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A study in healthy post-menopausal female volunteers to assess how the test medicine [14C]AZD9833 is taken up, broken down and removed from the body

Submission date 31/03/2022	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 05/05/2022	**Overall study status** Completed	
Last Edited 22/06/2023	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
The Sponsor is developing the test medicine AZD9833 for the potential treatment of oestrogen receptor (ER)-positive breast cancer. Breast cancer is the second most common type of cancer in the UK and worldwide. Most women diagnosed with breast cancer are over the age of 50 years, but younger women and men can also get breast cancer. Estrogen receptor (ER)-positive breast cancer means the cancer cells grow in response to the hormone oestrogen. AZD9833 has the potential to prevent ER activity and increase overall survival in advanced breast cancer patients. This single-part, healthy volunteer study will try to identify how the test medicine is taken up, broken down and removed from the body. To help investigate this, the test medicine is radiolabelled, which means that the test medicine has a radioactive component (carbon-14) which can be used to track where the test medicine is in the body. The safety and tolerability of the test medicine will also be studied.

Who can participate?
Post-menopausal female volunteers aged between 50 to 70 years

What does the study involve?
On Day 1, volunteers will receive a 75 mg dose of [14C]AZD9833 oral solution in the fasted state (on an empty stomach). Volunteers' blood, urine and faeces will be taken throughout the study for analysis of the test medicine and its breakdown products (metabolites) and for volunteer safety. Volunteers will remain in the clinical unit until Day 8, however, if the relevant radioactivity criteria have not been met, volunteers may be required to remain at the clinic until Day 10. If relevant criteria have not been met at this point, home collections of urine and/or faeces may be required. Volunteers are expected to be involved in this study for about 6 weeks from screening to discharge.

What are the possible benefits and risks of participating?
Participants will get no medical benefit from the test medicine, however, the development of a

treatment for breast cancer may benefit the population as a whole. As this is a Phase I study, the most relevant population is healthy volunteers. It is considered that the risk/benefit evaluation in this study supports the use of healthy volunteers. There is always a risk that the stipend in healthy volunteer studies could represent coercion. The time spent in the clinic, travel, inconvenience and other expenses factor in calculating the stipend. Perception of risk is not considered in this calculation. Volunteers may experience side effects from the test medicine. Full information on possible side effects is provided to volunteers in the participant information sheet (PIS)/informed consent form (ICF). When investigating new medicines there is also a risk of unexpected side effects and occasionally allergic reactions. All volunteers will be closely monitored during the study and safety assessments will be performed at regular intervals. Risks are further mitigated by ensuring that only volunteers who meet all inclusion/exclusion criteria are included and that if the safety of any volunteer represents a concern they will be withdrawn. There will be an extended period of fasting for the volunteers taking part in this study. Volunteers will be allowed water up to 1 hour before the scheduled dosing time and will be provided with 240 ml of water at 1-hour post-dose. Water will be allowed after 1-hour post-dose. Decaffeinated fluids will be allowed from lunchtime on the day of dosing. Blood samples will be collected during the study. Collection of these samples can cause soreness and bruising of the arms but these problems usually clear up within a few days to a few weeks. ECG stickers on volunteers' chests and limbs may cause some local irritation and may be uncomfortable to remove but volunteers will be closely monitored to ensure any local irritation does not persist. By taking part in the study the volunteers will be exposed to a small amount of radiation.

Where is the study run from?
AstraZeneca (Sweden)

When is the study starting and how long is it expected to run for?
March 2022 to June 2022

Who is funding the study?
AstraZeneca (Sweden)

Who is the main contact?
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Contact information

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT05364255

Clinical Trials Information System (CTIS)
2022-000834-40

Integrated Research Application System (IRAS)
1005259

Protocol serial number
D8532C00005

Study information

Scientific Title

A Phase I, open-label, single-dose, single-period study to assess the mass balance recovery, metabolite profile and metabolite identification of [14C]AZD9833 after oral administration in healthy post-menopausal female subjects

Acronym
QSC205863

Study objectives
1. To determine the mass balance recovery after a single oral dose of [14C]AZD9833
2. To perform metabolite profiling and structural identification from plasma, urine and faecal samples
3. To determine the routes and rates of elimination of [14C]AZD9833
4. To determine the oral pharmacokinetics (PK) of AZD9833 in plasma and total radioactivity in plasma and whole blood
5. To evaluate the extent of distribution of total radioactivity into blood cells
6. To provide additional safety and tolerability information for AZD9833

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 25/04/2022, Fast Track REC (Health Research Authority, 2 Redman Place, Stratford, London, E20 1JQ, UK; +44 (0)207 104 8012; fasttrack.rec@hra.nhs.uk), ref: 22/FT/0050

Primary study design
Interventional

Study design
Non-randomized study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
ER-positive, HER2-negative breast cancer

Interventions
This is a single-part, healthy volunteer study to identify how the test medicine is taken up, broken down and removed from the body. To help investigate this, the test medicine is radiolabelled, which means that the test medicine has a radioactive component (carbon-14) which helps track where the test medicine is in the body. The safety and tolerability of the test medicine will also be studied. This study will take place at one non-NHS site, and will consist of a single study period involving up to 6 post-menopausal female volunteers, aged between 50 to 70 years. On Day 1, volunteers will receive a 75 mg dose of [14C]AZD9833 oral solution in the fasted state. Volunteers' blood, urine and faeces will be taken throughout the study for analysis of the test medicine and its breakdown products (metabolites) and for volunteer safety. Volunteers will remain in the clinical unit until Day 8, however, if the relevant radioactivity criteria have not been met, volunteers may be required to remain at the clinic until Day 10. If relevant criteria have not been met at this point, home collections of urine and/or faeces may be required. Volunteers are expected to be involved in this study for approximately 6 weeks from screening to discharge.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
[14C]AZD9833

Primary outcome(s)
1. Mass balance recovery of total radioactivity in all excreta (urine and faeces): CumAe and Cum% Ae measured by accelerator mass spectrometry from samples taken at timepoints between Day 1 up to Day 10
2. Levels and structures of drug and metabolites in plasma, urine and faeces measured by ultra-performance liquid chromatography coupled to high-resolution mass spectrometry (hrMS)/mass spectrometry (MS) from samples taken at timepoints between Day 1 up to Day 10 (plus any additional samples taken beyond this period if warranted)

Key secondary outcome(s)
1. Mass balance recovery of total radioactivity in urine and faeces separately: Ae, %Ae, CumAe and Cum%Ae by interval measured by accelerator mass spectrometry from samples taken at timepoints between Day 1 up to Day 10
2. Assessment of the PK of AZD9833 and total radioactivity by calculation of tmax, Cmax, AUC0-t, AUC0-inf, AUC%extr, t1/2, λz, CL/F and Vz/F measured by LC-UV-MS from samples taken at timepoints between Day 1 up to Day 10
3. Whole blood:plasma concentration ratios for total radioactivity evaluated using samples taken at timepoints between Day 1 up to Day 10
4. Safety and tolerability information via measures including physical examinations, vital signs, ECGs and laboratory safety tests will be assessed by standard phase 1 unit monitoring at screening, from Day -1 to discharge from the ward on (up to) Day 10

Completion date
20/06/2022

Eligibility

Key inclusion criteria
1. Provision of signed and dated, written informed consent prior to any study-specific procedures
2. Aged between 50 to 70 years inclusive at the time of signing informed consent
3. Healthy post-menopausal females, defined as post-menopausal by fulfilling the following criterion:
3.1. Amenorrhoea for at least 12 months following cessation of all exogenous hormonal treatments and without an alternative medical or surgical cause and confirmed by an FSH result of ≥30 IU/l
4. Must be willing and able to communicate and participate in the whole study
5. Have a body mass index (BMI) between 19.0 to 35.0 kg/m², weigh at least 50 kg and no more than 100 kg inclusive as measured at screening.
6. Must have regular bowel movements (i.e. average stool production of ≥1 and ≤3 stools per day)

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Sex
Female

Total final enrolment
6

Key exclusion criteria
1. History of any clinically significant disease or disorder which, in the opinion of the Investigator, may either put the volunteer at risk because of participation in the study, or influence the results or the volunteer's ability to participate in the study
2. History or presence of GI, hepatic or renal disease, or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs
3. Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks of the first administration of IMP
4. History of or ongoing clinically significant visual disturbances including but not limited to visual hallucinations, migraine with visual symptoms, blurred vision, frequent floaters/flashes associated with other symptoms such as dizziness
5. Any clinically significant abnormalities in clinical chemistry, haematology, or urinalysis results, at screening as judged by the Investigator.
6. Any clinically significant abnormal findings in vital signs at screening as judged by the Investigator, including systolic BP <100 mmHg, diastolic BP <50 mmHg or heart rate <50 bpm. Vital signs outside these limits can be repeated once for confirmation
7. Any clinically significant abnormalities on 12-lead ECG at screening, as judged by the Investigator, including non-sinus rhythms, PR interval <120 msec or >220 msec, ventricular rate <50 bpm or >100 bpm, QRS interval >120 msec, or QTcF >470 msec as a mean of triplicate. ECGs can be repeated once in triplicate if parameters are outside these limits for confirmation
8. Evidence of renal impairment at screening, as indicated by an estimated creatinine clearance (CLcr) of <60 ml/min/1.73m² using the Cockcroft-Gault equation
9. Any positive result on screening for serum hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV Ab), and human immunodeficiency virus (HIV) 1 and 2 antibodies
10. Has received another new chemical entity (defined as a compound which has not been approved for marketing) within 4 weeks prior to Day 1, or less than 5 elimination half-lives + 6 days prior to Day 1, whichever is longer. Note: subjects consented and screened, but not administered IMP in this study or a previous Phase I study, are not excluded
11. Plasma donation within 1 month of screening or any blood donation/loss more than 500 ml during the 3 months prior to screening
12. History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the Investigator or history of hypersensitivity to drugs with a similar chemical structure or class to AZD9833. Hay fever is allowed unless it is active
13. Any known or suspected hypersensitivity or contraindication to the components of the study drug, AZD9833, judged to be clinically relevant by the investigator
14. Current smokers or those who have smoked or used nicotine products (including e-

cigarettes) within the 3 months prior to screening
15. A confirmed breath carbon monoxide reading of greater than 10 ppm at screening or admission
16. Positive screen for drugs of abuse at screening or on each admission to the study centre
17. Regular alcohol consumption >14 units per week (1 unit = ½ pint beer, or a 25 mL shot of 40% spirit, 1.5 to 2 units = 125 mL glass of wine, depending on type)
18. A confirmed positive alcohol breath test at screening or admission
19. Subjects who are taking, or have taken:
19.1. Any prescribed or over-the-counter drug (other than up to 4 g of paracetamol per day) or herbal remedies in the 14 days before IMP administration or longer if the medication has a long half-life. COVID-19 vaccines are accepted concomitant medications. Exceptions may apply, as determined by the Investigator, if each of the following criteria are met: medication with a short half-life if the washout is such that no PD activity is expected by the time of dosing with IMP; and if the use of medication does not jeopardise the safety of the trial subject; and if the use of medication is not considered to interfere with the objectives of the study
19.2. Atropine or atropine containing drugs, in the 14 days before IMP administration
19.3. Systemic oestrogen-containing hormone replacement therapy in the 6 months prior to IMP administration
20. Use of drugs with enzyme-inducing properties such as St John's Wort within 3 weeks or 5 half-lives (whichever is longer) or any drugs with a known risk, potential risk or conditional risk for QTca prolongation as defined and outlined in the Credible Meds website within 4 weeks prior to Day 1
21. Subjects who do not agree to avoid the use of warfarin or phenytoin (and other coumarin-derived vitamin K antagonist anticoagulants) for 2 weeks after administration of IMP
22. Excessive intake of caffeine-containing drinks or food (e.g., coffee, tea, chocolate) as judged by the Investigator. Excessive intake of caffeine defined as the regular consumption of more than 600 mg of caffeine per day (e.g., >5 cups of coffee) or would likely be unable to refrain from the use of caffeine-containing beverages during confinement at the clinical unit
23. Involvement of any AstraZeneca, Quotient or study site employee or their close relatives
24. Subjects who report having previously received AZD9833 in the last 12 months
25. Judgment by the Investigator that the volunteer should not participate in the study if they have any ongoing or recent (i.e., during the screening period) minor medical complaints that may interfere with the interpretation of study data or are considered unlikely to comply with study procedures, restrictions, and requirements
26. Evidence of current SARS-CoV-2 infection
27. Radiation exposure, including that from the present study, excluding background radiation but including diagnostic x-rays and other medical exposures, exceeding 5 mSv in the last 12 months or 10 mSv in the last 5 years. No occupationally exposed worker, as defined in the Ionising Radiation Regulations 2017, shall participate in the study
28. Vulnerable subjects, e.g., kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order
29. Subjects who do not have suitable veins for multiple venepunctures/cannulation as assessed by the Investigator or delegate at screening
30. Subjects with an anticipated need for major surgery and/or any surgery requiring general anaesthesia during the participation in the study (which may entail administration of atropine in an anaesthetic context)
31. Failure to satisfy the Investigator of fitness to participate for any other reason

Date of first enrolment
10/05/2022

Date of final enrolment
20/06/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Quotient Sciences Limited
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NG11 6JS

Sponsor information

Organisation
AstraZeneca (Sweden)

ROR
https://ror.org/04wwrrg31

Funder(s)

Funder type
Industry

Funder Name
AstraZeneca

Alternative Name(s)
AstraZeneca PLC, Pearl Therapeutics, AZ

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The SAS datasets are available after CSR submission and are retained for 1 year before disposal. Requests for data should be directed to the Data Protection Officer in the Data Privacy Office via email at Privacy@astrazeneca.com. Subjects consent to future use of data during the Screening and Enrolment process and are provided with the privacy notice as requested. All data will be anonymized and transferred via a secure, encrypted method.

IPD sharing plan summary
Available on request