Sponsor: Sanofi **Drug substance:** Amcenestrant	**Study Identifiers:** NCT04940026 **Study code:** BEX15859

Title of the study: A Phase 1, open-label, single center, one period, one sequence study to determine absorption, metabolism, and excretion of a single oral dose administration of radiolabeled ^{14}C-SAR439859 and an assessment of the absolute oral bioavailability using the microdosing technique in healthy post-menopausal women

Study center: This study was conducted at 1 center that enrolled healthy post-menopausal female participants in the United Kingdom.

Study period:

Date first participant enrolled: 16/Jun/2021

Date last participant completed: 19/Aug/2021

Study Status: Completed

Phase of development: Phase 1

Objectives:

Primary:

- To assess the excretion balance after oral and IV administration of [^{14}C]-amcenestrant
- To assess pharmacokinetics (PK) of total radioactivity, [^{14}C]-amcenestrant, and [^{14}C]-M7 after IV administration of [^{14}C]-amcenestrant, and PK of radioactivity, amcenestrant, and M7 after oral administration of amcenestrant alone or with [^{14}C] amcenestrant
- To assess IV clearance and absolute bioavailability (F) of amcenestrant given as microdose of [^{14}C]-amcenestrant tracer on top of a single tablet oral dose
- To assess relative bioavailability of amcenestrant given as tablet or solution

Secondary:

- To assess metabolic profile in plasma and excreta after oral administration of [^{14}C]-amcenestrant as solution, contribution in plasma of amcenestrant, and metabolite relative to total radioactivity and identify metabolites
- To assess safety and tolerance of amcenestrant

Methodology:

This was a single-center, open-label, 1-period, fixed-sequence study to determine absorption, metabolism, and excretion of [^{14}C]-amcenestrant, and to assess absolute oral bioavailability of amcenestrant in healthy post-menopausal women.

A single oral dose of amcenestrant (tablet) was administered on Day 1 in a fasted condition, followed 3 hours later by a single IV dose of [^{14}C]-amcenestrant. Following a 6-day washout, a single oral dose of [^{14}C]-amcenestrant (solution) was administered on Day 7 in a fasted condition.

Based on the elimination half-life of amcenestrant that was approximately 15.2 hours after a single dose of 400 mg, the release criteria were expected to be met within the first week following the oral administration on Day 7. The earliest possible discharge would have been on Day 11 if the combined cumulative excretion of radioactivity in urine and feces exceeded a mean of 90% of the administered dose for the cohort, with recovery being not less than 85% in any one individual. If by Day 11, the release criteria were still not met, participants were to be individually released if the total of urinary and fecal 24-hour excretion of radioactivity dropped below 0.5% of the dose on 2 consecutive days after Day 11 and not later than Day 16.

If the criteria were still not met on Day 16, all participants were to be discharged, but returned weekly to the clinical unit for collection of additional blood samples and to bring single 24-hour collections of urine and feces, for a maximum of 4 additional weeks, or until the cumulative total of urinary and fecal 24-hour excretion of radioactivity dropped below 0.5% of the dose.

Number of participants:

Six participants were enrolled as planned and completed the study. All 6 participants were included in the safety and PK populations.

Diagnosis and criteria for inclusion:

Healthy female participants who were post-menopausal or had had a post-bilateral surgical oophorectomy (not linked to a history of cancer) aged 40 to 75 years of age (inclusive), with a body weight between 40.0 and 95.0 kg, inclusive, and a body mass index between 18.0 and 32.0 kg/m^2 (inclusive).

Study products:

Investigational medicinal products:

Amcenestrant (SAR439859)

- Formulation: 200 mg tablet.
- Route of administration: oral.
- Dose regimen: 400 mg administered as a single dose on Day 1 in a fasted condition

[^{14}C]-amcenestrant (IV, Day 1)

- Formulation: solution for IV injection [^{14}C]-amcenestrant equivalent to 100 µg amcenestrant, containing no more than 37 kBq (1 µCi = microtracer)
- Route(s) of administration: IV (infusion): a light meal/snack could have been served at least 2 hours after the oral tablet dosing and 1 hour before IV [^{14}C]-amcenestrant administration. This light meal/snack should have been finished by the participants in around 30 minutes
- Dose regimen: single dose 100 µg on Day 1, 3 hours after oral dosing

[^{14}C]-amcenestrant (oral, Day 7)

- Formulation: oral solution containing equivalent of 400 mg [^{14}C]-amcenestrant corresponding to no more than 5.6 MBq (151.2 µCi)
- Route of administration: oral
- Dose regimen: 400 mg administered as a single dose on Day 7 in a fasted condition

Duration of study intervention:

The expected duration of the study per participant was 72 days maximum, including the steps described below:

- Screening: up to 27 days (minimum 2 days) (Day -28 to Day -2)
- Day -1: Admission.
- Treatment period: up to 16 days (dosing on Day 1 and Day 7)
- Washout: 6 days
- Follow-up/End of study Visit: 7 to 10 days after last collection of excreta or otherwise on the last follow-up visit on Day 44.

Criteria for evaluation:

Primary:

- Amount and percentage of radioactive dose, [^{14}C]-amcenestrant, and [^{14}C]-M7 excreted in urine and feces after IV (Day 1) and oral (Day 7) administration
- For radioactivity and for [^{14}C]-amcenestrant (plasma) after IV (Day 1): C_0, AUC_{last}, AUC, $t_{1/2z}$, CL, V_{ss}, and AUC ratios after IV (Day 1)
- For radioactivity (blood and plasma, Day 7) and for amcenestrant (plasma, Day 1 and Day 7) after oral administration: C_{max}, t_{max}, AUC_{last}, AUC, $t_{1/2z}$, and blood/plasma concentration and AUC ratios after oral

  For [^{14}C]-M7 (Day 1) and M7 (Day 1 and Day 7) in plasma: C_{max}, t_{max}, AUC_{last}, AUC, $t_{1/2z}$, R_{met} C_{max}, and AUC
- Clearance, F, and fraction absorbed after IV (Day 1) using [^{14}C] amcenestrant
- Relative bioavailability (F_{rel}) of tablet and oral solution dose

Secondary:

- Samples were to be analyzed according to metabolic analysis plan and results were to be documented in a separate report
- Clinical laboratory evaluations, vital signs, electrocardiogram (ECG) parameters, treatment-emergent adverse events (TEAEs) (serious and non-serious)

Statistical methods:

Pharmacokinetics: PK analysis was conducted on the PK population.

Concentrations (plasma radioactivity, blood radioactivity, plasma amcenestrant, plasma M7) and PK parameters were summarized using standard descriptive statistics by route and day of administration and for each appropriate matrix.

Absolute bioavailability (F), relative bioavailability (Frel), metabolic ratio (Rmet), and RAUC and $RAUC_{0-24}$ for amcenestrant and M7 were presented by individual listings and associated with descriptive statistics including 90% confidence intervals (CIs). Individual blood/plasma ratio of radioactivity concentration and AUC were tabulated by time point and/or study intervention group and summarized by descriptive statistics.

For the mass balance, radioactivity measured in urine and feces after oral and IV administration, was expressed as percent of dose administered. Individual amount excreted at each time interval and cumulative amount as well as total amount excreted were summarized per matrix. Cumulative amount of radioactivity excreted as function of time was presented by matrix and overall.

Safety: Safety analysis (adverse events [AEs], laboratory parameters, vital signs, ECGs was based on the review of individual values and descriptive statistics. The safety analysis focused on the TEAE periods.

Adverse events were coded according to the Medical Dictionary for Regulatory Activities (version 24.0). Their severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. The number (%) of participants experiencing TEAEs was summarized by NCI-CTCAE grade (all grades, Grade ≥3), by primary system organ class, preferred term, and TEAE periods. Clinical laboratory parameters covered by NCI-CTCAE criteria were also graded. Potentially clinically significant abnormalities (PCSAs) in clinical laboratory test results (clinical laboratory parameters not covered by the NCI CTCAE criteria only), vital signs, and ECGs were flagged and summarized using frequency tables.

Summary Results:

Demographic and other baseline characteristics:

All participants were female, the majority were White (66.7%), and the median age of participants in this study was 60.5 years old (min:max of 53:63 years).

Exposure:

A total of 6 participants were exposed to investigational medicinal products (amcenestrant oral tablet and [^{14}C]-amcenestrant IV on Day 1; and [^{14}C]-amcenestrant oral solution on Day 7) in this study. All participants received the planned doses of amcenestrant as per protocol.

Safety results:

Adverse events:

There were no treatment-emergent serious AEs or TEAEs leading to treatment discontinuation during the study and no AEs of special interest.

Treatment emergent AEs were reported by 3/6 (50%) and 6/6 (100%) participants during treatment with amcenestrant 400 mg oral tablet + [^{14}C]-amcenestrant 100 µg IV and [^{14}C]-amcenestrant 400 mg oral solution TEAE periods, respectively. No TEAEs were reported in the amcenestrant 400 mg oral tablet TEAE period.

The most frequent TEAE was throat irritation reported by 6/6 (100%) participants during treatment with [^{14}C]-amcenestrant 400 mg oral solution TEAE period. The next most frequently reported TEAE was nausea, reported in 1/6 (16.7%) and 4/6 (66.7%) participants during treatment with amcenestrant 400 mg oral tablet + [^{14}C]-amcenestrant 100 µg IV and [^{14}C]-amcenestrant 400 mg oral solution TEAE periods, respectively. Other TEAEs were single occurrences.

With the exception of 1 TEAE of Grade 2, all TEAEs were of Grade 1 intensity.

There were no PCSAs for vital signs except 1 single occurrence of systolic blood pressure of ≤95 mmHg and decrease from baseline ≥20 mmHg that was not considered clinically significant by the Investigator.

There were very few PCSAs for ECGs. The PCSAs were not symptomatic and consisted mainly of single occurrences that were not considered clinically relevant by the Investigator. There were 3/6 and 2/6 participants with PR interval >200 msec during treatment with amcenestrant 400 mg oral tablet + [^{14}C]-amcenestrant IV 100 µg and [^{14}C]-amcenestrant 400 mg oral solution TEAE periods, respectively, but none represented an increase from baseline ≥25%.

There were very few laboratory parameter NCI-CTCAE abnormalities. They consisted mainly of single occurrences except anemia, high cholesterol, and hypertriglyceridemia that were considered not clinically significant by the Investigator. Overall, there were no combined PCSAs reported for liver function.

Pharmacokinetic results:

[^{14}C]-amcenestrant oral solution

Mass balance following a single [^{14}C]-amcenestrant oral solution administration

Individual, mean, and standard deviation (SD) total radioactivity in urine and feces expressed as percentage of a 400 mg oral solution of [^{14}C]-amcenestrant administered as a single dose in healthy post-menopausal participants (N=6) under fasting conditions are presented in Table 1.

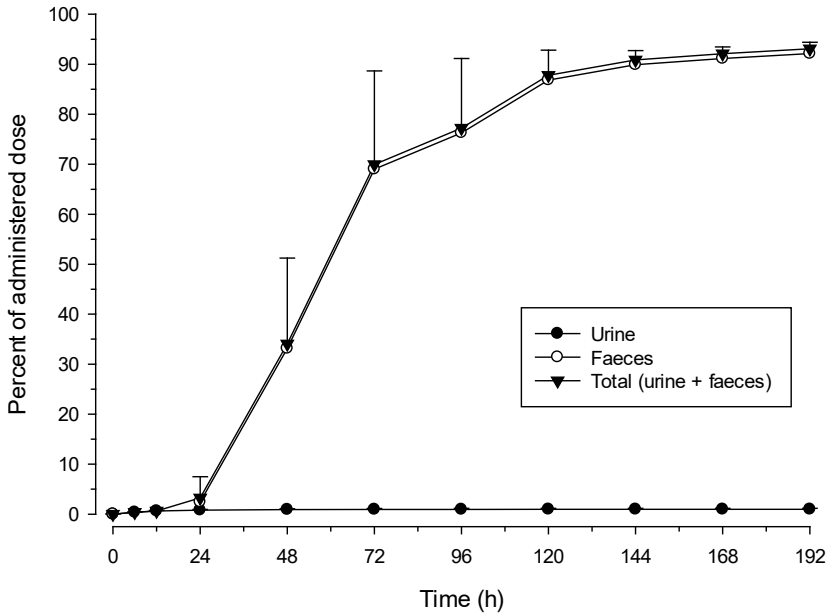
Table 1 - Individual and mean excretion balance of total radioactivity following a single [^{14}C]-amcenestrant (400 mg) oral solution administration in healthy post-menopausal women (N=6) under fasting conditions

	Percent of dose administered							
	Subject number							
	001	002	003	004	005	006	Mean	SD
Urine	0.74	1.33	0.98	1.02	0.78	0.88	0.96	0.21
Feces	92.51	94.64	92.32	92.98	87.84	92.46	92.13	2.27
Total	93.25	95.97	93.30	94.00	88.62	93.34	93.08	2.42

Excretion via feces was the major elimination pathway of the amcenestrant oral solution administered radioactive dose. On average, around 92% of the dose was excreted in feces and less than 1% in urine, over 192 hours.

Mean cumulative percent of radioactivity recovered in urine and feces up to 192 hours postdose is illustrated in Figure 1.

Figure 1 - Mean (+SD) cumulative percent of radioactive dose recovered in urine and feces at specified intervals following a single [^{14}C]-amcenestrant (400 mg) oral solution administration in healthy post-menopausal participants (N=6) under fasting conditions

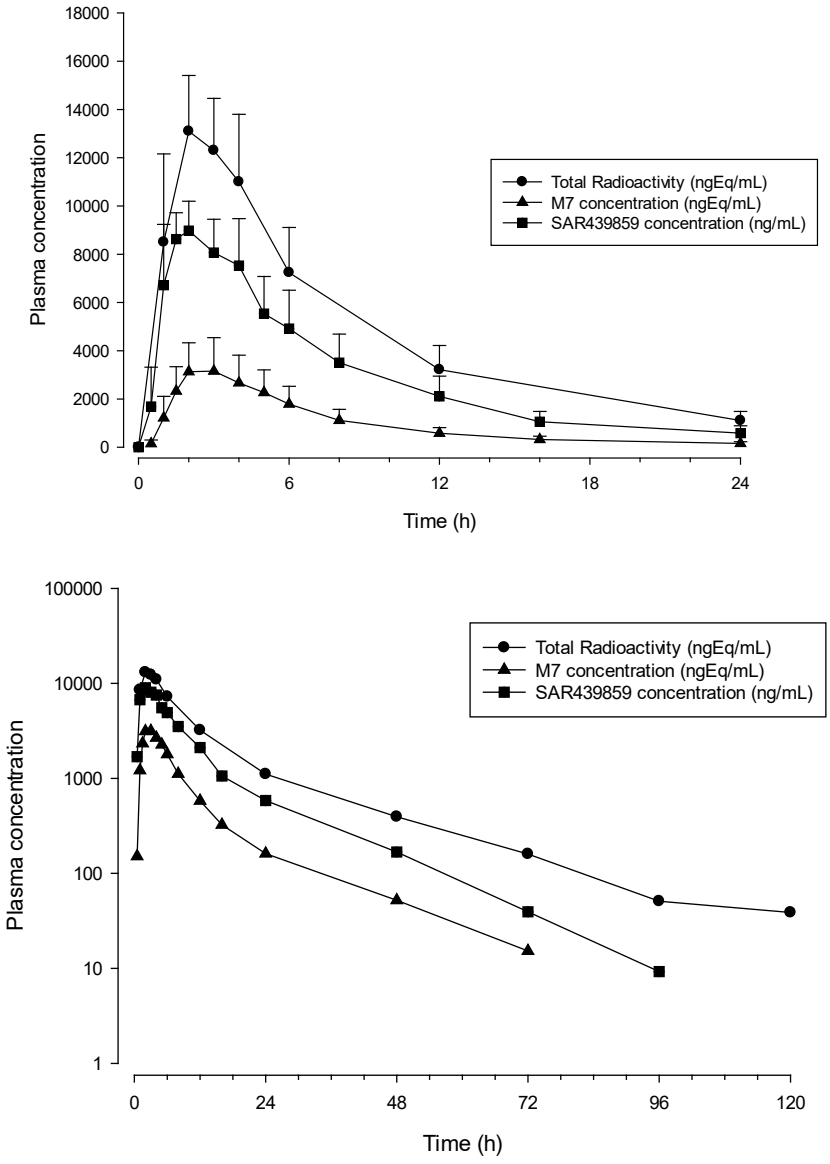


Overall, 90% of the administered radioactive dose was excreted within 144 hours after [14C]-amcenestrant oral solution administration.

PK following a single [^{14}C]-amcenestrant oral solution administration

Mean concentration-time profiles of total radioactivity, amcenestrant, and M7 in plasma are illustrated in Figure 2.

Figure 2 – Mean (+SD) plasma concentration-time profiles of radioactivity, amcenestrant, and M7 following a single [^{14}C]-amcenestrant (400 mg) oral solution administration (linear and log scale) in healthy post-menopausal women (N=6) under fasting conditions



Mean total radioactivity in plasma was quantifiable up to 120 hours post dosing. Mean amcenestrant concentrations were quantifiable up to 96 hours and up to 72 hours for the metabolite M7.

Descriptive statistics of PK parameters obtained for total radioactivity in plasma and blood and for amcenestrant and M7 in plasma after a single [^{14}C]-amcenestrant (400 mg) oral solution administration are presented in Table 2.

Table 2 - Summary of pharmacokinetic parameters for radioactivity (blood, plasma), amcenestrant, and M7 (plasma) following a single [^{14}C]-amcenestrant (400 mg) oral solution administration in healthy post-menopausal women under fasting conditions

N, Mean ± SD, (Geo. Mean) [CV%]	Total Radioactivity, blood	Total Radioactivity, plasma	N, Mean ±SD, (Geo. Mean) [CV%]	SAR439859, plasma	M7, plasma
Tmax (h) [a]	6 2.00 [2.00-4.00]	6 2.00 [2.00-4.00]	Tmax (h) [a]	6 1.75 [1.00-4.00]	6 2.50 [2.00-4.00]
Cmax (ngEq/mL)	6 8630 ± 1340 (8550) [15.5]	6 13500 ± 2430 (13300) [18.0]	Cmax (ng/mL)	6 9540 ± 1070 (9480) [11.2]	6 4380 ± 1650 (4140) [37.7]
AUClast (h*ngEq/mL)	6 90400 ± 20700 (88300) [22.9]	6 142000 ± 36000 (138000) [25.3]	AUClast (ng*h/mL)	6 83500 ± 23300 (80600) [27.9]	6 35200 ± 13900 (33000) [39.5]
AUC (h*ngEq/mL)	6 97000 ± 22700 (94800) [23.4]	6 147000 ± 36700 (143000) [25.0]	AUC (ng*h/mL)	6 84000 ± 23200 (81100) [27.6]	6 35600 ± 13900 (33300) [39.0]
t1/2z (h)	6 19.6 ± 7.13 (18.5) [36.4]	6 22.5 ± 10.9 (20.4) [48.4]	t1/2z (h)	6 12.2 ± 3.45 (11.8) [28.3]	6 13.2 ± 3.73 (12.8) [28.2]
			CL/F (L/h)	6 5.12 ± 1.62 (4.93) [31.6]	NA
			Vss/F (L)	6 54.5 ± 8.13 (54.0) [14.9]	NA

a: median [min - max]

Source = PKS Study : BEX15859 LSC; Scenario: RA-A-EV-OD, Version 7, for total radioactivity

Source = PKS Study : BEX15859; Scenario: P-D-A-EV-OD, Version 7, for amcenestrant and M7

Median t_{max} of total radioactivity in plasma was 2 hours. Amcenestrant and metabolite M7 t_{max} were similar to that of total radioactivity (1.75 and 2.5 hours, respectively), showing that amcenestrant was rapidly absorbed and metabolized to M7 and other circulating metabolites.

The mean (±SD) terminal half-life of plasma radioactivity was 22.5 (±10.9) hours and the mean elimination half-life was 12.2 (±3.45) hours for amcenestrant and 13.2 (±3.73) hours for metabolite M7.

In terms of C_{max}, amcenestrant and the metabolite M7 represented 71.5% (90%CI: 66.2% - 77.3%) and 23.7% (90%CI: 18.5% - 30.3%) of total radioactivity, respectively. In terms of AUC, amcenestrant and M7 represented 56.8% (90%CI: 50.9% - 63.4%) and 17.7% (90%CI: 13.4% - 23.4%) of total radioactivity, respectively. The sum of AUCs of the parent drug and the metabolite M7 indicated that other circulating metabolites existed, representing around 25% of circulating radioactivity.

Metabolic ratio was 33.1% (90%CI: 25.1% - 43.6%) and 31.2% (90%CI: 21.5% - 45.2%) for C_{max} and AUC, respectively, following administration of a single [^{14}C]-amcenestrant 400 mg oral solution.

Geometric mean ratio of blood to plasma AUC of total radioactivity was 66.3% (90%CI: 64.8% - 68.0%) indicating no affinity of amcenestrant or its metabolite for blood cells.

Amcenestrant oral tablet

Descriptive statistics of amcenestrant plasma PK parameters after a single amcenestrant (400 mg) oral tablet or [^{14}C]-amcenestrant (400 mg) oral solution administration are presented in Table 3.

Table 3 - Summary of amcenestrant plasma pharmacokinetic parameters after a single amcenestrant tablet or [^{14}C]-amcenestrant solution oral administration in healthy post-menopausal women under fasting conditions

Mean ± SD , Geo. Mean (CV%)	**amcenestrant (400 mg) tablet, plasma**	**^{14}C-amcenestrant (400 mg) solution, plasma**
N	6	6
Tmax (h) [a]	3.38 [2.72-5.02]	1.75 [1.00-4.00]
Cmax (ng/mL)	5100 ± 930	9540 ± 1070
	(5030) [18.2]	(9480) [11.2]
AUClast (ng*h/mL)	53700 ± 14600	83500 ± 23300
	(51800) [27.1]	(80600) [27.9]
AUC (ng*h/mL)	54100 ± 14300	84000 ± 23200
	(52400) [26.5]	(81100) [27.6]
t1/2z (h)	14.7 ± 4.91	12.2 ± 3.45
	(14.1) [33.4]	(11.8) [28.3]
CL/F (L/h)	7.92 ± 2.46	5.12 ± 1.62
	(7.64) [31.1]	(4.93) [31.6]
Vss/F (L)	111 ± 52.7	54.5 ± 8.13
	(104) [47.2]	(54.0) [14.9]

a: median [min - max]

Source = PKS Study : BEX15859; Scenario: P-D-A-EV-OD, Version 7, for tablet and solution

The F_{rel} of amcenestrant tablet compared to the solution was 64.6% (90%CI: 49.8% - 83.7%).

No t_{lag} was observed for both formulations. A shorter geometric mean tmax (median values: 1.75 versus 3.38 hours) and higher plasma exposure (geometric mean C_{max} and AUC) was observed for the solution compared to the tablet.

The apparent terminal half-life of elimination was similar for both formulations.

[^{14}C]-amcenestrant IV solution

Mass balance following a single [^{14}C]-amcenestrant IV solution administration

Individual, mean, and standard deviation (SD) total radioactivity in urine and feces expressed as percentage of a 100 µg IV solution of [^{14}C]-amcenestrant administered as a single dose in healthy post-menopausal participants (N=6) are presented in Table 4.

Table 4 Individual and mean excretion balance of total radioactivity following a single [^{14}C]-amcenestrant (100 µg) IV solution administration in healthy post-menopausal women (N=6)

Percent of dose administered								
	Subject number							
	0001	0002	0003	0004	0005	0006	Mean	SD
Urine	0.859	1.30	1.09	1.22	0.839	1.15	1.08	0.192
Feces	81.2	77.6	88.4	85.2	77.8	85.3	82.6	4.42
Total	82.1	78.9	89.5	86.4	78.6	86.4	83.7	4.47

Excretion via feces was the major elimination pathway of the amcenestrant IV solution administered radioactive dose. On average, around 82.6% of the dose was excreted in feces and 1.1% in urine, over 117 hours.

Overall, 83.7% of the administered radioactive dose was excreted within 117 hours after a single [^{14}C]-amcenestrant IV solution administration.

PK following single [^{14}C]-amcenestrant IV administration

Summary statistics of plasma PK parameters obtained for total radioactivity, amcenestrant and M7 after a single IV administration of [^{14}C]-amcenestrant 100 µg, are presented in Table 5.

Table 5 - Summary of plasma pharmacokinetic parameters for radioactivity, amcenestrant, and M7 following a single IV administration of [^{14}C]-amcenestrant 100 µg in healthy post-menopausal women

N, Mean ± SD, (Geo. Mean) [CV%]	Total Radioactivity, plasma	amcenestrant, plasma	M7, plasma
Cmax (ngEq/mL)	6 10.3 ± 1.42 (10.2) [14]	6 6.33 ± 0.968 (6.26) [15]	6 0.632 ± 0.323 (0.573) [51]
AUClast (h*ngEq/mL)	6 40.6 ± 8.36 (39.9) [21]	6 18.0 ± 4.74 (17.6) [26]	6 5.75 ± 1.75 (5.51) [30]
AUC_{0-24} (h*ngEq/mL)	6 35.2 ± 6.90 (34.7) [20]	6 16.6 ± 4.23 (16.2) [25]	6 5.03 ± 1.48 (4.83) [30]
AUC (h*ngEq/mL)	6 43.8 ± 8.96 (43.1) [20]	6 18.5 ± 4.82 (18.0) [26]	6 6.12 ± 1.93 (5.85) [32]
$t_{1/2z}$ (h)	6 13.6 ± 1.22 (13.6) [9]	6 9.46 ± 1.25 (9.39) [13]	6 11.6 ± 1.71 (11.5) [15]
CL (L/h)	NA	6 5.69 ± 1.26	NA

		(5.56) [22]	
Vss (L)	NA	6 44.1 ± 10.7 (43.0) [24]	NA

NA: Not Applicable

Source = PKS Study : BEX15859 AMS; Scenario: RA-B-EV-OD, Version 6, for total radioactivity

Source = PKS Study : BEX15859IV; Scenario: P-D-A-IN-OD, Version 7, for amcenestrant and M7

In terms of AUC, amcenestrant and M7 represented 41.7% (90% CI: 37.1% - 46.9%) and 13.6% (90% CI: 10.1% - 18.2%) of total radioactivity, respectively.

Metabolic ratio of M7 was 32.5% (90%CI: 22.0% - 48.1%) for AUC following administration of single IV administration of [^{14}C]-amcenestrant 100 µg.

The absolute oral bioavailability of amcenestrant 400 mg calculated using IV data was 72.8% (90% CI: 61.6% - 86.0%) when administered as a 200-mg tablet and 113% (90% CI: 94.5% - 134%) when administered as a solution.

An estimation of amcenestrant F_{abs} using an oral solution was done using the plasma AUC of radioactivity after oral and IV administration normalized by dose. The F_{abs} of amcenestrant 400 mg administered as a solution was 82.9% (90% CI: 75.3% - 91.2%).

Issue date: 10-Jul-2023