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| **Sponsor:** Sanofi<br>**Drug substance:** Amcenestrant | **Study Identifiers:** U1111-1244-1929; NCT05126329; EudraCT 2021-001784-24<br>**Study code:** POP16301 |
| **Title of the study:** An open-label pharmacokinetic and tolerability study of amcenestrant given as a single dose in female participants with mild and moderate hepatic impairment, and in matched participants with normal hepatic function | |
| **Study centers:** This study was conducted at 3 centers that enrolled participants in Germany and South Korea. | |
| **Study period:**<br>Date first participant enrolled: 15/Nov/2021<br>Date last participant completed: 17/May/2022<br>Study Status: Terminated. The study was terminated following the Sponsor's decision to prematurely stop the study, which was not linked to any safety concerns. | |
| **Phase of development:** Phase 1 | |
| **Objectives:**<br>**Primary**<br>To study the effect of mild and moderate hepatic impairment on the main PK parameters of amcenestrant<br>**Secondary**<br>● To study the effect of mild and moderate hepatic impairment on additional PK parameters of amcenestrant and M7<br>● To assess the tolerability of amcenestrant given as a single dose in participants with mild and moderate hepatic impairment in comparison with matched participants with normal hepatic function | |
| **Methodology:**<br>This was a Phase 1, parallel, open-label, 3-arm, single amcenestrant dose, multi-center study in female participants with mild and moderate hepatic impairment and matched participants with normal hepatic function.<br>The study was designed to evaluate the effects of mild and moderate hepatic impairment on the PK of amcenestrant as compared with matched participants with normal hepatic function and to assess the safety and tolerability of amcenestrant.<br>Participants with hepatic impairment or normal hepatic function were to be enrolled and assigned to receive a study intervention (ie, a single dose of amcenestrant 200 mg on Day 1). The hepatic impairment of the enrolled participants was assessed according to the Child-Pugh classification and using Child-Pugh total score (ie, 5 to 6 and 7 to 9 for participants with mild and moderate hepatic impairment, respectively). Participants who prematurely withdraw from the study could be replaced if insufficient data for PK evaluation were obtained from these participants. | |

**Number of participants (planned and analyzed) :**

Planned: Approximately 18 participants (at least 6 participants to be enrolled in each arm: participants with mild hepatic impairment, moderate hepatic impairment and normal hepatic function).

Actual: 13 participants (7 with mild and 6 with moderate hepatic impairment) were enrolled and treated. Participants with normal hepatic function have not been enrolled due to the early study termination decided by the Sponsor. All 13 participants were analyzed for PK and safety.

**Diagnosis and criteria for inclusion:**

Enrolled participants were female, 40 to 75 years of age at the time of signing the informed consent, were postmenopausal or post-bilateral surgical oophorectomy not linked to a history of cancer. Other key eligibility criteria for participants with mild and moderate hepatic impairment or normal hepatic function included the following:

Participants with hepatic impairment:

- Had stable chronic liver disease assessed by medical history, physical examination, and laboratory values
- Had a Child-Pugh total score ranging from 5 to 6 (mild) or 7 to 9 (moderate)
- Had laboratory parameters within the acceptable range; however, with an estimated glomerular filtration rate above or equal to 60 mL/min
- Had body weight within a range of 50 kg (40 kg for sites in South Korea) to 110 kg and body mass index (BMI) within a range of 18 to 36 kg/$m^2$

Matched participants with normal hepatic function:

- Were certified as healthy by a comprehensive clinical assessment (detailed medical history and complete physical examination)
- Had laboratory parameters within the normal range (or defined screening threshold for the investigator site), unless the investigator considered an abnormality to be clinically irrelevant. Had hepatic transaminases (aspartate aminotransferase and alanine aminotransferase) not exceeding 1.25x the upper laboratory normal value
- Had body weight within a range of 50 kg (40 kg for sites in South Korea) to 100 kg and BMI within a range of 18 to 36 kg/m2.

**Study interventions:**

Amcenestrant was provided in a 200 mg tablet formulation and was administered orally once on Day 1 in fed conditions.

**Duration of study interventions:**

The expected duration of the study per participant was up to 41 days, including the following steps:

- Screening period: up to 4 weeks (Day -28 to Day -2).
- Treatment period: 6 days (Day -1 to Day 5), including a single dose amcenestrant administration on Day 1, 4 days of compulsory institutional stay (Day -1 to Day 3), and 2 days of optional institutional stay (Day 4 and Day 5).

Follow-up period: up to 10 days (based on the variation of optional institutional stay, follow-up period could start from Day 4, Day 5, or Day 6 to the end of study (EOS) visit at Day 10 ±3 days).

**Criteria for evaluation:**

**Primary:**

PK parameters: $C_{max}$ and AUC of amcenestrant

**Secondary:**

- PK parameters: $AUC_{last}$, $t_{max}$, $C_{max,u}$ and $AUC_u$ of amcenestrant, and $C_{max}$, $AUC_{last}$, and AUC for M7
- Assessment of adverse events (AEs)/treatmentemergent adverse events (TEAEs)
- Clinical laboratory evaluations
- Vital signs
- Electrocardiogram (ECG)

Abbreviation: $AUC_u$ = unbound AUC; $C_{max,u}$ = unbound $C_{max}$; M7 = O-AcylGlucuronide; PK: pharmacokinetic.

**Statistical methods:**

A detailed description of the planned statistical methods is provided in the clinical study protocol and the statistical technical document. Statistical analyses compared with that specified in the protocol were reduced as the study was terminated early. That is, only descriptive analyses conducted on participants with mild or moderate hepatic impairment are provided in this report.

Pharmacokinetics (PK):

- PK analysis was conducted on the PK population.
- PK parameters and plasma concentrations of amcenestrant and its M7 metabolite O‑AcylGlucuronide were listed and summarized using descriptive statistics. Unbound plasma concentrations and PK parameters of amcenestrant were not determined due to the early termination of the study.

Safety:

- All the safety analyses were performed using the safety population.
- The safety analyses only focused on demography, disposition, protocol deviations, and adverse event (AE) part. Laboratory parameters, vital signs, and electrocardiogram data were not part of the statistical analyses.
- The safety analyses were based on the review of individual values and descriptive statistics and focused on the treatment-emergent period defined as the period from the investigational medicinal product (IMP) administration up to the EOS visit.
- AEs were coded according to the Medical Dictionary for Regulatory Activities. Their severities were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0. For participants with multiple occurrences of the same AE, the maximum (worst) grade by population group was used.
- Summaries were provided for treatment-emergent adverse events (TEAEs), including TEAEs by System Organ Class (SOC) and Preferred Term (PT), TEAEs by hepatic function population group, treatment-related TEAEs to amcenestrant; treatment-emergent adverse events of special interest (AESIs) by hepatic function population group and by both category and PT; treatment-emergent serious adverse events (SAEs) and treatment-related treatment-emergent SAEs; and TEAEs leading to permanent study discontinuation. Summaries were provided in two categories: 1) for all grades and 2) for Grades ≥3 (including Grade 5).
- All AEs reported in the study were listed, sorted by participant, onset date and time.

**Summary Results:**

A total of 13 participants with mild or moderate hepatic impairment were enrolled and treated in this study. No participants with normal hepatic function have been enrolled, at the time of terminating the study. The study was terminated following the Sponsor's decision to prematurely stop the study, which was not linked to any safety concerns.

During the study, none of the participants had critical or major deviations. All participants treated completed the study period.

**Demographic and other baseline characteristics:**

Overall, only female participants with mild (7 participants) and moderate (6 participants) hepatic impairment were enrolled, 9 (69.2%) out of 13 participants were White, and 4 (30.8%) were Asian. The participants enrolled were between 54 and 75 years, with a mean (SD) age of 63.5 (7.1) years. The mean (SD) baseline body weight for participants enrolled was 66.43 (14.91) kg.

**Exposure:**

All 13 participants received a single administration of amcenestrant 200 mg as per the protocol.

**Safety results:**

During the study, no SAEs or AESIs were reported. Only 1 participant with mild hepatic impairment experienced a TEAE; this event was a Grade 1 eye irritation and considered not related to the IMP. The event was resolved on Day 9 without any corrective treatment.

**Pharmacokinetic results:**

The geometric means (CV%) of exposure PK parameters ($C_{max}$ and AUC) of amcenestrant were 3490 ng/mL (25%) and 35 500 ng•h/mL (27%), respectively, in participants with mild hepatic impairment, and 2500 ng/mL (40%) and 40 500 ng•h/mL (46%), respectively, in participants with moderate hepatic impairment.

The geometric means (CV%) of exposure PK parameters ($C_{max}$ and AUC) of O-AcylGlucuronide were 2420 ng/mL (43%) and 22 600 ng•h/mL (53%), respectively, in participants with mild hepatic impairment, and 2620 ng/mL (55%) and 38 900 ng•h/mL (63%), respectively, in participants with moderate hepatic impairment.

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