO3 data).

Table 55: Other Secondary Efficacy Results (FAS) – TFST and TSST (DCO2)

	DCO1 28 November 2024		DCO2 30 June 2025	
	Camizestrant + CDK4/6i N = 157	AI + CDK4/6i N = 158	Camizestrant + CDK4/6i N = 157	AI + CDK4/6i N = 158
TFST				
Total number of patients with events, n (%)	65 (41.4)	92 (58.2)	88 (56.1)	117 (74.1)
Median, months (95% CI) b, c	16.85 (15.97, 20.14)	10.41 (7.62, 11.50)	16.89 (15.77, 20.37)	10.18 (7.72, 11.50)
HR (95% CI) ^d	0.44 (0.31, 0.61)		0.47 (0.35, 0.62)	
TSST				
Total number of patients with events, n (%)	45 (28.7)	52 (32.9)	60 (38.2)	77 (48.7)
Median, months (95% CI) b, c	21.52 (19.91, NC)	19.25 (14.98, 29.40)	24.64 (21.09, NC)	19.25 (16.10, 21.95)
HR (95% CI) ^d	0.62 (0.41, 0.93)		0.57 (0.40, 0.81)	

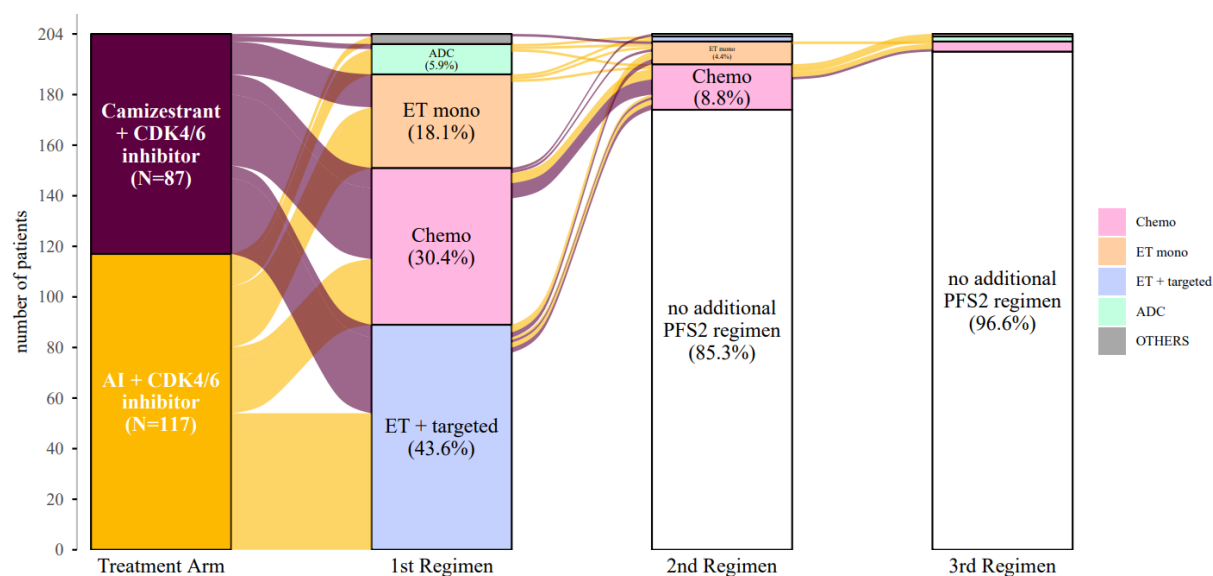
[a] Chemotherapy agents as well as ADCs were included to derive “chemotherapy-free survival” analysis.

[b] The calculation is based on the Kaplan-Meier method.

[c] The CI is derived based on Brookmeyer-Crowley method.

[d] The HR and its CI are estimated using a stratified Cox proportional hazards model stratified by disease site (only for TFST), *ESR1*m detectable at first versus subsequent ctDNA tests and time from initiation of AI + CDK4/6 inhibitor to randomisation. A HR < 1 favours camizestrant + CDK4/6 inhibitor.

Figure 50: Sankey Diagram: Representation of Subsequent Regimens Contributing to PFS2 Event by Treatment Arm (FAS)



Note: For one patient, a 4th regimen (details of the regimen are redacted to protect SERENA-6 data integrity (blinding)) is not displayed due to visualization constraints. All other regimens for all patients are included in the plot.

Chemotherapy-free survival – updated at DCO3 (02 January 2026)

Table 56: Chemotherapy-free Survival^a (FAS)

	DCO1 28 November 2024		DCO2 30 June 2025		DCO3 02 January 2026	
	Camizestrant + CDK4/6i N = 157	AI + CDK4/6i N = 158	Camizestrant + CDK4/6i N = 157	AI + CDK4/6i N = 158	Camizestrant + CDK4/6i N = 157	AI + CDK4/6i N = 158
Total number of patients with events, n (%)	46 (29.3)	50 (31.6)	66 (42.0)	76 (48.1)	85 (54.1)	98 (62.0)
Median, months ^b	21.59	23.62	22.74	18.69	22.57	18.66
95% CI ^c	19.91, NC	14.98, 29.40	20.27, 31.54	16.69, 24.71	19.29, 30.85	15.77, 22.14
HR (95% CI) ^d	0.75 (0.50, 1.12)		0.69 (0.49, 0.97)		0.64 (0.47, 0.87); nominal p = 0.00375	

[a] ADCs and chemotherapies were included in the chemotherapy-free survival analysis.

[b] The calculation is based on the Kaplan-Meier method.

[c] The CI is derived based on Brookmeyer-Crowley method.

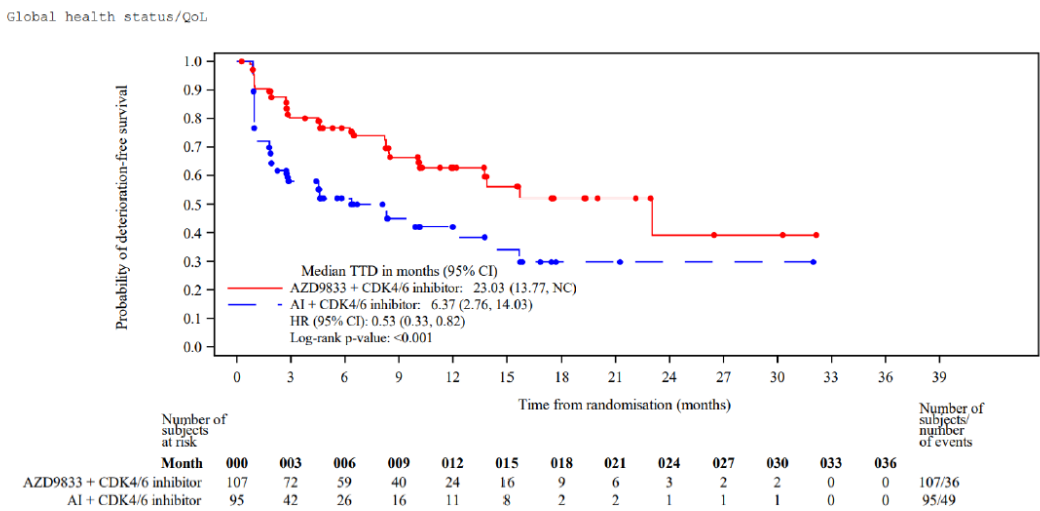
[d] The HR and its CI are estimated using a stratified Cox proportional hazards model stratified by disease site, *ESR1m* status detectable at first vs subsequent ctDNA tests and time from initiation of AI + CDK4/6 inhibitor to randomisation.

A HR < 1 favours camizestrant + CDK4/6 inhibitor.

With regards to subsequent therapies, more patients in the camizestrant arm received subsequent chemotherapy (45.6%) compared to patients in the AI arm (22.9%). There were no patients in the camizestrant arm who received an antibody-drug conjugate (ADC), while 12% did in the AI arm. Subsequent therapies also included endocrine-based therapy with CDK4/6i, mTORi, and ET monotherapy.

Clinical Outcomes Assessments/HRQoL

Figure 51: Kaplan-Meier Plot for Time to Deterioration (months) in GHS/QoL for EORTC QLQ-C30 (Full Analysis Set)



Dots represent censored observations. 2-sided p-value.

Subjects are included if they have a baseline score that would allow deterioration and at least one evaluable post-baseline assessment.

Source: see Figure 14.2.11.7.

- A reduction in the risk of deterioration in GHS/QoL was observed in the camizestrant arm compared to the AI (HR 0.53; 95%CI: 0.33, 0.82, with a prolonged median TTD [23.03 months in camizestrant arm vs 6.37 months in AI arm]).
- A reduction in the risk of deterioration in pain was observed in the camizestrant arm compared to the AI arm (HR 0.57; 95%CI: 0.37, 0.86, with a prolonged median TTD [16.56 months in camizestrant arm vs 6.47 months in AI arm]).
- A numerical reduction in the risk of deterioration in role functioning (HR 0.74; 95%CI: 0.49, 1.12), physical functioning (HR 0.77; 95%CI: 0.46, 1.30), breast symptoms (HR 0.60; 95%CI: 0.28, 1.25), and arm symptoms (HR 0.66; 95%CI: 0.32, 1.34) was observed in favour of the camizestrant arm compared to the AI arm.

Pre-defined and post-hoc subgroup analyses

PFS by investigator Assessment– subgroup analysis

Table 57:58 PFS Based on Investigator Assessment, Subgroup Analysis (FAS) – DCO1 and DCO2

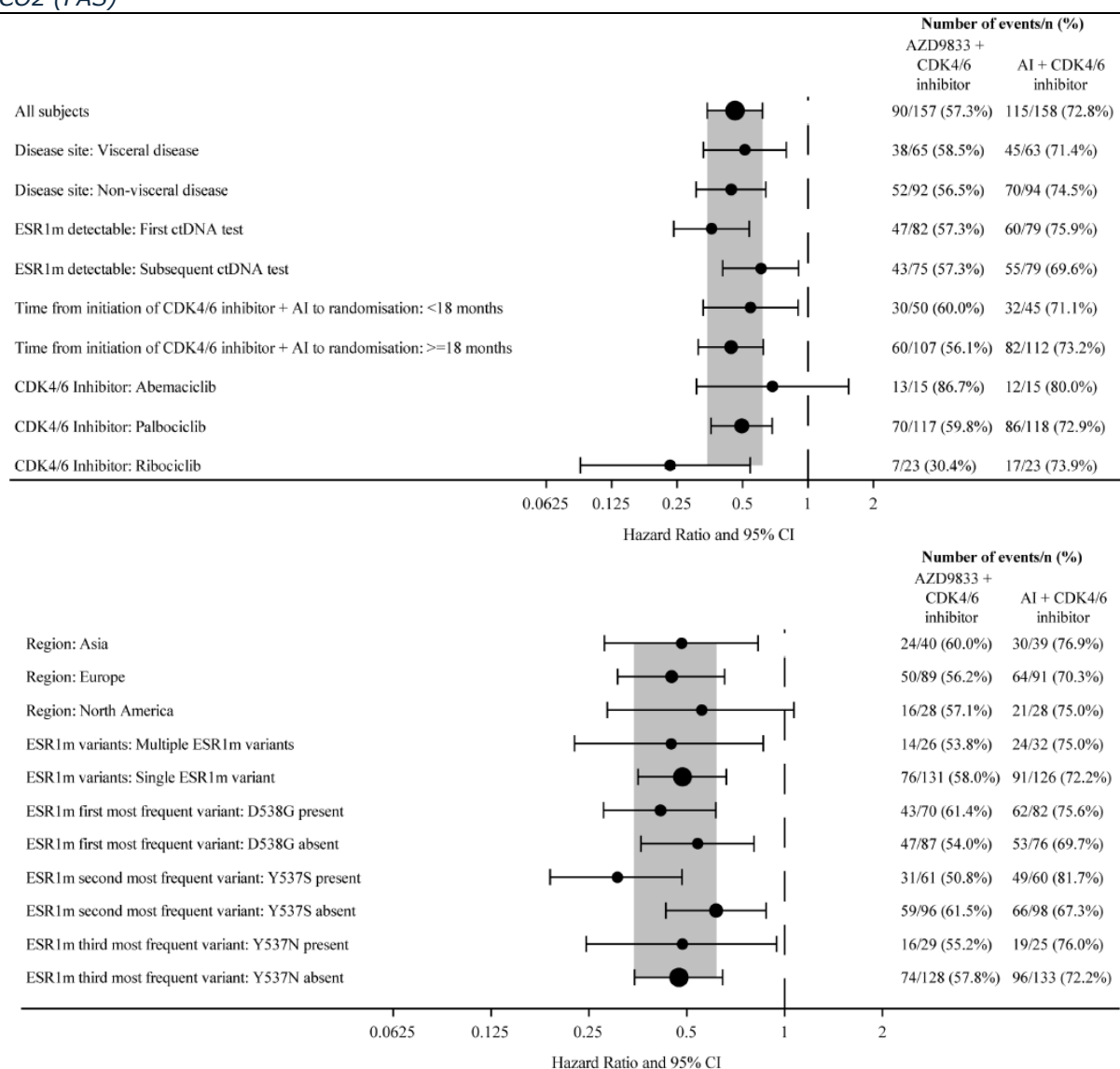
		DCO1 28 November 2024			DCO2 30 June 2025		
		Median PFS (months) (95% CI) ^a		HR (95% CI)	Median PFS (months) (95% CI) ^a		HR (95% CI)
		Camizestrant + CDK4/6i	AI + CDK4/6i		Camizestrant + CDK4/6i	AI + CDK4/6i	
All patients		15.97 (12.71, 18.23)	9.23 (7.23, 9.53)	0.44 (0.31, 0.60)	16.59 (14.72, 19.35)	9.23 (7.23, 9.66)	0.46 (0.34, 0.62)
Disease site							
Visceral disease	n/N (%)	32/65 (49.2)	37/64 (57.8)	0.57 (0.35, 0.92)	38/65 (58.5)	45/63 (71.4)	0.51 (0.33, 0.79)
		14.75 (11.07, 18.40)	9.46 (5.55, 14.92)		16.59 (11.30, 22.01)	9.23 (5.49, 13.24)	
Non-visceral disease	n/N (%)	39/92 (42.4)	63/92 (68.5)	0.38 (0.25, 0.56)	52/92 (56.5)	70/94 (74.5)	0.44 (0.31, 0.64)
		15.97 (11.66, 19.35)	7.39 (6.74, 9.36)		16.76 (14.72, 20.47)	8.90 (6.74, 9.66)	
ESR1m detectable							
First ctDNA test	n/N (%)	36/82 (43.9)	56/79 (70.9)	0.32 (0.20, 0.49)	47/82 (57.3)	60/79 (75.9)	0.36 (0.24, 0.54)
		15.74 (11.30, NC)	7.26 (4.67, 9.23)		16.43 (12.91, 21.88)	7.26 (4.67, 9.23)	
Subsequent ctDNA test	n/N (%)	35/75 (46.7)	44/79 (55.7)	0.64 (0.41, 0.99)	43/75 (57.3)	55/79 (69.6)	0.61 (0.41, 0.91)
		15.97 (11.24, 16.92)	10.12 (7.33, 14.78)		16.62 (11.83, 19.35)	10.02 (7.33, 14.59)	
Time from initiation of CDK4/6 inhibitor + AI to randomisation							
<18 months	n/N (%)	28/50 (56.0)	29/46 (63.0)	0.60 (0.35, 1.01)	30/50 (60.0)	32/45 (71.1)	0.55 (0.33, 0.90)

		DCO1 28 November 2024			DCO2 30 June 2025		
		Median PFS (months) (95% CI) ^a		HR (95% CI)	Median PFS (months) (95% CI) ^a		HR (95% CI)
		11.24 (8.34, 16.62)	7.26 (3.91, 9.53)		15.74 (9.46, 18.43)	7.26 (3.91, 9.46)	
≥ 18 months	n/N (%)	43/105 (41.0)	69/110 (62.7)	0.39 (0.26, 0.58)	60/107 (56.1)	82/112 (73.2)	0.44 (0.31, 0.62)
		16.76 (14.72, 21.88)	9.26 (7.16, 10.12)		16.76 (14.72, 22.01)	9.26 (7.23, 11.01)	
CDK4/6 inhibitor							
Palbociclib	n/N (%)	57/117 (48.7)	78/118 (66.1)	0.45 (0.32, 0.64)	70/117 (59.8)	86/118 (72.9)	0.50 (0.36, 0.68)
		16.59 (13.01, 19.35)	9.30 (7.26, 11.04)		16.76 (14.98, 19.35)	9.36 (7.39, 11.07)	
Ribociclib	n/N (%)	4/23 (17.4)	13/23 (56.5)	0.27 (0.08, 0.77)	7/23 (30.4)	17/23 (73.9)	0.23 (0.09, 0.54)
		NC (9.46, NC)	5.49 (3.84, 11.14)		14.62 (9.69, NC)	5.55 (4.01, 8.44)	
Abemaciclib	n/N (%)	10/15 (66.7)	9/15 (60.0)	0.63 (0.25, 1.59)	13/15 (86.7)	12/15 (80.0)	0.68 (0.31, 1.54)
		7.36 (3.68, 16.43)	4.21 (3.52, NC)		7.39 (3.68, 16.43)	4.67 (3.52, 14.62)	
ESR1m first most frequent variant							
D538G	n/N (%)	29/70 (41.4)	52/82 (63.4)	0.34 (0.21, 0.53)	43/70 (61.4)	62/82 (75.6)	0.41 (0.28, 0.61)
		16.76 (12.91, 24.87)	7.33 (6.74, 9.30)		16.76 (12.91, 19.35)	7.39 (6.74, 9.46)	
ESR1m second most frequent variant							
Y537S	n/N (%)	24/61 (39.3)	46/60 (76.7)	0.29 (0.17, 0.47)	31/61 (50.8)	49/60 (81.7)	0.31 (0.19, 0.48)
		16.92 (11.30, NC)	7.26 (4.34, 9.53)		18.23 (15.01, 31.08)	7.26 (4.67, 9.36)	

		DCO1 28 November 2024			DCO2 30 June 2025		
		Median PFS (months) (95% CI) ^a	HR (95% CI)		Median PFS (months) (95% CI) ^a	HR (95% CI)	
ESR1m third most frequent variant							
Y537N	n/N (%)	13/29 (44.8)	18/25 (72.0)	0.44 (0.21, 0.90)	16/29 (55.2)	19/25 (76.0)	0.48 (0.25, 0.94)
		16.62 (5.42, NC)	9.36 (3.71, 14.59)		16.62 (8.21, NC)	9.40 (3.71, 14.59)	

[a] Calculated using Kaplan-Meier method. For each subgroup level of a factor, the HR and 95% profile likelihood CIs are calculated from a Cox proportional hazards model with treatment, factor, and treatment by-factor as the only covariates. A HR < 1 favours camizestrant + CDK4/6 inhibitor. HRs and CIs are not produced for subgroups with < 20 events, except for CDK4/6 inhibitor subgroup. In such cases, only descriptive summaries are provided. Subjects without a progression event or who progress after 2 or more consecutive missed visits following the last assessment (or randomisation) are censored at the date of last evaluable assessment.

Figure 52 PFS Based on Investigator Assessment According to RECIST 1.1, Forest Plot by Subgroup, at DCO2 (FAS)



HR (camizestrant + CDK4/6 inhibitor: AI + CDK4/6 inhibitor) and 95% CI.

A HR < 1 implies a lower risk of progression on camizestrant + CDK4/6 inhibitor.

The overall analysis was performed using a stratified Cox proportional hazards model, stratified by disease site, *ESR1m* status detectable at first versus subsequent ctDNA tests, and time from initiation of CDK4/6 inhibitor + AI to randomisation. Profile likelihood methods are used to calculate CIs. Estimates for all subgroup categories are from a Cox proportional hazards model with treatment, factor, and treatment-by-factor as the only covariates. Size of the circle is proportional to the number of events. Grey band represents the 95% CI for the overall (all subjects) HR.

DCO2: 30 June 2025

Pre-defined and post-hoc sensitivity analyses

Not applicable.

Ancillary analyses

Please refer to the above section on predefined and ad hoc subgroup analysis.

5.3.3. Clinical studies in special populations

Table 59: Clinical studies in special populations

	Controlled (randomised) trials (SERENA-2 and SERENA-6)	Non-controlled (non-randomised) trials (SERENA-1, China PK and Japan PK Studies)
Renal impairment ^a patients (Subjects number/Total number)	(12/384)	(0/151)
Hepatic impairment ^b patients (Subjects number/Total number)	(1/384)	(0/151)
Paediatric patients < 18 years (Subjects number/Total number)	(0/384)	(0/151)
Age 65-74 (Subjects/total number)	(116/384)	(31/151)
Age 75-84 (Subjects/total number)	(25/384)	(14/151)
Age 85+ (Subjects/total number)	(2/384)	(2/151)

[a] Renal impairment was defined as having an eGFR value of 30-44 (Stage 3b), 15-29 (Stage 4), < 15 (Stage 5). The eGFR value was derived by applying the CKD-EPI Equation (2021).

[b] Hepatic impairment (moderate or severe) was defined as the following: total bilirubin > 1.5 x upper limit of normal with any aspartate aminotransferase value (NCI classification).

The following DCOs were used for each study: SERENA-6 (30 June 2025); SERENA-2 (09 December 2024); SERENA-1 (Parts A, B, C, and D; 09 September 2021); SERENA-1 (Parts G, H, K, and L; 16 September 2024); Study 7 China PK (07 September 2023); and Study 6 Japan PK (15 June 2022).

5.3.4. *In vitro* biomarker test for patient selection for efficacy

Background to diagnostic testing on SERENA-6

Guardant360 CDx (Guardant Health, Redwood City, CA, USA) was the diagnostic test used in the study. In STEP 1 of the SERENA-6 study, blood samples for ctDNA testing were taken every 2 to 3 months during routine clinical visits and screened for *ESR1m*, with ctDNA analysis centrally using Guardant360 CDx. If at any point during STEP 1 *ESR1m* was detected, and there was no evidence of clinical or radiographic disease progression, the patient was then eligible to move into the STEP 2 screening of the study.

Guardant360 CDx is a qualitative next generation sequencing-based *in vitro* diagnostic device that uses targeted high throughput hybridization-based capture technology for detection of single nucleotide variants (SNVs), insertions and deletions (indels) in 55 genes, copy number amplifications (CNAs) in two (2) genes, and fusions in four (4) genes. Guardant360 CDx utilises circulating cell-free DNA (cfDNA) from plasma of peripheral whole blood collected in Streck Cell-Free DNA Blood Collection Tubes (BCTs).

Scientific Rationale

Mutations in *ESR1* (*ESR1m*), the gene encoding ERα, are a frequent cause of acquired resistance to AI plus a CDK4/6 inhibitor (Bhave et al 2024, Bidard et al 2022, Cardoso et al 2023, Chaudhary et al 2024), which is considered the 1L standard of care therapy for ER-positive HER2-negative advanced breast cancer (ABC). In the pivotal SERENA-6 trial, an *ESR1m* test is considered positive, if one or more of the 11 most prevalent *ESR1m* (E380Q, V422del, S463P, L536H, L536P, L563R, Y537C, Y537D,

Y537N, Y537S, D538G) that occur in HR-positive mBC) are detected. These mutations are all gain-of function mutations that occur in the LBD and have been shown to confer constitutive ER activity in the absence of estradiol.

Camizestrant was previously shown to bind ER α containing several of the more common *ESR1*m (potency for mutant ER α was within 10-fold potency of wild-type ER α) (2.6.2). To expand this analysis and to confirm that camizestrant could inhibit the proliferation of *ESR1*m expressing cells, CRISPR-cas9 mediated genome editing was used to generate a comprehensive panel of clonal, isogenic MCF7 cells expressing 10 of the 11 most common *ESR1*m (D538G, Y537S, E380Q, Y537N/C/D, L536H/P/R and S463P). The clones generated were either heterozygous or homozygous for each mutation. Due to technical reasons, clones expressing the V422del mutation were unable to be generated using this method.

Cells expressing *ESR1*m showed enhanced growth in the absence of E2 (17 β -estradiol) compared to *ESR1*wt cells. The extent of E2-independent growth varied between mutations, as reported previously and also across the different clones (see Pharmacology Report ONC9833-013).

Parental MCF7 cells (MCF7 Luc or MCF7 PE) or MCF7 cells harbouring *ESR1*m were treated with camizestrant for 6 days to determine the anti-proliferative activity of camizestrant against a broad range of *ESR1*m. Camizestrant inhibited the proliferation of parental MCF7 cells with a mean IC₅₀ of 0.08 nM. The potency of camizestrant in MCF7 cells expressing 10 different *ESR1*m ranged from 0.15 to 8.71 nM.

Analytical validation aspects of the biomarker assay

Guardant360 CDx is performed by the Guardant Health Clinical Laboratory. Guardant360 CDx is composed of the following major processes:

- Whole Blood Collection and Shipping
- Plasma Isolation and cfDNA Extraction
- Library Preparation and Enrichment
- DNA Sequencing
- Data Analysis and Reporting

Whole blood is collected in Streck Cell-Free DNA BCTs, which stabilise cfDNA and nucleated blood cells for shipping.

Performance characteristics are detailed in the Guardant360 CDx Technical information, with summary performance characteristics for *ESR1*m below:

- Analytical Accuracy/Concordance with MassARRAY Comparator Method: PPA: 98%, NPA: 85%
- Limit of Blank (LoB): 0% false positive rate
- Limit of Detection (LoD): 1.1% MAF (5ng input), 0.3% MAF (30ng input)
- Precision: PPA: 95.2% with 5ng input.

The performance characteristics show the robustness of Guardant360 CDx for detecting *ESR1*m.

Clinical validation aspects

Guardant Health has received EU IVDR Certification for the Guardant360 CDx Liquid Biopsy for tumour mutation profiling across all solid cancers. This certification allows reporting of all *ESR1*m variants that are included in the biomarker definition for SERENA-6.

Additionally, clinical validation of the Guardant360 assay was demonstrated in the SERENA-6 study. Randomised patients had detectable *ESR1*m with ctDNA analysis centrally using Guardant360 CDx. Please refer to the section on clinical efficacy for details.

Table 60: Detection rates of *ESR1* variants in randomised patients (Full analysis set)

<i>ESR1</i> variants	AZD9833 + CDK4/6 inhibitor [N=157] N (%) [a]	AI + CDK4/6 inhibitor [N=158] N (%) [a]	Total [N=315] N (%) [a]
D538G	70 (44.6)	82 (51.9)	152 (48.3)
Y537S	61 (38.9)	60 (38.0)	121 (38.4)
Y537N	29 (18.5)	25 (15.8)	54 (17.1)
E380Q	15 (9.6)	18 (11.4)	33 (10.5)
Y537C	8 (5.1)	7 (4.4)	15 (4.8)
L536H	3 (1.9)	7 (4.4)	10 (3.2)
Y536P	3 (1.9)	6 (3.8)	9 (2.9)
L536R	2 (1.3)	2 (1.3)	4 (1.3)
V422del			3 (1.0)
S463P			1 (0.3)
Y537D	0	0	0

Source: Table 14.2.21.4. Percentages add up to greater than 100% because subjects can have multiple variants of *ESR1* mutation. Qualifying *ESR1* variants are: D538G; E380Q; L536H; L536P; L536R; S463P; V244del; Y537C; Y537D; Y537N; Y537S. Table is sorted by prevalence in the Total column.

Table 61: Number of *ESR1* variants detected in randomised patients (Full analysis set)

Number of <i>ESR1</i> variants detected	AZD9833 + CDK4/6 inhibitor (N=157) n (%)	AI + CDK4/6 inhibitor (N=158) n (%)	Total (N=315) n (%)
1	131	126	257 (81.6)
2	16	20	36 (11.4)
3	9	8	17 (5.4)
4	1	2	3 (1.0)
5			2 (0.6)

Source: Table 14.2.21.5. Qualifying *ESR1* variants are: D538G; E380Q; L536H; L536P; L536R; S463P; V244del; Y537C; Y537D; Y537N; Y537S. The maximum number of *ESR1* variants detected in any patient was 5.

Table 62: Frequency of *ESR1m*-detected Tests at Each Sequential Test Visit (All Screened Patients)

Sequential Test Visit	Total tests taken	Tests with <i>ESR1m</i> detected	95% CI
1	3209	285 (8.9%)	(7.9%, 9.9%)
2	2334	86 (3.7%)	(3.0%, 4.5%)
3	1717	55 (3.2%)	(2.4%, 4.1%)
4	1258	28 (2.2%)	(1.5%, 3.2%)
5	1015	33 (3.3%)	(2.2%, 4.5%)
6	802	24 (3.0%)	(1.9%, 4.4%)
7	606	14 (2.3%)	(1.3%, 3.8%)

Sequential Test Visit	Total tests taken	Tests with <i>ESR1</i> m detected	95% CI
8	464	12 (2.6%)	(1.3%, 4.5%)
9	328	5 (1.5%)	(0.5%, 3.5%)
10	214	3 (1.4%)	(0.3%, 4.0%)
11	131	2 (1.5%)	(0.2%, 5.4%)
12	75	0 (0.0%)	NC
13	41	0 (0.0%)	NC
14	22	1 (4.5%)	(0.1%, 22.8%)
15	14	0 (0.0%)	NC
16	10	0 (0.0%)	NC
17	8	0 (0.0%)	NC
18	7	0 (0.0%)	NC
19	2	0 (0.0%)	NC

Justification for the definition of the selected population

The cut-off is determined by the analytical sensitivity of the assay platform. The cut-off metrics is described in the Technical Information (see above) with ≥ 2 DNA molecules: $\geq 0.001\%$ MAF.

There is a scientific rationale for *ESR1*-mutation testing based on the mechanism of action for camizestrant and what is known for a comparable oral SERD Orserdu (elacestrant). It was approved in the EU under the IVDR regulation (IVDR 2017/746) as a companion diagnostic for elacestrant to aid in selection of patients with breast cancer with *ESR1* missense mutations in May 2024.

In the pivotal study SERENA-6, 3256 patients were tested with Guardant360 CDx, of which 548 patients had a detectable *ESR1*m. 12906 samples were tested, with 649 (5.0%) failing to give a valid result. Out of the 2885 patients eligible for STEP 1, 2861 patients were tested with Guardant360 CDx. Of those: 521 patients (18.2%; 521/2861) had detectable *ESR1*m; 266 patients had detectable *ESR1*m on the first test, reflecting a prevalence of 9.3% (266/2861) from the first test. D538G was the most prevalent *ESR1* variant (48.3% of randomised patients), and the majority of patients (81.6%) had a single *ESR1* variant.

The clinical data support the utility of using the Guardant360 CDx in selecting patients with a detectable *ESR1*-mutation.

5.3.5. Supportive studies

SERENA-1 Study

SERENA-1 is a first-in-human (FIH) study evaluating camizestrant as a monotherapy (Parts A and B) and in combination (Parts C through L) in pre- or post-menopausal women with advanced ER-positive, HER2-negative breast cancer. An overview of the SERENA-1 study is presented in Table 20. SERENA-1 enrolled patients with metastatic or locoregionally recurrent disease refractory or intolerant to existing standard therapies. Majority of patients had received prior CDK4/6 inhibitor.

Camizestrant (75 mg) in combination with a CDK4/6 inhibitor

Patients received a median of 2 to 3 prior regimens in the advanced setting, including 0 to 2 prior chemotherapy regimens and a median of 1 to 2 ETs. Patients treated with camizestrant (75 mg) in combination with palbociclib, abemaciclib, and ribociclib were generally heavily pre-treated (Table 64).

Despite extensive prior lines of therapy, camizestrant in combination with a CDK4/6 inhibitor exhibited clinical activity in patients with ER-positive ABC.

The clinical benefit rate (CBR) at 24 weeks, median PFS, and objective response rate (ORR) in patients with measurable disease at baseline, are summarised in Table 64. See also 5.3.1.

Table 63: Summary of SERENA-1 Patient Demographics, Baseline Characteristics, and Efficacy Data

	Number (%) of patients			
	Camizestrant 75 mg + palbociclib Parts C + D N = 25	Camizestrant 75 mg + abemaciclib Parts G + H N = 24	Camizestrant 75 mg + ribociclib 400 mg Parts K + L N = 28	Camizestrant 75 mg + ribociclib 600 mg Parts K + L N = 32
Median age, years (range)	58.0 (47 – 77)	61.0 (39 – 89)	58.0 (31 – 81)	55.0 (37 – 80)
Post-menopausal, n (%)	25 (100)	22 (91.7)	24 (85.7)	27 (84.4)
ECOG category 0, n (%)	10 (40.0)	11 (45.8)	14 (50.0)	17 (53.1)
Measurable disease, n (%)	17 (68.0)	19 (79.2)	18 (64.3)	24 (75.0)
Visceral disease, n (%) ^a	16 (64.0)	16 (66.7)	20 (71.4)	22 (68.8)
Number of prior hormonal regimens, median (range)	2.0 (0 – 4)	2.0 (1 – 5)	1.5 (0 – 4)	1.5 (0 – 5)
Number of prior cytotoxic chemotherapy regimens, median (range)	0 (0 – 2)	0 (0 – 2)	0 (0 – 1)	1.0 (0 – 2)
Prior chemotherapy, n (%)	12 (48.0)	11 (45.8)	7 (25.0)	17 (53.1)
Prior treatment with fulvestrant, n (%)	17 (68.0)	14 (58.3)	19 (67.9)	21 (65.6)
Prior treatment with CDK4/6 inhibitor, n (%) ^b	20 (80.0)	19 (79.2)	26 (92.9)	32 (100)
<i>ESR1</i> m detected at baseline, n (%)				
Detected	11 (44.0)	11 (45.8)	16 (57.1)	12 (37.5)
Not detected	14 (56.0)	12 (50.0)	12 (42.9)	20 (62.5)
Unknown	0	1 (4.2)	0	0
CBR at 24 weeks ^c	N = 25	N = 24	N = 27	N = 32
Number of patients with CBR at 24 weeks, n (%) ^d	7 (28.0)	15 (62.5)	15 (55.6)	16 (50.0)
80% CI ^e	16.32, 42.58	47.36, 75.94	41.51, 68.94	37.41, 62.59
PFS	N = 25	N = 24	N = 28	N = 32
Total number of events, n (%) ^f	18 (72.0)	17 (70.8)	14 (50.0)	17 (53.1)
Median, months (95% CI) ^g	3.71 (1.81, 5.65)	13.80 (5.32, 30.36)	8.15 (1.87, NC)	8.08 (1.97, NC)
ORR in patients with measurable disease at baseline ^d	N = 17	N = 19	N = 18	N = 24
Number of patients with objective response, n (%)	1 (5.9)	7 (36.8)	3 (16.7)	3 (12.5)
95% CI ^e	0.15, 28.69	16.29, 61.64	3.58, 41.42	2.66, 32.36

a. Visceral disease included patients with disease site at baseline of adrenal, brain/central nervous system, oesophagus, liver, lung/respiratory, pancreas, spleen, cardiovascular, gall bladder, gastrointestinal, genitourinary, and identified terms under other metastatic sites.

b. Patients may have received more than one prior CDK4/6 inhibitor.

- c. Percentages were calculated from the number of patients in the evaluable for response set. Percentage of patients who had a best objective response of complete response or partial response in the first 25 weeks (which allowed for a late assessment within the assessment window) or who had SD for at least 23 weeks after start of treatment (which allowed for an early assessment within the assessment window). Evaluable for response set: All dosed patients with a non-missing RECIST v1.1 assessment at baseline (whether measurable or non-measurable) (as per SAP Edition 4).
- d. Responses excluded unconfirmed responses.
- e. CIs calculated using the exact Clopper-Pearson method.
- f. Progression events that occurred after the DCO date of the statistical analysis were censored at the time of their last evaluable RECIST v1.1 assessment and therefore excluded in the number of events.
- g. Calculated using Kaplan-Meier method. CI was calculated using the exact Clopper-Pearson method.

SERENA-2 Study

SERENA-2 is an open-label, randomised Phase II study evaluating the efficacy and safety of camizestrant (75, 150, and 300 mg, oral QD) as a monotherapy in comparison with fulvestrant administered according to its label in post-menopausal women with advanced ER-positive, HER2-negative breast cancer. Prior chemotherapy and/or ET was permitted, albeit with no more than one line of chemotherapy and one line of ET for advanced disease. Prior treatment with CDK4/6-inhibitor was permitted.

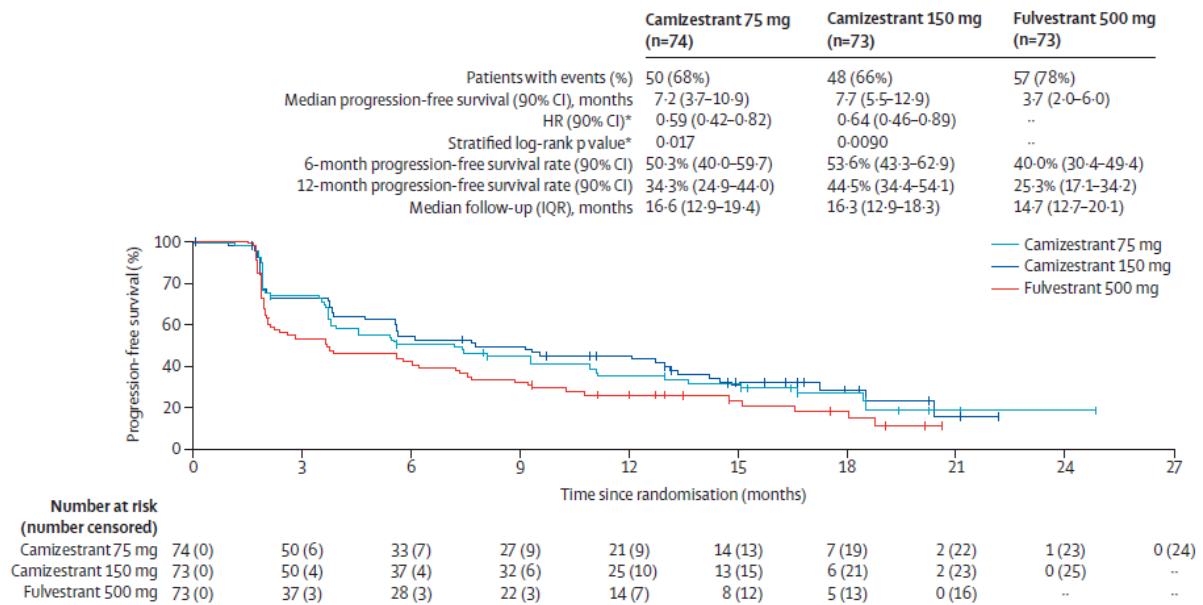
In total, 240 patients were randomised and received treatment. The age distribution was as expected and well balanced across treatment arms with approximately half of the patients (118 [49.2%] patients) in the ≥ 50 to < 65 years old age group. The majority of patients were White (226 [94.2%] patients). By design, half of the patients (119 [49.6%] patients) reported prior use of CDK4/6 inhibitors. The majority of these ABC patients had metastatic disease (224 [93.3%] patients). At least 1 *ESR1*m was detectable in 88 (36.7%) patients at study entry, with a slightly higher proportion observed in the fulvestrant treatment arm (35/73 [47.9%] patients).

During study conduct, review of the SERENA-1 Phase I camizestrant monotherapy data revealed no increment in efficacy with increases of dose above 150 mg, in terms of ORR, CBR at 24 weeks, and PFS. Based on this information, the Sponsor closed further recruitment to the 300 mg arm of SERENA-2 on 21 December 2020. Data accrued from the camizestrant 300 mg treatment arm were summarised and reported in the CSR as appropriate. See also 5.3.1.

Primary Endpoint - PFS

At the primary analysis (DCO date of 30 August 2022), camizestrant at both 75 mg and 150 mg showed a statistically significant and clinically meaningful improvement in PFS over fulvestrant (HR = 0.59; 90% CI: 0.42, 0.82; $p = 0.0167$ for the 75 mg dose arm and HR = 0.64; 90% CI: 0.46, 0.89; $p = 0.0090$ for the 150 mg dose arm) (Table 65). Median PFS by investigator assessment was 7.2 months (90% CI: 3.7, 10.9) in the camizestrant 75 mg arm, 7.7 months (90% CI: 5.5, 12.9) in the camizestrant 150 mg arm, and 3.7 months (90% CI: 2.0, 6.0) in the fulvestrant arm (Table 65).

Figure 53: PFS, Kaplan-Meier Plot (FAS)

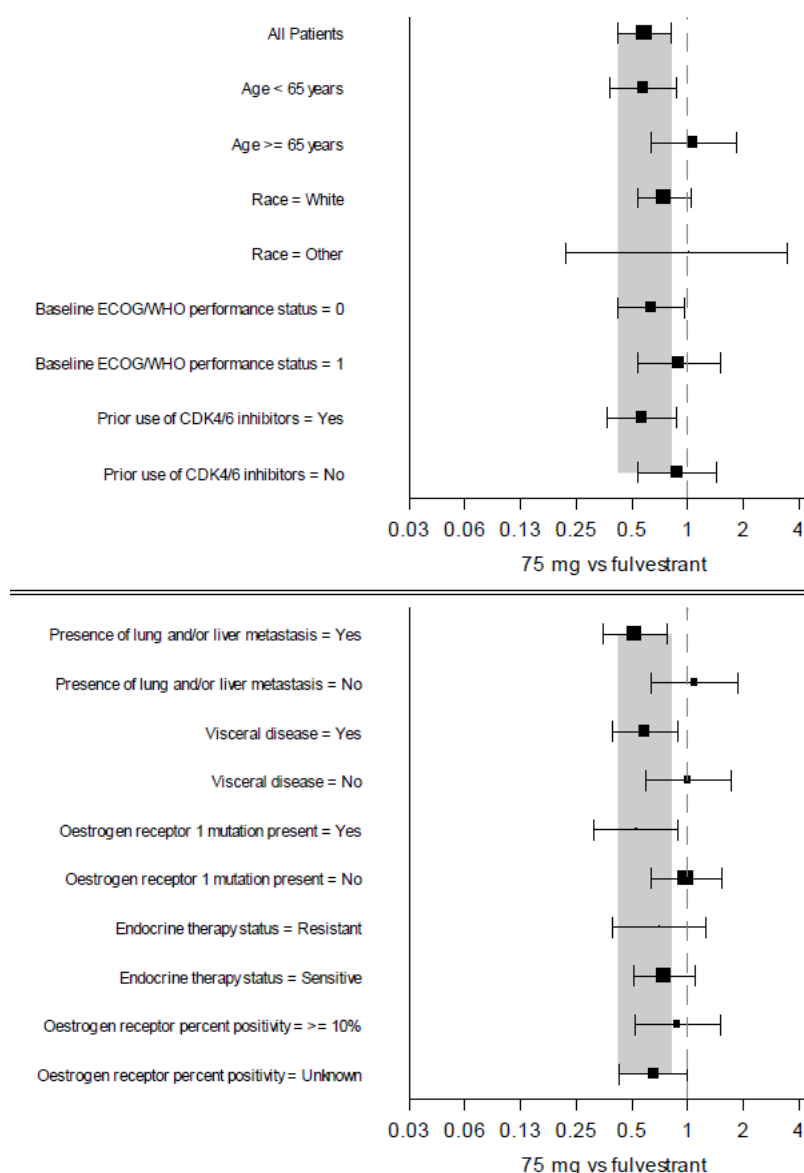


Vertical tick marks indicate a censored observation.

* HRs are based on a stratified Cox proportional hazards model, and the p-value is based on the stratified log-rank test. The stratification factors were previous use of CDK4/6 inhibitors and the presence of liver and/or lung metastases. Comparisons were just for the 75 mg and 150 mg doses of camizestrant versus fulvestrant 500 mg only; no comparisons were made between different camizestrant doses.

Subgroup Analyses

Figure 54: PFS, Forest Plot (FAS)



Squares present HR and lines 90% CI. Size of the square is proportional to the number of events.

A HR < 1 implies a lower risk of progression for camizestrant against fulvestrant.

Progression is determined by investigator assessment.

RECIST v1.1. Any subgroup containing less than 10 patients has been suppressed and is not presented in the output.

The secondary endpoints results (ORR, CBR at 24 weeks and OS) are presented in Table 65.

Table 64: Summary of SERENA-2 Efficacy Data

	Camizestrant 75 mg	Camizestrant 150 mg	Fulvestrant 500 mg
Primary endpoint			
PFS	N = 74	N = 73	N = 73
Total events ^a , n (%)	50 (67.6)	48 (65.8)	57 (78.1)
Median, months (90% CI) ^b	7.2 (3.7, 10.9)	7.7 (5.5, 12.9)	3.7 (2.0, 6.0)
HR (90% CI) ^{c, d}	0.59 (0.42, 0.82)	0.64 (0.46, 0.89)	
2-sided p-value ^{e, d}	0.0167 ^f	0.0090 ^f	
Secondary endpoints			
ORR	N = 70	N = 65	N = 68

	Camizestrant 75 mg	Camizestrant 150 mg	Fulvestrant 500 mg
Number (%) of patients with response ^g	11 (15.7)	11 (16.9)	8 (11.8)
Adjusted response rate, %	15.7	17.1	11.6
Odds ratio (90% CI)	1.42 (0.63, 3.31)	1.57 (0.69, 3.67)	
2-sided nominal p-value	0.4828	0.3691	
CBR at 24 weeks	N = 74	N = 73	N = 73
Number (%) of patients with disease control at 24 weeks ^g	35 (47.3)	36 (49.3)	28 (38.4)
Adjusted disease control rate, %	48.8	51.0	39.1
Odds ratio (90% CI)	1.48 (0.84, 2.64)	1.62 (0.91, 2.89)	
2-sided nominal p-value	0.2554	0.1658	
OS	N = 74	N = 73	N = 73
Deaths, n (%)	41 (55.4)	39 (53.4)	41 (56.2)
Median, months (90% CI) ^b	24.5 (18.6, 30.8)	33.5 (27.5, 36.8)	23.7 (19.6, 29.0)
HR (90% CI) ^c	0.90 (0.62, 1.29)	0.73 (0.50, 1.06)	
2-sided nominal p-value ^e	0.5591	0.1391	

- a. Only includes progression events that occur within 18 weeks of the last evaluable assessment.
- b. Calculated using the Kaplan-Meier method. CI for median PFS or OS derived based on Brookmeyer-Crowley method.
- c. The analysis was performed using a stratified Cox proportional hazards model (with ties = Efron and prior use of CDK4/6 inhibitors and presence of lung and/or liver metastasis as stratification factors) for the calculation of HR while the CIs were calculated using a profile likelihood approach. A HR < 1 favours camizestrant to be associated with a longer PFS or OS than fulvestrant.
- d. Comparisons of camizestrant against fulvestrant 500 mg only; no comparisons between different camizestrant doses presented.
- e. The analysis was performed using a stratified log-rank test adjusting for the prior use of CDK4/6 inhibitors and presence of lung and/or liver metastasis for the generation of the p-value.
- f. Statistically significant p-value.
- g. Responses included unconfirmed responses.

DCO date for OS was 30 March 2024 (OS analysis at 50% maturity) and DCO date for other endpoints was 30 August 2022 (primary analysis).

5.3.6. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

5.3.7. Observational data/Data from registries

Not applicable.

5.3.8. Patient experience data (PED)

As part of the study design process, consultations were held with 3 groups of breast cancer patients with clinical trial experience, as part of the Sponsor's Patient Partnership Program. Patients were provided with study background details, and draft patient communication materials (eg, ICF). Consultation was in the form of 1.5 hour meetings (one with each group of 3 to 4 patients), and written feedback provided by patients. The feedback focused on patient-impacting study design elements (eg, visit schedule, sample collection, study activities (eg, CT scans), storage and use of data, ICF process and wording, etc.). Patient feedback was very positive regarding the study concept

of monitoring disease in order to switch treatment, and to further understand the disease response to treatment.

This feedback provided by patients was used to optimise the study from a patient-centricity perspective, and to edit and develop the patient communication material.

In addition, see Figure 51: Kaplan-Meier Plot for Time to Deterioration (months) in GHS/QoL for EORTC QLQ-C30 (Full Analysis Set) in section 5.3.2.1.4. Results for patient reported outcomes (PROs) assessment in SERENA-6.

5.3.9. Healthcare professional engagement

Not applicable.

5.3.10. Overall discussion and conclusions on clinical efficacy

5.3.10.1. Discussion

Design and conduct of the clinical studies

The approval is primarily based on data from the pivotal study, SERENA-6, which is a randomised, phase 3, double-blind, placebo-controlled multicentre study. The design of the pivotal study, SERENA-6, has been considered overall acceptable and data from this study support the proposed indication. However, the applied indication will lead to a new treatment paradigm, as patients are switched early based on a biomarker-selection (*ESR1*-mutation), which is not part of the current standard of care. CHMP scientific advice underlined that from a clinical perspective the need for support from PFS2 data of high quality and OS data would be considered key.

Patients eligible for inclusion had advanced ER-positive, HER2-negative breast cancer, and were treated with an AI + CDK4/6 inhibitor in the first-line advanced setting.

During the evaluation, it was clarified that SERENA-6 allowed patients with bone-only evaluable disease (regardless of measurability). Moreover, patients with evaluable disease included both patients with measurable and non-measurable disease that can be assessed by CT or MRI in line with RECIST 1.1 guidelines. Those patients with bone disease only, in most cases, have a lytic component that can be distinguished in CT or MRI and were not excluded from the SERENA-6 study. This resulted in exclusion of 14 patients out of 406 patients (3.4%) during STEP2 screening and this low fraction of exclusions is considered reassuring, and it is agreed that this should not have any impact on the indication, since no different efficacy is expected based on presence of measurable (bone) disease or not.

Screening of 3050 patients led to randomisation of 315 patients in a 1:1 ratio, and the randomisation was stratified by time from initiation of CDK4/6 inhibitor + AI to randomisation (<18 months vs ≥18 months); *ESR1*m detectable at first ctDNA test; visceral vs non-visceral disease; and CDK4/6 inhibitor used (i.e. palbociclib vs abemaciclib vs ribociclib). Most of the stratification factors were endorsed as they were considered to be prognostic factors (e.g. visceral disease; early detection of *ESR1*-mutation indicating treatment resistance; and time on 1L therapy). However, type of CDK4/6i used may not be prognostic, but stratification can support relevant subgroup analyses, if sufficiently powered. It should be noted that in previous advice (EMA/SA/0000051172, dated April 22, 2021) it was questioned whether presence of *ESR1*m (first versus subsequent) was an adequate way to capture heterogeneity in the study population, but in this assessment the Applicant's choice of stratification factors has been considered acceptable. During the procedure, it was clarified that among the 91 enrolled patients with *ESR1*m, who were not subsequently randomised, 82.8% (n=83) were classified as "screen failure" or "failure to meet randomisation criteria". Most commonly, this was due to clinical or radiographic

progression: 52.7% (n=48); bone-only disease measurability: 15.4% (n=14); and Organ/marrow function: 8.8% (n=8). The reasons were noted and it was considered expected that some patients would be excluded due to non-measurable disease and organ/marrow dysfunction. However, the exclusion of 48 patients due to disease progression was considered substantial, and for this reason this aspect has been included in the revised wording of indication, clarifying that 'no progression' should be evident at the time of treatment switch to camizestrant.

Crossover within the study was not permitted and all randomised patients continued study treatment until objective radiological disease progression as defined by RECIST v1.1, unacceptable toxicity occurred, treatment discontinuation criterion was met, the patient withdrew consent, or death. This was considered acceptable.

The primary objective of the pivotal study SERENA-6 was showing superiority in PFS by Investigator of camizestrant + CDK4/6i over SoC (AI + CDK4/6i), which was considered a clinically relevant and acceptable primary endpoint in the studied first-line setting of advanced ER+, HER2-negative breast cancer. In the context of a double-blind, randomised placebo-controlled pivotal study, it was considered fully acceptable to have investigator-assessed PFS as the primary endpoint. PFS by BICR and assessment of early discrepancy rate (EDR) and late discrepancy rate (LDR) have been considered as indicators of quality.

Secondary objectives of key relevance were PFS2 and OS. Other secondary endpoints were time to first subsequent therapy (TFST), time to second subsequent therapy (TSST), and chemotherapy-free interval.

There were four amendments to the initial protocol and none of the changes have been considered to have had any major impact on the study results.

Efficacy data and additional analyses

The clinical DCO for this submission of the first interim analysis of SERENA-6 was 28 November 2024 and the median duration of follow-up was 13.1 months in the camizestrant arm and 12.1 months in the control (AI) arm. During the procedure, the Applicant provided updated data from DCO2 (30 June 2025) and further on from DCO3 (02 January 2026).

Baseline data showed that the median age was ~61 years, 63% of the patients were less than 65 years of age, and 37% of the patients were ≥65 years in the study population, which was considered reflective of the targeted patient population. Three male patients were included, all in the control arm, which was considered acceptable, since breast cancer is rare in men. Still, the results from the pivotal trial were considered extrapolatable to men with ER-positive, HER2-negative metastatic breast cancer in line with previous EMA decisions (see Orserdu (elacestrant) EPAR, Inluriyo (imlunestrant EPAR)), based on the common biological and pharmacological rationale. The majority of patients were either White (63.2%) or Asian (23.2%), which was equally distributed between both arms and the fraction of EU-like patients is considered acceptable for interpretation of the study results in an EU context. Less than half of the included patients had visceral metastases (43.5%) versus non-visceral disease (56.5%), which was a stratification factor and equally distributed between the treatment arms. Patients were generally of good ECOG Performance status (PS), and either of ECOG PS 0 (68.2% vs 62.0%, respectively) or ECOG PS 1 (30.6% vs 35.4%, respectively); which was skewed a bit in favour of the camizestrant arm. All approved CDK4/6 inhibitors were allowed in the pivotal SERENA-6 study, and approximately 75.0% of patients were randomised to palbociclib, compared with ~15.0% to ribociclib and ~10.0% to abemaciclib. While this distribution was not optimal, it is attributable to the initial study design, as CDK4/6 inhibitors other than palbociclib were permitted only later during the recruitment period following a protocol amendment.

It was noted that more than half of the patients had a detectable *ESR1* mutation at the first ctDNA test, having in mind that patients were treated for at least 6 months with an AI + CDK4/6i before the screening was initiated, while 46.7% had an *ESR1*-mutation detected at the subsequent ctDNA test. This translated into approximately one third (37.5%) with less than 18 months duration of first-line

SoC treatment with an AI + CDK4/6 before the *ESR1* mutation was detected indicating treatment resistance; while two-thirds had longer time on first-line treatment (>18 months) before an *ESR1* mutation were detected. These numbers were considered in line with the known median PFS for AI + palbociclib of 27.6 months in the PALOMA-2 study (R.Finn et al., 2016). Prior adjuvant CDK4/6i was allowed but was only given to a very small subset of the included patients, i.e. 3.8% (6/157 patients) and 7% (11/158 patients) of the patients in each arm, respectively. This is acceptable, in line with SoC treatment in the early breast cancer setting and is not considered to have had an impact on the study results.

At the time of DCO1, 45.2% versus 63.3% events were observed, respectively, and the primary endpoint of **PFS by Investigator** was improved from a median of 9.23 months in the AI arm to 15.97 months in the camizestrant arm. The difference of 6.74 months was statistically significant with a HR of 0.44 (95%CI: 0.31; 0.60). The KM curves separated early and stay separated, which was considered promising. At DCO2, mature PFS data were provided with 57.3% and 72.8% events in the camizestrant arm vs the control arm, respectively and a HR of 0.46 (95% CI: 0.34, 0.62), consistent with DCO1. At DCO3, there was 63.1% and 78.5% of PFS events in the camizestrant arm vs the control arm, respectively and a HR of 0.45 (95% CI: 0.34, 0.59), consistent with DCO1 and 2. The median PFS by INV was **16.76 months** in the camizestrant arm vs 9.23 months in the control arm, resulting in 7.53 months of improvement. The KM curves are clearly separating after 3 months of treatment.

PFS by BICR at DCO2 indicated 38.2% and 47.5% events in the camizestrant arm vs the control arm, respectively, HR 0.46 (95% CI: 0.32, 0.66). The median PFS by BICR was 18.43 months in the camizestrant arm vs 12.68 months in the control arm, resulting in 5.75 months of improvement (at DCO1 it was 7.75 months). Although the point estimate for HR of PFS by BICR (HR 0.43, 95%CI: 0.29, 0.63) was similar to that of PFS by Investigator (0.46), the median PFS by BICR was estimated to be longer according to BICR compared to by Investigator in the camizestrant arm (18.43 versus 16.59 months), while median PFS by BICR was also longer in the AI arm compared to by Investigator (12.68 vs 9.23 months). It was noted that the updated concordance between the investigator assessment and BICR was still poor, especially regarding RECIST progression disagreements, as there were less PD cases called in the camizestrant arm. However, since PFS by INV was the primary endpoint, this observation is not considered to have had a major impact on the interpretation of the study results.

PFS2 data at DCO2 in the FAS were reported to be 25.75 months with camizestrant compared to 19.35 months in the control arm, HR 0.56 (95%CI: 0.39; 0.80). At DCO3 (time of the planned primary analysis of PFS2), a statistically significant result was reported with a HR of 0.63; 95%CI: 0.46, 0.86; p-value 0.00373). Median PFS2 was 25.72 months in the camizestrant arm compared to 19.06 months in the control arm. This PFS2 result cannot be considered supportive due to the poor quality of the collected PFS2 data. Consequently, the approval was considered supported only by the positive outcome on PFS and the consistent result of updated PFS by BICR.

The SERENA-6 protocol did not mandate specific post-study treatments but recommended to follow ESMO and NCCN guidelines. Results show a high level of heterogeneity in subsequent treatment choices, partly not reflected in the treatment guidelines. Furthermore, tumor assessments by RECIST methods were not mandated but an assessment interval of 8-12 weeks was defined. Different types of progression contributed to the PFS2 analyses and only a subset of patients who received subsequent treatment were followed with RECIST methods (58/87 in the camizestrant arm and 60/117 in the control arm). It was clarified that only in 15 patients in each arm the assessment interval of 8-12 weeks was followed with RECIST methods. This poor data quality with large heterogeneity in subsequent treatment choices, heterogeneity in tumor assessments intervals including missing assessments led to consider the PFS2 data unreliable, and an overestimation of the median PFS2 in both arms was considered likely. The extent of the reported difference in PFS2 could not be clarified.

Summary of subsequent therapies showed that more patients in the camizestrant arm received subsequent chemotherapy (45.6%) compared to patients in the AI arm (22.9%). There were no

patients in the camizestrant arm who received an antibody-drug conjugate (ADC), while 12% did in the AI arm. Subsequent therapies also included endocrine-based therapy with CDK4/6i, mTORi, and ET monotherapy.

Since the pivotal study was testing whether an early switch of ET backbone therapy in combination with the same CDK4/6i at the time of detection of an *ESR1* mutation in ctDNA was better than awaiting radiological disease progression (PD) or even clinical progressive disease, for any PFS benefit to be considered clinically relevant, it must be supported by benefit in longer term time-to-event endpoints and at least no OS detriment. The new treatment paradigm can be considered as early second-line therapy, and entails multiple testings of the blood for *ESR1* mutations, which can be challenging for the patients emotionally, since the detection of an *ESR1* mutation is associated with treatment-resistance. On the other hand, it has been considered clinically meaningful to prolong time on first-line endocrine based therapy, since radiological and/or clinical progression is associated with symptoms that may be severe, including treatment-resistant pain as well as potentially severe disabilities and disease manifestations such as spinal cord compression resulting in paralysis and liver failure. In this context, it has been considered clinically relevant to detect an early sign of treatment-resistance and upcoming treatment failure and avoid the first progression on first-line therapy to be symptomatic. Therefore, the clinical study design of SERENA-6 has been considered to adequately answer the question on whether a switch to camizestrant from an AI backbone in combination with CDK 4/6i was really beneficial for patients, since the patients were randomised in a blinded and a placebo-controlled study at the time of detection of the known resistance mutation of *ESR1* in ctDNA and because a clinically relevant PFS prolongation has been observed in the camizestrant arm using this approach.

OS has further matured at DCO3 with ~30% events in both arms, HR: 0.87 (95% CI: 0.57, 1.30), which is an improvement of the HR from DCO1 and 2 (HR 0.91 and HR 0.92, respectively). At this time, there was no apparent detriment on OS but no clear OS benefit either. A *post-hoc* RMST analysis indicated no apparent detrimental effect on OS. It was considered still early to conclude on these updated OS data. The Applicant will submit the final OS data planned with 55% maturity (165 OS events) as a Post authorisation efficacy study (PAES) in Annex II.D by December 2028. These data are considered key to the B/R balance and will address criteria 2a of the Commission Delegated Regulation (EU) No. 357/2014 (*when an initial efficacy assessment that is based on surrogate endpoints, which requires verification of the impact of the intervention on clinical outcome or disease progression or confirmation of previous efficacy assumptions*).

Other secondary endpoints included Time to First Subsequent Therapy or death (TFST), Time to Second Subsequent Therapy or death (TSST), and Time to Second Subsequent Therapy or death. At DCO2, the PFS benefit was supported by longer TFST and TSST in the camizestrant arm compared to the control arm. Chemotherapy-free survival was also updated at DCO3. The interpretability of the reported difference was limited as the choice of post-study treatments was not prospectively defined. Due to heterogeneity in the choice of type of next-line treatment, more patients in the camizestrant + CDK 4/6i arm received classical chemotherapy and more patients in the control arm received ADCs post-progression. A descriptive analysis of the change in *ESR1*m VAF detected in plasma according to the treatment arm was provided. In the camizestrant arm, levels decline (median change of -100%) while levels rise (median +66.7%) in patients in the AI arm. Although these data are exploratory in nature, the observed decline in the treatment arm and rising ctDNA level in the control arm was considered supportive.

Subgroup analyses of the primary endpoint, PFS by Investigator, were performed regarding disease site; *ESR1*m-detection (first vs subsequent test); time from initiation of CDK4/6i to randomisation; type of CDK4/6i; and *ESR1* variants. Additionally, subgroup analyses of age groups and menopausal status are considered relevant to comment. Disease site (visceral vs non-visceral) subgroup analyses showed clinically relevant benefit in both subgroups with maybe a trend toward better outcomes for the patients with non-visceral disease (HR 0.51 vs HR 0.44 for patients with visceral vs non-visceral); however, this finding may be uncertain due to still few events in the camizestrant arm. Likewise, the benefit seems to be increased in patients with early detected *ESR1*m (first test) with a HR of 0.36

compared to later (HR 0.61); and this finding was considered due to the poorer outcomes for the patients in the control arm, who continued AI + CDK4/6 and was consistent with the knowledge that SERDs such as camizestrant primarily have shown relevant efficacy in patients with an *ESR1* mutation.

The updated subgroup analyses from the DCO2 continued to show benefit in favour of camizestrant and no discordant results for PFS in the requested subgroups were identified. Hence, the point estimate for HR was still below 1 across important subgroups including the stratification factors: CDK4/6 inhibitor combination partner (palbociclib, ribociclib, or abemaciclib), *ESR1*m detectable at first ctDNA test or subsequent ctDNA test, disease site (visceral vs non-visceral), and time from initiation of AI + CDK4/6 inhibitor to randomisation (< 18 months or ≥ 18 months). Results on the subgroups *ESR1*m detectable at first ctDNA test or subsequent ctDNA test were identified as interesting. For the camizestrant arm, the median PFS was comparable in both subgroups, while in the control arm the median PFS was longer in the subgroup with *ESR1*m detection at a subsequent test.

PFS according to type of CDK4/6i used was not conclusive, as the vast majority of patients (75%) received palbociclib, while very few patients received ribociclib or abemaciclib. This was considered acceptable and the type of CDK4/6i was not considered to be an important effect modifier for camizestrant, when combined. Importantly, the benefit was considered clinically relevant across subgroups of age categories and regarding menopausal status.

Results from the supportive clinical studies SERENA-1 and -2, respectively, were also provided and while the studies supported the proposed dose and continued clinical development, there was no need to have the data reflected in the SmPC. Overall, the benefit of camizestrant was based on the clinical data from the pivotal study SERENA-6.

5.3.10.2. Conclusions on the clinical efficacy

Overall, the efficacy assessment concluded that: SERENA-6 was testing a new treatment paradigm, i.e. proactively searching for the earliest timepoint to diagnose an *ESR1*-mutation in parallel to ongoing first-line treatment of ER+ HER2- mBC with the combination of an aromatase inhibitor (AI) + a CDK4/6 inhibitor, leading to replacement of the AI by camizestrant (still in combination with the CDK4/6i) without evidence of clinical and/or radiological progression. This new approach can be considered an early second-line therapy; however, without experiencing a symptomatic first-line treatment failure, which may include severe disease symptoms, including treatment-resistant pain as well as potentially severe disabilities and disease manifestations such as spinal cord compression resulting in paralysis and liver failure. The benefit of the new treatment paradigm was primarily based on the demonstrated PFS benefit of 7.53 months and the HR of 0.45 (95% CI: 0.34; 0.59) with camizestrant, considering the randomised, blinded and placebo-controlled study design. This positive outcome was supported by a consistent result of updated PFS by BICR which continued to support clinical benefit in favour of the camizestrant arm. Based on the available data and in the absence of an OS detriment, the efficacy of camizestrant has been considered sufficiently established to support its use in the proposed indication. In order to further characterise the efficacy of camizestrant, the MAH will submit the final OS analysis as a PAES in Annex II.D by December 2028.

5.4. Clinical safety

Please refer to the table of studies in section 5.1.2.

For the purpose of this document, the following definitions apply:

‘Adverse event – AE’ means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

‘Serious adverse event – SAE’ means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant

disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

‘Adverse drug reaction – ADR’ means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

The pivotal analysis of the safety and tolerability data of camizestrant + CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib) in the proposed indication is based on the pre-planned IA (DCO1) of data from the Phase III SERENA-6 study (DCO1 date: 28 November 2024). The overall clinical study pooling strategy used to support safety claims for this submission are presented in Table 66. The integrated safety datasets included:

- **Camizestrant + CDK4/6 inhibitor combination pool:** Combination pool included safety data from studies SERENA-6 and SERENA-1 (Parts C, D, G, H, K, and L) evaluating the same therapeutic combinations (camizestrant 75 mg QD + all CDK4/6 inhibitors, ie, camizestrant + palbociclib, camizestrant + ribociclib, and camizestrant + abemaciclib). Pooled data of camizestrant + CDK4/6 inhibitor combination was also presented by individual CDK4/6 inhibitor (ie, palbociclib, ribociclib, or abemaciclib).
- **Monotherapy pool:** The monotherapy pool included safety data of camizestrant from studies SERENA-1 (Parts A and B), SERENA-2, Japan and China Phase I studies.

Table 65: Safety Pooling Strategy

	Camizestrant + CDK4/6 inhibitor combination therapy pool	Camizestrant monotherapy pool
Eligible subjects	• Patients who took at least one dose of camizestrant 75 mg QD in combination therapy with either palbociclib, ribociclib, or abemaciclib. • Patients who received at least one dose of either palbociclib, ribociclib, or abemaciclib but not camizestrant were not included	• Patients who took at least one dose of camizestrant 75 mg QD as a monotherapy. • Patients who took other dose levels of camizestrant were not included
Treatment group(s)	• Combined CDK4/6 inhibitors ◦ camizestrant + CDK4/6 inhibitors (N = 263) • Individual CDK4/6 inhibitors ◦ camizestrant + palbociclib (N = 141) ◦ camizestrant + ribociclib (N = 83) ◦ camizestrant + abemaciclib (N = 39)	camizestrant (N = 117)
Studies to be integrated	SERENA-6 (N = 155) and SERENA-1 (Parts C, D, G, H, K, and L; N = 108)	SERENA-1 (Parts A and B; N = 24), SERENA-2 (N = 74), Japan Phase I study (N = 7), and China Phase I study (N = 12)

The analyses of pooled data included pooled analyses of AEs and laboratory data. The pooled data are presented side-by-side with the SERENA-6 safety data to provide comparative descriptive analysis.

In SERENA-6 study, after data unblinding, it was determined that a patient randomised to the AI + CDK4/6 inhibitor arm received treatment with camizestrant instead of with camizestrant-matching placebo for 1 cycle due to a study treatment kit dispensing error. According to the SAP, this patient should have been included in the camizestrant + CDK4/6 inhibitor arm for safety analysis but was analysed in the AI + CDK4/6 inhibitor arm based on the ITT principle.

Of note, data collection methodologies were comparable in the individual studies, which allows for meaningful comparisons of safety variables to be made.

Table 66: Safety Variables by Safety Population

Safety variable	SERENA-6 (combined and individual CDK4/6 inhibitor)	Pooled data	
		Combination therapy ^a	Monotherapy
Exposure to study drug	✓	✓	✓
Demographic and other baseline characteristics	✓	✓	✓
Adverse events			
Overall summary by category	✓	✓	✓
Common AEs	✓	✓	✓
AEs of CTCAE Grade 3 or higher	✓	✓	✓
SAEs	✓	✓	✓
Deaths	✓	✓	✓
AEs leading to dose discontinuation	✓	✓	✓
AEs leading to dose interruption	✓	✓	✓
AEs leading to dose reduction	✓	✓	✓
AESIs	✓	✓	✓
Clinical laboratory evaluations (haematology, clinical chemistry): CTCAE grade shifts from baseline	✓	✓	✓
Vital signs, physical findings, and ECGs ^b	✓		

a. Combination therapy includes both- camizestrant + CDK4/6 inhibitor (combined palbociclib, ribociclib, or abemaciclib) and camizestrant + individual CDK4/6 inhibitor

b. Presented at pivotal study level (not pooled)

The criteria used in recording of AEs in individual studies pooled for safety are summarised in Table 68.

Table 67: Criteria for AE Assessment

Criteria	Definition
AE	An AE is the development of any untoward medical occurrence (other than progression of the malignancy under evaluation) in a patient or clinical study patient administered a study treatment 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 study treatment.

Criteria	Definition
TEAE reporting period	The integrated analysis of AEs was based on all TEAEs from all studies. TEAEs for the patients on combination therapy, camizestrant/AI + CDK4/6 inhibitor, were defined as those AEs with onset or that worsen (by investigator report of a change in intensity) after the first dose of camizestrant, AI (anastrozole or letrozole), and CDK4/6 inhibitor (palbociclib, ribociclib or abemaciclib), whichever occurred first, and on or before the date of last dose of camizestrant/anastrozole/letrozole + 28 days. For patients on the camizestrant monotherapy, TEAEs were defined in a similar way but excluding the AI and CDK4/6 inhibitor dose. In SERENA-2 and SERENA-6, TEAEs were further restricted to those that occurred prior to the start of any subsequent cancer therapy.
TEAE variables collected	The following variables were collected for each TEAE: TEAE term (verbatim), TEAE start and stop date, maximum CTCAE grade, TEAE seriousness, investigator causality assessment against the study drug (yes or no), action taken with study drug, and outcome of the TEAE.
Coding of TEAEs	The most current version of MedDRA was used for coding of the AE data. Data from studies originally reported in previous versions of MedDRA were up-versioned for integration purposes.
Capturing TEAE severity	In SERENA-1 CTCAE Version 4.0 was used, whereas in China and Japan Phase I studies, SERENA-2, and SERENA-6 studies, CTCAE Version 5.0 was used. The AEs reported in this remained with the original CTCAE grading recorded in the individual studies by the investigator. The difference in CTCAE versions between the studies was not considered to have an impact on the interpretation of the AE summaries.
Causality assessment	All studies collected study drug relationship as assessed by the investigator with respect to camizestrant. For SERENA-6, it was also collected for CDK4/6 inhibitor and AI. The investigator assessed causal relationship between the study treatment and each AE and answered '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?'
Dosing action taken due to TEAE	All studies reported where camizestrant was discontinued due to an AE. The available action in the treatment management guidelines allowed for "Dose not changed", "Dose reduced", "Drug interrupted", "Drug permanently discontinued" and "Not applicable" in all studies.

5.4.2. Patient exposure

The ongoing blinded, active-controlled, pivotal Phase III SERENA-6 study provided the primary data for safety and SERENA-1, SERENA-2, Japan Phase I and China Phase I open-label studies provided the supportive safety data. An overview of all studies contributing to the safety data analysis is presented in Table 66.

Exposure to study drug in SERENA-6 and pooled studies is provided in Table 70.

Table 68 Patient exposure (cut off) DCO1

	Patients enrolled	Patients exposed to camizestrant ^a	Patients exposed at 75 mg camizestrant	Patients exposed at 75 mg camizestrant with ≥ 6 months safety data ^b	Patients exposed at 75 mg camizestrant with ≥ 12 months safety data ^b
Blinded studies (Active-controlled) (SERENA-6)	315	155	155	130	89
Open studies (SERENA-1, SERENA-2, Japan Phase I study, China Phase 1 study)	674	492	225	106	49
All pooled studies (SERENA-1, SERENA-2, SERENA-6, Japan Phase I study, China Phase 1 study)	989	647	380	236	138

[a] Received at least 1 dose of active treatment.

[b] This applies to 6 months and 12 months continuous exposure, or intermittent exposure.

The table includes camizestrant monotherapy and camizestrant combination therapy with CDK4/6 inhibitor

Table 69: Exposure to Camizestrant/Aromatase Inhibitor: SERENA-6 and Pooled Studies

Treatment Duration	SERENA-6		Pool	
	camizestrant + CDK inhibitor (N = 155)	AI + CDK inhibitor (N = 155)	camizestrant + CDK inhibitor (N = 263)	camizestrant monotherapy (N = 117)
Total (intended) treatment duration (months) - Camizestrant/AI + Any CDK4/6 inhibitor ^a				
N	155	155	263	0
Mean (SD)	11.2 (7.16)	7.7 (5.33)	9.9 (7.83)	NE (NE)
Median (Min, Max)	10.1	6.2	8.3 (0, 41)	NE (NE, NE)
Total treatment years ^b	144.9	99.0	217.7	0
Total (intended) treatment duration (months) - Camizestrant/AI ^c				
N	155	155	263	117
Mean (SD)	11.4 (7.11)	7.8 (5.37)	10.1 (7.80)	9.9 (11.62)
Median (Min, Max)	10.2	6.3	8.5 (0, 41)	5.1 (0, 52)
Total treatment years ^b	147.1	101.1	220.9	96.1
Actual treatment duration (months) - Camizestrant/AI ^d				
N	155	155	263	117
Mean (SD)	11.2 (7.07)	7.7 (5.16)	9.9 (7.68)	9.7 (11.49)
Median (Min, Max)	10.1	6.3	8.3 (0, 40)	5.0 (0, 51)
Total treatment years ^b	144.7	99.1	216.8	94.6
Total (intended) treatment duration (months) - CDK4/6 inhibitor ^c				
N	155	155	263	0
Mean (SD)	11.2 (7.15)	7.7 (5.33)	10.0 (7.80)	NE (NE)
Median (Min, Max)	10.1	6.3	8.5 (0, 41)	NE (NE, NE)
Total treatment years ^b	144.9	99.4	219.0	0
Actual treatment duration (months) - CDK4/6 inhibitor ^d				
N	155	155	263	0
Mean (SD)	8.6 (5.56)	5.9 (4.03)	7.8 (6.74)	NE (NE)
Median (Min, Max)	7.6	4.9	6.4 (0, 39)	NE (NE, NE)
Total treatment years ^b	110.5	76.8	170.4	0

	SERENA-6		Pool	
Treatment Duration	camizestrant + CDK inhibitor (N = 155)	AI + CDK inhibitor (N = 155)	camizestrant + CDK inhibitor (N = 263)	camizestrant monotherapy (N = 117)
Total (intended) treatment duration (months) - Camizestrant/AI + Palbociclib ^a				
N	117	117	141	0
Mean (SD)	12.4 (7.23)	8.4 (5.65)	11.1 (7.36)	NE (NE)
Median (Min, Max)	11.4	7.1	10.4 (0, 33)	NE (NE, NE)
Total treatment years ^b	121.4	81.6	131.0	0
Total (intended) treatment duration (months) - Palbociclib ^c				
N	117	117	141	0
Mean (SD)	12.4 (7.23)	8.4 (5.65)	11.1 (7.36)	NE (NE)
Median (Min, Max)	11.4	7.1	10.4 (0, 33)	NE (NE, NE)
Total treatment years ^b	121.4	81.8	131.0	0
Actual treatment duration (months) - Palbociclib ^d				
N	117	117	141	0
Mean (SD)	9.2 (5.45)	6.3 (4.17)	8.2 (5.54)	NE (NE)
Median (Min, Max)	8.7	5.3	7.8 (0, 25)	NE (NE, NE)
Total treatment years ^b	89.8	61.7	96.8	0
Total (intended) treatment duration (months) - Camizestrant/AI + Abemaciclib ^a				
N	15	15	39	0
Mean (SD)	8.7 (8.06)	5.7 (4.49)	13.0 (12.20)	NE (NE)
Median (Min, Max)	6.4	4.2	8.2 (0, 41)	NE (NE, NE)
Total treatment years ^b	10.9	7.1	42.4	0
Total (intended) treatment duration (months) - Abemaciclib ^c				
N	15	15	39	0
Mean (SD)	8.7 (8.06)	5.7 (4.46)	13.0 (12.20)	NE (NE)
Median (Min, Max)	6.4	4.2 (	8.2 (0, 41)	NE (NE, NE)
Total treatment years ^b	10.9	7.2	42.4	0
Actual treatment duration (months) - Abemaciclib ^d				
N	15	15	39	0
Mean (SD)	8.6 (8.11)	5.5 (4.42)	12.6 (11.84)	NE (NE)
Median (Min, Max)	6.4	4.2	7.2 (0, 39)	NE (NE, NE)
Total treatment years ^b	10.7	6.9	40.8	0
Total (intended) treatment duration (months) - Camizestrant/AI + Ribociclib ^a				
N	23	23	83	0
Mean (SD)	6.6 (2.67)	5.4 (2.75)	6.4 (3.81)	NE (NE)
Median (Min, Max)	6.2	5.2	6.3 (0, 13)	NE (NE, NE)

	SERENA-6		Pool	
Treatment Duration	camizestrant + CDK inhibitor (N = 155)	AI + CDK inhibitor (N = 155)	camizestrant + CDK inhibitor (N = 263)	camizestrant monotherapy (N = 117)
Total treatment years ^b	12.6	10.3	44.4	0
Total (intended) treatment duration (months) - Ribociclib ^c				
N	23	23	83	0
Mean (SD)	6.6 (2.65)	5.4 (2.75)	6.6 (3.80)	NE (NE)
Median (Min, Max)	6.2	5.2	6.5 (0, 13)	NE (NE, NE)
Total treatment years ^b	12.7	10.4	45.6	0
Actual treatment duration (months) - Ribociclib ^d				
N	23	23	83	0
Mean (SD)	5.2 (1.93)	4.3 (2.35)	4.7 (2.72)	NE (NE)
Median (Min, Max)	5.3	4.1	4.5 (0, 9)	NE (NE, NE)
Total treatment years ^b	9.9	8.2	32.8	0

Table 70: Exposure to Camizestrant/Aromatase Inhibitor: SERENA-6 and Pooled Studies– ECOG/WHO performance status = 0

ECOG/WHO Performance Status: 0

	SERENA-6		Combo Therapy Pool	Monotherapy pool
	Camiz + CDK4/6i (N=107)	AI + CDK4/6i (N=98)	Camiz + CDK4/6i (N=158)	Camizestrant (N=66)
Treatment duration (months)				
Total (intended) treatment duration (months) - Camizestrant/AI [a]				
n	107	98	158	66
Mean	11.4	8.2	10.5	11.2
SD	7.28	5.50	7.87	12.74
Median	10.2	7.0	9.2	6.3
Min			0	0
Max			41	52
Total treatment years	102.0	67.4	138.4	61.7
Actual treatment duration (months) - Camizestrant/AI [b]				
n	107	98	158	66
Mean	11.2	8.1	10.3	11.1
SD	7.20	5.24	7.77	12.62
Median	10.1	6.9	9.0	6.3
Min			0	0
Max			40	51
Total treatment years	100.2	65.9	135.9	60.9

Table 71: Exposure to camizestrant/aromatase inhibitor: SERENA-6 and Pooled Studies– ECOG/WHO performance status ≥ 1

	SERENA-6		Combo Therapy Pool	Monotherapy pool
	Cami + CDK4/6i (N=48)	AI + CDK4/6i (N=57)	Cami + CDK4/6i (N=103)	Camizestrant (N=49)
Treatment duration (months)				
Total (intended) treatment duration (months) - Camizestrant/AI [a]				
n	48	57	103	49
Mean	11.3	7.1	9.5	8.2
SD	6.81	5.10	7.73	10.00
Median	9.2	5.6	8.0	4.1
Min			0	1
Max			39	45
Total treatment years	45.1	33.7	81.3	33.6
Actual treatment duration (months) - Camizestrant/AI [b]				
n	48	57	103	49
Mean	11.1	7.0	9.3	8.1
SD	6.83	5.01	7.60	9.86
Median	9.1	5.6	7.7	4.1
Min			0	1
Max			37	45
Total treatment years	44.5	33.2	79.8	32.9

[a] Total treatment duration (months) = (min(date of last dose date where dose > 0, date of death, date of DCO) - first dose date + 1) / (365.25/12).

[b] Actual treatment duration = total intended treatment duration minus the total duration of dose interruptions (including any planned no dose periods occurring before the planned dose is resumed).

[c] Treatment duration calculation is similar to that in [a] but change the last dose date to the last dose of either camizestrant or CDK4/6, whichever occurs first and the first dose date to the first dose of camizestrant or CDK4/6, whichever occurs later
AI Aromatase Inhibitor; CDK4/6i Cyclin dependent kinase inhibitor;

n Number of subjects per category; N Number of subjects per treatment group; SD Standard Deviation.

Table 72: Exposure to camizestrant / AI: SERENA-6 and Pooled studies – disease site: liver visceral

Disease Site: Liver visceral

	SERENA-6		Combo Therapy Pool	Monotherapy pool
	Cami + CDK4/6i (N=26)	AI + CDK4/6i (N=24)	Cami + CDK4/6i (N=87)	Camizestrant (N=35)
Treatment duration (months)				
Total (intended) treatment duration (months) - Camizestrant/AI [a]				
n	26	24	87	35
Mean	10.0	5.5	8.2	6.8
SD	6.14	4.97	7.97	6.84
Median	9.8	4.4	6.3	3.7
Min			0	1
Max			39	32
Total treatment years	21.7	11.1	59.7	19.8
Actual treatment duration (months) - Camizestrant/AI [b]				
n	26	24	87	35
Mean	9.9	5.5	8.1	6.7
SD	6.14	4.91	7.85	6.76
Median	9.8	4.2	5.7	3.7
Min			0	1
Max			37	31
Total treatment years	21.4	10.9	58.7	19.6

Table 73: Exposure to camizestrant / AI: SERENA-6 and Pooled studies – disease site: non-liver visceral

Disease Site: Non-liver visceral

	SERENA-6		Combo Therapy Pool	Monotherapy pool
	Cami + CDK4/6i (N=38)	AI + CDK4/6i (N=38)	Cami + CDK4/6i (N=55)	Camizestrant (N=31)
Treatment duration (months)				
Total (intended) treatment duration (months) - Camizestrant/AI [a]				
n	38	38	55	31
Mean	11.5	9.2	10.5	11.0
SD	6.98	6.20	7.85	12.24
Median	10.5	7.3	8.9	5.8
Min			0	0
Max			41	49
Total treatment years	36.6	29.1	48.0	28.3
Actual treatment duration (months) - Camizestrant/AI [b]				
n	38	38	55	31
Mean	11.3	8.9	10.3	10.9
SD	6.91	5.64	7.71	12.22
Median	10.3	7.3	8.9	5.8
Min			0	0
Max			40	49
Total treatment years	35.9	28.1	47.0	28.0

Table 74: Exposure to camizestrant / AI: SERENA-6 and Pooled studies – disease site: non-visceral

Disease Site: Non-visceral

	SERENA-6		Combo Therapy Pool	Monotherapy pool
	Cami + CDK4/6i (N=91)	AI + CDK4/6i (N=90)	Cami + CDK4/6i (N=121)	Camizestrant (N=39)
Treatment duration (months)				
Total (intended) treatment duration (months) - Camizestrant/AI [a]				
n	91	90	121	39
Mean	11.7	7.9	11.2	13.5
SD	7.44	4.99	7.46	14.70
Median	9.5	6.9	9.4	9.1
Min			1	0
Max			35	52
Total treatment years	88.8	59.6	113.1	44.0
Actual treatment duration (months) - Camizestrant/AI [b]				
n	91	90	121	39
Mean	11.5	7.8	11.0	13.3
SD	7.40	4.94	7.37	14.48
Median	9.4	6.8	9.4	8.6
Min			1	0
Max			33	51
Total treatment years	87.4	58.7	111.0	43.2

Table 75: Summary of Demographics in Pivotal and Pooled Studies (Safety Analysis Set)

	SERENA-6		Pool	
Characteristics	camizestrant + CDK4/6 inhibitor (N = 155)	AI + CDK4/6 inhibitor (N = 155)	camizestrant + CDK4/6 inhibitor (N = 263)	camizestrant monotherapy (N = 117)
Age (years)				
n	155	155	263	117
Mean	58.9	59.6	58.7	61.0
SD	11.15	11.49	11.29	10.22
Median	61.0	60.0	60.0	61.0
Min			29	37
Max			89	89
Age group (years) n (%)				
< 45	20 (12.9)	20 (12.9)	34 (12.9)	6 (5.1)
≥ 45 to < 55	40 (25.8)	34 (21.9)	63 (24.0)	26 (22.2)
≥ 55 to < 65	33 (21.3)	48 (31.0)	72 (27.4)	42 (35.9)
≥ 65 to < 75	57 (36.8)	36 (23.2)	80 (30.4)	31 (26.5)
≥ 75	5 (3.2)	17 (11.0)	14 (5.3)	12 (10.3)
Sex n (%)				
Male	0	3 (1.9)	0	0
Female	155 (100)	152 (98.1)	263 (100)	117 (100)
Race n (%)				
Asian	38 (24.5)	33 (21.3)	38 (14.4)	19 (16.2)
White	96 (61.9)	100 (64.5)	199 (75.7)	94 (80.3)
Other	7 (4.5)	2 (1.3)	12 (4.6)	4 (3.4)
Missing	14 (9.0)	20 (12.9)	14 (5.3)	0
Ethnic group n (%)				
Hispanic or Latino	8 (5.2)	2 (1.3)	18 (6.8)	3 (2.6)
Not Hispanic or Latino	144 (92.9)	149 (96.1)	241 (91.6)	113 (96.6)
Missing	3 (1.9)	4 (2.6)	4 (1.5)	1 (0.9)
Weight (kg)				
n	155	155	263	117
Mean	69.6	72.1	69.1	70.3
SD	14.78	18.09	14.61	15.02
Median	67.6	68.0	66.4	68.0
Min			38	34
Max			113	112
Weight category (kg) n (%)				
<50	13 (8.4)	8 (5.2)	19 (7.2)	7 (6.0)
≥ 50 to < 70	75 (48.4)	76 (49.0)	137 (52.1)	55 (47.0)

	SERENA-6		Pool	
Characteristics	camizestrant + CDK4/6 inhibitor (N = 155)	AI + CDK4/6 inhibitor (N = 155)	camizestrant + CDK4/6 inhibitor (N = 263)	camizestrant monotherapy (N = 117)
≥ 70 to < 90	53 (34.2)	42 (27.1)	82 (31.2)	42 (35.9)
≥ 90	14 (9.0)	29 (18.7)	25 (9.5)	13 (11.1)
Pulse Rate (Beats/Min)				
n	155	155	263	117
Mean	78.0	77.6	79.3	79.8
SD	11.22	11.83	12.49	11.10
Median	78.0	77.0	78.0	78.0
Min			55	56
Max			128	120
Disease site n (%)				
Liver visceral				35 (29.9)
Non-Liver Visceral	38 (24.5)	38 (24.5)	55 (20.9)	31 (26.5)
Non-visceral	91 (58.7)	90 (58.1)	121 (46.0)	39 (33.3)
Missing				12 (10.3)
Prior chemotherapy n (%)				
Yes	6 (3.9)	11 (7.1)	52 (19.8)	22 (18.8)
No	149 (96.1)	144 (92.9)	211 (80.2)	95 (81.2)
Menopausal Status n (%)				
Male or pre- or peri- menopausal female	34 (21.9)	30 (19.4)	45 (17.1)	6 (5.1)
Post-menopausal female	121 (78.1)	125 (80.6)	218 (82.9)	111 (94.9)
WHO/ECOG performance status				
0	107 (69.0)	98 (63.2)	158 (60.1)	66 (56.4)
≥ 1	48 (31.0)	57 (36.8)	103 (39.2)	49 (41.9)
Missing	0	0	2 (0.8)	2 (1.7)

The Other category in race includes the following options in the Case Report Form: Black or African American, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and Other.

5.4.3. Adverse events

Table 76: Summary of adverse events (full analysis set) DCO1

	SERENA-6		Pool	
	camizestrant + CDK4/6 inhibitor (N = 155) n (%) ^a	AI + CDK4/6 inhibitor (N = 155) n (%) ^a	camizestrant + CDK4/6 inhibitor (N = 263) n (%) ^a	camizestrant monotherapy (N = 117) n (%) ^a
Any AE	145 (93.5)	135 (87.1)	252 (95.8)	100 (85.5)
Any AE possibly related to camizestrant/AI ^b	96 (61.9)	63 (40.6)	186 (70.7)	79 (67.5)

	SERENA-6		Pool	
	camizestrant + CDK4/6 inhibitor (N = 155) n (%)^a	AI + CDK4/6 inhibitor (N = 155) n (%)^a	camizestrant + CDK4/6 inhibitor (N = 263) n (%)^a	camizestrant monotherapy (N = 117) n (%)^a
Any AE possibly related to CDK4/6 inhibitor ^c	113 (72.9)	96 (61.9)	213 (81.0)	NA
Any AE of CTCAE Grade 3 or higher	93 (60.0)	71 (45.8)	165 (62.7)	20 (17.1)
Any AE of CTCAE Grade 3 or higher, possibly related to camizestrant/AI ^b	11 (7.1)	8 (5.2)	22 (8.4)	4 (3.4)
Any AE of CTCAE Grade 3 or higher, possibly related to CDK4/6 inhibitor ^c	79 (51.0)	55 (35.5)	135 (51.3)	NA
Any AE with outcome of death	3 (1.9)	0	4 (1.5)	0
Any AE with outcome of death, possibly related to camizestrant/AI ^b	1 (0.6)	0	1 (0.4)	0
Any SAE (including events with outcome of death)	16 (10.3)	19 (12.3)	34 (12.9)	15 (12.8)
Any SAE (including events with outcome of death), possibly related to camizestrant/AI ^b	1 (0.6)	5 (3.2)	3 (1.1)	4 (3.4)
Any SAE (including events with outcome of death), leading to discontinuation of camizestrant/AI	0	2 (1.3)	0	1 (0.9)
Any AE leading to discontinuation of camizestrant/AI	2 (1.3)	3 (1.9)	3 (1.1)	3 (2.6)
Any AE leading to dose interruption of camizestrant/AI	34 (21.9)	22 (14.2)	60 (22.8)	23 (19.7)
Any AE leading to dose reduction of camizestrant/AI ^d	9 (5.8)	2 (1.3)	9 (3.4)	3 (2.6)

a. Percentages are based on the total number of patients in the treatment group (N).

b. Possibly related to camizestrant/AI, as assessed by the investigator.

c. Possibly related to CDK4/6 inhibitor, as assessed by the investigator.

d. Dose reductions of AI in the control arm refer to dose reduction in camizestrant placebo.

Patients with events in more than one category are counted once in each of those categories.

Note: AEs with an onset date on/after date of first dose; AEs with onset date prior to dosing which worsen after dosing and AEs occurring up to 28 days following date of last dose.

CTCAE version 4.0 in SERENA-1 and version 5.0 in SERENA-2, -6, China, and Japan Phase I studies.

Table 77: Most Common Adverse Events (≥ 5% Patients in Any Arm) and Exposure-adjusted Incidence Rates in Pivotal and Pooled Studies (Safety Analysis Set) – DCO1

	SERENA-6		Combination therapy pool	Monotherapy pool
Preferred term/Grouped term (MedDRA version 28.0)	Camizestrant + CDK4/6 inhibitor (N = 155) n (%) [EAIR]^{a, b}	AI + CDK4/6 inhibitor (N = 155) n (%) [EAIR]^{a, b}	Camizestrant + CDK4/6 inhibitor (N = 263) n (%) [EAIR]^{a, b}	Camizestrant (N = 117) n (%) [EAIR] ^{a, b}
Patients with any AE	147 (94.8) [766.1]	140 (90.3) [563.7]	254 (96.6) [1132.6]	100 (85.5) [655.3]
Neutropenia	89 (57.4) [95.3]	71 (45.8) [99.8]	155 (58.9) [117.9]	6 (5.1) [6.6]
Anaemia	35 (22.6) [23.0]	33 (21.3) [30.7]	54 (20.5) [25.0]	18 (15.4) [19.8]

	SERENA-6		Combination therapy pool	Monotherapy pool
Preferred term/Grouped term (MedDRA version 28.0)	Camizestrant + CDK4/6 inhibitor (N = 155) n (%) [EAIR]^{a, b}	AI + CDK4/6 inhibitor (N = 155) n (%) [EAIR]^{a, b}	Camizestrant + CDK4/6 inhibitor (N = 263) n (%) [EAIR]^{a, b}	Camizestrant (N = 117) n (%) [EAIR]^{a, b}
Photopsia	32 (20.6) [21.9]	12 (7.7) [10.5]	62 (23.6) [30.4]	17 (14.5) [20.1]
Arthralgia	29 (18.7) [18.3]	29 (18.7) [27.6]	49 (18.6) [22.2]	9 (7.7) [10.2]
Leukopenia	28 (18.1) [17.7]	13 (8.4) [11.9]	40 (15.2) [17.6]	5 (4.3) [5.3]
Fatigue	24 (15.5) [14.6]	25 (16.1) [23.0]	53 (20.2) [24.7]	8 (6.8) [8.5]
Back pain	19 (12.3) [10.8]	17 (11.0) [14.8]	32 (12.2) [13.1]	8 (6.8) [8.7]
Dry eye	19 (12.3) [11.5]	11 (7.1) [9.6]	27 (10.3) [11.6]	2 (1.7) [2.1]
Diarrhoea	16 (10.3) [9.3]	20 (12.9) [18.3]	56 (21.3) [26.3]	12 (10.3) [14.0]
Nausea	16 (10.3) [9.5]	24 (15.5) [21.5]	55 (20.9) [24.9]	14 (12.0) [15.6]
Thrombocytopenia	15 (9.7) [8.6]	14 (9.0) [12.5]	32 (12.2) [13.2]	5 (4.3) [5.3]
Headache	14 (9.0) [8.1]	22 (14.2) [20.7]	26 (9.9) [10.9]	8 (6.8) [9.2]
Vitreous floaters	14 (9.0) [8.1]	4 (2.6) [3.4]	25 (9.5) [10.2]	4 (3.4) [4.3]
Asthenia	13 (8.4) [7.6]	9 (5.8) [7.7]	36 (13.7) [15.1]	10 (8.5) [11.3]
Vomiting	13 (8.4) [7.4]	11 (7.1) [9.3]	37 (14.1) [15.6]	6 (5.1) [6.5]
COVID-19	12 (7.7) [7.0]	5 (3.2) [4.2]	21 (8.0) [8.8]	6 (5.1) [6.4]
Cough	12 (7.7) [6.9]	8 (5.2) [6.8]	35 (13.3) [14.8]	8 (6.8) [8.8]
Hot flush	12 (7.7) [6.9]	7 (4.5) [6.0]	17 (6.5) [6.9]	7 (6.0) [7.9]
Vision blurred	12 (7.7) [6.8]	12 (7.7) [10.4]	16 (6.1) [6.5]	3 (2.6) [3.2]
Constipation	11 (7.1) [6.2]	15 (9.7) [13.0]	19 (7.2) [7.7]	9 (7.7) [9.9]
Dizziness	11 (7.1) [6.2]	7 (4.5) [6.0]	27 (10.3) [11.0]	9 (7.7) [10.1]
Urinary tract infection	11 (7.1) [6.2]	9 (5.8) [7.8]	26 (9.9) [10.8]	12 (10.3) [13.5]
Aspartate aminotransferase increased	9 (5.8) [5.0]	13 (8.4) [11.2]	25 (9.5) [10.0]	9 (7.7) [9.8]
Pneumonia	9 (5.8) [5.0]	3 (1.9) [2.5]	14 (5.3) [5.6]	2 (1.7) [2.1]
Pruritus	9 (5.8) [5.1]	6 (3.9) [5.1]	21 (8.0) [8.8]	6 (5.1) [6.6]
Pyrexia	9 (5.8) [5.1]	4 (2.6) [3.3]	17 (6.5) [6.9]	4 (3.4) [4.3]
Alanine aminotransferase increased	8 (5.2) [4.4]	13 (8.4) [11.3]	21 (8.0) [8.5]	4 (3.4) [4.3]
Alopecia	8 (5.2) [4.4]	5 (3.2) [4.2]	13 (4.9) [5.2]	4 (3.4) [4.4]
Bradycardia	8 (5.2) [4.4]	0	14 (5.3) [5.7]	4 (3.4) [4.4]
Dyspnoea	8 (5.2) [4.5]	8 (5.2) [6.8]	24 (9.1) [9.7]	5 (4.3) [5.4]
Gamma-glutamyl transferase increased	8 (5.2) [4.4]	12 (7.7) [10.3]	11 (4.2) [4.3]	1 (0.9) [1.0]
Nasopharyngitis	8 (5.2) [4.5]	3 (1.9) [2.5]	9 (3.4) [3.6]	1 (0.9) [1.0]
Stomatitis	8 (5.2) [4.5]	9 (5.8) [7.7]	13 (4.9) [5.2]	2 (1.7) [2.1]
Decreased appetite	7 (4.5) [3.9]	9 (5.8) [7.5]	22 (8.4) [8.9]	6 (5.1) [6.5]
Hypertension	7 (4.5) [3.9]	5 (3.2) [4.2]	24 (9.1) [9.9]	5 (4.3) [5.2]
Lymphocyte count decreased	7 (4.5) [3.9]	2 (1.3) [1.7]	19 (7.2) [7.7]	2 (1.7) [2.1]

	SERENA-6		Combination therapy pool	Monotherapy pool
Preferred term/Grouped term (MedDRA version 28.0)	Camizestrant + CDK4/6 inhibitor (N = 155) n (%) [EAIR]^{a, b}	AI + CDK4/6 inhibitor (N = 155) n (%) [EAIR]^{a, b}	Camizestrant + CDK4/6 inhibitor (N = 263) n (%) [EAIR]^{a, b}	Camizestrant (N = 117) n (%) [EAIR]^{a, b}
Blood creatinine increased	6 (3.9) [3.3]	11 (7.1) [9.7]	22 (8.4) [9.0]	0
Bone pain	6 (3.9) [3.3]	5 (3.2) [4.2]	14 (5.3) [5.5]	3 (2.6) [3.1]
Myalgia	6 (3.9) [3.3]	8 (5.2) [6.9]	13 (4.9) [5.2]	3 (2.6) [3.3]
Sinus bradycardia	6 (3.9) [3.3]	0	36 (13.7) [15.3]	18 (15.4) [21.0]
Upper respiratory tract infection	6 (3.9) [3.3]	9 (5.8) [7.9]	11 (4.2) [4.3]	3 (2.6) [3.2]
Visual impairment	6 (3.9) [3.4]	3 (1.9) [2.5]	27 (10.3) [11.4]	11 (9.4) [12.6]
Abdominal pain	5 (3.2) [2.7]	10 (6.5) [8.5]	18 (6.8) [7.3]	2 (1.7) [2.1]
Electrocardiogram QT prolonged	5 (3.2) [2.7]	2 (1.3) [1.7]	17 (6.5) [6.8]	8 (6.8) [8.7]
Hypokalaemia	5 (3.2) [2.7]	8 (5.2) [6.9]	8 (3.0) [3.1]	3 (2.6) [3.2]
Pain in extremity	5 (3.2) [2.8]	8 (5.2) [6.8]	12 (4.6) [4.8]	3 (2.6) [3.2]
Blood alkaline phosphatase increased	1 (0.6) [0.5]	9 (5.8) [7.5]	12 (4.6) [4.7]	5 (4.3) [5.3]
Hypoalbuminaemia				7 (6.0) [7.8]

[a] Percentages are based on the total number of patients in the treatment group (N).

[b] EAIR is defined as the number of patients with AEs divided by the total number of days at risk for AEs across all patients in a given group, multiplied by 365.25 multiplied by 100.

The table includes AEs reported in $\geq 5\%$ of subjects (any treatment group).

Table is sorted in descending frequency by preferred term (camizestrant + CDK4/6 inhibitor from SERENA-6).

Patients with multiple AEs are counted once for each preferred term.

Note: AEs with an onset date on/after date of first dose; AEs with onset date prior to dosing which worsen after dosing and AEs occurring up to 28 days following date of last dose.

The following PTs have been grouped: Neutropenia and Neutrophil count decreased into Neutropenia; Leukopenia and White blood cell count decreased into Leukopenia; Thrombocytopenia and Platelet count decreased into Thrombocytopenia; Urinary tract infection, Cystitis, Pyelonephritis, Pyelonephritis acute, and Escherichia urinary tract infection into Urinary tract infection; Pneumonia respiratory syncytial viral, Atypical pneumonia, Pneumonia, Respiratory tract infection into Pneumonia; Anaemia, Anaemia macrocytic, and Iron deficiency anaemia into Anaemia.

Table 78: Adverse Events Possibly Related to Camizestrant/AI and/or CDK4/6 Inhibitor in $\geq 5\%$ of Subjects, by System Organ Class and Preferred Term (Combined CDK4/6 Inhibitors) – DCO1

	SERENA-6		Combination therapy pool	Monotherapy pool
System organ class Preferred term/Grouped term (MedDRA version 28.0)	Camizestrant + CDK4/6 inhibitor (N = 155) n (%)^a	AI + CDK4/6 inhibitor (N = 155) n (%)^a	Camizestrant + CDK4/6 inhibitor (N = 263) n (%)^a	Camizestrant (N = 117) n (%)^a
Patients with any AE possibly related to camizestrant/AI and/or CDK4/6i ^b	131 (84.5)	110 (71.0)	235 (89.4)	79 (67.5)
Infections and infestations	9 (5.8)	8 (5.2)	18 (6.8)	5 (4.3)
Blood and lymphatic system disorders	93 (60.0)	79 (51.0)	161 (61.2)	15 (12.8)
Neutropenia	86 (55.5)	63 (40.6)	151 (57.4)	4 (3.4)
Anaemia	28 (18.1)	26 (16.8)	42 (16.0)	8 (6.8)
Leukopenia	26 (16.8)	11 (7.1)	38 (14.4)	2 (1.7)
Thrombocytopenia	11 (7.1)	12 (7.7)	26 (9.9)	4 (3.4)
Metabolism and nutrition disorders	7 (4.5)	10 (6.5)	23 (8.7)	11 (9.4)

	SERENA-6		Combination therapy pool	Monotherapy pool
System organ class Preferred term/Grouped term (MedDRA version 28.0)	Camizestrant + CDK4/6inhibitor (N = 155) n (%) ^a	AI + CDK4/6 inhibitor (N = 155) n (%) ^a	Camizestrant + CDK4/6 inhibitor (N = 263) n (%) ^a	Camizestrant (N = 117) n (%) ^a
Decreased appetite	3 (1.9)	4 (2.6)	15 (5.7)	2 (1.7)
Nervous system disorders	23 (14.8)	14 (9.0)	44 (16.7)	9 (7.7)
Headache	6 (3.9)	10 (6.5)	9 (3.4)	2 (1.7)
Eye disorders	62 (40.0)	23 (14.8)	119 (45.2)	36 (30.8)
Photopsia	31 (20.0)	10 (6.5)	57 (21.7)	17 (14.5)
Dry eye	12 (7.7)	6 (3.9)	19 (7.2)	1 (0.9)
Vitreous floaters	11 (7.1)	2 (1.3)	20 (7.6)	3 (2.6)
Vision blurred	9 (5.8)	5 (3.2)	11 (4.2)	2 (1.7)
Visual impairment	5 (3.2)	2 (1.3)	23 (8.7)	10 (8.5)
Cardiac disorders	19 (12.3)	2 (1.3)	54 (20.5)	23 (19.7)
Sinus bradycardia				17 (14.5)
Vascular disorders	16 (10.3)	8 (5.2)	23 (8.7)	10 (8.5)
Hot flush	11 (7.1)	6 (3.9)	14 (5.3)	5 (4.3)
Respiratory, thoracic and mediastinal disorders	9 (5.8)	8 (5.2)	15 (5.7)	4 (3.4)
Gastrointestinal disorders	30 (19.4)	34 (21.9)	86 (32.7)	20 (17.1)
Nausea	9 (5.8)	16 (10.3)	42 (16.0)	8 (6.8)
Vomiting	7 (4.5)	4 (2.6)	21 (8.0)	3 (2.6)
Diarrhoea	6 (3.9)	11 (7.1)	37 (14.1)	7 (6.0)
Skin and subcutaneous tissue disorders	24 (15.5)	10 (6.5)	40 (15.2)	12 (10.3)
Pruritus	9 (5.8)	3 (1.9)	15 (5.7)	3 (2.6)
Musculoskeletal and connective tissue disorders	20 (12.9)	21 (13.5)	33 (12.5)	6 (5.1)
Arthralgia	13 (8.4)	15 (9.7)	20 (7.6)	4 (3.4)
General disorders and administration site conditions	38 (24.5)	27 (17.4)	80 (30.4)	12 (10.3)
Fatigue	18 (11.6)	17 (11.0)	38 (14.4)	5 (4.3)
Asthenia	12 (7.7)	5 (3.2)	30 (11.4)	5 (4.3)
Investigations	22 (14.2)	20 (12.9)	67 (25.5)	23 (19.7)
Lymphocyte count decreased	7 (4.5)	2 (1.3)	19 (7.2)	1 (0.9)
Electrocardiogram QT prolonged				7 (6.0)
Aspartate aminotransferase increased	4 (2.6)	10 (6.5)	13 (4.9)	3 (2.6)
Alanine aminotransferase increased	3 (1.9)	10 (6.5)	9 (3.4)	3 (2.6)

[a] Percentages are based on the total number of patients in the treatment group (N).

[b] Possibly related to camizestrant/AI and/or CDK4/6 inhibitor, as assessed by the investigator.

The table includes AEs reported in ≥ 5% of subjects (any treatment group).

Table is sorted by international order for system organ class and descending frequency for preferred term (camizestrant + CDK4/6 inhibitor from SERENA-6).

Patients with multiple AEs are counted once for each system organ class/preferred term.

Note: AEs with an onset date on/after date of first dose; AEs with onset date prior to dosing which worsen after dosing and AEs occurring up to 28 days following date of last dose.

The following PTs have been grouped: Neutropenia and Neutrophil count decreased into Neutropenia; Leukopenia and White blood cell count decreased into Leukopenia; Thrombocytopenia and Platelet count decreased into Thrombocytopenia; Urinary tract infection, Cystitis, Pyelonephritis, Pyelonephritis acute, and Escherichia urinary

tract infection into Urinary tract infection; Pneumonia respiratory syncytial viral, Atypical pneumonia, Pneumonia, Respiratory tract infection into Pneumonia; Anaemia, Anaemia macrocytic, and Iron deficiency anaemia into Anaemia.

Table 79: Adverse Events of CTCAE Grade 3 or Higher, Possibly Related to Camizestrant/AI and/or CDK4/6 Inhibitor in $\geq 5\%$ of Subjects, by System Organ Class and Preferred Term (Combined CDK4/6 Inhibitors) – DCO1

	SERENA-6		Combination therapy pool	Monotherapy pool
System organ class Preferred term/Grouped term (MedDRA version 28.0)	Camizestrant + CDK4/6 inhibitor (N = 155) n (%) ^a	AI + CDK4/6 inhibitor (N = 155) n (%) ^a	Camizestrant + CDK4/6 inhibitor (N = 263) n (%) ^a	Camizestrant (N = 117) n (%) ^a
Patients with AE of CTCAE Grade 3 or higher, possibly related to camizestrant/AI and/or CDK4/6i ^b	85 (54.8)	61 (39.4)	142 (54.0)	4 (3.4)
Blood and lymphatic system disorders	78 (50.3)	56 (36.1)	126 (47.9)	2 (1.7)
Anaemia	6 (3.9)	10 (6.5)	6 (2.3)	1 (0.9)
Leukopenia	18 (11.6)	3 (1.9)	23 (8.7)	0
Neutropenia	72 (46.5)	49 (31.6)	118 (44.9)	0
Investigations	5 (3.2)	6 (3.9)	14 (5.3)	0

[a] Percentages are based on the total number of patients in the treatment group (N).

[b] Possibly related to camizestrant/AI and/or CDK4/6 inhibitor, as assessed by the investigator.

The table includes AEs reported in $\geq 5\%$ of subjects (any treatment group). A system organ class row will be included if there are AEs occurring in $\geq 5\%$ of subjects (any treatment group) for that system organ class, even if there are no preferred terms that meet the condition.

Table is sorted by international order for system organ class and descending frequency for preferred term (camizestrant + CDK4/6 inhibitor from SERENA-6). Patients with multiple AEs are counted once for each system organ class/preferred term.

Note: AEs with an onset date on/after date of first dose; AEs with onset date prior to dosing which worsen after dosing and AEs occurring up to 28 days following date of last dose.

The following PTs have been grouped: Neutropenia and Neutrophil count decreased into Neutropenia; Leukopenia and White blood cell count decreased into Leukopenia; Thrombocytopenia and Platelet count decreased into Thrombocytopenia; Urinary tract infection, Cystitis, Pyelonephritis, Pyelonephritis acute, and Escherichia urinary tract infection into Urinary tract infection; Pneumonia respiratory syncytial viral, Atypical pneumonia, Pneumonia, Respiratory tract infection into Pneumonia; Anaemia, Anaemia macrocytic, and Iron deficiency anaemia into Anaemia.

Table 80: Most Common Adverse Events and Exposure-adjusted Incidence Rates of CTCAE Grade ≥ 3 (≥ 2 Patients in any arm) in Pivotal and Pooled Studies (Safety Analysis Set)

	SERENA-6		Pool	
Preferred term (MedDRA version 27.1)	Camizestrant + CDK4/6 inhibitor (N = 155) n (%) [EAIR] _{a, b}	AI+ CDK4/6 inhibitor (N = 155) n (%) [EAIR] _{a, b}	Camizestrant + CDK4/6 inhibitor (N = 263) n (%) [EAIR] _{a, b}	Camizestrant monotherapy (N = 117) n (%) [EAIR] _{a, b}
Patients with any AE of CTCAE Grade ≥ 3	100 (64.5) [99.4]	82 (52.9) [105.7]	172 (65.4) [133.6]	20 (17.1) [23.3]
Neutropenia ^c	76 (49.0) [62.4]	58 (37.4) [66.6]	122 (46.4) [72.1]	2 (1.7) [2.1]
Anaemia	7 (4.5) [4.8]	8 (5.2) [8.0]	7 (2.7) [3.2]	1 (0.9) [1.0]
Leukopenia ^d	19 (12.3) [10.0]	4 (2.6) [3.2]	24 (9.1) [9.2]	1 (0.9) [1.0]
Thrombocytopenia	4 (2.6) [1.9]	1 (0.6) [0.8]	4 (1.5) [1.4]	1 (0.9) [1.0]
Hypokalaemia	2 (1.3) [1.0]	1 (0.6) [0.8]	3 (1.1) [1.1]	1 (0.9) [1.1]
Lymphocyte count decreased				0
Pneumonia	3 (1.9) [1.4]	2 (1.3) [1.5]	4 (1.5) [1.4]	0
Urinary tract infection	2 (1.3) [1.0]	1 (0.6) [0.8]	2 (0.8) [0.7]	0
Back pain	1 (0.6) [0.5]	0	3 (1.1) [1.1]	0
Electrocardiogram QT prolonged				1 (0.9) [1.1]
Hypertension	1 (0.6) [0.5]	2 (1.3) [1.5]	7 (2.7) [2.5]	3 (2.6) [3.1]
Hypertriglyceridaemia				0
Pulmonary embolism				0

	SERENA-6		Pool	
Preferred term (MedDRA version 27.1)	Camizestrant + CDK4/6 inhibitor (N = 155) n (%) [EAIR] a, b	AI+ CDK4/6 inhibitor (N = 155) n (%) [EAIR] a, b	Camizestrant + CDK4/6 inhibitor (N = 263) n (%) [EAIR] a, b	Camizestrant monotherapy (N = 117) n (%) [EAIR] a, b
Syncope				0
Vomiting	1 (0.6) [0.5]	1 (0.6) [0.8]	2 (0.8) [0.7]	0
Abdominal pain				0
Alanine aminotransferase increased				0
Aspartate aminotransferase increased				0
Diarrhoea				0
Dyspnoea				0
Fatigue	1 (0.6) [0.5]	1 (0.6) [0.8]	3 (1.1) [1.1]	0
Gamma- glutamyltransferase increased	1 (0.6) [0.5]	5 (3.2) [3.9]	1 (0.4) [0.4]	0

a. Percentages are based on the total number of patients in the treatment group (N).

b. EAIR is defined as the number of patients with AEs divided by the total number of days at risk for AEs across all patients in given group, multiplied by 365.25 multiplied by 100.

c. Neutropenia and Neutrophil count decreased have been regrouped into neutropenia

d. Leukopenia and white blood cell count decreased have been regrouped leukopenia

Table is sorted in descending frequency by preferred term (camizestrant + CDK4/6 inhibitor from SERENA-6).

Patients with multiple AEs are counted once for each preferred term.

Note: AEs with an onset date on/after date of first dose; AEs with onset date prior to dosing which worsen after dosing and AEs occurring up to 28 days following date of last dose.

CTCAE version 4.0 in SERENA-1 and version 5.0 in SERENA-2, and -6.

5.4.3.1. Adverse drug reactions

Table 81: Adverse Drug Reaction by Grouped Term and Preferred Term (SERENA-6) – DCO3

	SERENA-6		Pool	
ADR grouped term Preferred term (MedDRA version 27.1)	Camizestrant + CDK4/6 inhibitor (N=155) n (%) Category ^{a, b}	AI + CDK4/6 inhibitor (N=155) n (%) Category ^{a, b}	Camizestrant + CDK4/6 inhibitor (N=263) n (%) Category ^{a, b}	Camizestrant monotherapy (N=117) n (%) Category ^{a, b}
Infections	61 (39.4) Very Common	50 (32.3) Very Common	101 (38.4) Very Common	34 (29.1) Very Common
Neutropenia	91 (58.7) Very Common	76 (49.0) Very Common	157 (59.7) Very Common	6 (5.1) Common
Anaemia	37 (23.9) Very Common	35 (22.6) Very Common	56 (21.3) Very Common	18 (15.4) Very Common
Leukopenia	29 (18.7) Very Common	13 (8.4) Common	41 (15.6) Very Common	5 (4.3) Common
Thrombocytopenia	17 (11.0) Very Common	15 (9.7) Common	34 (12.9) Very Common	5 (4.3) Common
Lymphopenia	3 (1.9) Common	2 (1.3) Common	9 (3.4) Common	2 (1.7) Common
Febrile neutropenia	1 (0.6) Uncommon	0	1 (0.4) Uncommon	1 (0.9) Uncommon
Decreased appetite	7 (4.5) Common	9 (5.8) Common	22 (8.4) Common	6 (5.1) Common
Hypokalaemia	6 (3.9) Common	8 (5.2) Common	9 (3.4) Common	3 (2.6) Common
Hypophosphatemia	4 (2.6) Common	4 (2.6) Common	5 (1.9) Common	1 (0.9) Uncommon
Hypocalcaemia	4 (2.6) Common	1 (0.6) Uncommon	5 (1.9) Common	3 (2.6) Common
Dizziness	11 (7.1) Common	7 (4.5) Common	27 (10.3) Very Common	9 (7.7) Common
Headache	15 (9.7) Common	22 (14.2) Very Common	27 (10.3) Very Common	8 (6.8) Common
Dysgeusia				0
				0
Syncope				
Visual effects	51 (32.9) Very Common	26 (16.8) Very Common	107 (40.7) Very Common	34 (29.1) Very Common
Dry eye	20 (12.9) Very Common	11 (7.1) Common	28 (10.6) Very Common	2 (1.7) Common
Bradycardia	16 (10.3) Very common	0	52 (19.8) Very Common	22 (18.8) Very Common
Torsades de Pointes	0	0		

	SERENA-6		Pool	
ADR grouped term Preferred term (MedDRA version 27.1)	Camizestrant + CDK4/6 inhibitor (N=155) n (%) Category ^{a, b}	AI + CDK4/6 inhibitor (N=155) n (%) Category ^{a, b}	Camizestrant + CDK4/6 inhibitor (N=263) n (%) Category ^{a, b}	Camizestrant monotherapy (N=117) n (%) Category ^{a, b}
Deep vein thrombosis	4 (2.6) Common	1 (0.6) Uncommon	4 (1.5) Common	0
Embolism				0
Cough	14 (9.0) Common	8 (5.2) Common	37 (14.1) Very Common	8 (6.8) Common
Dyspnoea	8 (5.2) Common	9 (5.8) Common	24 (9.1) Common	5 (4.3) Common
Pulmonary embolism	1 (0.6) Uncommon	2 (1.3) Common	2 (0.8) Uncommon	0
Diarrhoea	16 (10.3) Very Common	21 (13.5) Very Common	56 (21.3) Very Common	12 (10.3) Very Common
Nausea	17 (11.0) Very Common	24 (15.5) Very Common	56 (21.3) Very Common	14 (12.0) Very Common
Vomiting	13 (8.4) Common	11 (7.1) Common	37 (14.1) Very Common	6 (5.1) Common
Constipation	11 (7.1) Common	16 (10.3) Very Common	19 (7.2) Common	9 (7.7) Common
Abdominal pain	6 (3.9) Common	10 (6.5) Common	19 (7.2) Common	2 (1.7) Common
Stomatitis	9 (5.8) Common	9 (5.8) Common	14 (5.3) Common	2 (1.7) Common
Pruritus	9 (5.8) Common	6 (3.9) Common	21 (8.0) Common	6 (5.1) Common
Alopecia	9 (5.8) Common	5 (3.2) Common	14 (5.3) Common	4 (3.4) Common
Back pain	19 (12.3) Very Common	17 (11.0) Very Common	32 (12.2) Very Common	8 (6.8) Common
Fatigue	25 (16.1) Very Common	27 (17.4) Very Common	54 (20.5) Very Common	8 (6.8) Common
Asthenia	13 (8.4) Common	10 (6.5) Common	36 (13.7) Very Common	10 (8.5) Common
Pyrexia	9 (5.8) Common	4 (2.6) Common	17 (6.5) Common	4 (3.4) Common
Aspartate aminotransferase increased	9 (5.8) Common	13 (8.4) Common	25 (9.5) Common	9 (7.7) Common
Alanine aminotransferase increased	8 (5.2) Common	13 (8.4) Common	21 (8.0) Common	4 (3.4) Common
Blood creatinine increased	7 (4.5) Common	12 (7.7) Common	23 (8.7) Common	0
Electrocardiogram QT prolonged	6 (3.9) Common	2 (1.3) Common	18 (6.8) Common	8 (6.8) Common

a. Percentages are based on the total number of patients in the treatment group (N).

- b. Category is defined based on CIOMS III convention before rounding: (1) very common ($\geq 1/10$), (2) common ($\geq 1/100$ to $< 1/10$), (3) uncommon ($\geq 1/1,000$ to $< 1/100$), (4) rare ($\geq 1/10,000$ to $< 1/1,000$), (5) very rare ($< 1/10,000$), and (6) NK (not known -cannot be estimated from available data)

Table is sorted in alphabetical order by ADR grouped term and descending frequency for preferred term (camizestrant + CDK4/6 inhibitor from SERENA-6).

Patients with multiple ADRs are counted once for each grouped term/preferred term.

Note: ADRs with an onset date on/after date of first dose; ADRs with onset date prior to dosing which worsen after dosing and ADRs occurring up to 28 days following date of last dose.

A screening process for ADRs was conducted when a summary table of overall frequencies of AEs by treatment group was available for the SERENA-6 study.

The approach to identify the ADRs was as follows:

- 1 All AEs (by PT) reported in at least 10% (or an alternative appropriate threshold chosen) of patients in the camizestrant + CDK4/6 inhibitor arm in SERENA-6 with at least 5% difference (or an alternative appropriate threshold) between the 2 treatment arms were considered as potential ADRs and subject to clinical review.
- 2 A similar approach was applied to Grade 3-4 or higher events only, whereby a 2% difference (or an alternative appropriate threshold) was used to screen for potential ADRs.
- 3 Clinical review of all safety data from SERENA-6, SERENA-1, SERENA-2, China and Japan Phase I studies was performed to identify any ADR candidates not selected by the above screening strategy (eg, ADR candidates with a very low occurrence rate, or single cases, or reported in SERENA-1 SERENA-2, China and Japan Phase I studies only). These were added to the list of ADRs if deemed medically relevant and suspected to be treatment related.

Table 82: Summary of ADRs as presented in the SmPC – DCO3 ^a

MedDRA SOC	MedDRA Term	All Grades (%) category	Grade 3 or 4 (%) category
Infections and infestations	Infections ^{d,e,f,g}	Very common (38.4%)	Common (3.4%)
Blood and lymphatic system disorders	Neutropenia ^{e,f,g,h}	Very common (59.7%)	Very common (46.4%)
	Anaemia ^{e,f,g,i}	Very common (21.3%)	Common (3.4%)
	Leukopenia ^{e,f,g,j}	Very common (15.6%)	Common (9.1%)
	Thrombocytopenia ^{e,f,g,k}	Very common (12.9%)	Common (1.5%)
	Lymphopenia ^{f,g}	Common (3.4%)	Uncommon (0.4%)
	Febrile neutropenia ^{e,f,g}	Uncommon (0.4%)	Uncommon (0.4%)
Metabolism and nutrition disorders	Decreased appetite ^{e,f,g}	Common (8.4%)	Uncommon (3.4%)
	Hypokalaemia ^g	Common (3.4%)	Common (1.1%)

	Hypophosphatemia ^g	Common (1.9%)	Uncommon (0.8%)
	Hypocalcaemia ^g	Common (1.9%)	Uncommon (0.4%)
Nervous system disorders	Dizziness ^{f,g}	Very common (10.3%)	Uncommon (0.4%)
	Headache ^{f,g}	Very common (10.3%)	Uncommon (0.8%)
	Dysgeusia ^{e,f}	Common (3.8%)	Uncommon (0.4%)
	Syncope ^g	Common (1.1%)	Uncommon (0.8%)
Eye disorders	Visual effects ^b	Very common (40.7%)	Uncommon (0.4 %)
	Dry eye ^{e,g}	Very common (10.6%)	-
Cardiac disorders	Bradycardia ^c	Very common (19.8%)	-
Vascular disorders	Deep vein thrombosis ^{e,f}	Common (1.5%)	Uncommon (0.8%)
	Embolism ^e	Uncommon (0.8%)	Uncommon (0.8%)
Respiratory, thoracic and mediastinal disorders	Cough ^g	Very common (14.1%)	-
	Dyspnoea ^g	Common (9.1%)	Uncommon (0.8%)
	Pulmonary embolism ^{e,f}	Uncommon (0.8%)	Uncommon (0.8%)
Gastrointestinal disorders	Diarrhoea ^{e,f,g}	Very common (21.3%)	Common (1.5%)
	Nausea ^{e,f,g}	Very common (21.3%)	Uncommon (0.4%)
	Vomiting ^{e,f,g}	Very common (14.1%)	Uncommon (0.8%)

	Constipation ^g	Common (7.2%)	-
	Abdominal pain ^g	Common (7.2%)	Common (1.1%)
	Stomatitis ^{e,f,g}	Common (5.3%)	-
Skin and subcutaneous tissue disorders	Pruritus ^{f,g}	Common (8.0%)	-
	Alopecia ^{e,f,g}	Common (5.3%)	-
Musculoskeletal and connective tissue disorders	Back pain ^g	Very common (12.2%)	Common (1.1%)
General disorders and administration site conditions	Fatigue ^{e,f,g}	Very common (20.5%)	Common (1.1%)
	Asthenia ^{e,g}	Very common (13.7%)	Uncommon (0.4%)
	Pyrexia ^{e,f,g}	Common (6.5%)	Uncommon (0.3%)
Investigations	Aspartate aminotransferase increased ^{e,f,g}	Common (9.5%)	Uncommon (0.8%)
	Alanine aminotransferase increased ^{e,f,g}	Common (8.0%)	Common (2.3%)
	Blood creatinine increased ^{e,g}	Common (8.7%)	-
	Electrocardiogram QT prolonged ^g	Common (6.8%)	Common (1.5%)

^a Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

^b Visual effects include photopsia, vision blurred, visual impairment, diplopia, and photophobia of eye disorders MedDRA SOC, and visual perseveration of nervous system disorders MedDRA SOC. In addition to camizestrant, vision blurred is an ADR for palbociclib and photopsia is an ADR for abemaciclib.

^c Bradycardia includes bradycardia and sinus bradycardia.

^d All PTs under the Infections and Infestation SOC.

^e ADR for camizestrant and palbociclib combination.

^f ADR for camizestrant and abemaciclib combination.

^g ADR for camizestrant and ribociclib combination.

^h Neutropenia includes neutropenia and neutrophil count decreased.

ⁱ Anaemia includes anaemia, anaemia macrocytic and iron deficiency anaemia.

^j Leukopenia includes leukopenia and white blood cell count decreased.

^k Thrombocytopenia includes thrombocytopenia and platelet count decreased.

The common serious adverse reactions ($\geq 1\%$) reported in patients receiving Etcamah in combination with a CDK4/6 inhibitor included infections (3.4%) and pyrexia (1.1%).

5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events

5.4.4.1. Bradycardia

This AESI was evaluated by a review of grouped PTs, comprising bradycardia and sinus bradycardia.

Based on the non-clinical toxicology and clinical safety findings observed across the camizestrant clinical program, bradycardia was an identified risk for camizestrant and classified as an AESI for further risk characterisation in the SERENA-6 study.

Table 83: Characterisation of Bradycardia in Pivotal and Pooled Studies (Safety Analysis Set)– DCO3

Statistic	SERENA-6		Pool	
	Camizestrant + CDK4/6 inhibitor (N = 155)	AI + CDK4/6 inhibitor (N = 155)	Camizestrant + CDK4/6 inhibitor (N = 263)	Camizestrant monotherapy (N = 117)
Patients with any AESI n (%) ^a				22 (18.8)
Serious AESI n (%) ^a	0	0	0	0
Number of AESI per subject (among subjects with ≥ 1 AESI)				
Min			1	1
Median			1.0	1.0
Max			4	4
Time-to-onset of first AESI per subject (days)				
Min			1	8
Median			15.0	18.5
Max			465	1149
Maximum reported CTCAE grade				
Total				22 (18.8)
Grade 1				21 (17.9)
Grade 2				1 (0.9)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Unknown	0	0	0	0
AESI leading to dose modification or discontinuation of camizestrant/AI n (%) ^a				3 (2.6)
AESI leading to discontinuation of camizestrant/AI n (%) ^a	0	0	0	0
AESI leading to dose reduction of camizestrant/AI n (%) ^{a, b}				1 (0.9)
AESI leading to dose interruption of camizestrant/AI n (%) ^a				2 (1.7)
AESI possibly related to camizestrant/AI ^c n (%) ^a				21 (17.9)

	SERENA-6		Pool	
Statistic	Camizestrant + CDK4/6 inhibitor (N = 155)	AI + CDK4/6 inhibitor (N = 155)	Camizestrant + CDK4/6 inhibitor (N = 263)	Camizestrant monotherapy (N = 117)
Outcome of AESI				
Recovered/Resolved n (%) ^{a, d}				16 (13.7)
Recovering/Resolving n (%) ^a	0	0	3 (1.1)	0
Recovered/Resolved with Sequelae n (%) ^a	0	0	1 (0.4)	0
Not Recovered/Not Resolved n (%) ^a				7 (6.0)
Fatal n (%) ^a	0	0	0	0
Time of resolution of AESI with an outcome recovered/resolved				
On-treatment ^e n (%) ^a				13 (11.1)
Follow-up ^f n (%) ^a				5 (4.3)
Post-treatment ^g n (%) ^a	0	0	2 (0.8)	0

- a. Percentages are based on the total number of patients in the treatment group (N).
- b. Dose reductions of AI in the control arm refer to dose reduction in camizestrant placebo.
- c. Possibly related to camizestrant/AI, as assessed by the investigator.
- d. Each patient was counted once per category, a patient was counted in more than one category if the outcomes were different.
- e. On-treatment includes AEs with end date up to and including the date of last dose of investigational product.
- f. Follow-up includes AEs with end date within 28 days following the date of last dose of investigational product.
- g. Post-treatment includes AEs with end date more than 28 days following the date of last dose of investigational product.

CTCAE version 4.0 in SERENA-1 and version 5.0 in SERENA-2, -6, China, and Japan Phase I studies.

Note: AESIs with an onset date on/after date of first dose; AESIs with onset date prior to dosing which worsen after dosing and AESIs occurring up to 28 days following date of last dose.

Table 84: AESI bradycardia - Electrocardiogram results over time (Safety Set) – DCO1

ECG Heart Rate (Beats/Min)								
Group								
Timepoint	Result							
	n	Mean	SD	Min	Q1	Median	Q3	Max
AZD9833 + CDK4/6 inhibitor N=155								
Baseline	145	73.7	11.3	49	65.7	73.0	81.0	111
Cycle 1, Day 1	69	75.1	11.6	49	67.0	76.0	82.7	102
Cycle 1, Day 15	129	59.5	7.9	40	53.0	59.0	65.0	83
Cycle 2, Day 1	134	60.9	9.7	42	54.3	60.0	66.3	106
Cycle 3, Day 1	123	61.0	8.5	40	54.0	60.0	66.0	90
Cycle 5, Day 1	115	60.9	9.0	41	54.0	59.3	67.0	88
Cycle 7, Day 1	105	60.2	8.7	42	53.7	59.3	67.0	82
Cycle 9, Day 1	86	60.2	9.3	40	53.7	58.8	66.0	95
Cycle 11, Day 1	72	60.5	8.9	44	53.8	60.5	65.8	86
Cycle 13, Day 1	61	60.5	9.0	45	55.7	58.7	66.0	93
Cycle 15, Day 1	46	60.6	9.1	43	55.0	59.8	65.0	94
Cycle 17, Day 1	38	59.6	7.3	43	56.0	58.0	65.0	73
Cycle 19, Day 1	26	63.1	6.4	52	58.0	64.8	68.0	80
Cycle 21, Day 1	22	61.4	9.7	42	55.0	58.5	70.0	83
Cycle 23, Day 1	13	59.2	6.6	45	54.3	61.0	63.0	69

Cycle 25, Day 1	9	62.9	9.7	53	57.0	61.0	65.0	86
Cycle 27, Day 1	8	63.9	14.2	50	54.5	61.0	67.5	95
Cycle 29, Day 1	7	57.6	8.4	48	50.0	56.0	63.0	73
Cycle 31, Day 1	5	63.8	10.4	57	57.0	58.0	66.5	81
Cycle 33, Day 1	4	56.8	2.1	54	55.5	57.0	58.0	59
Cycle 35, Day 1	4	56.3	5.7	49	52.7	56.7	60.0	63
End of Treatment	52	66.6	13.1	45	55.7	66.0	74.5	109
Safety Follow-up	20	75.3	15.3	51	62.5	74.0	86.5	106

Group Timepoint	Change from Baseline							
	n	Mean	SD	Min	Q1	Median	Q3	Max
AZD9833 + CDK4/6 inhibitor N=155								
Baseline	145							
Cycle 1, Day 1	69	0.0	9.4	-27	-6.7	0.3	7.0	21
Cycle 1, Day 15	129	-14.5	9.9	-39	-21.7	-14.0	-8.3	11
Cycle 2, Day 1	134	-12.1	10.6	-35	-17.7	-12.5	-6.7	54
Cycle 3, Day 1	123	-12.8	10.0	-36	-20.3	-12.7	-7.3	25
Cycle 5, Day 1	115	-13.1	9.8	-40	-19.0	-12.3	-8.0	13
Cycle 7, Day 1	105	-13.5	10.0	-37	-20.7	-14.0	-8.0	11
Cycle 9, Day 1	86	-12.6	10.2	-39	-18.3	-12.0	-8.0	21
Cycle 11, Day 1	72	-13.0	9.3	-42	-18.5	-11.7	-7.2	8
Cycle 13, Day 1	61	-12.6	12.3	-38	-20.3	-11.0	-6.3	41
Cycle 15, Day 1	46	-12.9	9.7	-39	-19.7	-12.0	-6.7	9
Cycle 17, Day 1	38	-14.5	9.8	-36	-19.7	-11.0	-6.7	0
Cycle 19, Day 1	26	-9.9	8.4	-30	-12.0	-7.8	-5.7	6
Cycle 21, Day 1	22	-11.8	10.2	-29	-18.0	-14.3	-5.0	17
Cycle 23, Day 1	13	-12.7	8.8	-33	-17.0	-12.0	-10.7	11
Cycle 25, Day 1	9	62.9	9.7	53	57.0	61.0	65.0	86
Cycle 27, Day 1	8	63.9	14.2	50	54.5	61.0	67.5	95
Cycle 29, Day 1	7	57.6	8.4	48	50.0	56.0	63.0	73
Cycle 31, Day 1	5	63.8	10.4	57	57.0	58.0	66.5	81
Cycle 33, Day 1	4	56.8	2.1	54	55.5	57.0	58.0	59
Cycle 35, Day 1	4	56.3	5.7	49	52.7	56.7	60.0	63
End of Treatment	52	66.6	13.1	45	55.7	66.0	74.5	109
Safety Follow-up	20	75.3	15.3	51	62.5	74.0	86.5	106

Among the 19.8% patients with bradycardia reported, 85% patients had bradycardia reported as asymptomatic CTCAE Grade 1, while the remaining 15% had Grade 2 adverse reactions reported. Bradycardia exhibited a time-dependent onset where a gradual decrease in heart rate can reach a stable nadir at approximately 14 days and generally recovered following treatment cessation in a similar time course.

QTc prolongation has been reported as an adverse reaction in 18 patients (6.8%) within the Etcamah and CDK4/6 inhibitor combination. Of those, 14 were reported as Grade 1 or Grade 2; 3 were reported as Grade 3 and one as Grade 4 (all Grade 3 and 4 were in combination with ribociclib). There was one report of CTCAE Grade 4 QT prolongation for camizestrant in combination with ribociclib in a phase 1 study where ribociclib and camizestrant were administered concomitantly and ribociclib dose modification guidance was not followed. The case was also confounded by multiple contributing factors and the patient recovered.

5.4.4.2. Visual effects

This AESI was evaluated by a review of grouped PTs, comprising photopsia, vision blurred, visual impairment, diplopia, photophobia, visual perseveration, and glare.

Table 85: Number of Patients with Ophthalmological Assessments (SERENA-6)– DCO1

Ophthalmological Assessment	Number of patients with assessment at baseline and at least one post-baseline assessment	
	Camizestrant + CDK4/6 inhibitor	AI + CDK4/6 inhibitor
Fundoscopy	39	38
Slit lamp examination	36	35
Pupillary light reflex test – right/left	36	32
Extraocular muscle movement test – right/left	37	32
Optical coherence tomography -right/left	31	33
Visual field	41	39
Intraocular pressure ^a	30	32
Visual acuity – right/left	36/35	35/35

a. For intraocular pressure the number of patients shown is those that had a reading at baseline and at end of treatment.

Of the 40.7% patients who reported visual effects, the majority (92.5%) experienced CTCAE Grade 1 adverse reactions, while 6.5% patients experienced CTCAE Grade 2 adverse reactions and 0.9% CTCAE Grade 3 adverse reaction (photopsia) occurred. The most common visual effect was photopsia (24.0%). The median time to the onset of the first visual effect was 9 days. Visual effects ADRs were typically intermittent, of brief duration, and not continuous throughout the day (typically reported in the evening or morning). Visual effects were reported not to worsen over time in patients. Ophthalmological review of patients reporting visual effects showed no evidence of structural effects on the eye or clinically meaningful changes in visual acuity attributed to camizestrant.

Table 86: Characterisation of Visual Effects in Pivotal and Pooled Studies (Safety Analysis Set)– DCO3

Statistic	SERENA-6		Pool	
	Camizestrant + CDK4/6 inhibitor (N = 155)	AI + CDK4/6 inhibitor (N = 155)	Camizestrant + CDK4/6 inhibitor (N = 263)	Camizestrant monotherapy (N = 117)
Patients with any AESI n (%) ^a	51 (32.9)	26 (16.8)	107 (40.7)	34 (29.1)
Serious AESI n (%) ^a	0	1 (0.6)	0	0
Number of AESI per subject (among subjects with ≥ 1 AESI)				
Min	1	1	1	1
Median	1.0	1.0	1.0	1.0
Max	3	4	3	3
Time-to-onset of first AESI per subject (days)				
Min	1	1	1	1
Median	8.0	26.5	9.0	10.5
Max	364	444	364	159
Maximum reported CTCAE grade				
Total	51 (32.9)	26 (16.8)	107 (40.7)	34 (29.1)
Grade 1	46 (29.7)	25 (16.1)	99 (37.6)	33 (28.2)
Grade 2	4 (2.6)	1 (0.6)	7 (2.7)	1 (0.9)
Grade 3				0
Grade 4	0	0	0	0
Grade 5	0	0	0	0

Unknown	0	0	0	0
AESI leading to dose modification or discontinuation of camizestrant/AI n (%) ^a				0
AESI leading to discontinuation of camizestrant/AI n (%) ^a	0	0	0	0
AESI leading to dose reduction of camizestrant/AI n (%) ^{a, b}	0	0	0	0
AESI leading to dose interruption of camizestrant/AI n (%) ^a				0
AESI possibly related to camizestrant/AI ^c n (%) ^a	45 (29.0)	16 (10.3)	93 (35.4)	32 (27.4)
Outcome of AESI				
Recovered/Resolved n (%) ^{a, d}	41 (26.5)	23 (14.8)	79 (30)	26 (22.2)
Recovering/Resolving n (%) ^a				0
Recovered/Resolved with Sequelae n (%) ^a	0	0	0	1 (0.9) ^e
Not Recovered/Not Resolved n (%) ^a	10 (6.5)	4 (2.6)	30 (11.4)	10 (8.5)
Fatal n (%) ^a	0	0	0	0
Time of resolution of AESI with an outcome recovered/resolved				
On-treatment ^f n (%) ^a	28 (18.1)	20 (12.9)	53 (20.2)	17 (14.5)
Follow-up ^g n (%) ^a	12 (7.7)	1 (0.6)	25 (9.5)	9 (7.7)
Post-treatment ^h n (%) ^a	2 (1.3)	2 (1.3)	6 (2.3)	0

- Percentages are based on the total number of patients in the treatment group (N).
- Dose reductions of AI in the control arm refer to dose reduction in camizestrant placebo.
- Possibly related to camizestrant/AI, as assessed by the investigator.
- Each patient was counted once per category, a patient was counted in more than one category if the outcomes were different.
- One patient in the camizestrant 75 mg monotherapy pool experienced CTCAE Grade 1 photopsia from Day 21 to Day 175, reported as possibly related and recovered with sequelae; the dose of camizestrant was not changed. An AE of cataract was also reported in the same patient on Day 175 which was considered as not related to camizestrant (see Appendix 16.2.7.1, Japan Phase I study, Module 5.3.3.2).
- On-treatment includes AEs with end date up to and including the date of last dose of investigational product.
- Follow-up includes AEs with end date within 28 days following the date of last dose of investigational product.
- Post-treatment includes AEs with end date more than 28 days following the date of last dose of investigational product.

CTCAE version 4.0 in SERENA-1 and version 5.0 in SERENA-2, -6, China, and Japan Phase I studies.

Note: AESIs with an onset date on/after date of first dose; AESIs with onset date prior to dosing which worsen after dosing and AESIs occurring up to 28 days following date of last dose.

5.4.4.3. Deaths

Table 87: All deaths (combined CDK 4/6i) – DCO1

	SERENA-6		Combo Therapy Pool	Monotherapy Pool
	Cam1 + CDK4/6i (N=155) n (%) [a]	AI + CDK4/6i (N=155) n (%) [a]	Cam1 + CDK4/6i (N=263) n (%) [a]	Camizestrant (N=117) n (%) [a]
Primary cause of death				
Any	20 (12.9)	18 (11.6)	21 (8.0)	46 (39.3)
Related to disease under investigation [b]	13 (8.4)	14 (9.0)	13 (4.9)	43 (36.8)
AE	2 (1.3)	1 (0.6)	2 (0.8)	0
On treatment [c]	2 (1.3)	0	2 (0.8)	0
Post-treatment [d]	0	1 (0.6)	0	0
Other [e]	5 (3.2)	3 (1.9)	6 (2.3)	3 (2.6)
Secondary cause of death				
Any	2 (1.3)	4 (2.6)	2 (0.8)	0
Related to disease under investigation [b]	0	2 (1.3)	0	0
AE	0	1 (0.6)	0	0
On treatment [c]	0	1 (0.6)	0	0
Post-treatment [d]	0	0	0	0
Other [e]	2 (1.3)	1 (0.6)	2 (0.8)	0

[a] Percentages are based on the total number of patients in the treatment group (N).

[b] Death related to disease under investigation is determined by the investigator.

[c] On treatment includes adverse events with an onset date or that worsen on or after the date of first dose of IP up to and including 28 days following the date of last dose of IP and prior to the start of any subsequent cancer therapy.

[d] Post-treatment includes adverse events with an onset date more than 28 days after last dose of IP or once subsequent cancer therapy started, whichever comes first.

[e] Subjects who died and are not captured in the earlier categories

SERENA-1 study eCRF does not collect information pertinent to AE regardless of primary or secondary cause of death, while SERENA-2 study eCRF does not collect analyzable data for secondary cause of death.

Categories within each primary and secondary cause of death are mutually exclusive.

AI Aromatase Inhibitor; CDK4/6i Cyclin dependent kinase inhibitor;

n Number of subjects per category; N Number of subjects per treatment group.

5.4.5. Discontinuation due to adverse events

5.4.6. Adverse events leading to discontinuation of treatment

Table 88: Adverse Events Leading to Discontinuation of Camizestrant/AI in Pivotal and Pooled Studies (Safety Analysis Set)– DCO1

Preferred Term (MedDRA version 27.1)	SERENA-6		Pool	
	Camizestrant + CDK4/6 inhibitor (N=155) n (%) [EAIR] a, b	AI + CDK4/6 inhibitor (N=155) n (%) [EAIR] a, b	Camizestrant + CDK4/6 inhibitor (N=263) n (%) [EAIR] a, b	Camizestrant monotherapy (N=117) n (%) [EAIR] a, b
Patients with any AE leading to dose discontinuation of camizestrant/AI	2 (1.3) [1.4]	3 (1.9) [3.0]	3 (1.1) [1.4]	3 (2.6) [3.1]
Aspartate aminotransferase increased				0
Cholestasis				0
Dermatitis allergic	0	0	0	1 (0.9) [1.0]

Preferred Term (MedDRA version 27.1)	SERENA-6		Pool	
	Camizestrant + CDK4/6 inhibitor (N=155) n (%) [EAIR] a, b	AI + CDK4/6 inhibitor (N=155) n (%) [EAIR] a, b	Camizestrant + CDK4/6 inhibitor (N=263) n (%) [EAIR] a, b	Camizestrant monotherapy (N=117) n (%) [EAIR] a, b
Fatigue				0
Gamma-glutamyltransferase increased				0
Gastrooesophageal reflux disease				0
Gingivitis	0	0	0	1 (0.9) [1.0]
Hepatic cytolysis				0
Neutropenia	0	0	1 (0.4) [0.5]	0
Pneumonia				0
Swelling face	0	0	0	1 (0.9) [1.0]

a. Percentages are based on the total number of patients in the treatment group (N).

b. EAIR is defined as the number of patients with AEs divided by the total number of days at risk for AEs across all patients in given group, multiplied by 365.25 multiplied by 100.

Table is sorted by alphabetical order for preferred term.

Patients with multiple AEs leading to dose discontinuation of investigational product are counted once for each preferred term.

Note: AEs with an onset date on/after date of first dose; AEs with onset date prior to dosing which worsen after dosing and AEs occurring up to 28 days following date of last dose.

At DC03, the adverse reactions leading to treatment discontinuation of Etcamah in patients receiving camizestrant in combination with a CDK4/6 inhibitor were neutropenia (0.4%) and electrocardiogram QT prolonged (0.4%).

5.4.7. Adverse events leading to dose modifications

The CSP guidance on dose modifications differed between the SERENA-1, SERENA-2, and SERENA-6 studies; and therefore, the dose modifications between SERENA-6 and the pooled data, including the monotherapy pool, were not comparable. At DCO3, the most common adverse reactions ($\geq 2\%$) leading to dose modification of camizestrant in patients receiving camizestrant in combination with a CDK4/6 inhibitor were infections (6.8%), neutropenia (6.5%), bradycardia (4.2%), electrocardiogram QT prolonged (3.4%), diarrhoea (2.3%), vomiting (2.3%) and visual effects (2.3%)

SERENA-6

Table 89: Incidence of Adverse Events Leading to Dose Modification, Dose Reduction, and Dose Interruption of Camizestrant/AI, CDK4/6 Inhibitor, and LHRH Agonist in SERENA-6 Study (Safety Analysis Set)– DCO1

AE category	Camizestrant + CDK4/6 inhibitor	AI + CDK4/6 inhibitor
	N = 155 n (%)	N = 155 n (%)
Any AE leading to dose modification of ^a		
camizestrant/AI	39 (25.2)	23 (14.8)
CDK4/6 inhibitor	78 (50.3)	60 (38.7)
Any AE leading to dose reduction of		
camizestrant/AI ^b	9 (5.8)	2 (1.3)
CDK4/6 inhibitor	18 (11.6)	17 (11.0)
Any AE leading to dose interruption of		
camizestrant/AI	34 (21.9)	22 (14.2)
CDK4/6 inhibitor	75 (48.4)	53 (34.2)
LHRH agonist	1 (3.1)	1 (3.3)

a. Dose modification describes an AE where action taken is either dose reduction or drug interruption.

b. Dose reductions of AI in the control arm refer to dose reduction in camizestrant placebo.

The table includes AEs with an onset date or that worsen on or after the date of first dose of IP up to and including 28 days following the date of last dose of IP and prior to the start of any subsequent cancer therapy.

Patients with multiple occurrences in the same category are counted once per category regardless of the number of occurrences.

Table 90: Incidence of Adverse Events leading to Dose Modification, Dose Reduction, and Dose Interruption of Camizestrant/AI, CDK4/6 Inhibitor, and LHRH Agonist in SERENA-6 Study by Individual CDK4/6 Inhibitors (Safety Analysis Set)– DCO1

AE category	camizestrant + palbociclib N = 117 n (%)	AI + palbociclib N = 117 n (%)	camizestrant + ribociclib N = 23 n (%)	AI + ribociclib N = 23 n (%)	camizestrant + abemaciclib N = 15 n (%)	AI + abemaciclib N = 15 n (%)
Any AE leading to dose modification of ^a						
camizestrant/AI	30 (25.6)	20 (17.1)	7 (30.4)	2 (8.7)	2 (13.3)	1 (6.7)
CDK4/6 inhibitor	66 (56.4)	49 (41.9)	9 (39.1)	8 (34.8)	3 (20.0)	3 (20.0)
Any AE leading to dose reduction of						
Camizestrant/AI ^b			5 (21.7)	2 (8.7)	0	0
CDK4/6 inhibitor ^c	14 (12.0)	14 (12.0)	3 (13.0)	3 (13.0)		
Any AE leading to dose interruption of						
Camizestrant/AI	29 (24.8)	20 (17.1)	3 (13.0)	1 (4.3)	2 (13.3)	1 (6.7)

CDK4/6 inhibitor	63 (53.8)	44 (37.6)	9 (39.1)	6 (26.1)	3 (20.0)	3 (20.0)
LHRH agonist ^c	1 (4.8)	1 (6.3)	0	0	0	0

a. Dose modification describes an AE where action taken is either dose reduction or drug interruption.

b. Dose reductions of AI in the control arm refer to dose reduction in camizestrant placebo.

c. For LHRH agonist, n = 21 for camizestrant + palbociclib arm and n = 16 for AI + palbociclib arm.

The table includes AEs with an onset date or that worsen on or after the date of first dose of IP up to and including 28 days following the date of last dose of IP and prior to the start of any subsequent cancer therapy.

Patients with multiple occurrences in the same category are counted once per category regardless of the number of occurrences.

5.4.8. Safety in special populations

Table 91: AEs by age range (AEs by Elderly and Special Population Data in the SERENA-6 Study (Safety Analysis Set) – DCO1

Age Group	Camizestrant + CDK4/6 inhibitor N = 155				AI + CDK4/6 inhibitor N = 155			
	< 65 N = 93 n (%)	65-74 N = 57 n (%)	75-84 N = n (%)	≥ 85 N = n (%)	< 65 N = 102 n (%)	65-74 N = 36 n (%)	75-84 N = n (%)	≥ 85 N = n (%)
Any AE	88 (94.6)	52 (91.2)	5		90 (88.2)	30 (83.3)	14	
Any SAE	9 (9.7)	6 (10.5)	1	0	12 (11.8)	6 (16.7)	1	0
Fatal			0	0			0	0
Hospitalization/prolong existing hospitalization	9 (9.7)	5 (8.8)	1	0	11 (10.8)	6 (16.7)	1	0
Life-threatening	0		0	0	0		0	0
Disability/incapacity			0	0			0	0
Other (medically significant)	1 (1.1)	2 (3.5)	0	0	5 (4.9)	1 (2.8)	0	0
AE leading to discontinuation of any IP		2 (3.5)	0	0		1 (2.8)	0	0
AE leading to discontinuation of Camizestrant/AI		2 (3.5)	0	0		1 (2.8)	0	0
AE leading to discontinuation of CDK4/6 inhibitor		2 (3.5)	0	0		1 (2.8)	0	0
Psychiatric disorders	4 (4.3)	1 (1.8)		0	8 (7.8)	2 (5.6)		0
Nervous system disorders	17 (18.3)	15 (26.3)	1	0	22 (21.6)	8 (22.2)	5	0
Accidents and injuries	1 (1.1)			0	3 (2.9)			0

Cardiac disorders	11 (11.8)	10 (17.5)	0	0	3 (2.9)	2 (5.6)	0	0
Vascular disorders	12 (12.9)	10 (17.5)		0	8 (7.8)	5 (13.9)		0
Cerebrovascular disorders			0	0			0	0
Infections and infestations	31 (33.3)	16 (28.1)	2		28 (27.5)	7 (19.4)	5	
Anticholinergic syndrome	0	0	0	0	0	0	0	0
Quality of life decreased	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures	4 (4.3)	8 (14.0)	1	0	6 (5.9)	1 (2.8)	3	0

Table includes AEs with an onset date or that worsen on or after the date of first dose of IP up to and including 28 days following the date of last dose of IP and prior to the start of any subsequent cancer therapy.

5.4.9. Immunological events

Not applicable.

5.4.10. Safety related to drug-drug interactions and other interactions

Camizestrant is primarily metabolized by CYP3A4, and thus inducers of CYP3A4 can reduce exposure levels of camizestrant. Since ribociclib is a potent inhibitor of CYP3A4, camizestrant exposure is increased approximately two-fold when administered together with ribociclib 400 mg and three-fold when co-administered with ribociclib 600 mg, which corresponds to the exposure reached with camizestrant 150 mg QD monotherapy.

Camizestrant is an inhibitor of CYP2B6, CYP2C9 and CYP2C19.

5.4.11. Vital signs and laboratory findings

5.4.12. Clinical laboratory evaluations

Table 92: Laboratory Abnormalities Occurring in $\geq 10\%$ of Patients in Any Arm in SERENA-6 and Combination Therapy Pool (Safety Set)– DCO1

Laboratory Abnormality	SERENA-6								Combination therapy pool			
	Camizestrant + CDK4/6i (N = 155)		Camizestrant + CDK4/6i (N = 155)		AI + CDK4/6i (N = 155)		AI + CDK4/6i (N = 155)		Camizestrant + CDK4/6i (N = 263)		Camizestrant + CDK4/6i (N = 263)	
	Any grade		Grade 3 or 4		Any grade		Grade 3 or 4		Any grade		Grade 3 or 4	
	n/Nobs	(%)	n/Nobs	(%)	n/Nobs	(%)	n/Nobs	(%)	n/Nobs	(%)	n/Nobs	(%)
B-Hemoglobin (hypo) (g/L)	120/155	(77.4)	9/155	(5.8)	122/154	(79.2)	15/154	(9.7)	206/262	(78.6)	9/262	(3.4)
B-Leukocytes (hypo) ($10^9/L$)	145/155	(93.5)	44/155	(28.4)	137/154	(89.0)	35/154	(22.7)	244/262	(93.1)	74/262	(28.2)
B-Lymphocytes (hypo) ($10^9/L$)	94/137	(68.6)	17/137	(12.4)	84/137	(61.3)	17/137	(12.4)	182/244	(74.6)	30/244	(12.3)
B-Neutrophils (hypo) ($10^9/L$)	126/144	(87.5)	69/144	(47.9)	119/143	(83.2)	65/143	(45.5)	219/251	(87.3)	115/251	(45.8)
B-Platelets (hypo) ($10^9/L$)	75/155	(48.4)	4/155	(2.6)	60/154	(39.0)	4/154	(2.6)	128/262	(48.9)	5/262	(1.9)
S-Triglycerides (hyper) (mmol/L)	39/153	(25.5)	3/153	(2.0)	29/148	(19.6)	1/148	(0.7)	39/153	(25.5)	3/153	(2.0)
S/P-Alanine Aminotransferase (hyper) (ukat/L)	30/155	(19.4)			42/154	(27.3)			63/262	(24.0)	7/262	(2.7)
S/P-Albumin (hypo) (g/L)	23/151	(15.2)	0/151		26/153	(17.0)	0/153		35/258	(13.6)	0/258	
S/P-Alkaline Phosphatase (hyper) (ukat/L)	19/153	(12.4)	1/153	(0.7)	46/153	(30.1)	3/153	(2.0)	58/260	(22.3)	1/260	(0.4)
S/P-Aspartate Aminotransferase (hyper) (ukat/L)	45/155	(29.0)	4/155	(2.6)	66/154	(42.9)	2/154	(1.3)	101/262	(38.5)	6/262	(2.3)
S/P-Calcium (hypo) (mmol/L)	0/0		0/0		0/0		0/0		34/107	(31.8)	2/107	(1.9)
S/P-Calcium Corrected for Albumin (hyper) (mmol/L)	9/151	(6.0)	1/151	(0.7)	19/153	(12.4)	1/153	(0.7)	9/151	(6.0)	1/151	(0.7)
S/P-Calcium Corrected for Albumin (hypo) (mmol/L)	39/151	(25.8)			25/153	(16.3)			39/151	(25.8)	0/151	

	SERENA-6								Combination therapy pool			
	Camizestrant + CDK4/6i (N = 155) Any grade		Camizestrant + CDK4/6i (N = 155) Grade 3 or 4		AI + CDK4/6i (N = 155) Any grade		AI + CDK4/6i (N = 155) Grade 3 or 4		Camizestrant + CDK4/6i (N = 263) Any grade		Camizestrant + CDK4/6i (N = 263) Grade 3 or 4	
	n/Nobs	(%)	n/Nobs	(%)	n/Nobs	(%)	n/Nobs	(%)	n/Nobs	(%)	n/Nobs	(%)
Laboratory Abnormality												
S/P-Creatinine (hyper) (umol/L)	48/155	(31.0)	2/155	(1.3)	61/154	(39.6)	2/154	(1.3)	87/262	(33.2)	2/262	(0.8)
S/P-Gamma Glutamyl Transferase (hyper) (ukat/L)	33/149	(22.1)	4/149	(2.7)	49/152	(32.2)	15/152	(9.9)	33/149	(22.1)	4/149	(2.7)
S/P-Magnesium (hypo) (mmol/L)	10/151	(6.6)	0/151		16/151	(10.6)	0/151		30/258	(11.6)	0/258	
S/P-Potassium (hypo) (mmol/L)	15/155	(9.7)	6/155	(3.9)	15/154	(9.7)	2/154	(1.3)	31/262	(11.8)	8/262	(3.1)
S/P-Sodium (hypo) (mmol/L)	23/155	(14.8)	2/155	(1.3)	20/154	(13.0)	4/154	(2.6)	46/262	(17.6)	6/262	(2.3)

Percentages are calculated as n/Nobs*100.

5.4.13. Vital signs and physical findings

Apart from the changes in heart rate described in section 4.4.1, no relevant changes were observed in vital sign measurements.

5.4.14. Electrocardiogram data

Table 93: QTC prolongation - Electrocardiogram results over time (Safety Set) – DCO1

QTcF Duration (ms)								
Group								
Timepoint	Result							
	n	Mean	SD	Min	Q1	Median	Q3	Max
AZD9833 + CDK4/6 inhibitor								
N=155								
Baseline	145	415.2	16.8		404.0	415.0	424.0	
Cycle 1, Day 1	69	412.5	18.4		399.0	411.3	425.3	
Cycle 1, Day 15	129	425.7	21.4		410.0	426.0	438.3	
Cycle 2, Day 1	134	419.2	19.8		406.0	420.0	431.0	
Cycle 3, Day 1	123	421.1	21.8		407.0	420.0	433.3	
Cycle 5, Day 1	115	417.8	20.0		403.0	417.0	432.0	
Cycle 7, Day 1	105	418.9	21.4		403.0	418.0	434.0	
Cycle 9, Day 1	86	416.2	19.2		402.0	414.5	432.0	
Cycle 11, Day 1	72	417.6	21.8		402.0	415.0	432.0	
Cycle 13, Day 1	61	419.0	20.5		404.0	416.0	429.0	
Cycle 15, Day 1	46	416.1	25.2		392.0	421.8	432.0	
Cycle 17, Day 1	38	418.2	25.0		398.5	420.0	435.0	
Cycle 19, Day 1	26	420.1	22.3		405.0	417.0	433.0	
Cycle 21, Day 1	22	419.8	19.5		408.0	421.5	437.0	
Cycle 23, Day 1	13	420.3	19.6		410.0	417.0	431.0	
Cycle 25, Day 1	9	418.2	13.1		411.0	416.0	427.0	
Cycle 27, Day 1	8	425.6	20.1		409.5	426.3	443.5	
Cycle 29, Day 1	7	413.1	22.9		394.0	400.0	438.0	
Cycle 31, Day 1	5	414.7	27.2		398.5	399.0	427.0	
Cycle 33, Day 1	4	433.2	13.4		424.0	431.3	442.3	
Cycle 35, Day 1	4	411.8	20.3		396.2	408.7	427.5	
End of Treatment	52	417.0	22.3		401.5	413.3	432.2	
Safety Follow-up	20	406.0	21.9		392.0	409.0	421.0	

Group	Change from Baseline							
Timepoint	n	Mean	SD	Min	Q1	Median	Q3	Max
AZD9833 + CDK4/6 inhibitor								
N=155								
Baseline	145							
Cycle 1, Day 1	69	-3.8	16.7		-12.3	-3.3	6.3	
Cycle 1, Day 15	129	9.9	16.9		-2.7	9.0	19.5	
Cycle 2, Day 1	134	3.8	17.1		-6.7	3.0	16.0	
Cycle 3, Day 1	123	5.9	16.3		-7.0	6.3	15.7	
Cycle 5, Day 1	115	2.6	16.8		-9.0	3.3	14.7	
Cycle 7, Day 1	105	3.2	16.6		-7.7	0.7	16.3	
Cycle 9, Day 1	86	1.5	16.4		-10.3	4.5	12.0	
Cycle 11, Day 1	72	3.1	19.6		-11.7	0.5	15.8	
Cycle 13, Day 1	61	2.0	17.8		-9.3	2.0	13.3	
Cycle 15, Day 1	46	-1.2	21.6		-12.0	-1.3	13.7	
Cycle 17, Day 1	38	1.4	18.4		-8.3	-2.3	12.3	
Cycle 19, Day 1	26	3.2	16.3		-6.7	2.5	7.0	
Cycle 21, Day 1	22	1.3	16.3		-7.7	-2.5	9.3	
Cycle 23, Day 1	13	4.5	13.5		-2.7	7.0	14.0	
Cycle 25, Day 1	9	-4.3	9.5		-9.3	-3.7	3.7	
Cycle 27, Day 1	8	6.1	13.8		-7.3	9.7	14.4	
Cycle 29, Day 1	7	-2.0	13.0		-9.0	-1.7	12.7	
Cycle 31, Day 1	5	5.4	6.0		-0.7	8.3	10.0	
Cycle 33, Day 1	4	17.1	16.9		2.7	17.0	31.5	
Cycle 35, Day 1	4	-4.3	4.4		-8.0	-4.8	-0.5	
End of Treatment	52	1.6	16.9		-12.8	-0.8	14.0	
Safety Follow-up	20	-9.6	15.7		-21.3	-8.0	1.3	

QTcF Duration (ms)								
Group Timepoint	Change from Baseline							
	n	Mean	SD	Min	Q1	Median	Q3	Max
AI + CDK4/6 inhibitor N=155								
Baseline	139							
Cycle 1, Day 1	72	-5.7	13.3		-15.0	-7.2	3.0	
Cycle 1, Day 15	124	-1.7	15.5		-14.0	-0.2	7.8	
Cycle 2, Day 1	128	-2.0	15.1		-10.3	-1.8	7.0	
Cycle 3, Day 1	122	-4.4	15.8		-13.0	-3.3	6.7	
Cycle 5, Day 1	95	-5.2	16.1		-16.7	-5.0	7.3	
Cycle 7, Day 1	70	-4.3	14.6		-12.0	-4.5	7.0	
Cycle 9, Day 1	49	-5.6	15.9		-15.3	-6.3	5.0	
Cycle 11, Day 1	40	-6.5	15.1		-17.7	-4.7	3.0	
Cycle 13, Day 1	31	-4.7	15.3		-13.7	-9.0	4.7	
Cycle 15, Day 1	15	-5.2	13.1		-12.7	-5.0	1.0	
Cycle 17, Day 1	13	-6.1	15.3		-20.0	-3.7	6.0	
Cycle 19, Day 1	10	-1.8	22.6		-24.3	1.7	16.0	
Cycle 21, Day 1	6	-17.9	8.3		-24.0	-20.8	-9.3	
Cycle 23, Day 1	4	-16.9	17.9		-30.8	-17.2	-3.0	
Cycle 25, Day 1	3	-14.4	20.8		-38.3	-5.0	0.0	
Cycle 27, Day 1	1		NC					
End of Treatment	69	-1.8	17.5		-14.0	-4.0	9.7	
Safety Follow-up	30	-7.1	19.1		-16.3	-10.0	1.7	

Treatment emergent electrocardiogram abnormalities by pre-defined criteria (Safety set)

	AZD9833 + CDK4/6 inhibitor N=155		AI + CDK4/6 inhibitor N=155	
	n/Nobs	(%)	n/Nobs	(%)
QTcF (ms)				
>450	33/145	(22.8)	10/139	(7.2)
>480	/145		/139	
>500	0/145		0/139	
Increase from baseline >30	42/145	(29.0)	10/139	(7.2)
Increase from baseline >60	/145		/139	
>450 and increase from baseline >30	21/145	(14.5)	1/139	(0.7)
>500 and increase from baseline >60	0/145		0/139	

5.4.15. Post-marketing experience

Not applicable.

5.4.16. Overall discussion and conclusions on clinical safety

5.4.16.1. Discussion

5.4.16.1.1. Overall assessment of available safety data

Safety data from both SERENA-6 arms (155 patient in both arms), and a camizestrant + CDK4/6 inhibitor combination therapy pool (n= 263), which pools data from SERENA-6 with patients from SERENA-1 treated with camizestrant 75 mg and a CDK4/6 inhibitor, were submitted. Although a monotherapy indication was not sought, additional data from 117 patients treated with camizestrant 75 mg in SERENA-1 was also provided. The 263 patients in the combination therapy pool were regarded as the primary safety pool. The median **treatment exposure** to camizestrant was 8.3 months in the combination therapy pool, which should be compared to the median PFS in SERENA-6 of 15.97 months. Although the exposure was considered rather short, given that the sought indication is treatment until progression, the safety database is considered sufficient for approval, and the Applicant has committed to provide final safety data post-authorisation, as a recommendation.

The most common **adverse events** in the combined camizestrant+CDK4/6i pool were hematological (neutropenia/neutrophil count decreased, anemia, leukopenia/white blood cell count decreased), and eye-related (photopsia, dry eyes, visual impairment), but other burdensome AEs were also very common (arthralgia, fatigue, nausea, back pain, diarrhoea, headache, vomiting, asthenia). As expected, most AE rates were comparable between the combination therapy pool and the AI arm of SERENA-6, since both arms received CDK4/6 inhibitors. Especially photopsia was more frequent in the camizestrant arm than the AI arm of SERENA-6 (21.3% vs. 7.7%), and even more frequent in the pooled camizestrant+CDK4/6i population (24%). Similar to all AEs, the most frequent grade ≥ 3 AEs in the camizestrant+CDK4/6i populations were hematological. Other notable grade ≥ 3 AEs in the combination therapy pool were syncope, QT prolonged, hypertension, vomiting, diarrhoea, abdominal pain, and infections. This has been reflected accordingly in the SmPC section 4.8.

Adverse events of special interest were bradycardia and visual effects. 52 (19.8%) patients in the combination therapy safety pool experienced one or more bradycardia events. Overall, the bradycardic effects of camizestrant appeared well-tolerated in most patients. The maximum reported CTCAE grade

was 2 (8 patients). No patients discontinued treatment due to bradycardia. One case of torsades de pointes arrhythmia was observed in a patient treated with camizestrant and ribociclib and with concurrent bradycardia and QTc-prolongation. A causal link between camizestrant and the case of torsades de pointes has not been firmly established, but is considered a possibility. Furthermore, 2 syncope events and one death of unknown causes occurred in the combination therapy pool, which could theoretically be related to arrhythmias. The size of the safety pool and the duration of exposure did not appear sufficient to rule out a risk of other rare, life-threatening arrhythmias, including bradyarrhythmias, associated with conduction disturbances caused by camizestrant, especially (but not only) when combined with ribociclib which is known to cause QT-prolongation. In relation to this concern, it is noteworthy that many patients with cardiac disease or risk factors were excluded from SERENA-6 (including atrioventricular block, heart failure, and QT prolongation). Based on the observed case of torsades des pointes and the above concerns, a warning about the potential arrhythmogenic effects of camizestrant in combination with ribociclib has been included in section 4.4 of the SmPC.

The AESI "visual effects" was analysed by a grouping of the PTs photopsia, vision blurred, visual impairment, diplopia, photophobia, visual perseveration, and glare. Of these, photopsia was the most common. Most events were mild, with only seven grade 2 and one grade 3 event in the combined safety pool, and no treatment discontinuations or dose reductions due to visual effects. PRO data also indicated that the visual effects were generally well-tolerated. Data from comprehensive ophthalmologic examinations for a small subset of the SERENA-6 patients (approximately 41 patients) were provided, and no structural eye damage was identified. Data on ophthalmological examinations were additionally provided, which seemed to rule out a risk of more serious ophthalmological adverse effects, including retinal damage.

Both AESIs have the potential to affect patient's ability to drive and use machines, either due to vision disturbances and possibly dizziness or syncope from bradycardia, and this is included in the SmPC.

The number of **deaths** due to any cause was 22 (8%) in the camizestrant + CDK4/6 inhibitor pool, 20 (12.9%) in the camizestrant arm of SERENA-6 and 18 (11.6%) in the AI arm of SERENA-6 at DC01. Of 22 deaths in the combination therapy pool, 13 were attributed to the disease under investigation by the investigator, and five to "other" causes. Possible treatment-related deaths were two patients who died from ADRs which may have been linked to interstitial lung disease, a known ADR for CDK4/6 inhibitors, one unexplained death (discussed above), and one death after life-threatening anemia. None of these deaths have been considered related to study treatment.

Serious adverse events included five serious infections, of which two also appeared to have sepsis and neutropenia.

There were only three AEs leading to camizestrant **discontinuation** in the combination therapy pool. In SERENA-6, nine patients experienced AEs leading to dose **reductions**, of which four were bradycardia. Importantly, dose reductions will not be possible in the post-approval setting, as only one tablet strength was included in the application.

Patients with moderate and severe renal and hepatic impairment were not included in SERENA-6, and patients with hepatic impairment are expected to have increased exposure to camizestrant due to reduced elimination. Therefore, a warning has been included in section 4.4. of the SmPC that camizestrant should be avoided in patients with moderate and severe hepatic impairment. There are no apparent patterns observed in the tables on clinical studies in special populations (see Table 92), probably due to the very small subgroups, so no firm conclusions can be made.

Shifts in **laboratory** measurements of grade ≥ 3 , and measurements at grade 3 or higher were observed for all hematology measurements as well as liver transaminases, which is expected given the known safety profile of the CDK4/6 inhibitors.

There was no potential or confirmed Hy's law cases in the camizestrant arm of SERENA-6, nor in the rest of the combination and monotherapy pools.

Electrocardiogram data showed an increase in mean QTcF by 9.9 msec between baseline and day 15 in the SERENA-6 camizestrant arm, but not the AI arm. This is considered a quite large increase in QTc considering that the threshold for regulatory concern is 10 msec (including 95% confidence limits). Some AEs of QT prolonged were observed in the camizestrant safety pools, including one grade 3 event in the monotherapy pool. PK/PD exposure-safety modeling predicted the largest QT-prolonging effects of camizestrant in patients also receiving ribociclib 600 mg. Additionally a warning about the cardiac safety of the camizestrant + ribociclib combination has been added to the SmPC along with ECG monitoring guidelines. Moreover the SmPC was revised to reflect that QT prolonged is considered an ADR to the camizestrant + CDK4/6 inhibitor combination therapy regardless of CDK4/6 inhibitor.

It is considered that overall the SmPC adequately reflects the safety profile of the camizestrant + CDK4/6i as studied.

5.4.16.1.2. Adverse drug reactions (ADRs) in the SmPC

The ADRs presented in the SmPC are described in section 5.4.3. above.

5.4.16.2. Conclusions on clinical safety

Overall, the safety profile of camizestrant in combination with CDK4/6 inhibitors appeared acceptable. The majority of the observed serious side effects (including neutropenia and infections) were known from the CDK4/6 inhibitors, with the exception of bradycardia and visual disturbances, which appeared to be specific ADRs for camizestrant. The concern of cardiotoxicity of the camizestrant + CDK4/6i combination has been addressed in the SmPC (warning in 4.4., updated guidance on ECG monitoring in 4.2, list of products to be avoided in 4.5, description of selected AEs in 4.8).

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

Table 94: Summary of safety concerns in the proposed RMP

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

6.1.2. Discussion on proposed safety specification

Patients with a known or family history of severe structural or ischaemic heart disease were excluded from SERENA-1 and SERENA-6. It remains uncertain whether the bradycardic properties of camizestrant do not confer an additional risk in patients with e.g. structural heart disease or heart failure, as these patients were excluded upfront. Patients with a resting heart rate < 55 bpm, unexplained syncope,

symptomatic hypotension, second- and third-degree heart block, or clinically significant sinus pause or sinoatrial block were excluded from the camizestrant clinical studies. The observation that a product with bradycardic properties is safe in patients without pre-existing bradycardia or other bradyarrhythmias cannot be used to infer that the product is also safe in patients with pre-existing bradycardia or other bradyarrhythmias. Consequently, a warning has been included in the SmPC section 4.4, making clear to the prescriber that the use of camizestrant together with ribociclib can result in cardiotoxicity. In addition, QTc prolongation has been added as a new ADR in the SmPC section 4.8, with a corresponding footnote indicating that it is a known ADR associated with ribociclib. The SmPC section 4.2. has been additionally updated with specific guidance on ECG monitoring, section 4.4 with warnings and precautions on the risk of QT prolongation, and section 4.5 with a list of other products whose concomitant use should be avoided. The case of Torsade de Pointes (TdP) has been mentioned in 4.4, 4.5 and 4.8. Finally, studying a wide spectrum of cardiac comorbidities ("level of cardiotoxicity") in the indicated patient population with advanced breast cancer is not considered feasible. Therefore, adequate information in the PI on which patients that have not been studied is deemed sufficient, no further risk characterisation is considered necessary and no addition to the RMP was considered warranted as the warnings included in the SmPC are considered sufficient to mitigate the risk of QTc prolongation.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

In the approved RMP version 1.4, routine pharmacovigilance activities were considered sufficient to monitor the safety profile of the product.

No additional pharmacovigilance activities have been proposed.

6.2.2. Discussion on the pharmacovigilance plan

6.2.2.1. Routine pharmacovigilance activities

Routine pharmacovigilance has been considered sufficient to identify and characterise the risks of the product.

Routine PhV have been considered as sufficient to monitor the effectiveness of the risk minimisation measures.

6.2.2.2. Additional pharmacovigilance activities

There are no planned additional pharmacovigilance activities.

6.3. Plans for post-authorisation efficacy studies

Table 95: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
SERENA-6 study (ongoing)	In order to further characterise the long term efficacy of camizestrant in combination with a CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib) for the treatment of adult patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer upon detection of <i>ESR1</i> mutation and without disease progression during first-line endocrine therapy in combination with a CDK4/6 inhibitor, the MAH shall submit the results of the final OS analysis from the SERENA-6 study, a phase III, randomised, double-blind study.	Overall survival (no detriment)	the timing of DCO4 (achieving 165 OS events) is predicted to be September 2028	31 December 2028
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

No additional risk minimisation measures were proposed.

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

Routine risk minimisation measures are considered sufficient to minimise the risks of the product in the proposed indication(s).

6.4.2.2. Additional risk minimisation measures

Having considered the data submitted, no additional risk minimisation measures are considered required.

6.5. RMP summary and RMP annexes overall conclusion

Having considered the data submitted and the raised concerns, the RMP v1.4 is considered acceptable as the PI includes adequate warnings and the Applicant confirmed that cardiac toxicity/QT prolongation will be followed in the PSUR as a routine pharmacovigilance measure.

6.6. Overall conclusion on the Risk Management Plan

The CHMP and PRAC consider that the risk management plan version 1.4 is acceptable.

7. Pharmacovigilance

7.1. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. Periodic safety update reports (PSURs) submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new list of Union reference dates (EURD list) entry uses the European birth date (EBD) or the international birth date (IBD) to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request an alignment of the PSUR cycle with the IBD. The IBD is 29 May 2025.

8. Product information

8.1. Summary of product characteristics (SmPC)

See the attached commented product information.

8.1.1. SmPC section 4.1 justification

The approved indication is supported by the results of the pivotal clinical study submitted in the dossier, Serena-6, which evaluated camizestrant + a CDK4/6i versus continuing an AI + a CDK4/6i in the treatment of ER-positive, HER2-negative locally advanced or metastatic breast cancer upon detection of an *ESR1* mutation and without disease progression during first-line endocrine-based treatment. The target population in the indication is fully aligned with the population studied in the pivotal trial, including disease and baseline characteristics. The proposed treatment setting is new, as camizestrant is indicated to a biomarker-restricted population based on the emergence of an *ESR1* mutation in circulating tumor (ct)DNA during first-line treatment with SoC.

8.1.2. SmPC section 4.3 justification

Camizestrant is contraindicated when breastfeeding, which is in line with other products of the same class (eg. fulvestrant and imlunestrant).

8.2. Labelling

8.2.1. User consultation

8.2.1.1. Conclusion from the checklist for the review of user consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the

readability of the label and package leaflet of medicinal products for human use.

8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Etcamah (camizestrant) is included in the additional monitoring list since it contains a new active substance which, in 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

9. Benefit-risk assessment

9.1. Therapeutic context

The final agreed indication is:

"Etcamah in combination with a CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib) is indicated for the treatment of adult patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer upon detection of ESR1-mutation and without disease progression during first-line endocrine therapy in combination with a CDK4/6 inhibitor (for biomarker based patient-selection, see section 4.2 and 5.1).

In pre- or peri-menopausal women and in men, camizestrant plus a CDK4/6 inhibitor should be combined with a luteinizing hormone releasing hormone (LHRH) agonist or antagonist."

9.1.1. Disease or condition, proposed therapeutic indication

Although many patients are cured of their early-stage disease, advanced breast cancer remains incurable. Approximately 70% of patients present with ER-positive, HER2-negative disease (American Cancer Society 2024-2025), making it the most common subtype in both women and men. Various studies have reported that the frequency of *ESR1*m is low (approximately 4%) at the initial diagnosis; while approximately 40% of patients at the end of first-line (1L) treatment with an aromatase inhibitor (AI) + a CDK4/6i have detectable *ESR1*m in ctDNA, and the prevalence of *ESR1*m rises further to > 50% in patients who have been treated with AI + CDK4/6 inhibitor for more than one year (Bhave et al 2024, Bidard et al 2022, Cardoso et al 2023, Chaudhary et al 2024).

9.1.2. Available therapies and unmet medical need

For a detailed description, please see section 2.1. of this document.

The preferred standard-of-care first-line therapy for patients with estrogen receptor-positive (ER+), HER2-negative advanced breast cancer is a CDK4/6 inhibitor (CDK4/6i) in combination with endocrine therapy (ET), with improved PFS and OS observed in several phase 3 trials.

There are currently no 1L therapies specifically approved for the treatment of these patients with emergent *ESR1*m, ahead of disease progression. Progression beyond 1L is often associated with increased toxicities of therapy regimens and diminished treatment efficacy, likely due to the increased genetic complexity of disease and increased tumour burden. Currently, Orserdu (elacestrant) and Inluriyo

(imlunestrant) are monotherapy options for patients with *ESR1*m who have progressed on ET + CDK4/6 inhibitor, and modest activity has been shown (median PFS 3.8 months with elacestrant vs 1.9 months for ET's (including AI and fulvestrant) and mPFS 5.5 months with imlunestrant vs 3.8 months for ET's (including AI and fulvestrant). Both Orserdu (elacestrant) and Inluriyo (imlunestrant) are indicated after disease progression under endocrine based regime therapy, placing them as a second line option for patients with an *ESR1*m detected. According to ESMO Guidelines (Gennari et al 2021, ESMO guideline), evidence based available options for second-line therapy (other than *ESR1*m targeted options) are fulvestrant-alpelisib (for PIK3CA mutated tumours), PARP inhibitors (for tumours harbouring genomic BRCA mutations), exemestane-everolimus, fulvestrant monotherapy, aromatase inhibitors (AI), trastuzumab deruxtecan (for HER2-low tumours), and chemotherapy. At least two lines of endocrine based therapy are preferred before moving to chemotherapy (Gennari et al, Annals of Oncology, 2021). Thus, there is a need for better treatment options that could be met by earlier identification of patients, who may benefit from therapies that address resistance to current ET in 1L, ahead of clinical and radiological disease progression by targeting the resistance mechanisms that emerge during 1L treatment. This strategy is considered to have the potential to extend the benefit of endocrine based 1L therapy, leading to better patient outcomes for patients with ER-positive, HER2-negative advanced breast cancer.

9.2. Main clinical studies

The application is primarily based on data from the single pivotal study, SERENA-6, which is a randomised, phase 3, double-blind, placebo-controlled multicentre study. Patients eligible for inclusion were adult female (pre/peri-menopausal or post-menopausal) and male patients with advanced ER-positive, HER2-negative breast cancer and who were treated with an AI + CDK4/6 inhibitor in the first-line advanced setting and who had no evidence of progressive disease. 3325 patients were screened for the presence of an *ESR1* mutation using ctDNA, and 315 were randomised 1:1 to continue with standard of care (SoC) or switch the ET backbone for camizestrant, while the CDK4/6i is continued without changes in both arms.

The studied dose of camizestrant was 75mg QD. Study treatment was continued until disease progression or unacceptable toxicity.

The primary efficacy endpoint was PFS as assessed by investigator in the ITT. OS and PFS2 were key secondary endpoints.

Of note, the SERENA-6 study investigates a new treatment paradigm, as patients are switched early based on a biomarker-selection (*ESR1*-mutation) without having a clinical or radiological progression, which is not part of the current standard of care.

9.3. Favourable effects

As of the DCO3 corresponding to the third interim analysis of the pivotal study SERENA-6 (02 January 2026), the median duration of follow-up was approximately 23 months.

The primary endpoint of PFS by Investigator was improved by 7.53 months from a median of 9.23 months in the AI arm to 16.76 months in the camizestrant arm. The HR was 0.45 (95%CI: 0.34; 0.59).

At DCO2, the secondary endpoint of PFS by BICR showed a similar HR of 0.46 (95%CI: 0.32, 0.66

At DCO3, the secondary endpoint of PFS2 was met at the time of the planned primary analysis of PFS2 with a HR of 0.63; 95%CI: 0.46, 0.86; p-value 0.00373). Median PFS2 was 25.72 months in the camizestrant arm compared to 19.06 months in the control arm, a difference of 6.66 months.

Immature OS data are available at DCO3, with 30% events observed overall, HR: 0.87 (95%CI: 0.57, 1.30).

Updated subgroup analyses were provided from the DCO2 showing benefit in favour of camizestrant and no discordant results for PFS in the requested subgroups were observed. Hence, the point estimate for HR was still below 1 across important subgroups including the stratification factors: CDK4/6 inhibitor combination partner (palbociclib, ribociclib, or abemaciclib), ESR1m detectable at first ctDNA test or subsequent ctDNA test, disease site (visceral vs non-visceral), and time from initiation of AI + CDK4/6 inhibitor to randomisation (< 18 months or ≥ 18 months).

9.3.1. Uncertainties and limitations about favourable effects

The collected PFS2 data are considered insufficient to establish a long-term benefit. These data are considered unreliable due the limited number of patients who were continuously followed with tumour assessments according to RECIST 1.1 at appropriate intervals, as well as the heterogeneity in post-study treatment choices.

Although no detrimental effect on OS has been observed at DCO3, the OS data available are immature (30%). Final OS data should be submitted post-authorisation as an Annex II condition to further characterize the efficacy of camizestrant and rule out a detrimental effect on OS.

Finally, the following uncertainties on the biomarker aspects have been considered:

No clinical thresholding for the cut-point defining a tumour as biomarker positive or negative was performed. Due to this, it cannot be excluded that in the threshold definition of biomarker-positivity applied in the pivotal study, patients who may not benefit are included.

9.4. Unfavourable effects

The safety data from both SERENA-6 arms (155 patient in both arms), and a camizestrant + CDK4/6 inhibitor combination therapy pool (n= 263), which pools data from SERENA-6 with patients from SERENA-1 treated with camizestrant 75 mg and a CDK4/6 inhibitor, have been provided. The 263 patients in the combination therapy pool have been regarded as the primary safety pool. The median **treatment exposure** to camizestrant was 8.3 months in the combination therapy pool.

The most common **adverse events** in the combined camizestrant+CDK4/6i pool were hematological (neutropenia/neutrophil count decreased, anemia, leukopenia/white blood cell count decreased), and eye-related (photopsia, dry eyes, visual impairment), but other burdensome AEs were also very common (arthralgia, fatigue, nausea, back pain, diarrhoea, headache, vomiting, asthenia). As expected, most AE rates were comparable between the combination therapy pool and the AI arm of SERENA-6, since both arms received CDK4/6 inhibitors. Of note, photopsia was more frequent in the camizestrant arm than the AI arm of SERENA-6 (20% vs. 7.7%), and even more frequent in the pooled camizestrant+CDK4/6i population (23.2%). Similar to all AEs, the most frequent grade ≥3 AEs in the camizestrant+CDK4/6i populations were hematological. Other notable grade ≥ 3 AEs in the combination therapy pool were syncope, QT prolonged, hypertension, vomiting, diarrhoea, abdominal pain, and infections.

Two ADRs were identified for camizestrant (bradycardia and visual effects), which were also identified as **adverse events of special interest**. 48 (18.3%) patients in the combination therapy safety pool experienced one or more bradycardia events. Bradycardia is especially concerning given that camizestrant also can prolong the QT interval and may be given together with ribociclib which also prolongs the QT interval. One case of torsades de pointes arrhythmia was observed in a patient treated with camizestrant and ribociclib. The AESI “visual effects” was analysed by a grouping of the PTs photopsia, vision blurred,

visual impairment, diplopia, photophobia, visual perseveration, and glare. Of these, photopsia was the most common.

The number of **deaths** due to any cause was 22 (8%) in the camizestrant + CDK4/6 inhibitor pool, 20 (12.9%) in the camizestrant arm of SERENA-6 and 18 (11.6%) in the AI arm of SERENA-6. Of 22 deaths in the combination therapy pool, 13 were attributed to the disease under investigation by the investigator, and five to “other” causes.

Serious adverse events included five serious infections, of which two also appeared to have sepsis and neutropenia. Other noteworthy SAEs were rare cases of pulmonary embolism, venous thrombosis and unspecified embolisms (one event each), and the above-mentioned case of torsades de pointes.

There were three AEs leading to camizestrant **discontinuation** in the combination therapy pool. In SERENA-6, nine patients experienced AEs leading to dose **reductions**, of which four were bradycardia.

Shifts in **laboratory** measurements of grade ≥ 3 , and measurements at grade 3 or higher were observed for all hematology measurements as well as liver transaminases, which is expected given the known safety profile of the CDK4/6 inhibitors.

There was no potential or confirmed Hy’s law cases in the camizestrant arm of SERENA-6.

9.4.1. Uncertainties and limitations about unfavourable effects

The median **treatment exposure** to camizestrant was 8.3 months in the combination therapy pool, which is considered rather short, given that the sought indication is treatment until progression, and median PFS in SERENA-6 was 15.97 months. Key limitations of the safety database include its relatively small size in view of the potentially large target population, which limits the detection of rare adverse events, as well as the limited data for the ribociclib and abemaciclib combinations.

The exclusion of patients with significant cardiac comorbidities or severe hepatic impairment upfront further restricts the external validity of the findings.

9.5. Effects table

Table 96: Effects Table for ETCAMAH in the treatment of ER-positive, HER2-negative advanced breast cancer with a detectable ESR1 mutation during 1L treatment (data cut-off: DCO3: 02 January 2026).

Effect (short description)	Treatment Camizestrant + CDK4/6i N=157		Control AI + CDK4/6i N=158	Uncertainties/ Strength of evidence
Favourable effects				
PE: PFS by INV	Progression-free survival by investigator (months)	16.76	9.23	HR 0.45 (95%CI: 0.34;0.59) SoE: Double-blind, placebo-controlled RCT.
OS	Overall survival (months)	41.2	40.21	HR 0.87 (95%CI: 0.57; 1.30) SoE: Hard endpoint Unc: SE, Immature data (~30% events)
Unfavourable effects				
Grade ≥ 3 AEs	Incidence (%)	60	45.8	

<i>Effect (short description)</i>	<i>Treatment Camizestrant + CDK4/6i N=157</i>		<i>Control AI + CDK4/6i N=158</i>	<i>Uncertainties/ Strength of evidence</i>
SAEs	Incidence (%)	10.3	12.3	SoE: Double-blind, placebo-controlled RCT. Unc: No possible disentanglement of the safety of camizestrant alone, only for the applied combination of camizestrant + CDK4/6i.
AEs leading to discontinuation	Incidence (%)			
Deaths	Incidence (%)	1.9	0	AEs leading to death
Bradycardia	Incidence (%)			ADR
Visual impairment	Incidence (%)	3.9	1.9	ADR

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; HR: Hazard ratio; PE: primary endpoint; SE: secondary endpoint.

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

PFS by INV (primary endpoint) at the DCO3 of 02 January 2026, is mature with 63.1% and 78.5% events in the camizestrant arm vs the control arm, respectively, and a **HR of 0.45** (95% CI: 0.34, 0.59). The median PFS by INV was **16.76 months** in the camizestrant arm vs **9.23 months** in the control arm, resulting in 7.53 months of improvement (at DCO1 it was 6.74 months). The KM curves are clearly separating after 3 months of treatment.

Time to second progression, PFS2, reported a HR 0.63, although the collected data have been considered insufficient to establish long-term benefit. Their reliability is limited by the small number of patients with continuous tumour assessments performed at appropriate intervals according to RECIST 1.1, together with the heterogeneity in post-study treatment choices.

At diagnosis of metastatic breast cancer (MBC), the 5-year survival rate is approximately 38% (Allemani et al., 2018). CDK4/6 inhibitors combined with endocrine therapy (ET) are the standard of care for ER-positive, HER2-negative MBC, demonstrating improved progression-free survival (PFS; median ~2 years), overall survival (OS), and a favourable safety profile (ESMO guidelines).

Following progression on ET plus a CDK4/6 inhibitor, assessment of somatic *PIK3CA* and *ESR1* mutations (optional if further AI is considered), as well as germline *BRCA1/2* and *PALB2* mutations, is recommended (ESMO guidelines). Second-line ET provides more limited benefit (median PFS 2–4 months for monotherapy; 5–8 months when combined with targeted agents), and the optimal treatment sequence after CDK4/6 inhibitors remains uncertain, depending on prior therapies, duration of response, disease burden, patient preference, and availability (ESMO guidelines).

Early detection of *ESR1* mutations, associated with resistance to aromatase inhibitors (AI), may help anticipate treatment failure. In the SERENA-6 study, early switching to camizestrant (plus CDK4/6 inhibitor) based on *ESR1* mutation detection resulted in clinically relevant PFS improvement compared with continuing AI until radiological or clinical progression.

However, as this approach involves switching ET prior to disease progression, any PFS benefit should be supported by favourable long-term outcomes and no OS detriment. Moreover, this strategy effectively represents early second-line therapy and entails multiple testings of the blood for *ESR1* mutations,

which can be challenging for the patients emotionally, since the detection of an *ESR1* mutation is associated with treatment-resistance. Only about 10% of the screened population were included in the SERENA-6 trial.

At DCO3, OS is still considered immature with overall 30% events, HR: 0.87 (95% CI: 0.57, 1.30). At this time, there is no apparent detriment on OS, but no clear OS benefit either. In order to further characterise the efficacy of camizestrant, the MAH will submit the final OS analysis as an Annex II.D condition by December 2028.

The benefit of switching to camizestrant is primarily based on the PFS benefit established in the context of a well-conducted randomised, blinded, placebo-controlled study and in the absence of an apparent OS detriment: the efficacy of camizestrant is considered to be sufficiently demonstrated.

Overall, the safety profile of the oral SERD camizestrant in the proposed target population in combination with CDK4/6 inhibitors is similar to that known for endocrine therapies. The majority of the observed serious side effects (including neutropenia and infections) are known from the CDK4/6 inhibitors. The main differences observed are bradycardia and visual disturbances, which appear to be specific ADRs for camizestrant. An increased risk of serious arrhythmia, including torsade des pointes, remains a concern, and guidelines for ECG monitoring after treatment initiation have been included in the SmPC along with a warning about the concern for cardiotoxicity.

9.6.2. Balance of benefits and risks

The benefit-risk balance is considered positive for camizestrant + CDK4/6i.

9.6.3. Additional considerations on the benefit-risk balance

9.6.3.1. Questions to be posed to additional experts

Not applicable.

9.6.3.2. Input from additional experts

Not applicable at this time.

9.6.3.3. Third party intervention(s)

The CHMP received, during the assessment of this application, a correspondence signed by European physicians being specialised in treating breast cancer (hereinafter referred to as "third party") expressing the third party views about the SERENA-6 pivotal trial results, about the treatment lines options as well as unmet medical need and supporting the proposed new strategy to target emerging resistance before clinical deterioration. The third party shared in addition a manuscript under press providing a discussion on the rationale, the design, the results and the third party's interpretation of SERENA-6.

The CHMP considered those interventions in the context of its assessment and concluded that the observations put forward by the third party were already known by CHMP, and as such had no impact on the CHMP assessment or its conclusions.

9.7. Benefit-risk conclusions

The benefit-risk balance is considered positive for camizestrant + CDK4/6i in the sought indication for adult patients with ER positive, HER2-negative locally advanced or metastatic breast cancer upon detection of ESR1-mutation and without disease progression during first-line endocrine therapy in combination with a CDK4/6 inhibitor.

10. Appendices

Divergent position(s) to the majority recommendation

APPENDIX

DIVERGENT POSITION DATED 21 May 2026

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation in the following indication:

"Etcamah" in combination with a CDK4/6 inhibitor (palbociclib, ribociclib, or abemaciclib) indicated for the treatment of adult patients with ER-positive, HER2-negative, locally advanced or metastatic breast cancer upon detection of ESR1-mutation and without disease progression during first-line endocrine therapy in combination with a CDK4/6 inhibitor (for biomarker based patient-selection, see section 4.2 and 5.1).

In pre- or peri-menopausal women and in men, Etcamah plus a CDK4/6 inhibitor should be combined with a luteinizing hormone releasing hormone (LHRH) agonist or antagonist."

The reasons for the divergent opinion are as follows:

The treatment strategy evaluated in the single pivotal SERENA-6 trial does not reflect current standard clinical practice. The study does not adequately answer the clinically relevant question whether early switching endocrine therapy at first detection of an *ESR1* mutation, and prior to radiographic or clinical progression, improves long-term patient outcome compared with the established strategy of continuing treatment until progression and switching treatment thereafter.

In particular, this is based on the following issues:

- The SERENA-6 trial primarily evaluates an early-switch treatment strategy triggered by first detection of molecular progression while on first-line treatment. The added clinical value of camizestrant, when introduced at the time when switch of treatment would be indicated as to current standard of care, i.e. at clinical or radiological progression, is not part of the study design.
- Early switching may expose patients with ongoing disease control under the existing regimen to additional treatment-related risks, biomarker-testing burden, and potential loss of time on an effective and tolerated regimen, without robust evidence that the early initiation of camizestrant improves long-term outcome.
- The experimental arm incorporates earlier use of a subsequent endocrine treatment option before conventional first-line treatment failure has been documented.

In consequence, the observed PFS advantage cannot be interpreted in the same manner as in a conventional treatment strategy. It remains to be clarified, whether camizestrant improves the overall treatment sequence or long-term patient outcome compared with the established practice. Therefore, PFS is not considered sufficient as a stand-alone endpoint for pivotal B/R assessment in this context. However, no robust evidence of long-term clinical benefit has been provided to overcome these limitations:

- At present, OS data remain insufficiently mature to be informative (maturity approximately 30%) and do not provide robust evidence that the early-switch strategy improves long-term outcome.
- The submitted PFS2 analysis is considered unreliable due to (i) the heterogeneity in choice and timing of subsequent therapy (partly not reflecting current scientific guideline recommendations), and (ii) the insufficiently standardised assessment of second progression (only a small number of patients was continuously followed with tumour assessments based on RECIST 1.1 methods in appropriate time intervals).

Therefore, based on the currently available SERENA-6 data, we cannot conclude on a positive benefit-risk balance for Etcamah in the proposed indication.

Janet König

Jan Müller-Berghaus

Paolo Gasparini

Eva Skovlund

Carolina Prieto Fernandez

Sol Ruiz

Peter Mol

Hrefna Gudmundsdottir

Christian B. Roes