AMENDED CLINICAL TRIAL PROTOCOL 06

Protocol title:	**An open-label randomized Phase 2 trial of amcenestrant (SAR439859), versus endocrine monotherapy as per physician's choice in patients with estrogen receptor-positive, HER2-negative locally advanced or metastatic breast cancer with prior exposure to hormonal therapies**
Protocol number:	**ACT16105**
Amendment number:	**06**
Compound number (INN/Trademark):	**SAR439859 (Amcenestrant/Not Applicable)**
Brief title:	**Phase 2 study of amcenestrant (SAR439859) versus physician's choice in patients with locally advanced or metastatic ER-positive breast cancer (AMEERA-3)**
Acronym:	**AMEERA-3**
Study phase:	**Phase 2**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**1 Avenue Pierre Brossolette 91380 Chilly-Mazarin**
Monitoring Team's Representative Name and Contact Information	Click here to type

Regulatory agency identifying number(s):

EudraCT number:	2018-004593-98
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WHO number:	U1111-1217-2774
NCT number:	NCT04059484
EUDAMED	Not applicable
Other	Not applicable

Date: 10-Dec-2021 Total number of pages: 158

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 06	All	10 December 2021, version 1 (electronic 6.0)
Amended Clinical Trial Protocol 05	All	23 September 2021, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 04	All	17 December 2020, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 03	All	30 June 2020, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 02	All	13 February 2020, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	08 August 2019, version 1 (electronic 1.0)
Original Protocol		11 December 2018, version 1 (electronic 1.0)

Amended protocol 06 (10 December 2021)

This amended protocol 06 (Amendment 06) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for the amendment

The objective of the amendment is to update the protocol with the following key changes:

- To update the cut of date (COD) definition for the final progression free survival (PFS) analysis.
- To update the censoring and event scheme of the PFS primary analysis.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis and 9.2 Sample size determination and 9.5.2 Interim analysis for overall survival	The definition of the COD for the final PFS and OS analysis has been changed	To allow more flexibility for the COD definition for final PFS and OS analyses.
1.1 Synopsis and 9.4.1.1 Analysis of the primary efficacy endpoint	The definition of the censoring and event scheme for the PFS analysis has been changed.	To align AMEERA-3 with the general FDA recommendation to censor patients after initiation of further anti-cancer therapy or if the documented progression or death occurred after

Section # and Name	Description of Change	Brief Rationale
		two or more non-evaluable tumor assessments.
1.1 Synopsis and 4.1 Overall design	The sections indicating the safety data to be collected after the COD for the final PFS analysis have been updated: "(…) and all new **serious or** related AEs ~~(serious or not)~~ occurring post-COD (…)"	To clarify that SAEs are in scope of data to be collected post-COD, even if not related to IMP.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

An open-label randomized Phase 2 trial of amcenestrant (SAR439859), versus endocrine monotherapy as per physician's choice in patients with estrogen receptor-positive, HER2-negative locally advanced or metastatic breast cancer with prior exposure to hormonal therapies

Brief title:

Phase 2 study of amcenestrant (SAR439859) versus physician's choice in patients with locally advanced or metastatic ER-positive breast cancer (AMEERA-3)

Rationale:

The treatment of metastatic/advanced breast cancer without visceral crisis is based on hormonal therapies given as monotherapy (tamoxifen, aromatase inhibitors [AI], fulvestrant) and in combination with targeted agents such as everolimus + exemestane and AI or fulvestrant + CDK4/6 inhibitors. These treatments were more often assessed in clinical studies in first and second lines, but few studies explore the efficacy in later lines. The purpose of this study is to evaluate the activity of amcenestrant, a potent, orally bioavailable, and selective estrogen receptor (ER) inhibitor that belongs to the selective estrogen receptor degrader (SERD) class of compounds in comparison with other endocrine treatments approved for the treatment of breast cancer, including fulvestrant, selective ER modulators (tamoxifen), and AIs (anastrozole, exemestane, and letrozole). Amcenestrant antagonizes the binding of estradiol to ER and promotes the transition of ER to an inactive conformation that leads to up to 98% receptor degradation at nanomolar concentrations in cellular assays. These dual properties of amcenestrant translate in a deeper inhibition of ER pathways and a more effective antiproliferative activity in ER-dependent breast cancer cell lines driven by mutant or wild type ER compared to fulvestrant. Fulvestrant is the only SERD currently marketed and is administered by intramuscular (IM) route. The other endocrine treatments listed above are given per os (PO).

Amcenestrant recommended dose was established at 400 mg once daily (QD), based on the safety, pharmacokinetic and pharmacodynamic data review of the ongoing first in human study TED14856, from advanced breast cancer participants.

Objectives and endpoints

Objectives	Endpoints
Primary	
To determine whether amcenestrant 400 mg per os improves progression-free survival (PFS) when compared with an endocrine monotherapy of the choice of the physician, in participants with metastatic or locally advanced breast cancer.	Progression-free survival is defined as the time interval from the date of randomization to the date of first documented tumor progression as per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) assessed by independent central review (ICR) or death (due to any cause), whichever comes first.
Secondary	
To compare the overall survival in the 2 treatment arms.	Overall survival is defined as the time interval from the date of randomization to the date of documented death (due to any cause).
To assess the objective response rate in the 2 treatment arms.	Objective response rate is defined as the proportion of participants who have a confirmed complete response (CR) or partial response (PR), as best overall response (BOR) derived from overall response determined by ICR as per RECIST 1.1, from the date of randomization to the date of end of treatment.
To evaluate the disease control rate in the 2 treatment arms.	Disease control rate is defined as the proportion of participants who have a confirmed CR, PR, stable disease (SD), or Non-CR/ Non-PD as BOR determined by ICR as per RECIST 1.1 from the date of randomization to the date of end of treatment.
To evaluate the clinical benefit rate in the 2 treatment arms.	Clinical benefit rate is defined as the proportion of participants who have a confirmed CR, PR, SD, or Non-CR/ Non-PD for at least 24 weeks determined by ICR as per RECIST 1.1, from the date of randomization to the date of end of treatment.
To evaluate the duration of response in the 2 treatment arms.	Duration of response is defined as the time from first documented evidence of CR or PR until progressive disease (PD) as determined by ICR as per RECIST 1.1 or death from any cause, whichever occurs first.
To evaluate the PFS according to the estrogen receptor 1 gene (ESR1) mutation status in the 2 treatment arms.	Progression-free survival as per ESR1 status determined at Cycle 1 Day 1.
To evaluate the pharmacokinetics of amcenestrant as single agent.	Amcenestrant plasma concentrations during the treatment period.
To evaluate health-related quality of life in the 2 treatment arms.	Disease-specific and generic health-related quality of life, disease and treatment-related symptoms, health state utility, and health status will be evaluated using the European Organisation for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30), the EORTC QLQ breast cancer specific module (BR23) and the EuroQoL questionnaire with 5◦dimensions and 5 levels per dimension (EQ-5D-5L), from Cycle 1 Day 1 until 90 days after last dose of the study treatment.
To evaluate the overall safety profile in the 2 treatment arms.	Adverse events/serious adverse events and laboratory abnormalities.

For China, please see Section 10.8 for details.

Overall design:

This is an international, prospective, open-label, Phase 2 randomized study. Men, postmenopausal women and premenopausal women on a gonadotropin-releasing hormone analog with locally advanced or metastatic breast cancer will be randomly (1:1) assigned to one of the following treatment arms: amcenestrant or an endocrine monotherapy of the choice of the physician.

The population will be stratified according to the presence of visceral metastasis (defined by at least 1 liver or lung metastasis) (Yes or No), prior treatment with CDK4/6 inhibitors (Yes or No), and Eastern Cooperative Oncology Group status (0 or 1).

Number of participants:

Overall, 282 participants will be randomly assigned to study intervention with a balanced randomization ratio (141 participants randomized per treatment arm) in the global part of the study. The number of participants naïve to CDK4/6 inhibitors should not be higher than 20% of the overall sample size.

After completion of randomization in the global part of the study (ie, all countries/sites including China), randomization will continue in China only until approximately 90 Chinese participants (including Chinese participants from the global part) are randomized.

Intervention groups and duration:

Participants will be treated (starting at a maximum of 3 days after randomization) with either amcenestrant or a single endocrine therapy of choice of the physician, depending on the randomization allocation. The potential control treatment should be selected in accordance with the Investigator's best clinical judgment before randomization. Study treatment may continue until precluded by unacceptable toxicity, disease progression, upon participant's request to stop treatment, or Investigator decision whichever occurs first.

Study intervention(s)

Investigational medicinal products (IMP)

Amcenestrant:

- Formulation: 100 mg capsules
- Route(s) of administration: PO
- Dose regimen: 4 capsules QD, given in the morning, regardless of food status. Capsules should be taken approximately at the same time every day (±3 hours). A cycle is artificially defined as a 4-week period.

Control:

Only 1 of the following single agent control treatments is allowed per participant randomized to the control arm. The treatment will be selected before randomization in accordance with the Investigator's best clinical judgment:

- Fulvestrant (Faslodex®):
  - Formulation: 50 mg/mL injection for IM administration
  - Route(s) of administration: IM
  - Dose regimen: 500 mg IM as two 250-mg (5 mL) injections, 1 injection in each buttock (gluteal area), on Cycle 1 Days 1 and 15, and at Day 1 of each 28-day cycle thereafter.
- Or AIs (a cycle is artificially defined as 4-week period):
  - Formulation: in accordance with the approved label
  - Route of administration: PO
  - Dose Regimen:
    - Anastrozole 1 mg QD, to be taken approximately at the same time every day, regardless of food status
    - Letrozole 2.5 mg QD, to be taken approximately at the same time every day, regardless of food status
    - Exemestane 25 mg QD to be taken approximately at the same time every day after a meal.
- Or Selective estrogen receptor modulator (a cycle is artificially defined as 4-week period):

  Tamoxifen:
  - Formulation: in accordance with the approved label
  - Route of administration: PO
  - Dose regimen: 20 mg/day to be taken QD or twice a day, approximately at the same time every day, regardless of food status.

Statistical considerations:

Sample size determination

Global population

In the global part of the study, a total of 201 progression-free survival (PFS) events assessed by independent central review (ICR) will be needed to detect a hazard ratio (HR) of 0.65 using a logrank test at the one-sided level of 2.5% and approximately 85% power. Assuming proportional hazards under exponential model and based on an anticipated median PFS time of 4.5 months in the control arm, this is expected to correspond to a median PFS of 6.9 months in the amcenestrant arm. In the global part of the study, based on an expected accrual rate 23.5 participants per month, accomplished over a period of about 12 months, and an annual dropout rate of 10%, a total of

282 participants are expected to be randomized in a 1:1 ratio into the amcenestrant arm and the control arm. The sample size calculation considers 1 futility interim analysis at 50% of the planned number of events. Under this current assumption, the cut-off date (COD) for final PFS is approximately 18 months after first participant randomized.

Chinese population

Chinese participants from the global part of the study and from the China extension part will be pooled for the purpose of the analysis of the Chinese population. Approximately 90 Chinese participants would need to be enrolled to reach 65 PFS events.

Analysis populations:

Enrolled population: All participants who sign the informed consent form.

Intent-to-treat (ITT) population: All participants from the enrolled population and for whom there is a confirmation of successful allocation of a randomization number by Interactive Response Technology (IRT). Participants will be analyzed according to the treatment arm assigned at randomization. This is the primary population for all efficacy parameters.

Safety population: All participants randomly assigned to study intervention and who took at least 1 dose of study intervention. Participants will be analyzed according to the treatment arm they actually received. This population is the primary population for the analysis of all safety parameters.

Pharmacokinetic-evaluable population: All participants from the safety population who receive at least 1 dose of amcenestrant and with at least 1 evaluable plasma concentration post-treatment.

Chinese participant populations will be defined for the efficacy and safety analyses in the China extension study.

Primary analysis

Primary analysis will consist of PFS comparison between the amcenestrant arm and the control arm through a logrank test procedure stratified by the stratification factors as entered in the IRT. A one-sided Type I error rate of 2.5% will be used for statistical testing.

The analysis of PFS will be based on the following censoring rules:

- If progression and death are not observed before the COD for final PFS, PFS will be censored at the date of the last valid disease assessment with no evidence of a disease progression prior to the initiation of a further anticancer therapy (if any).
- A participant without an event (death or disease progression) and without any valid postbaseline disease assessments will be censored at the day of randomization (Day 1).
- A participant with an event documented after two or more non-evaluable tumor assessments will be censored at the date of the last evaluable tumor assessment documenting no progression prior to the initiation of a further anticancer therapy.

The COD for final PFS analysis will be the date when approximately 201 PFS events assessed by ICR have been observed or when all participants from the global cohort have been followed-up for at least 10 months (or discontinued treatment), whichever is earlier.

The HR estimates and corresponding 95% two-sided confidence intervals will be provided using the Cox proportional hazard model stratified by the same stratification factors as those used for the logrank test described above. The median PFS and probabilities of being progression-free at different time points (calculated using the Kaplan-Meier methods) as well as corresponding 95% CIs will be presented by treatment arm. The Kaplan-Meier PFS curves will also be provided.

Sensitivity analyses of PFS will be performed (eg, different censoring rules and PFS assessed by the Investigator). Subgroup analyses of PFS will also be conducted as specified in the statistical analysis plan finalized before database lock.

Analysis of key secondary efficacy endpoint

Overall survival (OS) will be evaluated as a key secondary efficacy endpoint. In the absence of observation of death, survival time will be censored to the last date the participant is known to be alive.

In order to ensure a strong control of the overall Type I error rate at a one-sided 2.5%, a hierarchical testing strategy will be used. In other words, comparison between arms on the OS will be performed only if the primary analysis of the PFS is statistically significant.

In case of statistically significant PFS, OS will be compared between treatment arms through a logrank test procedure stratified by the stratification factors as entered in the IRT. Otherwise, descriptive statistics of OS will be provided at the time of final PFS analysis.

The COD for final OS analysis will be the date when approximately 196 death events have been observed (approximately 70% of the participants have died).

Analysis of secondary efficacy endpoints

Except for overall survival (OS), secondary endpoints will be analyzed at the time of the PFS analysis only. For these secondary endpoints, no formal statistical testing will be performed. The primary analysis will be based on ICR assessment and a sensitivity assessment will be based on the Investigator assessment.

Objective response rate (ORR) will be summarized for the ITT population based on ICR assessment with descriptive statistics by treatment arm. The 95% two-sided CIs will be computed using the Clopper-Pearson method.

The disease control rate and clinical benefit rate will be summarized for the ITT population with descriptive statistics by treatment arm. The 95% two-sided CIs will be computed using the Clopper-Pearson method. Similar analyses will be performed for the ITT population with measurable disease at study entry. Of note, the best overall response for each participant will also be summarized by treatment arm.

For the following time-to-event endpoints, similar methods to those described for the PFS will be used with the exception that no statistical test will be performed:

- Duration of response will be summarized for the ITT population for participants who have achieved a confirmed partial response or complete response as best overall response with descriptive statistics by treatment arm. For participants with ongoing response at the time of the analysis, duration of response will be censored at the date of the last valid disease assessment not showing disease progression performed before the initiation of a new anticancer treatment (if any). Similar analyses will be performed for the ITT with measurable disease at study entry.
- Progression-free survival by estrogen receptor 1 gene mutation status will be analyzed with similar methods to the PFS, with the exception that no statistical test will be performed.

Description and analysis of patient reported outcomes (PRO) endpoints

Analysis of the PRO endpoints will be based on participants from the safety population who have completed the baseline and at least 1 postbaseline assessment.

The PRO analysis will be conducted on the European Organisation for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30), the breast cancer specific module (QLQ-BR23), and the EuroQoL questionnaire with 5 dimensions and 5 levels per dimension (EQ-5D-5L). For each treatment group and at each time point, the number and percentage of participants who completed these instruments will be summarized, as well as the reasons for non-completion of these measures.

For the QLQ-C30 (15 total scales), QLQ-BR23 (8 scales), and EQ-5D-5L (health index and visual analogue scale) instruments, descriptive statistics on the absolute value and changes from baseline will be done for each treatment arm at each time point, at end of treatment (EOT) and 90 days after the last study administration (follow-up). Between treatment comparisons of the change from baseline over time will be provided for the QLQ-C30 (15 total scales), QLQ-BR23 (8 scales), and EQ-5D-5L (health index and visual analogue scale).

Analysis of safety endpoints

The observation period will be divided into 3 segments:

- The pre-treatment period is defined as the time from when the participants give informed consent to the first administration of the IMP.
- The on-treatment period is defined as the time from the first dose of IMP up to 30 days after the last dose of IMP.
- The post-treatment period is defined as the time starting 31 days after the last dose of IMP to study closure.

Number and percentage of participants experiencing treatment-emergent adverse events (TEAEs) by Medical Dictionary for Regulatory Activities primary system organ class and preferred term will be summarized by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 grade (all grades and Grade ≥3) for the safety population. Similar

summaries will be prepared for treatment-related TEAEs, TEAEs leading to definitive discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, adverse events (AEs) of special interest, and AEs/serious AEs (SAEs) occurring during the post-treatment period. For participants with multiple occurrences of the same AE within the treatment period, the worst grade will be used.

Hematology and clinical chemistry results will be graded according to the NCI-CTCAE v5.0, when applicable. Number and percentage of participants with laboratory abnormalities (ie, all grades and by grade) using the worst grade during the treatment period will be provided for the safety population.

Interim analysis

An interim analysis is planned based on the primary PFS endpoint at 50% of the planned total number of PFS events (ie, approximately 101 PFS events). The interim analysis of PFS will be performed for futility without possible claim for overwhelming evidence of efficacy (therefore, no Type I error rate adjustment will be performed). The stopping boundary for futility is based on the observed HR based on Cox proportional hazard model, ie, an HR>1.1.

Comparison between treatment arms on the OS will be performed only if the primary analysis of the PFS is statistically significant. Therefore, a maximum of 2 analyses are planned for OS: at the time of the primary analysis of PFS and at the final OS analysis. A gamma error spending function ($\gamma = -8$) will be used along with the hierarchical testing strategy to strongly control the Family Wise Error Rate (overall Type I error rate). If the value of the test statistic exceeds the efficacy boundary ($z \leq -3.716$, $p \leq 0.0001$), superiority of OS will be claimed but survival data will continue to be collected until the end of study when approximately 196 death events have been observed.

Planned cutoff date for the global study

Estimated COD will be approximately 18 months after first randomized participant for the PFS analysis. No pharmacokinetic sample will be taken after Cycle 6 or COD for final PFS, whichever comes first. After COD for final PFS analysis, no more efficacy assessments will be performed except collection of survival status (not applicable to Chinese participants for whom the efficacy assessment would continue until the planned COD for China). The COD for the final analysis of OS will be approximately 46 months after the PFS analysis, when approximately 196 death events have been observed. If a participant treated continues to benefit from the treatment after the COD for OS analysis, the participant may continue until treatment is precluded by toxicity, progression, upon participant's request to stop treatment, or Investigator decision. For cycles completed after the COD for final PFS analysis for the main cohort, only all ongoing SAEs (related or not), all related nonserious AEs ongoing at the COD, and all new serious or related AEs occurring post-COD and associated concomitant medication, as well as IMP administrations and reason for EOT will continue to be collected.

Planned cutoff date for the Chinese participants

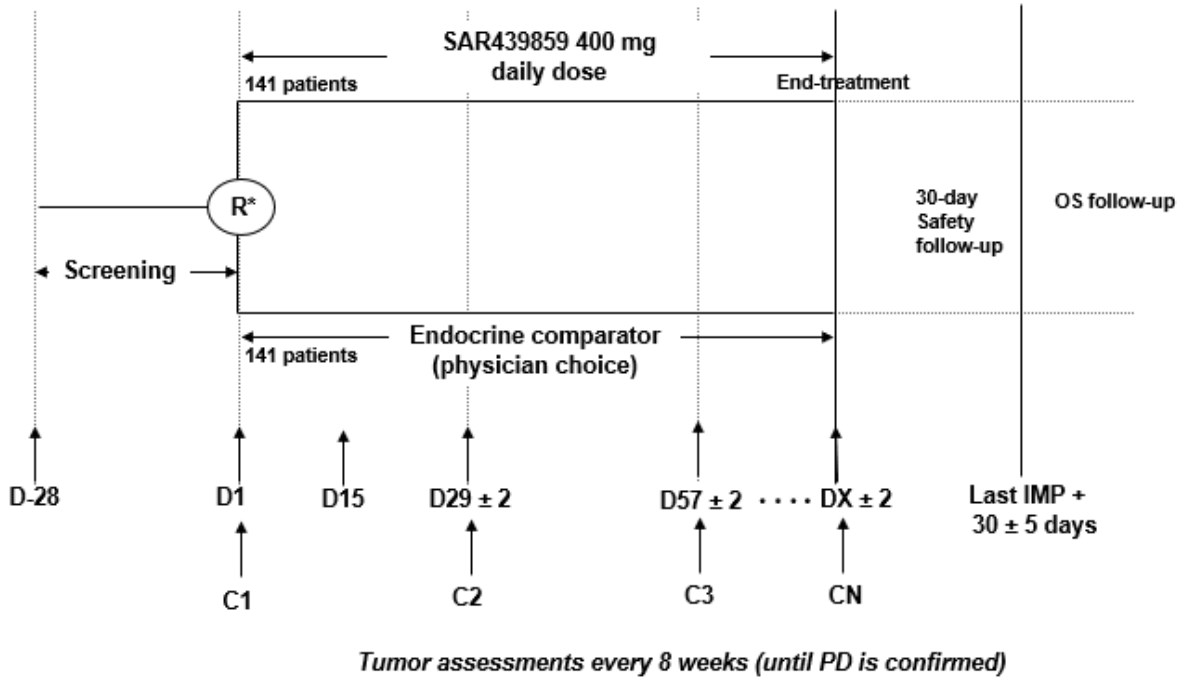
Assuming that the first Chinese participant is planned to be enrolled 11 months after the first randomized participant of the global part and a 17-month enrollment period for Chinese

participants, the estimated China COD will be approximately 5 months after last Chinese participant enrolled.

Data Monitoring Committee: Yes

1.2 SCHEMA

Figure 1 - Graphical study design



Note: For the China extension study, refer to Section 10.8.
C = Cycle; D = day; IM = intramuscular; IMP = investigational medicinal product; OS = overall survival; PD = progressive disease; PFS = progression-free survival; R = randomization.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening (up to 28 days before randomization)	Treatment Cycle 1		Subsequent cycles	EOT	Follow-up (±5) (every 2 months)	Notes
		D1	D15 (±2)	D1 (±2)	D30 (±5) (after last study treatment administration)		
Inclusion/exclusion criteria/informed consent	X						Section 5.1 Section 5.2 Section 8
Randomization	X						Participants will be randomized within 3 days prior to first dosing (C1D1) Section 6.3
Demography, medical/surgical and disease history	X						
Height	X						Section 8.2.1
ECOG performance status/body weight	X	X	X	X	X		Section 8.2.1
Vital signs, physical examination/signs and symptoms	X	X[a]	X	X	X		[a] In C1D1, vital signs will also be assessed approximately 2 hours after dosing Section 8.2.1
Hematology	X		X	X	X		Section 8 Section 10.2 (Appendix 2)
Coagulation	X						Section 8 Section 10.2 (Appendix 2)

Procedure	Screening (up to 28 days before randomization)	Treatment Cycle 1		Subsequent cycles	EOT	Follow-up (±5) (every 2 months)	Notes
		D1	D15 (±2)	D1 (±2)	D30 (±5) (after last study treatment administration)		
Follicle-stimulating hormone and estradiol (premenopausal women only)	X			X[a]	X[a]		[a] For patients receiving Fulvestrant as IMP, the local estradiol sample will not be required Section 10.2 (Appendix 2)
Pregnancy test (WOCBP only) - Local labs	x[a]			x[b]	x[b]		[a] Serum pregnancy test (β-hCG) to be done before starting study treatment. [b] Urine pregnancy test (dipstick) to be done on D1 of each cycle, and at EOT Section 10.2 (Appendix 2) Urine pregnancy test must have a sensitivity of at least 25 mIU/mL
Clinical chemistry	X		X	X	X		Section 8 Section 10.2 (Appendix 2)
12-lead ECG	X			X[a]	X		[a] Cycle 2 Day 1 only. On C2D1, ECG will be measured at least 1 hour after study treatment administration. Section 8.2.3
Urinalysis (dipstick)	X				X		Section 8 Section 10.2 (Appendix 2)
Control arm physician's choice: fulvestrant administration		X	X	X			Section 6.1

Procedure	Screening (up to 28 days before randomization)	Treatment Cycle 1		Subsequent cycles	EOT	Follow-up (±5) (every 2 months)	Notes
		D1	D15 (±2)	D1 (±2)	D30 (±5) (after last study treatment administration)		
Control arm Physician's choice: oral endocrine therapy		Continuous once daily					Section 6.1
Amcenestrant administration		Continuous once daily					Section 6.1
Concomitant medications		Continuous throughout study period					Section 6.5
AE review		Continuous throughout study period					Section 8.3
Tumor assessments	X			X[a]	X[b]	X[c]	*a* Every 8 weeks after randomization, ±7 days or when clinically indicated *b* If not done at the immediate previous cycle *c* If no radiological PD at last tumor assessment during the treatment period, disease assessment will continue to be performed every 8 weeks ±7 days (projected from last tumor assessment) up to PD Section 8.1.1

Procedure	Screening (up to 28 days before randomization)	Treatment Cycle 1		Subsequent cycles	EOT	Follow-up (±5) (every 2 months)	Notes
		D1	D15 (±2)	D1 (±2)	D30 (±5) (after last study treatment administration)		
Bone scans	X			X[a]			[a] If at screening, lesions are detected in the bone scan but not in the CT/MRI (RECIST 1.1) scan, further bone scans should be conducted every 8 weeks ±7 days after randomization. If the lesions seen in the bone scan are no longer visible, these assessments should be conducted every 16 weeks ±7 days after randomization. If lesions are detected in the bone scan and CT/MRI (RECIST 1.1) scan, further bone scan assessments will be conducted every 16 weeks ±7 days after randomization. Section 8.1.2
Further anticancer therapy						X	Section 6.7
Survival assessment						X	
QLQ-C30, QLQ-BR23, and EQ-5D-5L		X		X[a]	X	X[b]	[a] Every cycle from Cycle 1 to Cycle 4 and every 2 cycles thereafter [b] First follow-up visit only Section 8.1.3

Procedure	Screening (up to 28 days before randomization)	Treatment Cycle 1 D1	Treatment Cycle 1 D15 (±2)	Subsequent cycles D1 (±2)	EOT D30 (±5) (after last study treatment administration)	Follow-up (±5) (every 2 months)	Notes
Amcenestrant PK assessment		X[a]	X[b]	X[c]			*a* Postdose time windows: 1.5 h ±0.5 h; 4 h ±1 h *b* Predose *c* Cycle 2 Day 1: Predose Postdose time windows: 1.5 h ±0.5 h; 4 h ±1 h; 8 h ±1 h Cycles 3, 4, and 6: Day 1: predose No PK sample will be taken after Cycle 6 or PFS cut-off date, whichever comes first Section 8.5
Tumor specimen/ biopsy (optional procedures)	X[a]			X[b]			*a* Most recent archived biopsied tumor within past 3 months prior to initiation of study treatment, or fresh tumor biopsy collected from time of inclusion to C1D1 pre-treatment (optional) *b* Cycle 3 Day 1 (allowed up to Cycle 3 Day 15 or within 14 days after first radiological tumor assessment after baseline). Tumor biopsy should be performed only after radiological assessment (optional) Section 8.6
ESR1 analysis of cfDNA (plasma)		X		X[a]			*a* Cycle 3 Day 1 Section 8.7.1

Procedure	Screening (up to 28 days before randomization)	Treatment Cycle 1		Subsequent cycles	EOT	Follow-up (±5) (every 2 months)	Notes
		D1	D15 (±2)	D1 (±2)	D30 (±5) (after last study treatment administration)		
Mutation profiling in cfDNA (plasma)		X			X		Section 8.7.2
Normal tissue reference DNA (saliva)		X					Section 8.7.2 and Section 10.15.5
Estradiol (serum)		X[a]		X[b]			*a* Predose Cycle 1 Day 1 *b* Cycle 3 Day 1 Section 8.6.2
Genetic sample (DMET genotyping)		X					Sample collected in amcenestrant treatment arm only Section 8.7.4

C = cycle; cfDNA = cell-free deoxyribonucleic acid; CT = computed tomography; DMET = drug metabolizing enzymes and transporters; DNA = deoxyribonucleic acid; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; EQ-5D-5L = EuroQoL questionnaire with 5 dimensions and 5 levels per dimension; ESR1 = estrogen receptor 1 gene; MRI = magnetic resonance imaging; PFS = progression-free survival; PK = pharmacokinetics; QLQ-BR23 = EORTC QLQ breast cancer specific module; QLQ-C30 = EORTC core quality of life questionnaire; WOCBP = women of childbearing potential

2 INTRODUCTION

Amcenestrant is a potent, orally bioavailable, and selective estrogen receptor (ER) inhibitor that belongs to the selective ER degrader (SERD) class of compounds. amcenestrant antagonizes the binding of estradiol to ER and promotes the transition of ER to an inactive conformation that leads to up to 98% receptor degradation at nanomolar concentrations in cellular assays (1). These dual properties of amcenestrant translate in a deeper inhibition of ER pathways and a more effective antiproliferative activity in ER-dependent breast cancer cell lines driven by mutant or wild type ER compared to fulvestrant.

In locally advanced/metastatic breast cancer patients who progress after 1 or more lines of hormonal therapy, the current choice of further single agent treatment is mainly represented by 3 classes of compounds:

- Selective ER degraders: Fulvestrant (Faslodex®) is a potent approved SERD that binds and degrades ER. Recent data with fulvestrant administered 500 mg monthly to participants with recurrent hormone receptor-positive/human epidermal growth factor receptor 2 (HER2) negative breast cancer indicate significant antitumor activity in first line therapy, as well as after both antiestrogen and aromatase inhibitor (AI) failure. Fulvestrant is currently indicated for the treatment of postmenopausal women with metastatic hormone receptor-positive breast cancer:
  - Who have not previously been treated with endocrine therapy as monotherapy
  - Following the failure of endocrine therapy, as monotherapy and in combination with palbociclib or abemaciclib
  - For the first line treatment in combination with anastrozole.
- Selective ER modulators (SERM) (tamoxifen): SERMs are cytostatic agents that competitively bind to ER in tumor cells and breast tissue, producing receptor dimerization and a nuclear complex that decreases deoxyribonucleic acid (DNA) synthesis and inhibits estrogenic effects. There are multiple approved indications for tamoxifen in breast cancer:
  - Adjuvant treatment of early stage ER-positive breast cancer
  - Treatment of ER-positive metastatic breast cancer
  - Treatment of women with ductal carcinoma in situ following breast surgery and radiation, to reduce the risk of invasive breast cancer
  - Treatment of hormone receptor-positive, HER2-negative metastatic breast cancer in postmenopausal women with secondary AI resistance, in combination with everolimus
  - Adjuvant treatment of breast cancer, to reduce the occurrence of contralateral breast cancer
  - Breast cancer prophylaxis in women who are at high risk for developing breast cancer.
- Aromatase inhibitors (exemestane, anastrozole, and letrozole): Aromatase is a cytochrome P450 (CYP) enzyme involved in the synthesis of estrogen. Therefore, AIs function as

antiestrogens by decreasing the biosynthesis of estrogen from androgens, the primary estrogen biosynthesis pathway in postmenopausal women. There are 2 categories of AIs: the steroidal inhibitor exemestane and nonsteroidal inhibitors such as anastrozole and letrozole. Exemestane, a type 1 steroidal AI, binds irreversibly to aromatase, causing permanent inactivation of the enzyme even after the drug is cleared from circulation. Nonsteroidal (type 2) AIs, such as anastrozole and letrozole, bind reversibly to aromatase, thereby inhibiting the synthesis of estrogen.

Exemestane is approved for the following indications:

- Treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy
- Adjuvant treatment of ER-positive early breast cancer in postmenopausal women who have already received 2 to 3 years of tamoxifen therapy, and who are switched to exemestane for completion of a total of 5 consecutive years of adjuvant hormonal therapy
- Treatment of ER-positive, HER2-negative, locally advanced or metastatic breast cancer in postmenopausal women refractory to letrozole or anastrozole, in combination with everolimus.

Letrozole is approved for the following indications:

- Adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer
- Extended adjuvant treatment of early breast cancer in postmenopausal women who have received 5 years of adjuvant tamoxifen therapy
- First line treatment of postmenopausal women with hormone receptor-positive or hormone receptor status unknown, locally advanced or metastatic breast cancer
- Treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy.
- Neoadjuvant treatment of postmenopausal women with hormone receptor-positive, HER2-negative breast cancer where chemotherapy is not suitable and immediate surgery not indicated (European Union only).

Anastrozole is approved for the following indications:

- Adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer
- Adjuvant treatment of ER-positive early breast cancer in postmenopausal women who have received 2 to 3 years of tamoxifen therapy to complete a total of 5 consecutive years of adjuvant hormonal therapy
- First line treatment of hormone receptor-positive or hormone receptor status unknown, locally advanced or metastatic breast cancer in postmenopausal women
- In postmenopausal women with disease progression following tamoxifen therapy
- First line treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women, in combination with fulvestrant.

In prospective comparative studies conducted with fulvestrant monotherapy in postmenopausal women with breast cancer after progression to hormonal therapy and/or chemotherapy, time to progression (TTP)/progression-free survival (PFS) was between 3.5 and 5 months in the fulvestrant single agent arm. In a recent study comparing fulvestrant 500 mg combined with palbociclib with fulvestrant 500 mg alone in 521 participants, median PFS was 9.5 months (95% confidence interval [CI)]9.2 to 11.0) in the fulvestrant plus palbociclib group and 4.6 months (3.5 to 5.6) in the fulvestrant plus placebo group (hazard ratio [HR] = 0.46, 95% CI 0.36-0.59, p<0.0001) (2). In a Phase 2 study conducted in 131 participants of fulvestrant 500 mg combined with everolimus versus fulvestrant, the PFS was 5.1 months for fulvestrant single agent (3). In a Phase 3 study, fulvestrant given at 500 mg intramuscularly (IM) on Day 0, 250 mg on Days 14, 28, and 250 mg every 28 days thereafter was compared to exemestane 25 mg per os (PO) in 693 women; median TTP was 3.7 months in both groups (4).

In prospective comparative studies conducted with AIs in postmenopausal women with breast cancer after progression to hormonal therapy and/or chemotherapy, TTP/ PFS was about 4.1 months in the exemestane single agent arm (5, 6). A comparative study including 3 arms (fulvestrant, fulvestrant combined with anastrozole, and exemestane) was conducted in 723 breast cancer patients who failed after prior hormonal therapy. The median PFS was of 3.4 months, 4.8 months and 4.4 months, respectively (7).

Finally, in metastatic breast cancer patients who progressed after 1 or 2 lines of hormonal therapy and who received a further hormonal single agent therapy, the efficacy results indicate a PFS of 3.4 to 5.1 months and this result is consistent across studies.

2.1 STUDY RATIONALE

The objective of this study is to compare the efficacy, safety, and pharmacodynamic (PDy) characteristics of amcenestrant and an endocrine monotherapy of the choice of the physician (AIs, tamoxifen, or fulvestrant) in participants with locally advanced/metastatic breast cancer who have failed to other hormonal therapies/chemotherapy. This condition represents an unmet need in this patient population and amcenestrant may represent a new therapeutic option expected to have a better risk/benefit ratio than approved endocrine monotherapy.

The first in human (FIH) study with amcenestrant, TED14856, started in November 2017. This study was designed in several parts and includes ER-positive, HER2-negative, postmenopausal women presenting with measurable locally advanced/metastatic breast cancer who progressed after several therapies including hormonal as well as chemotherapies.

Part A is a dose escalation phase evaluating several dose levels from 20 mg to 600 mg in a once daily (QD) regimen, with 3 evaluable participants planned per dose, with the aim of assessing safety (including dose-limiting toxicities), pharmacokinetics (PK), and PDy, and defining the recommended dose as single agent. Part B is an expansion phase of amcenestrant single agent in the same population. Part C is a dose escalation of amcenestrant in combination with palbociclib followed by Part D, an expansion phase with this combination.

As of 29 May 2019, a total of 16 postmenopausal participants presenting with locally advanced/metastatic breast cancer participated in the dose escalation (Part A) of the study. Participants were enrolled at 20 mg (3 participants), 150 mg (3 participants), 200 mg (4 participants), 400 mg (3 participants), and 600 mg (3 participants). In addition, 48 participants started the treatment in the expansion cohort (Part B). Dose escalation of amcenestrant QD in combination with palbociclib (Part C) started in January 2019 and is ongoing with amcenestrant 200 mg and 400 mg QD, with 6 participants recruited so far. A total of 8 participants discontinued the study treatment due to progressive disease (PD) and 8 are currently in the treatment.

From the TED14856 FIH study, analyses of heavily pretreated postmenopausal women presenting with metastatic breast cancers showed promising activity. A total of 16 participants treated with amcenestrant from 20 to 600 mg daily dose were part of the dose escalation phase. No dose-limiting toxicity was observed at all dose levels. amcenestrant was considered well tolerated with adverse events (AEs) generally of low grade. The results of ^{18}fluoroestradiol (^{18}FES)-positron emission tomography (PET) scans indicate an almost 90% or more occupancy of ER receptors by amcenestrant was reached from 150 mg. Pharmacokinetics of amcenestrant indicated limited accumulation and dose proportional increase of exposure up to 400 mg after repeated administration while limited gain at 600 mg. The impact of food is minimal, and the compound can be administered with or without food. The average plasma concentration observed before treatment administration (C_{trough}) reached after repeated 400 mg QD was around 4 times above threshold concentration allowing 90% of signal inhibition at ^{18}FES-PET scans. Taking into account all these parameters, the 400 mg dose level is considered as the recommended dose for the expansion cohort and will be explored in dose escalation combination with palbociclib of TED14856.

Inhibition and down-regulation of ER are considered as pre-requisites for SERD compounds to be effective as well as to maintain the control of the disease. Amcenestrant and fulvestrant share the same mechanism of action. However, to optimize the beneficial effect, a 24-hour saturation of the receptor is expected for almost all participants, and significant residual ER availability has been observed during fulvestrant therapy in 38% of patients only, using ^{18}FES-PET (8). Available PDy data indicate that with amcenestrant, high levels of inhibition of the signal were observed starting from the 150 mg dose level and up: 100% inhibition at this dose level and more than 87% in all other patients treated at further dose levels. Another point of differentiation of amcenestrant versus fulvestrant is its ability to be given PO compared to IM injection. This may have a substantial impact on the quality of life of the participants: the participants will be prescribed capsules and have a daily intake at home, not needing to go to their hospital/physicians to get their monthly injection. Another advantage of the PO route is its suitability for a subgroup of participants receiving anticoagulant therapy for whom IM injections are a risk, even if fulvestrant is carefully administered.

2.2 BACKGROUND

Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer death in women (9). In the United States, in 2019, a total of 268 600 new cases of invasive breast cancer as well as 62 930 additional cases of in situ breast cancer are estimated. From 2006 to 2015, invasive female breast cancer incidence rates increased slightly, by 0.4% per year.

Approximately 41 760 women are expected to die from breast cancer in 2019. In men, 2670 new cases of invasive breast and 500 deaths were estimated in the United States, in 2019 (10).

Both endogenous and exogenous steroid hormones such as estrogen and progesterone have been implicated in the pathogenesis of breast cancer. Clinical treatment decisions are driven by the expression of ERs, progesterone receptors (PgRs), and HER2 receptor status into HER2-positive, ER-positive/HER2-negative and triple negative clinical subtypes (10). About 75% of breast cancers express ER alpha, a hormone regulator transcription factor (11). Estrogen receptor-positive breast cancers respond well to therapy targeting ER signaling either through competitive binding of ER antagonists, such as tamoxifen, or by blocking the production of estrogen by AIs (12).

According to the National Comprehensive Cancer Network guidelines (Version 1, 2020), sequential hormonal therapy (alone or in combination) is the standard of care in the metastatic breast cancer setting for ER-positive and HER2-negative participants without rapidly progressing visceral or symptomatic metastases. Common classes of drugs used after progression of hormonal treatment for this purpose include SERMs (eg, tamoxifen), AIs (eg, letrozole, anastrozole, or exemestane), and SERDs (fulvestrant). Because few men have been historically included in breast cancer clinical trials, recommendations regarding management of breast cancer in men are generally extrapolated from findings in clinical trials focusing on breast cancer in women.

Unfortunately, not all participants respond to first line hormonal therapy, instead presenting primary or de novo resistance. Moreover, some participants who initially respond subsequently present breast cancer progression (acquired resistance). Resistance to endocrine therapies is frequent but relapsed tumors remain dependent on ER, which is highlighted by patient responses to second- and third-line endocrine therapies after failure of an earlier line of hormonal therapy. Estrogen receptor alpha signaling reactivation can occur due to changes in ligand sensitivity and specificity or by new mutations of estrogen receptor 1 gene (ESR1) (13). Estrogen receptor 1 gene mutation was recently evaluated in clinical studies with a high prevalence (25% to 40%) reported in relapse participants after AI therapy and limited benefit with current monotherapy (14). The continued dependence of breast cancer tumors on ERs provides a strong rationale to continue targeting ERs in both first line and relapsed/advanced settings.

Selective ER degraders are competitive ER antagonists that also induce conformational changes that degrade ERs via a ubiquitin-proteasome system (15). This unique dual-function of SERDs may enable them to block ER signaling in cellular settings where other endocrine agents, such as tamoxifen or AIs, have failed. The clinical effect of fulvestrant as a treatment for recurrent endocrine-resistant disease supports this matter. Although fulvestrant has served as an important proof of concept for the SERD approach, this therapy is limited by its poor pharmaceutical properties which require IM administration and limit the applied dose, exposure, and receptor engagement (16, 17). The fulvestrant 500 mg regimen (500 mg on Days 1, 15, 29; monthly thereafter) exhibited improvement in PFS and overall survival (OS) over the initially marketed 250 mg dose (18). However, the fulvestrant 500 mg dose does not fully saturate ER binding in participants, as the inhibition of ^{18}FES-PET scan uptake was incomplete in 38% (6/16) of participants. This lack of receptor occupancy was associated with lack of clinical benefit (17, 19).

These data demonstrate that SERDs have the potential to provide effective and well-tolerated therapy for postmenopausal women with advanced breast cancer and highlight the need for the

development of new SERD compounds with optimized characteristics: improved route of administration (PO versus IM), bioavailability, and long-term maintenance of ER receptor blockade combined with a strong antitumor activity. It would also be important to further understand the potential benefit and safety of SERDs in men with breast cancer, in alignment with the Food and Drug Administration draft guidance "Male Breast Cancer: Developing Drugs for Treatment", which recommends the inclusion of both men and women in breast cancer clinical trials.

2.3 BENEFIT/RISK ASSESSMENT

Detailed information about the known and expected benefits and risks and reasonably expected AEs of amcenestrant may be found in the Investigator's Brochure (IB). Information on the selected control (endocrine therapy of choice of the physician) should be found in the approved package label.

2.3.1 Benefits

2.3.1.1 Amcenestrant

Amcenestrant has been administered to humans since November 2017, in the FIH TED14856 study. Efficacy was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria in 16 participants; the best overall responses (BOR) have been partial response (PR) in 1 participant treated at 150 mg, stable disease (SD) in 8 participants, and PD in 7 participants. Long-term SD (24 weeks or more) was seen in 7 participants so far. Clinical benefit (PR + SD ≥24 weeks) was therefore observed in 8 participants (29 May 2019).

2.3.1.2 Fulvestrant

Fulvestrant monotherapy is indicated for the treatment of ER-positive, locally advanced or metastatic breast cancer in postmenopausal women not previously treated with endocrine therapy or with disease relapse or progression on or after antiestrogen therapy.

Fulvestrant is also indicated in combination with palbociclib for treatment of hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer in women who have received prior endocrine therapy.

A Phase 3 randomized double-blind study comparing fulvestrant plus palbociclib with fulvestrant plus placebo was performed on 521 women with metastatic breast cancer, regardless of their menopausal status, whose disease progressed after prior endocrine therapy (2). Efficacy results for fulvestrant plus palbociclib and fulvestrant plus placebo included median PFS (9.5 and 4.6 months, respectively), objective response (19.0% and 8.6%, respectively), and clinical benefit (66.6% and 39.7%, respectively). The results from this study give some information on the expected PFS with fulvestrant single treatment in a population who relapsed to 1 or more prior hormonal-content therapy.

2.3.1.3 Aromatase inhibitors

2.3.1.3.1 Anastrozole

In postmenopausal women, anastrozole at a daily dose of 1 mg produced estradiol suppression of greater than 80%.

Anastrozole was studied in 2 controlled studies (20) in postmenopausal women with advanced breast cancer with PD following tamoxifen therapy for either advanced or early breast cancer. A total of 764 patients were randomized to receive either anastrozole or megestrol acetate. In both studies, efficacy results (TTP, objective response rate [ORR]), prolonged SD, rate of progression, and OS were similar between treatments.

2.3.1.3.2 Letrozole

Letrozole inhibits the aromatase enzyme by competitively binding to the heme of the aromatase CYP, resulting in a reduction of estrogen biosynthesis in all tissues where present. In postmenopausal patients with advanced breast cancer, daily doses of 0.1 mg to 5 mg suppressed plasma concentration of estradiol, estrone, and estrone sulfate by 75% to 95% from baseline in all patients treated. With doses of 0.5 mg and higher, many values of estrone and estrone sulfate were below the limit of detection in the assays, indicating that higher estrogen suppression is achieved with these doses.

Two letrozole doses (0.5 mg and 2.5 mg) were compared with megestrol acetate and with aminoglutethimide, respectively, in postmenopausal women with advanced breast cancer previously treated with anti-estrogens (21, 22). Letrozole showed comparable efficacy compared with megestrol, with the 2.5 mg dose showing higher objective tumor response and time to treatment failure. Compared with aminoglutethimide, letrozole showed better TTP, time to treatment failure, and OS.

2.3.1.3.3 Exemestane

In postmenopausal women, exemestane significantly lowered serum estrogen concentrations starting from a 5 mg dose, reaching maximal suppression (>90%) with a dose of 10 to 25 mg. In postmenopausal breast cancer patients treated with the 25 mg daily dose, whole body aromatization was reduced by 98%.

In a randomized controlled clinical study, exemestane at the daily dose of 25 mg has demonstrated statistically significant prolongation of survival, TTP, and time to treatment failure as compared to a standard hormonal treatment with megestrol acetate in postmenopausal patients with advanced breast cancer that had progressed following, or during, treatment with tamoxifen either as adjuvant therapy or as first line treatment for advanced disease.

2.3.1.4 Selective estrogen receptor modulators

2.3.1.4.1 Tamoxifen

In breast cancer patients, at the tumor level, tamoxifen acts primarily as an anti-estrogen, preventing estrogen binding to the ER. Tamoxifen leads to reductions in levels of blood total cholesterol and low-density lipoproteins in postmenopausal women of the order of 10% to 20%. Tamoxifen does not adversely affect bone mineral density.

2.3.2 Potential and identified risks

2.3.2.1 amcenestrant

Based on the nonclinical data available for amcenestrant and the safety profile observed in compounds of the same class approved and in development, the following are potential side effects and risks anticipated in humans:

- Gastrointestinal toxicities, including anorexia, nausea, vomiting, diarrhea (and possibly dehydration and electrolyte imbalance in severe cases), and upper and/or lower abdominal pain.
- Changes in liver function, including elevated liver enzymes and bilirubin.
- Hematological toxicities potentially presenting with laboratory abnormalities (leukopenia, neutropenia, thrombocytopenia, anemia), infections, and neutropenic fever.
- Effects in the female reproductive system (ovary, uterus, cervix, vagina, mammary glands).
- Risk of male infertility.
- Risk of photosensitivity.
- Risk of severe rash.
- Theoretical risk of osteoporosis, due to the mechanism of action of SAR439849, in case of long-term exposure.
- Risk of drug-drug interaction: in vitro, amcenestrant is mainly metabolized by uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A1 and UGT1A4, and to a lesser extent by CYP enzymes (<20%) CYP2C8 and/or CYP3A. Therefore, drugs that are potential inhibitors of UGTs (ie, atazanavir and probenecid) should not be administered with amcenestrant, as well as drugs that are strong inducers of CYP3A, since they may also induce UGTs. In vitro studies results showed that amcenestrant has the potential to induce CYP3A4, and to a lesser extent CYP2B6, CYP2Cs, and UGTs. In vivo study result showed that amcenestrant is a moderate inducer of CYP3A.

Preliminary safety results in humans from the FIH TED14856 study are as follows: as of 29 May 2019, 16 participants have been treated in the dose escalation part at doses from 20 to 600 mg (Part A) of TED14856 study, and 48 participants have been treated in the dose expansion part at the recommended dose of 400 mg (Part B). The safety was assessed in 16 participants in the dose escalation part of study. No dose-limiting toxicities were observed during Cycle 1 at any

tested dose levels. All of them presented with at least 1 treatment-emergent AE (TEAE), regardless of relationship. The most frequently reported TEAEs by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) were hot flush, diarrhea, constipation, and nausea in 6 participants, each (37.5%), decreased appetite in 5 participants (31.3%), asthenia and fatigue 4 participants, each (25.0%), hyperesthesia, night sweat, and arthralgia in 3 participants, each (18.8%). Updated safety information from July 2019 shows the following results regarding liver function tests (LFTs). Two of 16 participants from Part A of the TED14856 study developed treatment-emergent LFT abnormalities Grade ≥3. One participant (treated with amcenestrant 200 mg) developed Grade 3 aspartate aminotransferase (AST) and alkaline phosphatase increase with Grade 1 alanine aminotransferase (ALT) increase and normal total bilirubin. Another participant (treated with amcenestrant 600 mg) developed Grade 4 AST and total bilirubin increase with Grade 3 ALT and alkaline phosphatase increase. Both participants had liver metastasis and Grade 1 AST increase at baseline. These LFT abnormalities were observed concomitantly with disease progression in the liver.

Please see the last updated version of the IB for details.

Details on dose selection are described in Section 4.3.

2.3.2.2 Fulvestrant

Risks associated with fulvestrant include bleeding, increased exposure in patients with hepatic impairment, injection site reactions, embryo-fetal toxicity, and falsely elevated estradiol levels due to fulvestrant interfering with estradiol measurement by immunoassay.

The most common adverse reactions occurring in ≥10% of patients treated with fulvestrant monotherapy include: hypersensitivity reactions, hot flushes, nausea, elevated hepatic enzymes (ALT, AST, and alkaline phosphatase), rash, joint and musculoskeletal pain, asthenia, and injection site reactions.

Refer to current local label for further reference safety information.

2.3.2.3 Aromatase inhibitors

2.3.2.3.1 Anastrozole

Risks associated with anastrozole include reduction in bone mineral density, ischemic cardiovascular events, increase serum cholesterol, increased exposure in patients with hepatic impairment, and hypersensitivity reactions. Anastrozole is contraindicated in patients with hypersensitivity to the drug or any excipients (eg, lactose).

The most common adverse reactions occurring in ≥10% of patients treated with anastrozole monotherapy include: vasodilation (hot flushes), asthenia, pain, arthritis, arthralgia, pharyngitis, depression, hypertension, nausea, rash, osteoporosis, back pain, fracture, headache, and accidental injury (23).

Refer to current local label for further reference safety information.

2.3.2.3.2 Letrozole

Risks associated with letrozole include reduction in bone mineral density, hypercholesterolemia, fatigue, dizziness, increased exposure (two-fold) in patients with cirrhosis and severe liver impairment.

The most common adverse reaction occurring in ≥10% of patients treated with letrozole monotherapy (first line treatment in advance breast cancer) include: bone pain, hot flushes, dyspnea, back pain, nausea, arthralgia, cough, constipation, and pain in limb.

The most common adverse reaction occurring in ≥10% of patients treated with letrozole monotherapy (second line treatment in advance breast cancer) include: musculoskeletal reaction (including musculoskeletal pain, skeletal pain, back pain, leg pain), and nausea.

Refer to current local label for further reference safety information.

2.3.2.3.3 Exemestane

Risks associated with exemestane include reduction in bone mineral density. Exemestane is contraindicated in patients with hypersensitivity to the drug or any of excipients (glucose).

The most common adverse reaction occurring in ≥10% of patients treated with exemestane monotherapy (advanced breast cancer) include: fatigue, nausea, hot flushes, pain, depression, insomnia, anxiety, and dyspnea.

Refer to current local label for further reference safety information.

2.3.2.4 Selective estrogen receptor modulators

2.3.2.4.1 Tamoxifen

Risks with tamoxifen include: increased incidence of endometrial changes (including hyperplasia, polyps, cancer, and uterine sarcoma), and venous thromboembolism. Tamoxifen is contraindicated in patients with galactose intolerance.

The most common adverse reactions occurring in ≥10% of patients treated with tamoxifen monotherapy include: fluid retention, hot flushes, nausea, skin rash, vaginal bleeding, vaginal discharge, and fatigue.

Note: The ATAC trial reports that the most common adverse reactions occurring in ≥10% of patients treated with tamoxifen monotherapy include: hot flushes, asthenia, pain, arthralgia, pharyngitis, rash, depression, hypertension, nausea, lymphoedema, arthralgia, back pain, accidental injury, and urinary tract infection (23).

Refer to current local label for further reference safety information.

2.3.3 Conclusion

Based on amcenestrant experience and the observed safety profile in the ongoing TED14856 study, as well as on safety precautions that have been established to safeguard the wellbeing of the participants, the benefit-to-risk assessment is deemed acceptable within the context of the planned ACT16105 study.

Moreover, the clinical benefit is expected to be relevant in patients, as preclinical findings and clinical PDy show a very high saturation of the ER at the tumor level. This current comparative study aims to show a relevant improvement of the efficacy of amcenestrant versus a single endocrine therapy of the choice of the physician.

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
To determine whether amcenestrant 400 mg per os improves progression-free survival (PFS) when compared with an endocrine monotherapy of the choice of the physician, in participants with metastatic or locally advanced breast cancer.	Progression-free survival is defined as the time interval from the date of randomization to the date of first documented tumor progression as per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) assessed by independent central review (ICR) or death (due to any cause), whichever comes first.
Secondary	
To compare the overall survival in the 2 treatment arms.	Overall survival is defined as the time interval from the date of randomization to the date of documented death (due to any cause).
To assess the objective response rate in the 2 treatment arms.	Objective response rate is defined as the proportion of participants who have a confirmed complete response (CR) or partial response (PR), as best overall response (BOR) derived from overall response determined by ICR as per RECIST 1.1, from the date of randomization to the date of end of treatment.
To evaluate the disease control rate in the 2 treatment arms.	Disease control rate is defined as the proportion of participants who have a confirmed CR, PR, stable disease (SD), or Non-CR/ Non-PD as BOR determined by ICR as per RECIST 1.1 from the date of randomization to the date of end of treatment.
To evaluate the clinical benefit rate in the 2 treatment arms.	Clinical benefit rate is defined as the proportion of participants who have a confirmed CR, PR, SD, or Non-CR/ Non-PD for at least 24 weeks determined by ICR as per RECIST 1.1, from the date of randomization to the date of end of treatment.
To evaluate the duration of response in the 2 treatment arms.	Duration of response is defined as the time from first documented evidence of CR or PR until progressive disease (PD) as determined by ICR as per RECIST 1.1 or death from any cause, whichever occurs first.
To evaluate the PFS according to the estrogen receptor 1 gene (ESR1) mutation status in the 2 treatment arms.	Progression-free survival as per ESR1 status determined at Cycle 1 Day 1.
To evaluate the pharmacokinetics of amcenestrant as single agent.	Amcenestrant plasma concentrations during the treatment period.
To evaluate health-related quality of life in the 2 treatment arms.	Disease-specific and generic health-related quality of life, disease and treatment-related symptoms, health state utility, and health status will be evaluated using the European Organisation for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30), the EORTC QLQ breast cancer specific module (BR23) and the EuroQoL questionnaire with 5◦dimensions and 5 levels per dimension (EQ-5D-5L), from Cycle 1 Day 1 until 90 days after last dose of the study treatment.
To evaluate the overall safety profile in the 2 treatment arms.	Adverse events/serious adverse events and laboratory abnormalities.

Objectives	Endpoints
Tertiary/exploratory	
To evaluate in participants the gene mutation profile of the tumor over time (baseline and end of treatment) by cell-free deoxyribonucleic acid (cfDNA) analysis, and ESR1 mutation analysis (pre- and on-treatment) by cfDNA.	The gene mutation profile of the tumor over time (Cycle 1 Day 1 [pre-treatment] and end of treatment) by cfDNA analysis, and ESR1 mutation analysis by cfDNA analysis pre-treatment and at Cycle 3 Day 1.
To evaluate in participants tumor biomarkers over time such as estrogen receptor (ER), Ki67, Bcl-2, and progesterone receptor (PgR) protein, and ribonucleic acid (RNA) gene expression profiles (for participants with tumor sites accessible for biopsy who accept biopsies at study entry and on treatment).	Tumor ER, Ki67, Bcl-2, and PgR protein, and RNA gene expression profiles in optional paired biopsies at Cycle 1 Day 1 (pre-treatment) and at Cycle 3, Day 1 (allowed up to Day 15; or within 14 days after first radiological tumor assessment after baseline).
To explore pharmacokinetic/pharmacodynamics relationship of amcenestrant.	Pharmacokinetic exposure and response, or safety endpoints during the treatment period.
To evaluate the time to first use of chemotherapy after disease progression in the 2 treatment arms.	Time to first use of chemotherapy after disease progression is defined as the time from randomization to start of the first use of chemotherapy after disease progression.

For China, please see Section 10.8 for details.

3.1 APPROPRIATENESS OF MEASUREMENTS

Each of the efficacy, safety, PK, PDy, and patient reported outcomes (PRO) assessments selected for this study are considered well established and relevant in an oncology Phase 2 study setting.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is an international, prospective, open-label, Phase 2 randomized study comparing the efficacy and safety of amcenestrant versus a single endocrine therapy of the choice of the physician in men, postmenopausal women or premenopausal women on a gonadotropin-releasing hormone (GnRH) analog with ER-positive and HER2-negative advanced and/or metastatic breast cancer.

Participants will be randomly assigned (1:1) to either amcenestrant 400 mg QD PO, or a control arm (potential control treatment of the choice of the physician depending on each participant's medical condition and in accordance with the approved label).

The control arm may include 1 of the following treatments to be selected before randomization and used as monotherapy:

- Fulvestrant 500 mg, given as two 5-mL IM injections on Cycle 1 Days 1 and 15, and at Day 1 of each treatment 28-day cycle thereafter
- Aromatase inhibitors (PO, QD):
  - Anastrozole 1 mg to be taken approximately at the same time every day, regardless of food status
  - Letrozole 2.5 mg to be taken approximately at the same time every day, regardless of food status
  - Exemestane 25 mg to be taken approximately at the same time every day after a meal.
- Selective ER modulator (PO, QD or two times a day):
  - Tamoxifen 20 mg/day to be taken approximately at the same time every day, regardless of food status.

The population will be stratified according to the presence of visceral metastasis (defined by at least 1 liver or lung metastasis) (Yes or No), prior treatment with CDK4/6 inhibitors (Yes or No), and Eastern Cooperative Oncology Group (ECOG) status (0 or 1).

Study duration for an individual participant will include:

- A period to assess eligibility (screening period) of up to 4 weeks (28 days) before randomization
- A treatment period of 28 days of study treatment per cycle, and
- An end of treatment (EOT) visit at least 30 days (or until the participant receives another anticancer therapy, whichever is earlier) following the last administration of the investigational medicinal product (IMP).

Study treatment may continue until precluded by unacceptable toxicity, disease progression, upon participant's request to stop treatment, or Investigator decision, whichever occurs first.

Participants will continue treatment after the last cut-off date (COD). Participants who discontinue the study treatment without documented PD will be followed every 8 weeks until PD is documented or primary analysis COD, whichever occurs first.

For the global study, estimated COD for final PFS will be approximately 18 months after first randomized participant. No PK sample will be taken after Cycle 6 or COD for final PFS, whichever comes first. After the COD for final PFS analysis, no more efficacy assessment will be performed except collection of survival status. For all participants alive at the COD for final PFS analysis, the first follow-up visit will be conducted at the site and subsequent telephone follow-up assessments will be conducted every 2 months to record survival data and further therapies, which will be collected until COD for OS analysis, or participant death, or upon participant's request, whichever occurs first.

If a participant treated continues to benefit from the treatment after the COD for OS analysis, the participant may continue until treatment is precluded by toxicity, progression, upon participant's request to stop treatment, or Investigator decision. For cycles completed after the COD for final PFS analysis for the main cohort, only all ongoing serious AEs (SAEs) (related or not), all related nonserious AEs ongoing at the COD, and all new serious or related AEs occurring post-COD and associated concomitant medication, as well as IMP administrations and reason for EOT will continue to be collected.

For the China extension, assuming that the first Chinese participant is planned to be enrolled 11 months after the first randomized participant of the global part and a 17-month enrollment period for the Chinese participants, the estimated China COD will be approximately 5 months after last Chinese participant enrolled.

Study design specific to the China extension is described in Section 10.8.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

There is currently an unmet need in participants with advanced/metastatic breast cancer who have failed previous lines of hormonal therapies/chemotherapy. Fulvestrant is an approved SERD for participants who fail prior endocrine therapy, but despite demonstrated efficacy, this therapy is limited by its poor pharmaceutical properties which require IM administration and limit the applied dose, exposure, and receptor engagement (16, 17). Aromatase inhibitors and tamoxifen are alternative options that may benefit patients after relapse to prior hormonal therapies. Progression-free survival was found to be from 3 to 5 months in this population (2, 3, 4, 5, 6, 7).

The objective of this study is to compare the efficacy, safety, and PDy of amcenestrant with a single agent endocrine therapy in participants with advanced/metastatic breast cancer.

4.3 JUSTIFICATION FOR DOSE

The amcenestrant 400 mg dose was selected based on the preliminary safety, PK, and PDy data obtained from the TED14856 Phase 1 study with advanced breast cancer participants (detailed below).

Pharmacodynamics was assessed using ^{18}FES-PET scans; all the participants had 1 examination at baseline and a second one between 11 and 15 days after the first administration of amcenestrant, close to the time of PK trough prior to the next dose. Preliminary results show high levels of inhibition of the signal from the 150 mg dose level: 100% inhibition at this dose level and more than 87% in all participants treated at further dose levels. ^{18}fluoroestradiol-PET has been validated as an accurate method for localizing ER-expressing tumors (24, 25) and as a predictive assay for breast cancer endocrine therapy (24, 26, 27). The ^{18}FES-PET scan results indicated an inhibition of ER binding from 88% to 100% in participants treated with amcenestrant 400 mg QD.

Pharmacokinetic data of amcenestrant in humans was obtained after a single oral dose in healthy postmenopausal women (TDU16074 study) and after single and multiple QD doses in patients (TED14856 study). Amcenestrant was generally well absorbed but showed a high within and total-participant variability of exposure parameters. Amcenestrant is characterized by a large apparent volume of distribution (105 to 158 L) in both healthy and patient populations and a low apparent systemic clearance (from 9.8 L/h to 13.4 L/h after single or multiple dose). Pharmacokinetic profiles generally showed a biphasic elimination with a mean apparent terminal half-life estimated around 24 hours across doses after single dose administration. After multiple QD dosing in patients, a moderate accumulation was observed up to 200 mg while no accumulation was observed at 400 and 600 mg, suggesting possible non-linearity of amcenestrant PK with time. Exposure maximum concentration (C_{max}) and area under the curve (AUC) increased with dose and did not deviate significantly from dose proportionality after single dose, or after multiple doses between 20 and 600 mg. When given with a moderate fat breakfast in pilot food effect studies, amcenestrant exposure increased by 27% at 200 and 300 mg in healthy participants and by 45% between 200 and 600 mg in patients. Amcenestrant was recommended to be given regardless of food status in subsequent clinical studies. Please refer to the IB for more information on amcenestrant PK.

A strong PK/PDy relationship was established between plasma concentrations of amcenestrant, measured just before ^{18}FES administration and concomitant inhibition of ^{18}FES-PET signal. ^{18}FES-PET inhibition >87% was generally observed when plasma concentrations were above 100 ng/mL. This threshold is considered to allow amcenestrant occupancy of ER.

Estrogen receptor 1 gene mutations were assessed prior to treatment, with data available on 16 participants from Part A. In the cell-free deoxyribonucleic acid (cfDNA), 11 of 16 participants had detectable ESR1 mutations, and the proportion of the cfDNA that showed an ESR1 mutation varied widely between participants (0.1% to 47%). To date, there is no obvious correlation between presence of an ESR1 mutation and PK characteristics or ^{18}FES-PET occupancy.

Based on the aforementioned, PK, PDy, and safety data described in Section 2.3.2, the recommended amcenestrant dose was fixed at 400 mg QD.

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date of the last visit/last contact of the last participant in the study or the last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the study globally.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be 18 years of age (inclusive) or older, at the time of signing the informed consent or country's legal age of majority if the legal age is more than 18 years.

Type of participant and disease characteristics

I 02. Participants with histological or cytological proven diagnosis of adenocarcinoma of the breast.

I 03. Participants with evidence of either locally advanced not amenable to radiation therapy or surgery in a curative intent, and/or metastatic disease.

I 04. Documentation of ER-positive (≥1% positive stained cells) based on most recent tumor cell staining by immunohistochemistry (IHC) assay consistent with local standards.

- Note that if the primary tumor is ER-positive and any further metastatic lesion is ER-negative, the participant cannot be selected for inclusion.

I 05. Documentation of HER2 non over-expressing based on most recent tumor sample by IHC (0, 1+), or in situ hybridization-negative based on single-probe average HER2 copy number <6.0 signals/cell or dual-probe HER2/centromeric probe for chromosome 17 (CEP17) ratio <2 with an average HER2 copy number <6.0 signals/cell as per American Society of Clinical Oncology guidelines (28).

- Note that if the primary tumor is HER2-negative and any further metastatic lesion is HER2-positive, the participant cannot be selected for inclusion.

I 06. I 06 deleted in amended protocol 03.

I 07. Prior chemotherapy (including antibody-drug conjugates) or targeted therapy is allowed: participants must have received no more than 1 prior chemotherapeutic **or** 1 targeted therapy regimen for advanced/metastatic disease.

For participants for whom CDK4/6 inhibitors are available (ie, approved in their region and can be reimbursed), prior treatment with a CDK4/6 inhibitor in combination with fulvestrant or an AI is mandatory.

Note: The number of participants naïve to CDK4/6 inhibitors should not be higher than 20% of the overall sample size.

I 08. Participants must have received at least 6 months of a continuous prior endocrine therapy for advanced breast cancer and have progressed while on endocrine therapy (in single agent or in combination). The number of prior hormonal lines will be limited to 2.

Participants with a relapse while on adjuvant endocrine therapy but after the first 2 years, or with a relapse within 12 months of completing adjuvant endocrine therapy are also eligible.

Weight

Not applicable.

Sex

I 09. Male or Female

A) Postmenopausal women, as defined by one of the following:

- Women ≥60 years of age.
- Women <60 years of age:
  - With spontaneous cessation of menses >12 months prior to randomization in the absence of chemotherapy, tamoxifen, and toremifene.
  - Or with cessation of menses of duration ≤12 months or secondary to hysterectomy AND have follicle-stimulating hormone (FSH) level in the postmenopausal range according to institutional standards (or >34.4 IU/L if institutional range is not available) prior to randomization.
  - Or who have received hormonal replacement therapy but have discontinued this treatment AND have FSH level in the postmenopausal range according to institutional standards (or >34.4 IU/L if institutional range is not available) prior to randomization.
  - Or with status post bilateral surgical oophorectomy.
  - Or postbilateral ovarian ablation through pelvic radiotherapy.

B) Pre/perimenopausal women, ie, not meeting the criteria for being postmenopausal.

C) Male participants.

Note: Male with no prior bilateral orchiectomy and pre/perimenopausal women should be on a GnRH agonist for at least 4 weeks prior to randomization (to be continued during study treatment).

Informed Consent

I 10. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.2) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Criteria added in amended protocol 02

I 11. Participants must be considered clinically eligible by the Investigator to receive single agent endocrine therapy.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Eastern Cooperative Oncology Group performance status ≥2 (Section 10.10 [Appendix 10]).

E 02. Significant concomitant illness, including psychiatric condition that, in the opinion of the Investigator or Sponsor, would adversely affect the participant's participation in the study.

E 03. Medical history or ongoing gastrointestinal disorders potentially affecting the absorption of oral IMP. Participants unable to swallow normally and to take capsules. Predictable poor compliance to oral treatment.

E 04. Participants not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to the study procedures (ie, unwillingness and inability to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions).

E 05. Major surgery within 4 weeks prior to randomization.

E 06. Participant with any other cancer. Adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer or any other cancer from which the participant has been disease free for >3 years are allowed.

E 07. Any medical conditions that are contraindicated to endocrine treatment of physician's choice (refer to approved label for details).

E 08. Participants with abnormal coagulation profiles or any history of coagulopathy within the 6 months prior to the first dose of IMP, including history of deep vein thrombosis or pulmonary embolism. However, participants with the following conditions will be allowed to participate:

- Participants with adequately treated catheter-related venous thrombosis that occurred more than 1 month prior to the first dose of IMP.

- Participants being treated with an anticoagulant (eg, warfarin or heparin) for a thrombotic event that occurred more than 6 months before enrollment, or for an otherwise stable and allowed medical condition (eg, well-controlled atrial fibrillation), provided that dose and coagulation parameters (as defined by local standard of care) are stable for at least 1 month prior to the first dose of IMP.

Exclusion criteria related to the disease

E 09. Participants with a life expectancy <3 months.

E 10. E 10 deleted in amended protocol 02.

E 11. Participants with known brain metastases that are untreated, symptomatic or require therapy to control symptoms. Participants with brain metastases are eligible if they:

- Have completed treatment (whole brain radiotherapy, radiosurgery, or combination) at least 4 weeks prior to start of study treatment, and
- Have recovered from the effects of this treatment, and
- Are neurologically stable.

Any corticosteroid use for brain metastases must have been discontinued without the subsequent appearance of symptoms for ≥2 weeks prior to first IMP.

E 12. No improvement of any prior treatment-related adverse reaction to < Grade 2, except for alopecia according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 (Section 10.3 [Appendix 3]).

Prior/concomitant therapy

E 13. Prior treatment with mammalian target of rapamycin inhibitors or any other SERD compound, except fulvestrant if stopped for at least 3 months before randomization.

E 14. Treatment with drugs that have the potential to inhibit UGT, including, but not limited, to atazanavir and probenecid, for less than 2 weeks before randomization or 5 elimination half-lives whichever is longer.

E 15. Treatment with strong CYP3A inducers within 2 weeks before randomization or 5 elimination half-lives whichever is longer (Section 10.11 [Appendix 11]).

E 16. Ongoing treatment with drugs that are sensitive substrate of OATP1B1/B3 (asunaprevir, atorvastatin, bosentan, danoprevir, fexofenadine, glyburide, nateglinide, pitavastatin, pravastatin, repaglinide, rosuvastatin, and simvastatin acid).

NOTE: *Refer to FDA website: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-1*

Prior/concurrent clinical study experience

E 17. Treatment with anticancer agents (including investigational drugs) less than 3 weeks before randomization.

Diagnostic assessments

E 18. Inadequate hematological function including neutrophils $<1.5 \times 10^9$/L; platelet count $<100 \times 10^9$/L.

E 19. Prothrombin time/international normalized ratio (INR) >1.5 times the upper limit of normal (ULN) or outside therapeutic range if receiving anticoagulation that would affect the prothrombin time/INR.

E 20. Inadequate renal function with serum creatinine ≥1.5 × ULN or between 1.0 and 1.5 × ULN with glomerular filtration rate <60 mL/min/1.73 m^2 as estimated using the abbreviated Modification of Diet in Renal Disease formula (Section 10.13 [Appendix 13]).

E 21. Liver function:

- Aspartate aminotransferase >3 × ULN, or ALT >3 × ULN.
- Total bilirubin >1.5 × ULN.
- Note: In the presence of hepatic metastases, AST and ALT <5 × ULN are acceptable.

Other exclusions

E 22. Participants accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 23. Participants dependent on the Sponsor or Investigator (in conjunction with Section 1.61 of the International Council for Harmonisation-Good Clinical Practice Ordinance E6).

E 24. Employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals.

E 25. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Activity (Sun protection)

Preclinical toxicity studies using amcenestrant indicate a potential risk for phototoxicity; in addition, 1 participant from Part 1 of the TED14856 study experienced Grade 1 sunburn while exposed to the sun without protection, an event considered related to amcenestrant (described in the IB). For this reason, participants should avoid direct exposure to natural or artificial sunlight during study treatment and for at least 5 days after last IMP dose. It is recommended to advise to

wear protective clothing, lip balm, and broad spectrum sunscreen with a high sun protection factor (eg, ≥30) to cover UVA and UVB light exposure when outdoors with frequent re-application as necessary.

5.3.2 Osteoporosis

Due to anti-estrogenic properties of amcenestrant, fulvestrant, and aromatase inhibitors being potent estrogen lowering agents, there exists potential risk of osteoporosis. Lifestyle changes that preserve bone mineral density [eg, stopping or reducing smoking and drinking, and increasing physical activity, especially weight-bearing exercises), and adequate nutrition (protein, calcium, and supplementary vitamin D3)] are recommended. Investigators will monitor Bone Mineral Density if clinically indicated, taking into account full medical history of patients, all confounding factors, previous anti-cancer treatments and considering the anti-estrogenic properties of the study drugs.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Participants who do not meet the criteria for participation in this study may be retested during the screening period (≤28 days) and included, providing they meet at that time all inclusion and exclusion criteria. These participants are not considered screen failures.

Participants who do not meet the criteria for participation during the screening period will be labeled screen failures and may be rescreened once. A different participant identification will be issued, while the other identification for this participant should be recorded as screen failure. There is no requirement for a waiting period between a screen failure date and the rescreening date. Participants that are rescreened must sign a new consent form and all screening procedures must be repeated.

5.5 CRITERIA FOR TEMPORARILY DELAYING ADMINISTRATION OF STUDY INTERVENTION

During a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, if the site is unable to adequately follow protocol mandated procedures, contingency measures proposed in Section 10.16 (Appendix 16) should be considered.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Between the protocol-scheduled on-site visits, interim visits may be required for IMP dispensing. As an alternative to these visits, IMPs may be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations and approved by the participant (Section 10.16 [Appendix 16]).

Table 2 - Overview of study interventions administered

Study intervention name	amcenestrant	Fulvestrant (Faslodex®)	Aromatase inhibitors	Tamoxifen
Dosage formulation	Capsules for oral use	Concentrate for solution for intramuscularly injection	In accordance with the approved label	In accordance with the approved label
Unit dose strength(s)	100 mg capsule	250-mg (5 mL) solution for injections	Anastrozole Letrozole Exemestane In accordance with the approved label	In accordance with the approved label
Route of administration	Per os	Intramuscular	Per os	Per os
Dosing instructions	4 capsules once a day given in the morning with or without food, at approximately the same time every day (±3 hours)[a]	Two 250-mg (5 mL) injections for intramuscular use in Cycle 1 Day 1, Cycle 1 Day 15, and Day 1 of each 28-day cycle thereafter[a]	Anastrozole 1 mg and letrozole 2.5 mg: Once daily, approximately at the same time every day, regardless of food status[a] Exemestane 25 mg: once daily, approximately at the same time every day after a meal[a]	20 mg once daily or 10 mg twice a day, approximately at the same time every day, regardless of food status[a]
Packaging and labeling	Study intervention will be provided in blisters containing capsules. Each blister will be labeled as required per country requirement	In accordance with the approved label	In accordance with the approved label	In accordance with the approved label
Manufacturer	Sanofi-Aventis R&D	AstraZeneca	Not determined[b]	Not determined[b]

a In study visit days, participants should only be dosed after the predosing pharmacokinetic sampling collection.
b Brand and generic products can be used, according to country availability.
Aromatase inhibitors approved for breast cancer treatment include letrozole, anastrozole, and exemestane.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 General rules

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual and/or monitoring plan.

Partially-used and used IMP will be destroyed at the study site according to the standard practices of the site after an accurate accountability has been performed and signed by the Investigator (or the pharmacist). A detailed treatment log form of the destroyed IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team.

The Investigator must not destroy the unused IMP unless sanofi provides written authorization.

Any quality issue noticed with the receipt or use of amcenestrant (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.7).

A potential defect in the quality of amcenestrant or any comparator supplied globally may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the amcenestrant and eliminate potential hazards. When control treatments are recalled, the dispensing pharmacist or the site are responsible for notifying the participant, according to local regulation.

Under no circumstances will the Investigator supply IMP to a third party (except for DTP shipment, for which a courier company has been approved by the Sponsor), allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

6.2.2 Storage conditions

Investigators or other authorized persons (eg, pharmacists) will be responsible for storing amcenestrant and control treatments in a secure and safe location with restricted access, in accordance with local regulations, labeling specifications, policies, and procedures.

6.2.2.1 Amcenestrant

Control of amcenestrant storage conditions, especially temperature (eg, refrigerated storage), and information on in-use stability and instructions for handling this IMP should be managed in accordance with the rules provided by the Sponsor.

Amcenestrant is to be stored at +2°C to +8°C (36°F to 46°F) and protected from light. All capsules must be kept in their box until use.

6.2.2.2 Control products

Please refer to package insert for storage conditions.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

All participants will be centrally assigned to randomized study intervention using an Interactive Response Technology (IRT). The IRT generates the participant randomization list and allocates the intervention number and the corresponding intervention kits to the participants according to it. Before the study is initiated, the telephone number and call-in directions for the Interactive Voice Response System and/or the log in information and directions for the Interactive Web Response System will be provided to each site. The IRT centralized randomization system will be used to prevent the Investigators from knowing in advance the treatment assignment.

Investigational medicinal product will be dispensed at the study visits summarized in the Schedule of Activities (SoA). Participants will be randomized within 3 days prior to first IMP dosing (Cycle 1 Day 1).

Returned study intervention should not be re-dispensed to the participants.

Participants cannot be randomized more than once.

This is an open-label study; however, the specific intervention to be taken by a participant will be assigned using an IRT system. The site will contact the IRT prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable case report form, if required. Potential bias will be reduced by the following steps:

- Central randomization
- Randomization will be stratified according to the presence of visceral metastasis (defined by at least 1 liver or lung metastasis) (Yes or No), prior treatment with CDK4/6 inhibitors (Yes or No), and ECOG status (0 or 1) (Note: The number of participants naïve to CDK4/6 inhibitors should not be higher than 20% of the overall sample size)
- Assessment of tumor response by independent central review (ICR) blinded to study treatment arms.

During the trial, IMP administration will be open-label, and no attempts will be made to blind administration. Blinding rules for the Sponsor study team will be detailed in a separate document.

6.4 STUDY INTERVENTION COMPLIANCE

A patient diary will be provided to participants receiving oral therapy (amcenestrant or controls given PO) at every visit during treatment.

The person responsible for drug dispensing is required to maintain adequate records of the study treatment. These records (eg, product accountability and inventory forms at site level) include the date the study treatment is received from the Sponsor, dispensed to the participant and destroyed or returned to the Sponsor. The packaging batch number on the pack must be recorded on the drug accountability form.

Compliance to amcenestrant/controls given PO intake will be assessed using the patient diary. On Day 1, while the participant is in the clinic, the study staff will demonstrate to the participant how to record information in the patient diary. Participants will note every day the hours of amcenestrant/controls given PO intake and food conditions. If vomiting occurred after the intake of capsules/tablets, they need to report it in the same diary. In case of an early vomiting event, the administered dose of amcenestrant/controls given PO should not be repeated, and the participant should be instructed not to make it up the next day and resume the treatment the next day as prescribed. This information should be recorded in the diary. The diary will then be completed by the participant each day for each dose and will be returned to the study personnel at the end of each cycle. Participants who inadvertently take 1 extra dose during a day must be instructed to skip the next day's dose. Also refer to Section 8.4 for further details.

Participants will be requested to return all unused amcenestrant/controls given PO to the study site at the end of the treatment period for each cycle for a full compliance assessment. Clinic staff will record the study medication dosing information including the actual clock time of each dose based on information from the patient diary.

Administration of fulvestrant will be supervised at the study site by the Investigator or Subinvestigator.

In case of oral dosing omission or IM injection delay greater than 2 weeks, the participant will be withdrawn from the study treatment, unless a clear benefit is identified and after discussion with the Medical Monitor (Section 6.6).

6.5 CONCOMITANT THERAPY

All treatments being taken by the participant from the date of the consent form to the first study treatment administration, at any time during the treatment period and up to 30 days after the last dose are regarded as prior and concomitant treatments respectively, and will be reported on the appropriate screen of the electronic case report form (eCRF).

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, GnRH analogs, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use;
- dates of administration including start and end dates.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

Bisphosphonates and receptor activator of nuclear factor-kappa B ligand inhibitors are allowed.

Special caution should be taken regarding the following therapies:

- No additional investigational or commercial anticancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy other than amcenestrant or the selected control will be permitted during the active treatment phase. In general, any drugs containing "for the treatment of breast cancer" on the product label are not permitted on study.
- Palliative radiotherapy may be given for control of pain for palliative intents. The Sponsor team should be notified to obtain agreement prior to treatment if palliative radiotherapy is being considered, and prior to resuming therapy on the study. The irradiated area should be as small as possible and should never involve more than 20% of the bone marrow in any given 3-week period. In all such cases, the possibility of tumor progression should be ruled out by physical and radiological assessments of the tumor. If the only evaluable lesions are to be irradiated, the participant will stop the study treatment. The irradiated area cannot be used as a parameter for response assessment.
- Drugs which are sensitive substrates of CYP3A, CYP2B6, CYP2Cs, and/or UGT should be closely monitored (see list Section 10.12 [Appendix 12]) since there may be loss of efficacy of these drugs by concomitant use of amcenestrant due to a potential induction effect of amcenestrant.

The following therapies/medications are prohibited throughout the active treatment phase for the amcenestrant treatment arm:

- Drugs that are strong inducers of CYP3A, since they may decrease amcenestrant exposure (see full list in Section 10.11 [Appendix 11]).
- Herbal medications and food supplements including St John's Wort and genistein during treatment period, since they could decrease amcenestrant exposure.
- Drugs that are sensitive substrates of OATP1B1/1B3 including asunaprevir, atorvastatin, bosentan, danoprevir, fexofenadine, glyburide, nateglinide, pitavastatin, pravastatin, repaglinide, rosuvastatin and simvastatin acid, since amcenestrant is a potential inhibitor and may decrease their elimination.
- Drugs that have UGT inhibition potential and are contraindicated with UGT substrates, including, but not limited to, atazanavir and probenecid, since amcenestrant is substrate of UGT1A1 and UGT1A4.

Regarding the control arm, please refer to the approved label of the selected control for contraindications and precautions regarding concomitant medications.

Prophylactic vaccination is recommended for influenza A and B virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; ie COVID-19), Pneumococci, and Haemophilus influenza.

6.5.1 Rescue medicine

Not applicable.

6.6 DOSE MODIFICATION

Dose adjustment (omission, reduction) is permitted for oral drug IMP only. The fulvestrant dose cannot be adjusted; its dosing can only be delayed or interrupted.

If a dose of PO-given IMP is vomited or omitted, the participant should not take the dose later or 2 doses at the next planned dose, and this information has to be recorded in the patient diary.

Oral IMP dose omission is allowed in case of severe toxicity and the reason should be documented in the eCRF. Doses omitted for toxicity are not to be replaced within the same cycle.

Conditions for dose modifications are aligned in Table 3. Please refer to the selected control label information on additional specific contraindications and events requiring use precaution.

In case of oral dosing omission or IM injection delay greater than 2 weeks, the participant will be withdrawn from the study treatment, unless a clear benefit is identified and after discussion with the Medical Monitor.

Table 3 - Recommended dose modification and management of amcenestrant related toxicities

NCI-CTCAE grade	Dose modifications
Amcenestrant-related toxicities other than increase of ALT	
Grade 1 or 2	No dose adjustment required
Grade 3 (if persisting despite optimal medical treatment)	Omit amcenestrant until symptoms resolve to Grade ≤1 and administer amcenestrant at the same dose. In case of recurrence of the same Grade 3 event, and after symptoms resolve to Grade ≤1, a dose reduction to 200 mg QD can be considered, but no further re-escalation is allowed. In case of a second recurrence, if already reduced at first event recurrence, amcenestrant will be definitely stopped.
Grade 4 (if persisting despite optimal medical treatment)	Omit amcenestrant until symptoms resolve to Grade ≤1. After that, reintroduction of amcenestrant at the same dose or at reduced dose (200 mg QD) can be considered if the participant is clinically benefiting and with the agreement of the Medical Monitor. After dose reduction, no further re-escalation is allowed. In case of recurrence of the same event at Grade ≥3, and after symptoms resolve to Grade ≤1, the dose should be reduced to 200 mg QD (if not previously implemented) or permanent discontinuation of the drug could be considered.
Isolated increase of ALT Confounding factors such as, liver metastasis, hepato-biliary disorders, concomitant medications, etc should be excluded prior to dose modifications	
Grade 0 or 1	No dose adjustment is required
Grade 2	Omit amcenestrant administration until recovery to Grade ≤1, and then restart endocrine therapies at the same dose. In case of recurrence of the same Grade 2 event: administer at the same dose if restart is possible.
Grade 3	Omit amcenestrant administration. Repeat LFTs within 2-3 days. If ALT levels not recovered, monitor LFTs weekly (or more frequently, if clinically indicated) until recovery to Grade ≤1 ALT increased (or baseline grade). On recovery, restart endocrine therapies at the same dose. In case of first recurrence of the same Grade 3 event: administer at the same dose if restart is possible. In case of second recurrence of the same Grade 3 event: permanently discontinue endocrine therapies.
Grade 4	Permanently discontinue study treatment

NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; QD = once daily.

Liver function tests (LFTs) include AST, ALT, ALP (isoenzymes if Grade >2), total bilirubin (fractionated if >2 x ULN direct), GGT, and INR (if total bilirubin >2.5 ULN).

6.7 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

As per discretion of the Investigator.

In case a new anticancer therapy is administered during the follow-up stage of the study, before recovery or consolidation of any related AEs or SAEs, or before documented disease progression at the time of study treatment discontinuation, the start date, end date, and the name of further therapy until first chemotherapy will be collected in the eCRF.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1 (Section 10.1.8).

Pregnancy will lead to permanent treatment discontinuation in all cases.

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

Participants may withdraw from study treatment if they decide to do so, at any time and irrespective of the reason, or this may be done at the discretion of the Investigator. All efforts should be made to document the reason(s) for discontinuation and this should be documented in the eCRF.

Treatment with the study treatment should be discontinued in any of the following cases:

- At the participant's request, at any time and irrespective of the reason (consent's withdrawal), or at the request of their legally authorized representative. "Legally authorized representative" is considered to be an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the procedure(s) involved in the research. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for nonparticipant contact follow-up, eg, medical records check. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study. Participants who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. The participant should preferably withdraw consent in writing and, if the participant or the participant's representative refuses or is physically unavailable, the site should document any case of withdrawal of consent.
- If, in the Investigator's opinion, continuation of the study treatment would be detrimental to the participant's wellbeing, such as:
  - Disease progression
  - Unacceptable AE
  - Poor compliance to the study protocol
  - Any other reason such as intercurrent illness that prevents further administration of study treatment.
- Participant is lost to follow-up (Section 7.3).

Handling of participants after permanent intervention discontinuation

Participants will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of intervention, the participants will be assessed using the procedure normally planned for the EOT visit.

All cases of permanent intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for nonparticipant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be rerandomized/reallocated (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

  Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA. The ICF can be signed more than 28 days prior to randomization. Screening time indicates in which time frame examinations used to support eligibility have to be done prior to randomization.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples (refer to the study manual for details).
- Assessments should be performed when possible prior to administration of study treatment unless otherwise indicated in the SoA (Section 1.3). Every effort should be made to keep the SoA on time for each participant. All visits should be performed on the day specified, unless otherwise noted.
- Additional safety tests (eg, electrocardiogram [ECG]) can be performed whenever clinically indicated.

  Randomization: to take place once the consented participant has completed all the necessary screening procedures and is deemed eligible for study entry by the Investigator or designee. All eligible participants must be randomized using IRT. Every effort should be made to start treatment within 3 working days of randomization.
- Before Cycle 1, evaluations such as body weight, signs and symptoms, physical examination, ECG, hematology, coagulation tests, blood chemistry, and urinalysis should be repeated within 2 or 3 days before Cycle 1 Day 1 if abnormal or performed more than 7 days before Cycle 1 Day 1. Pregnancy test will be repeated (by dipstick) at Cycle 1 Day 1 for premenopausal patients if screening test >7 days before Cycle 1 Day 1.
- During treatment, additional hematology, coagulation, blood chemistry, and urinalysis assessments can be performed when clinically indicated.
- Cycle 1 Day 1 refers to the day the participant receives the initial dose of study treatment which will be a single administration of amcenestrant, or control selected by the physician.

- Cycle 1 Day 15 corresponds for participants randomized in the control arm and treated by fulvestrant to the second fulvestrant injection.
- A cycle duration is 28 days. Day 1 of Cycle 1 refers to the day the participant receives the first study treatment administration. Day 1 of each subsequent cycle corresponds to the visit performed on Day 29 ±2 days of previous cycle.

8.1 EFFICACY ASSESSMENTS

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

8.1.1 Criteria for response (antitumor activity)

The primary and secondary efficacy endpoints will be assessed by the RECIST 1.1 (Section 10.14 [Appendix 14]) criteria. Tumor assessments will be reviewed centrally by ICR. Copies of all imaging sets will be systematically collected for the purpose of ICR (refer to imaging charter and manual).

Tumor assessment will be performed at fixed intervals as described in SoA, and the assessment window is not impacted by dose delay or dose omission.

Chest, abdomen, and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans and any other examinations as clinically indicated will be performed to assess disease status within the screening period and before first study treatment as baseline. Positron emission tomography-CT is not authorized. Afterwards, chest, abdomen, and pelvis CT or MRI scans (whichever used at baseline) will be performed every 8 weeks or when clinically indicated during treatment, whenever disease progression is suspected (eg, symptomatic deterioration), and at the end of study treatment (in accordance with RECIST 1.1 for solid tumors). Considering the 8 weeks period between 2 tumor assessments, the confirmation of PR or CR is not necessary 4 weeks apart.

Tumor assessment should not be repeated at EOT if performed at the immediate previous cycle.

Participants who discontinue the study treatment without documented PD will be followed every 8 weeks (projected from last tumor assessment) until PD is documented or COD for final PFS, whichever occurs first.

The same evaluation method should be used for all evaluations in the same participant.

8.1.2 Bone scans

Bone scans will be performed in line with the SoA (Section 1.3). In the applicable cycles, bone scans and tumor assessments (Section 8.1.1) should be performed during the same period.

If at baseline, lesions are detected in the bone scan but not in the CT/MRI (RECIST 1.1) scan, further bone scans should be conducted every 8 weeks ±7 days after randomization until disease progression documented or COD for final PFS, whichever occurs first. If the lesions seen in the

bone scan are no longer visible, these assessments should be conducted every 16 weeks ±7 days after randomization until disease progression documented or COD for final PFS, whichever occurs first.

If bone lesions are detected in the bone scan and in CT/MRI (RECIST 1.1) scan at baseline, further bone scans will be conducted every 16 weeks ±7 days after randomization until disease progression documented or COD for final PFS, whichever occurs first.

If at screening, lesions are not detected in the bone scan nor in the CT/MRI (RECIST 1.1) scan, further bone scans are not required unless clinically indicated.

Bone scans will be assessed centrally by ICR.

8.1.3 Patient reported outcomes

Patient reported outcomes will be assessed in this study in line with the SoA (Section 1.3). While on treatment, PROs are to be administered prior to treatment and prior to discussion of participant's health status.

The European Organisation for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30) is a cancer specific instrument that contains 30 items and provides a multidimensional assessment of health-related quality of life (HRQL) (29, 30, 31). The validity and reliability of the QLQ-C30 has been established in various types of cancers (32). This instrument provides a comprehensive assessment of the principal HRQL dimensions identified as relevant by cancer patients (physical functioning, emotional functioning, cognitive functioning, role functioning, social functioning, global HRQL, impact of symptoms, and impact of toxicities). The QLQ-C30 is one of the standard instruments used in oncology for the evaluation of new cancer therapies.

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include 5 functional scales (physical, role, emotional, cognitive, and social functioning), 3 symptom scales (fatigue, nausea and vomiting, and pain), a Global Health Status (GHS)/quality of life scale, and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). All of the scales and single-item measures range in score from 0 to 100. A higher score for a functional scale/GHS represents a higher/healthier level of functioning/HRQL, where a higher score for symptoms/items represents a higher level of symptomatology/problems. The recall period for this instrument is 1 week.

The EORTC QLQ breast cancer specific module (QLQ-BR23) is a disease-specific HRQL measure that is used in conjunction with the QLQ-C30. The QLQ-BR23 assesses the impact breast cancer and the side effects of treatment in breast cancer patients.

The QLQ-BR23 contains 23 items: 8 assessing functioning which includes body image (4 items), sexual functioning (2 items), sexual enjoyment (1 item), and future perspective (1 item), and 15 items assessing symptoms of disease or treatment including arm symptoms (3 items), breast symptoms (4 items), systemic therapy side effects (7 items), and upset by hair loss (1 item).

The QLQ-C30 and QLQ-BR23 are reliable and valid measures of HRQL in cancer patients. The 2 measures together (53 items) take approximately 9 minutes to complete. The instruments have been translated, validated, and used in many countries.

The EuroQoL questionnaire with 5 dimensions and 5 levels per dimension (EQ-5D-5L) is a standardized measure of health status that provides a simple, generic measure of health utility, and consists of 2 sections: descriptive and visual analogue scale (VAS). The descriptive section consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The VAS records the participant's self-rated health on a 20 cm vertical VAS with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine'. This information can be used as a quantitative measure of health as judged by the individual participants.

The instrument is designed for self-completion by the participants. Response options are measured with a 5-point Likert scale with higher scores indicating better HRQL.

For EQ-5D-5L**,** VAS will be described as given by the participant and health utility index will be calculated according to EuroQoL-specific country algorithms/crosswalk developed by B. van Hout (33). In case a specific country algorithm is missing, the value sets based on the United Kingdom population will be used to generate health utility scores.

It is important that the PROs are completed by each study participant, after study participant has signed the informed consent and prior to any treatment- or study-related activities, including administration of drug, laboratory work, radiological assessments, discussion with the participant regarding their treatment or health status, and similar activities. This ensures the objectivity of the data.

Site staff must not complete the PRO data on behalf of participant.

Detailed site training on PROs will be provided at the Investigator meeting and in separate PRO training materials.

8.2 SAFETY ASSESSMENTS

This section presents safety assessments other than adverse events which are presented in Section 8.3.

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical examinations

- A physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height (at screening only) and weight will also be measured and recorded.
- Performance status as measured by the ECOG.

- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any new finding or worsening of previous finding during treatment period should be reported as a new AE.

8.2.2 Vital signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed by a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure, respiratory rate, and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

8.2.3 Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.
- Electrocardiograms will be done in accordance with the SoA (Section 1.3), and can be repeated as clinically indicated.

8.2.4 Clinical safety laboratory tests

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.

- The Investigator must review the laboratory report, document this review. The laboratory reports must be filed with the source documents.
- Liver function tests Grade ≥3 during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline. If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified if not related to underlying disease. If related to IMP refer to dose modification Table 3 (Section 6.6).
- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA.
- Any laboratory abnormalities are to be recorded as AEs only if they are serious or impact study treatment (ie, lead to dose omission, reduction, delay, or discontinuation).

8.2.5 Suicidal risk monitoring

Not applicable.

8.3 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

- **Pregnancy of a female participant entered in a study, as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP**:
  - Pregnancy occurring in a female participant or female partner of a male participant entered in the clinical study will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
- **Symptomatic overdose (serious or nonserious) with IMP**.
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug.
  - Injectable administration: at least twice the dose during the planned intervals.
  - Of note, asymptomatic overdose has to be reported as a standard AE.
- **Increase in ALT Grade ≥3**.
  - Omit study-treatment study-intervention administration, and repeat LFTs within 2-3 days. If not recovered, monitor LFTs weekly until recovery to Grade ≤1 (or baseline grade). Confounding factors such as, liver metastasis, hepato-biliary disorders, concomitant medications, etc should be excluded prior to dose modifications. Please refer to the dose modification guidelines for management of isolated increase of ALT (Table 3, Section 6.6).
  - Close monitoring of study participants is recommended in cases of increase of Grade ≥3 ALT. LFTs should be performed in patients with onset of otherwise unexplained nausea, jaundice, right upper abdominal pain, fever, or rash.
  - LFTs include AST, ALT, ALP (isoenzymes if Grade >2), total bilirubin (fractionated if >2 x ULN direct), GGT, and INR (if total bilirubin >2.5 ULN).
  - An ultrasound, or other imaging, should be considered based on the clinical presentation.
  - A consultation with a hepatologist should be undertaken if there is,
    - Unexplained or persistent Grade ≥3 ALT despite dose omissions
    - ALT >3 ULN and concomitant jaundice (total bilirubin >2.5 ULN), in patients with normal ALT and total bilirubin at baseline.

to exclude hepato-biliary disorders (eg, hepatotropic virus infections, autoimmune or alcoholic hepatitis, Non-Alcoholic Steatohepatitis, etc) or drug induced liver injury.

- Further hepatic virology will be undertaken as per the site's local guidelines for the treatment of cancer patients, taking into account the local and national recommendations.

- Photosensitivity
  - If photosensitivity is suspected in study participants, consider dermatologist consultation. Confounding factors such as other dermatological disorders, drug eruptions resulting from concomitant medication use, etc should be excluded prior to any dose modification (Refer to Section 6.6 Dose modification). In case of study intervention discontinuation because of photosensitivity reaction, study participant should be followed for possibility of development of other manifestations of photosensitivity such as photo-onycholysis, lichenoid reaction or actinic granuloma.

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the IMP (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs (regardless of seriousness or relationship with IMP) will be collected from the signing of the ICF until 30 days after the last dose of the IMP (Section 1.3).

All SAEs and AESIs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the prespecified study end-date, all SAEs, and nonserious AESIs (as defined in Section 8.3), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and Investigators.
- The Investigator is obligated to assess the relationship between study intervention (IMP) and each occurrence of AE/SAE (Section 10.3). Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- Serious adverse events that are considered expected will be specified in the reference safety information of the IB or approved label for the control arm.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and, therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants or female partners of male participants will be collected after the start of study intervention and until 30 days after the last dose.
- Participants are not expected to be in this situation, assuming that all participants are postmenopausal per definition, or receiving long-term GnRH therapy. Non-hormonal methods of contraception should be employed during the study in premenopausal participants and in male participants without prior orchiectomy on a GnRH analog as per label (please see Section 10.4 [Appendix 4] for details).

If a pregnancy is reported in female participants or female partners of male participants, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- In the event of pregnancy, study treatment should be discontinued.
- Follow-up of pregnancy is mandatory until outcome has been determined.

8.3.6 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable.

8.3.7 Guidelines for reporting product complaints

Any defect in the IMP supplied centrally by Clinical Supplies (amcenestrant and control arm treatments in the United States and Poland) must be reported as soon as possible by the Investigator to the monitoring team responsible for completing a product complaint form, within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 TREATMENT OF OVERDOSE

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until the IMP can no longer be detected systemically (at least 7 days for amcenestrant and 5 times the half-life time of the control treatment for the selected control IMP).
3. Obtain a plasma sample for PK analysis within 7 days from the date of the last dose of amcenestrant if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5 PHARMACOKINETICS

- Pharmacokinetic sampling is planned only in participants randomized in amcenestrant treatment arm.
- Blood samples of approximately 1 mL will be collected for measurement of plasma concentrations of amcenestrant as specified in the SoA (Section 1.3) using a validated liquid chromatography-mass spectrometry/mass spectrometry assay with a limit quantification of 5 ng/mL (method reference DOH1434). Instructions for the collection and handling of biological samples will be provided by the Sponsor and detailed in the laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded.
- Timing of blood sampling for PK assessments will be detailed in the laboratory manual.
- It is of utmost importance to collect all blood samples at the specified time windows and according to the specifications (refer to the laboratory manual).
- Samples missed or lost for any reason should be recorded. Actual dates and times of blood collection should be recorded in the eCRF. Actual dates and times of previous drug administration and food status should also be precisely recorded.
- For the comfort of the participants, some PK samplings may be deleted during the course of the study if they are no longer deemed necessary by the Sponsor.
- Pharmacokinetic samplings will be stopped at the end of Cycle 6 or at the COD for final PFS, depending which one comes first.
- A population PK analysis will be performed and reported in a standalone report.
- Pharmacokinetic sample handling procedures will be described in the laboratory manual.

8.6 PHARMACODYNAMICS

For additional parameters, please see Section 8.7 and Section 8.8.

8.6.1 Tumor biopsy to assess estrogen receptor degradation (optional procedures)

Participants with an accessible tumor who consented to the optional paired biopsy will be asked to contribute the most recent archived biopsied tumor (within past 3 months prior to initiation of study treatment) or preferably a fresh tumor biopsy that can be collected between the time of ICF signature and Cycle 1 Day 1 prior to treatment. After baseline, these participants will be asked to provide a biopsy of either a primary or secondary tumor site. This on-treatment biopsy should take place at approximately Cycle 3 Day 1 (allowed up to Cycle 3 Day 15 or within 14 days after first radiological tumor assessment visit after baseline) and should be taken from the same site as the previous biopsy, when feasible (not applicable for archive samples). Tumor biopsy should be performed only after radiological assessment has taken place.

The collected tissue should be fixed and preserved. Approximately 9 formalin fixed paraffin embedded (FFPE) slides (5-µm each for IHC analysis) and 3 FFPE slides (10-µm each for

ribonucleic acid [RNA] analysis, if possible), or the biopsy tissue block (preferred option) will be collected from each biopsy.

Special procedures for biopsy, tissue fixation, handling, storage and shipment will be described in a separate laboratory manual which will be available at the investigational site.

The presence of ER will be determined by central IHC and the ER score prior to the start of IMP treatment and on treatment will be compared to assess ER degradation. Protein expression levels of cancer-related proteins, such as Ki67, Bcl-2, and PgR, will also be evaluated by IHC. In addition, RNA extracted from the tumor may be used for sequencing and/or other analyses (see Section 8.7.3). These data will provide information on the activity of the IMP in the tumor.

8.6.2 Estradiol

Estradiol is the natural ligand to ER and amcenestrant antagonizes the binding of estradiol to ER. Serum samples will be collected to explore the possible influence of circulating levels of estradiol on amcenestrant efficacy. Circulating estradiol will be measured before and after treatment in accordance with the SoA (Section 1.3).

Special procedures for collection, handling, storage and shipment of samples will be described in a separate laboratory manual which will be available at the investigational site.

8.7 GENETICS

See Section 10.5 (Appendix 5) for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the laboratory manual.

8.7.1 Estrogen receptor 1 gene mutation status in cell-free DNA

Estrogen receptor 1 mutations have emerged as a resistance mechanism to endocrine therapies. While rarely present in tumors prior to endocrine therapy, a significant proportion of ER-positive breast cancer tumors will acquire ESR1 mutations, the gene encoding ER, after prolonged/repeated treatment with endocrine therapies (in particular AIs). The presence of an ESR1 mutation is linked to a poor prognosis in these participants.

Estrogen receptor 1 activating mutations render the ERs no longer dependent on estradiol for activity, thereby making the tumor less sensitive to certain endocrine therapies.

Samples to potentially assess 12 mutations of the ESR1 gene, including hotspot mutations described in the ligand domain, will be obtained from all participants at baseline (predose Cycle 1 Day 1) and at Cycle 3 Day 1, and cfDNA may be extracted from the plasma in order to assess the effects of the IMP on the tumor.

Special procedures for collection, handling, storage and shipment will be described in a separate laboratory manual which will be available at the investigational site.

8.7.2 Mutation profiling in cell-free DNA

Cancer gene mutations present in the tumor at baseline might influence the response to the IMP. It is also possible that mutations arising during the IMP treatment might constitute the root cause of the escape mechanism to the IMP treatment. To evaluate potential intrinsic and emerging resistance mutations, plasma will be collected at baseline and at the EOT visit, and cfDNA will be extracted.

In addition, saliva will be collected at baseline to extract DNA which will be used as a normal reference tissue for the mutation analysis. The mutation status of cancer-related genes will be determined by sequencing, and these data will be used to explore the potential link between specific mutations and intrinsic or acquired resistance to the IMP treatment.

Special procedures for collection, handling, storage and shipment will be described in a separate laboratory manual which will be available at the investigational site.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.16 (Appendix 10.16).

8.7.3 RNA transcriptome analysis

Transcriptome studies of the optional tumor biopsy may be conducted using microarray, sequencing, and/or alternative similar techniques, which facilitates the simultaneous measurement of the relative abundances and sequences of thousands of RNAs, resulting in a transcriptome profile for each biopsy sample. This will enable the evaluation of changes in transcriptome profiles that may correlate with biological response relating to breast cancer or the action of the IMP.

The same samples may also be used to confirm findings by application of alternative technologies.

The optional tumor biopsy taken for the assessments referred in Section 8.6.1 can be used for these analyses.

8.7.4 Drug metabolizing enzymes and transporters DNA sample

In accordance with the SoA (Section 1.3), a blood sample will be collected to investigate allelic variants of drug metabolizing enzymes (eg, variants of UGT1A1 and UGT1A4), drug transporters and/or other absorption, distribution, metabolism, and excretion-related genes as potential intrinsic factors associated with PK or PD variability of amcenestrant. This sample will be used for this specific analysis and not for other future research.

8.8 BIOMARKERS

Please see Section 8.6 and Section 8.7 for further details on the collection of samples for biomarker research.

Samples may be stored for a maximum of 15 years, if future use of samples is consented to, or according to local regulations, following the last participant last visit at a facility selected by the Sponsor to enable further analysis of biomarker responses to the IMP.

8.8.1 Future use of samples

Not all of the samples collected during this study may be required for the tests planned in this clinical trial. For participants who have consented to it, the samples that are unused or left over after testing may be used for other research purposes (including genetic analysis that may provide information on the likelihood of developing cancer and related diseases) related to oncology than those defined in the present protocol.

These other research analyses will help to understand either the disease or IMP response, or to develop and/or validate a bioassay method, or to identify new drug targets or biomarkers. These samples will remain labeled with the same identifiers used during the study. They will be transferred to a sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting participant confidentiality and personal data.

8.9 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

This study is designed to test:

- The null hypothesis that the survival distribution functions (SDF) for the PFS of the amcenestrant arm is lower than or equal to the SDF of the control arm.
  - H_0: SDF (amcenestrant) ≤ SDF (Control)

  versus
- The alternative hypothesis that the SDF for the PFS of the amcenestrant arm is superior to the SDF of the control arm.
  - H_1: SDF (amcenestrant) > SDF (Control)

Similar statistical hypotheses will be tested for the key secondary hypothesis for OS.

9.2 SAMPLE SIZE DETERMINATION

The sample size for the global part of this study is determined based on following assumptions: the median PFS for the control arm is assumed to be 4.5 months (2, 3, 4, 5, 6, 7) and an improvement of 53% to a median PFS of 6.9 months (corresponding to a HR = 0.65) would be considered clinically meaningful.

A total of 201 ICR-assessed PFS events in the 2 treatment arms for the global part of the study to have will provide approximately 86% power to detect an increase in PFS, assuming a true HR of 0.65 (representing a 53% increase in median PFS from 4.5 to 6.9 months under exponential model), tested at a one-sided significance level of alpha = 0.025.

For the global part of the study, assuming a uniform accrual rate of 23.5 participants per month accomplished over a period of about 12 months, an annual dropout rate of 10% and a COD for final PFS is approximately 18 months after first participant randomized, a total sample size of approximately 282 participants (randomized in a 1:1 ratio) is required. The sample size calculation considers 1 futility interim analysis at 50% of the planned number of events.

Sample size calculation was performed using East 6.5.

Power calculations for overall survival

Comparison between treatment arms on the OS will be performed only if the primary analysis of the PFS is statistically significant. Therefore, a maximum of 2 analyses are planned for OS. The interim analysis of OS is planned at the time of PFS analysis, ie, approximately 18 months from the start of study randomization. The final OS analysis is planned to be performed at approximately 196 death events (approximately 70% OS data maturity, ie, when approximately 70% of randomized participants have died).

Marginal power calculations for OS with 196 events is provided in Table 4 under several hypothetical alternative assumptions.

Table 4 - Marginal power for overall survival

OS Hazard Ratio	Marginal power for OS[a]
0.60	0.95
0.65	0.85
0.70	0.70
0.75	0.52
0.80	0.35

a Marginal power conditional to statistically significance of PFS.
Note: number have been rounded. Calculations were made using East 6.5 software.
OS = overall survival; PFS = progression-free survival.

Assuming the median OS for the control arm is 28 months and an improvement of 33% to a median OS of 37 months (corresponding to HR = 0.75) in the amcenestrant arm, the COD for OS is approximately 64 months after the first randomized participant (ie, 46 months after PFS analysis) assuming a 5% dropout rate.

Chinese population

Sample size determination for the Chinese population is described in Section 10.8.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined (Table 5):

Table 5 - Populations for analyses

Population	Description
Enrolled	All participants who sign the ICF.
Intent-to-treat (ITT)	All participants from the enrolled population and for whom there is a confirmation of successful allocation of a randomization number by IRT. Participants will be analyzed according to the treatment arm assigned at randomization.
Safety	All participants randomly assigned to study intervention and who took at least 1 dose of study intervention. Participants will be analyzed according to the treatment arm they actually received.
Pharmacokinetic-evaluable	All participants from the safety population who receive at least 1 dose of amcenestrant and with at least 1 evaluable plasma concentration post-treatment.

ICF = informed consent form; IRT = Interactive Response Technology; ITT = intention to treat.
Note: For the Chinese populations on the extension part, refer to Section 10.8.

9.4 STATISTICAL ANALYSES

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.16 (Appendix 10.16).

Planned date for analysis cut-off for the global part:

Estimated COD for the final PFS analysis will be approximately 18 months after first randomized participant. The COD for final analysis of OS will be approximately 64 months after the first randomized participant.

For the estimated COD for China extension participants please refer to Appendix 8 (Section 10.8).

Actual COD for final PFS analysis will be the date when approximately 201 PFS events assessed by ICR have been observed or when all participants from the global cohort have been followed-up for at least 10 months (or discontinued treatment), whichever is earlier.

Actual COD for final OS analysis will be the date when approximately 196 death events have been observed (approximately 70% of the participants have died).

9.4.1 Efficacy analyses

All efficacy analyses for the global part will be performed on the intent-to-treat (ITT) population unless stated otherwise. All primary and secondary efficacy endpoints based on radiological assessments of tumor burden (ie, PFS, BOR, ORR, disease control rate [DCR], clinical benefit rate [CBR], and duration of response [DOR]) will be derived using the ICR tumor assessment. Analysis based on local radiologist's/Investigator's assessment will be considered as supportive analyses.

A summary of efficacy analyses is provided in Table 6.

Table 6 - Efficacy analyses

Endpoint	Statistical Analysis Methods
Primary	
PFS	Stratified logrank for statistical testing. Stratified Cox proportional hazard model for HR. Kaplan-Meier method for probabilities of being event free at different time points.
Key secondary	
OS	Stratified logrank for statistical testing. Stratified Cox proportional hazard model for HR. Kaplan-Meier method for probabilities of being event free at different time points.

Secondary	
ORR, DCR, CBR	No statistical testing will be performed. Descriptive statistics by treatment arm and Clopper-Pearson method for CI calculation.
DOR	Kaplan-Meier method for probabilities of being event free at different time points.
PFS by ESR1 mutation status	Stratified Cox proportional hazard model for HR. Kaplan-Meier method for probabilities of being event free at different time points.
Exploratory	Will be described in the SAP finalized before database lock.

CBR = clinical benefit rate; CI = confidence interval; DCR = disease control rate; DOR = duration of response; ESR1 = estrogen receptor 1 gene; HR = hazard ratio; OS = overall survival; ORR = objective response rate; PFS = progression-free survival; SAP = statistical analysis plan.

9.4.1.1 Analysis of primary efficacy endpoint

Progression-free survival is defined as the time from the date of randomization to the date of the first documentation of objective PD according to RECIST 1.1 definitions or death due to any cause in the absence of documented PD, whichever occurs first. Primary efficacy analysis will consist of PFS comparison between the amcenestrant arm and the control arm through a logrank test procedure stratified by the stratification factors as entered in the IRT (Section 6.3). A one-sided Type I error rate of 2.5% will be used for statistical testing.

The primary analysis of PFS will be based on the following censoring rules:

- If progression and death are not observed before the COD for final PFS, PFS will be censored at the date of the last valid disease assessment with no evidence of a disease progression prior to the initiation of a further anticancer therapy (if any).
- A participant without an event (death or disease progression) and without any valid postbaseline disease assessments will be censored at the day of randomization (Day 1).
- A participant with an event documented after two or more non-evaluable tumor assessments will be censored at the date of the last evaluable tumor assessment documenting no progression prior to the initiation of a further anticancer therapy.

The HR estimates and corresponding 95% two-sided CIs will be provided using the Cox proportional hazard model stratified by the same stratification factors as those used for the logrank test described above. Progression-free survival for the 2 treatment arms will be summarized using Kaplan-Meier methods and displayed graphically. The median event time and associated 95% CI will be provided, along with probabilities of being progression-free at different time points.

Sensitivity analyses (eg, different censoring rules and PFS assessed by the Investigator) and subgroup analyses of PFS will be performed as specified in the SAP finalized before database lock.

9.4.1.2 Analysis of secondary efficacy endpoints

Analysis of response-based endpoints (ie, ORR, DCR, CBR, and DOR) will be performed for the global part primarily on the ITT population and supported by the analyses based on the ITT population with measurable disease at study entry. Except for OS, secondary endpoints will be analyzed at the time of the PFS analysis only. Of note, the BOR for each participant will also be summarized by treatment arm.

Key secondary endpoint:

Overall survival

Overall survival is defined as the time from date of randomization to date of documented death due to any cause. In the absence of observation of death, survival time will be censored to the last date the participant is known to be alive. In case of statistically significant PFS, OS comparison between the amcenestrant arm and the control arm will be performed through a logrank test procedure stratified by the stratification factors as entered in the IRT (Section 6.3). Otherwise, descriptive statistics of OS will be provided at the time of final PFS analysis.

The HR estimates and corresponding 95% two-sided CI will be provided using the Cox proportional hazard model stratified by the same stratification factors as those used for the PFS analysis described above. Overall survival for the 2 treatment arms will be summarized using Kaplan-Meier methods and displayed graphically. The median event time and associated 95% CI will be provided.

The 1-year survival probability and its 95% CI will be estimated using the Kaplan-Meier method and a log-log approach based on a normal approximation following the Greenwood's formula. Similar approaches will be used for 2-year and 3-year survival probabilities, if appropriate.

In order to ensure a strong control of the overall Type I error rate at a one-sided 2.5%, a hierarchical testing strategy will be used. In other words, comparison between arms on the OS will be performed only if the primary analysis of the PFS is statistically significant.

Other secondary endpoints:

Objective response rate

The ORR on each randomized treatment arm will be estimated by dividing the number of participants with objective response (confirmed CR or PR as BOR, according to RECIST 1.1) by the number of participants from the analysis population of the respective treatment arm. In addition, 95% two-sided CIs will be computed using the Clopper-Pearson method.

Disease control rate

The DCR on each randomized treatment arm will be estimated by dividing the number of participants with disease control (confirmed CR or PR, SD, or Non-CR/Non-PD as BOR, according to RECIST 1.1) by the number of participants from the analysis population of the respective treatment arm. In addition, 95% two-sided CIs will be computed using the Clopper-Pearson method.

Clinical benefit rate

The CBR on each randomized treatment arm will be estimated by dividing the number of participants with clinical benefit (confirmed CR or PR as BOR, SD or Non-CR/Non-PD lasting at least 24 weeks, according to RECIST 1.1) by the number of participants from the analysis

population of the respective treatment arm. In addition, 95% two-sided CIs will be computed using the Clopper-Pearson method.

Duration of response

The DOR will only be summarized on the subgroup of participants who have achieved objective response in the respective analysis population. For participants with ongoing response at the time of the analysis, DOR will be censored at the date of the last valid disease assessment not showing disease progression performed before the initiation of a new anticancer treatment (if any). Duration of response for the 2 treatment arms will be summarized using Kaplan-Meier methods and displayed graphically, if appropriate. The median event time and associated 95% CI will be provided.

Progression-free survival according to ESR1 mutation status at baseline

Progression-free survival according to ESR1 mutation status at baseline will be assessed following the procedures in Section 9.4.1.1, with the exception that no statistical test will be made.

9.4.2 Safety analyses

All safety analyses for the global part will be performed on the safety population. A summary of safety analyses is provided in Table 7.

Table 7 - Safety analyses

Endpoint	Statistical Analysis Methods
Primary	No primary endpoint is defined for safety analyses.
Secondary	
AEs/SAEs and laboratory abnormalities	Descriptive statistics
Exploratory	Will be described in the SAP finalized before database lock

AE = adverse event; SAE = serious adverse event; SAP = statistical analysis plan.

9.4.2.1 Analyses of adverse events

The observation period will be divided into 3 segments:

- The pre-treatment period is defined as the time from when the participants give informed consent to the first administration of the IMP.
- The on-treatment period is defined as the time from the first dose of IMP up to 30 days after the last dose of IMP.
- The post-treatment period is defined as the time starting 31 days after the last dose of IMP to study closure.

Pre-treatment AEs are defined as any AE occurring during the pre-treatment period. Treatment-emergent AEs are defined as AEs that develop, worsen (according to the Investigator's

opinion), or become serious during the on-treatment period. Post-treatment AEs are defined as AEs that are reported during the post-treatment period. The primary focus of AE reporting will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

Treatment-emergent AEs will be coded according to MedDRA. Adverse events will be graded according to the NCI-CTCAE v5.0. The grade will be taken into account in the summary. For participants with multiple occurrences of the same PT, the maximum grade will be used.

An overall summary of TEAEs will be provided. The number and percentage of participants who experience any of the following will be provided:

- Treatment-emergent AEs
- Grade ≥3 TEAEs
- Grade 5 TEAEs (any TEAE with a fatal outcome during the on-treatment period)
- Serious TEAEs
- Treatment-emergent AEs leading to definitive treatment discontinuation
- Treatment-related TEAEs
- Treatment-related TEAEs Grade ≥3
- Serious treatment-related TEAEs.
- AESIs

Number and percentage of participants experiencing TEAEs by primary system organ class and PT will be summarized by NCI-CTCAE v5.0 grade (all grades and Grade ≥3) for the safety population. Similar summaries will be prepared for treatment-related TEAEs, TEAEs leading to definitive discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, AESIs, and AEs/SAEs occurring during the post-treatment period.

9.4.2.2 Analyses of clinical laboratory evaluations

Hematology and clinical chemistry results will be graded according to the NCI-CTCAE v5.0, when applicable. Number and percentage of participants with laboratory abnormalities (ie, all grades and by grade) using the worst grade during the on-treatment period will be provided for the safety population.

When the NCI-CTCAE v5.0 grading scale is not applicable, the number of participants with laboratory abnormality out-of-normal laboratory range value will be displayed.

9.4.3 Other analyses

9.4.3.1 Analyses of patient reported outcome endpoints

Patient reported outcomes endpoints for each of the 3 selected PRO/HRQL and health utility instruments (EORTC QLQ-C30, QLQ-BR23, and EQ-5D-5L) will be analyzed in participants from the safety population who have completed the baseline and at least 1 postbaseline assessment.

For each questionnaire the compliance profile over time will be summarized on the safety population (number and percentage of forms received versus expected, and number and percentage of forms evaluable versus expected). Reasons for non-completion will be summarized on the safety population. For the QLQ-C30 (15 total scales), QLQ-BR23 (8 scales), and EQ-5D-5L (health index and VAS) instruments, descriptive statistics on the absolute value and changes from baseline will be done for each treatment arm at each time point, at EOT and 60 to 90 days after the last study administration (follow-up). Between treatment comparisons of the change from baseline for each cycle to EOT and to follow-up will be provided for the QLQ-C30 (15 total scales), QLQ-BR23 (8 scales), and EQ-5D-5L (health index and VAS).

A more detailed SAP for the 3 PROs will be detailed in the study SAP finalized before database lock.

9.4.3.2 Analyses of other endpoints

Further therapy, PK, PDy, and biomarker exploratory analyses will be described in the SAP finalized before database lock. A population PK analysis will be planned and reported separately from the global clinical study report. In case a PK/PDy analysis is planned, a dedicated SAP will be prepared.

9.5 INTERIM ANALYSES

9.5.1 Interim analysis for progression-free survival

An interim analysis on PFS is planned for futility at 50% of the planned total number of PFS events (ie, approximately 101 PFS events). Without possible claim for overwhelming evidence of efficacy, no Type I error rate adjustment will be performed. The stopping boundary for futility is based on the observed HR based on Cox proportional hazard model, ie, an HR>1.1

A summary of the PFS analyses is provided in Table 8.

Table 8 - Progression-free survival analyses

Analysis	Months after FPI (approx. under PFS HR=0.65)	Planned accrual	Number of events (under PFS HR=0.65)	Information fraction	Cumulative Power (under PFS HR=0.65)	Futility boundary	Efficacy boundary
PFS IA (futility only)	10	239	101	50%		HR > 1.1	NA
PFS Final analysis	18	282	201	100%	86%	p >0.025 (HR[a] >0.758)	p ≤0.025 (HR[a] ≤0.758)

a HR is provided only for information purposes. The interim and final decisions will be based on p-values.
Note: numbers have been rounded. Calculations were made using East 6.5 software.
FPI = first participant in; HR = hazard ratio; IA = interim analysis; NA = not applicable; PFS = progression-free survival.

The SAP will describe the planned interim analyses in greater detail.

9.5.2 Interim analysis for overall survival

Comparison between arms on the OS will be performed only if the primary analysis of the PFS is statistically significant. Therefore, a maximum of 2 analyses are planned for OS: at the time of the primary analysis of PFS and at the final OS analysis.

A gamma error spending function ($\gamma = -8$) will be used, along with the hierarchical testing strategy to strongly control the family-wise error rate (FWER; overall Type I error rate). This guarantees the protection of the 2.5% FWER across hypotheses associated with PFS and OS and the repeated testing of the OS hypotheses at interim and the final analysis (34). If the value of the test statistic exceeds the efficacy boundary ($z \leq -3.716$, $p \leq 0.0001$), superiority of OS will be claimed but survival data will continue to be collected until the end of study when approximately 196 death events have been observed.

A summary of the OS analyses is provided in Table 9.

Table 9 - Overall survival analyses

Analysis	Months after FPI (approx.)	Planned accrual	Number of deaths (approx.)	Information fraction	Cumulative Power[a] (under HR=0.75)	Futility boundary	Efficacy boundary
OS IA (at PFS final analysis)	18	282	63	32%	0.5%	NA	p ≤0.0001 (HR[b] ≤0.392)
Final analysis	64	282	196	100%	52%	p >0.0249 (HR[b] >0.756)	p ≤0.0249 (HR[b] ≤0.756)

a Marginal power conditional to statistically significance of PFS.
b HR is provided only for information purposes. The interim and final decisions will be based on p-values.
Note: number have been rounded. Calculations were made using East 6.5 software. Assume a 5% dropout rate at 64 months after first participant randomized.
FPI = first participant in; HR = hazard ratio; IA = interim analysis; NA = not applicable; OS = overall survival.

Selected independent statisticians/programmers will perform the interim analysis; individual participant identification will not be released to anyone who is involved in the conduct of the study.

9.5.3 Data Monitoring Committee

This study will use an independent Data Monitoring Committee (DMC). Details on DMC structure and role are presented in Section 10.1.4.

The first DMC meeting will be set up to review early safety results (eg, after approximately 25 participants have completed at least 2 cycles in the amcenestrant arm, or after 6 months after first participant randomized), and then periodically. Ad hoc DMC meetings may also be held if a significant safety issue or an issue deemed important for discussion arises on this or other amcenestrant studies. After each meeting, the DMC will make recommendations to the Sponsor's representatives regarding the continued safety of treating ongoing and future study participants, as well as the course of action regarding the conduct of the study.

The DMC will also oversee the interim analyses on PFS detailed in Section 9.5.1.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations.
- The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require national Health Authority and IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of serious adverse events (SAEs) or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.2 Informed consent process

- The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and

Data Protection requirements including those of the Global Data Protection Regulation (GDPR) and of the French law, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. Participant agreement will be required to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.16 (Appendix 16).

10.1.3 Data protection

All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR (Global Data Protection Regulation).

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study because these data are required by several regulatory agencies (eg, on African American population for the Food and Drug Administration or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan).

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

10.1.4 Committees structure

Data Monitoring Committee

This study will use an independent Data Monitoring Committee (DMC). The DMC membership and governance are outlined in a separate charter. The DMC will be in charge of reviewing the safety data and the progress of the study (including overseeing interim analyses) and advising the Sponsor on potential modifications or communications that may be necessary to ensure the participant safety or protect the scientific integrity of the study. The Sponsor will make the final decision(s) regarding study participants according to the charter. The DMC will make a recommendation as to whether or not the study should continue based on ongoing reviews of safety data.

Independent Central Review

An independent central review will be assigned to centrally perform tumor assessments within the scope of the primary and secondary efficacy endpoints. A third-party entity will provide this service.

10.1.5 Dissemination of clinical study data

Sanofi shares information about clinical trials and results on accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinical trial register (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

10.1.6 Data quality assurance

- All participant data relating to the study will be recorded on electronic case report form (eCRF) unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. The planned frequency and nature of data monitoring during the study will be tailored to the specific data priorities and risks identified.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the end of the clinical study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator’s site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Monitoring plan.

10.1.8 Study and site closure

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development
- Information on the product leads to doubt as to the benefit/risk ratio

10.1.9 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 10 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 10 - Protocol-required safety laboratory assessments

Laboratory assessments	Parameters			
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit		White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical chemistry[a,b]	Blood urea nitrogen or urea	Potassium	Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT)	Total and conjugated bilirubin
	Creatinine	Sodium	Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT)	Chloride
	Magnesium	Calcium	Alkaline phosphatase	Serum albumin
	Phosphate	Glucose	Lactate dehydrogenase	Gamma-glutamyl transferase
	GFR			
Coagulation[c]	Prothrombin time	International normalized ratio (INR)		
Routine urinalysis[d]	• pH, glucose, protein, blood, ketones, and leukocytes by dipstick • Microscopic examination (if blood or protein is abnormal), if clinically indicated.			
Other tests[e]	• Follicle-stimulating hormone and estradiol (as needed in women <60 years of age and premenopausal women on a gonadotropin-releasing hormone analog). • Pregnancy tests (serum and then urine) for WOCBP. The results of each test must be entered into the electronic case report form.			

a Hematology to be performed at screening, repeated within 2 or 3 days before randomization, in case of abnormal evaluations on parameters such as body weight, signs and symptoms, physical examination, electrocardiogram, hematology, coagulation tests, blood chemistry, and urinalysis, and repeated at Cycle 1 Day 1 if screening test >7 days of Day 1 Cycle 1, then performed on Day 1 of every subsequent cycle, at the end of treatment visit, and as clinically indicated. In the event of Grade 3 or 4 neutropenia, absolute neutrophil count (ANC) is assessed every 2 to 3 days until ANC ≥0.5 x 10^9/L and at least weekly thereafter until ANC ≥1.0 x 10^9/L (test to be done prior to study treatment administration). Hematological abnormalities will be recorded as adverse events only if they are serious or lead to study treatment modification or discontinuation.

b Clinical chemistry analyses will be performed in accordance with Section 1.3 and when clinically relevant. In case of Grade 3 or higher liver function abnormal tests, additional tests will be done every 2 to 3 days until recovery to normal or baseline value. Blood biochemistry to be performed at screening and repeated within 1 day prior to Cycle 1 Day 1 if screening test >7 days of Day 1 Cycle 1. Biochemistry will be performed prior to study treatment administration on Day 1 for subsequent cycles.

c Coagulation tests can be performed after Cycle 1 Day 1, if clinically indicated.

d Urinalysis will be performed in accordance with Section 1.3 and when clinically relevant. Participants with 3+ or greater urine protein dipstick reading should undergo further assessment with a 24-hour urine collection for determination of proteinuria.

e For patients receiving Fulvestrant as IMP, Estradiol will not be needed after screening test. Pregnancy test to be performed at screening, repeated (by dipstick) at Cycle 1 Day 1 if screening test >7 days prior to Cycle 1 Day 1.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

DEFINITION OF ADVERSE EVENT (AE)

Adverse event definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition

- Vital signs and electrocardiogram (ECG) are to be recorded as AEs only if they are symptomatic and/or requiring corrective treatment and/or leading to treatment discontinuation and/or modification of dosing and/or fulfilling a seriousness criterion.
- Clinically significant laboratory abnormalities are to be recorded as AEs only if they are serious or impact study treatment (ie, lead to dose omission, reduction, delay, or discontinuation).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

Events NOT meeting the AE definition

- Any abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be a serious AE (SAE) even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a) Results in death

b) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

DEFINITION OF UNEXPECTED ADVERSE DRUG REACTION

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved investigational medicinal product).

RECORDING AND FOLLOW-UP OF AE AND/OR SAE

Adverse event and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the electronic case report form (eCRF).
- It is not acceptable for the Investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it using National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] v5.0.

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.

- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

REPORTING OF SAES

Serious AE reporting to Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the monitoring team by fax or email.
- Contacts for SAE reporting can be found in the reference manual.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Male participants

Not applicable for men with prior bilateral orchiectomy.

- Male participants with heterosexual partners of reproductive potential are eligible to participate if they agree to use the following during the protocol-defined timeline:
  - Refrain from donating sperm

    and

  - Agree to be on a gonadotropin-releasing hormone analog for at least 4 weeks (to be continued during study treatment) as per label and use a male condom during intercourse during study treatment until 1 week after stopping the study treatment or after the time indicated by the GnRH analog label (eg 12 weeks after last injection of Goserelin) whichever is the longest, and should not father a child in this period. A condom is required to be used also by vasectomized men, as well as during intercourse with a male partner, in order to prevent delivery of the drug via seminal fluid.
- Men with a pregnant or breast-feeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom for the time defined in the protocol.
- Male participants should consider sperm preservation prior to beginning therapy with study IMPs because exposure to amcenestrant has the potential risk of testicular injury with partial or permanent infertility. Because exposure to amcenestrant, has the potential risk of testicular injury with partial or permanent infertility.

Woman of childbearing potential (WOCBP)

Not applicable for postmenopausal women.

Non-hormonal methods of contraception should be employed during the study in premenopausal women on a gonadotropin-releasing hormone analog as per label. These include: intrauterine device, bilateral tubal occlusion, vasectomy partner, sexual abstinence.

The duration of the contraception will be determined from drug-labels, taking into account that the duration selected will be the one of the GnRH analog or the IMP, whichever is longer.

- For participants with amcenestrant: 7 days
- For participants with tamoxifen: 9 months
- For participants with fulvestrant: 2 years
- Duration varies among aromatase-inhibitors (eg, letrozole: 3 weeks, exemestane: 4 weeks)
- Duration varies among GnRH analogs (eg, goserelin: 12 weeks)

COLLECTION OF PREGNANCY INFORMATION:

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date but may last up to one year. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue the investigational medicinal product.

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant’s female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner’s pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date but may last up to one year. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.5 APPENDIX 5: GENETICS

Use/Analysis of deoxyribonucleic acid (DNA)/ ribonucleic acid (RNA)

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and Institutional Review Boards/Independent Ethics Committees allow, a blood and a saliva sample will be collected for DNA analysis from consenting participants. In addition, plasma will be collected to isolate cell-free DNA (cfDNA) that will be used to assess for tumor mutations, including estrogen receptor 1 gene. The saliva sample will be used as a reference comparison for the tumor mutation analysis.
- DNA samples will be used for research related to the IMPs or breast cancer and related diseases. They may also be used to develop tests/assays including diagnostic tests related to IMPs and breast cancer. Genetic research may consist of the analysis of 1 or more candidate genes, or the analysis of genetic markers throughout the genome, or analysis of the entire genome (as appropriate) and may include sequencing.
- RNA may be isolated from the optional tumor biopsy in order to assess effects of IMP on the tumor. Analyses may include microarray, sequencing, and/or alternative similar techniques, resulting in a transcriptome profile. The analyses may include RNA of selected genes or all of the genome.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to amcenestrant or interventions of this class to understand breast cancer or related conditions.
- The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The Sponsor will store the DNA/RNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained for up to 5 years, or 15 years if future use of samples is consented to, or other period as per local requirements, following the last participant last visit.

10.6 APPENDIX 6: LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Not applicable.

10.7 APPENDIX 7: MEDICAL DEVICE INCIDENTS: DEFINITION AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

CHINA EXTENSION STUDY

1 INTRODUCTION

The decision for China to participate in the global study was taken later than for other countries, and consequently enrollment of the first Chinese participant may be 11 months after the first participant is randomized in the global study. The aims of the China extension study include an evaluation of the efficacy, safety, and pharmacokinetics (PK) of amcenestrant in Chinese participants. Enrollment of participants in China will continue as an extension study after enrollment into the global study is completed, until the required number of Chinese participants has been achieved.

2 STUDY DESIGN

The design of the China extension study is the same as that of the global study (Figure 1).

At the time of Amended Clinical Protocol 02 submission, there was no experience of amcenestrant in Chinese patients. However, based on available data, no ethnic difference in amcenestrant safety profile is expected between Chinese and non-Chinese patients. For the ACT16105 study, a safety observation period will be set for Chinese participants to secure safety. A safety run in step will consist in the sequential treatment of 6 participants with amcenestrant (ie, approximately 12 randomized participants). None of the first 3 participants of amcenestrant arm will be treated for first dose on the same day. The safety review will occur when 6 Chinese participants have been exposed to amcenestrant and completed a minimum of 1 cycle duration (approximately 4 weeks) of treatment. If 0 to 1 out of 6 evaluated participants had a treatment related adverse event of special interest (AESI) or treatment related AE leading to the treatment discontinuation, enrollment will continue in China. If at least 2 out of 6 evaluated amcenestrant treated participants have a treatment related AESI, or a treatment related AE leading to treatment discontinuation, enrollment will be on hold in China and further safety and PK assessment will be performed.

3 OBJECTIVES

Overall, the main objectives and endpoints of the China extension are the same as those for the global study. A secondary objective has been added, to evaluate the full PK profile of amcenestrant in 12 Chinese participants in the amcenestrant treatment arm in the extension study. Chinese participants in the amcenestrant treatment arm in the global study and all other participants in the amcenestrant treatment arm in the extension study will have samples taken for sparse PK analysis, consistent with sampling in the global study.

Table 11 - China extension additional objectives and endpoints

Objectives	Endpoints
Secondary	
To evaluate the pharmacokinetics (PK) of amcenestrant as single agent.	amcenestrant plasma concentrations during the treatment period. amcenestrant PK parameters will be evaluated in 12 participants from the amcenestrant treatment arm

4 STUDY POPULATION

Participants will be selected based on the study inclusion and exclusion criteria as defined in Section 5 of the global study protocol and will have agreed to participate in this extension study. A dedicated cohort of up to approximately 90 participants will be included.

Note: In this extension cohort, previous treatment with a CDK 4/6 inhibitor will not be mandatory, and there will be no limitation to the number of participants naïve to CDK4/6 inhibitors.

4.1.1 Additional inclusion criteria

Not applicable.

4.1.2 Addition exclusion criteria

Not applicable.

5 STUDY INTERVENTION ADMINISTERED

The study treatment to be administered is the same as that used in the global study and is administered in the same way. However, for those participants who will take part in the full PK profile assessment, amcenestrant administration at Cycle 1 Day 1 will be done after an overnight fast of at least 10 hours. A meal will be authorized from 2 hours after drug administration.

Then, from Day 2 onwards, the drug will be administered with or without food, as described for the global study. From Day 2, the fasting condition (without food) is when no meal is taken within 2 hours of amcenestrant administration and the fed condition (with food) is when a meal is taken within 2 hours of amcenestrant administration.

Full PK sampling will be collected in accordance with Table 12.

6 STUDY PROCEDURES

Participants enrolled in the extension study will have the main safety and efficacy assessments scheduled for the global part (see Section 1.3 of the global study protocol). Specific PK and pharmacodynamic evaluations will be performed. Biopsy samples and blood samples will be taken in accordance with local regulations for all participants from China (global and extension part).

Pharmacokinetic evaluation

In the extension study, 12 participants in the amcenestrant arm will have blood samples taken for PK analysis according to the following PK flowchart (full PK sampling; Table 12). When sampling is difficult for patients, full PK sampling could only be limited to Cycle 1 Day 1/2 and Cycle 2 Day 1 samples, other planned samples may be omitted based on investigator decision. For the remaining participants of the extension cohort, a sparse sampling approach for PK will be taken as presented in the Schedule of Activities (Section 1.3) of the global study protocol. Pharmacokinetic procedures (handling procedure and bioanalytical method) will be as described for the global study (Section 8.5 of the global study protocol).

Table 12 - Pharmacokinetic flowchart for full pharmacokinetic sampling

Cycle	**Cycle 1**										
Day within cycle	**Day 1/2**										**Day 15**
Relative nominal time	**0h**	**0.5h**	**1h**	**2h**	**3h**	**4h**	**6h**	**8h**	**10h**	**24h**	**0h**
Time window	**[-24h, 0h]**	**±5m**	**±10m**	**±15m**	**±15m**	**±30m**	**±30m**	**±30m**	**±1h**	**±1h**	**[-1h, 0h]**
Indicative clock time	**8:00 AM**	**8:30 AM**	**9:00 AM**	**10:00 AM**	**11:00 AM**	**12:00 noon**	**2:00 PM**	**4:00 PM**	**6:00 PM**	**8:00 AM**	**8:00 AM**
Amcenestrant administration[b]											
Once daily	X									X	X
Amcenestrant pharmacokinetics											
Plasma	P00[a]	P01	P02	P03	P04	P05	P06	P07	P08	P09[a]	P10[a]

Cycle	**Cycle 1**										**Cycle 2**
Day within cycle	**Day 22/23**										**Day 1**
Relative nominal time	**0h**	**0.5h**	**1h**	**2h**	**3h**	**4h**	**6h**	**8h**	**10h**	**24h**	**0h**
Time window	**[-1h, 0h]**	**±5m**	**±10m**	**±15m**	**±15m**	**±30m**	**±30m**	**±30m**	**±1h**	**±1h**	**[-1h, 0h]**
Indicative clock time	**8:00 AM**	**8:30 AM**	**9:00 AM**	**10:00 AM**	**11:00 AM**	**12:00 noon**	**2:00 PM**	**4:00 PM**	**6:00 PM**	**8:00 AM**	**8:00 AM**
Amcenestrant administration[b]											
Once	X										X
Amcenestrant pharmacokinetics											
Plasma	P11[a]	P12	P13	P14	P15	P16	P17	P18	P19	P20[a]	P21[a]

a Sample collected just before amcenestrant administration.

b Capsules should be taken approximately at the same time every day.

After Cycle 2, pharmacokinetic sample collection is as described in the study Schedule of Activities (see Section 1.3).

All blood samples for PK analysis must be collected at the specified times and according to the specifications. Samples missed or lost, for any reason should be recorded. Actual times of blood collection should be recorded in the electronic case report form. The days of sampling and times of drug administration should also be precisely recorded for the day of PK. The total blood volumes to be collected from each participant for PK analysis is outlined in Table 13.

Table 13 - Blood sample volume collected per participant during extension part

		Volume (mL)/ sample	Number of samples	Volume (mL)/ participants
PK amcenestrant	Full sampling	1 mL	25	25 mL
	Sparse sampling	1 mL	10	10 mL

PK = pharmacokinetics.

Pharmacokinetic parameters

Pharmacokinetic analyses will be carried out by the Pharmacokinetics, Dynamics and Metabolism department at Sanofi. Pharmacokinetic parameters will be determined by non-compartmental analysis using PKDMS (running Phoenix® software). The parameters will include, but may not be limited to, the following (Table 14):

Table 14 - List of pharmacokinetic parameters and definitions

Parameters	Drug	Matrix	Definition/calculation
t_{lag}	amcenestrant	Plasma	Lag time, interval between administration time and the sampling time preceding the first concentration above the lower limit of quantification
t_{max}	amcenestrant	Plasma	First time to reach C_{max}
C_{max}	amcenestrant	Plasma	Maximum concentration observed
AUC_{0-24}	amcenestrant	Plasma	Area under the plasma concentration versus time curve calculated using the trapezoidal method over the dosing interval (24 hours)
C_{trough}	amcenestrant	Plasma	Plasma concentration observed just before treatment administration during repeated dosing
CL_{ss}/F	amcenestrant	Plasma	Apparent total body clearance after repeated extra-vascular (EV) doses of a drug at steady state from the matrix (plasma) calculated using the following equation: $CL_{ss}/F = \frac{Dose_{EV}}{AUC_{0-\tau EV}}$

Pharmacodynamic evaluation

For participants enrolled in China, samples for estrogen receptor 1 gene (ESR1) analysis of cell-free deoxyribonucleic acid (cfDNA) will be collected at Cycle 1 Day 1 (predose). The other samples for ESR1 analysis of cfDNA will not be collected and exploratory pharmacodynamic endpoints will not be assessed in this extension study.

Note: These specificities apply also for participants from China enrolled in the global part of the study.

7 STATISTICAL ANALYSIS

7.1 SAMPLE SIZE DETERMINATION

Chinese participants from the global study and from the China extension part will be pooled for the purpose of the analysis of the Chinese population data.

Assuming the hazard ratio (HR) of progression-free survival (PFS) in the amcenestrant arm relative to the control arm is 0.65, a total of 65 PFS events in the Chinese population would provide an 80% probability of observing a HR inferior to 0.80 in the Chinese population, given that the primary analysis of PFS is statistically significant in the global study.

Approximately 90 Chinese participants would need to be enrolled to reach 65 PFS events. Assuming the first Chinese participant enrolls 11 months after the first randomized participant of the global study and Chinese participants have a 17-month enrollment period, the cut-off date (COD) for PFS analysis is estimated to occur 5 months after the last Chinese participant is enrolled.

The COD of the Chinese cohort is independent of the COD of the global study. The actual COD of the Chinese cohort will be the date with approximately 65 PFS events in Chinese population.

7.2 POPULATION FOR ANALYSES

For purposes of analysis, the following populations are defined (Table 15):

Table 15 - Populations for analyses

Population	Description
Chinese ITT	All Chinese participants from the global part of the study and from the China extension part who have given their informed consent and for whom there is confirmation of successful allocation of a randomization number by the IRT. All analyses using this population will be based on the treatment assigned at randomization.
Chinese Safety	All Chinese ITT participants who took at least 1 dose of study intervention. Participants will be analyzed according to the treatment arm they actually received.

ITT = intent-to-treat; IRT = Interactive Response Technology.

7.3 STATISTICAL ANALYSIS

Definition of the primary endpoint and secondary endpoints and the related analysis methods will be as described for the global study. Further details may be specified in a separate document.

For the 12 participants of the Chinese cohort with full PK sampling:

- Individual plasma concentrations and PK parameters of amcenestrant will be tabulated with standard descriptive statistics. Individual and mean profiles will be presented graphically.
- Accumulation ratio (Day 22/Day 1) for C_{max} and area under the plasma concentration curve within 0 to 24 hours (AUC_{0-24h}) will be estimated with 90% confidence intervals using a linear fixed effects model on log transformed parameters. Individual listing will be provided.
- Within-participant and total standard deviations for log (C_{max}) and log (AUC_{0-24}) will be estimated.

The decision to continue or not with the recruitment of Chinese patients will be based on the results of the statistical analyses performed in the global population.

8 SAFETY REPORTING

Adverse events and serious adverse events will be captured and reported in accordance with the global study (see Section 8.3).

9 ADMINISTRATION

9.1 INFORMED CONSENT

An informed consent (ICF) shall be obtained from participants who voluntarily agree to participate in the extension study. Participants who agree to have samples taken for the full PK profile assessment will sign a separate section in the informed consent for this aspect of the study.

The informed consent form reflecting this study and the full PK profile sampling will be submitted for review and approval to the Institutional Review Board/Independent Ethics Committee (IRB/IEC) charged with this responsibility.

9.2 CONFIDENTIALITY

Data collection and handling by the Sponsor for this study will be in accordance with that described in the global study protocol (see Section 10.1 [Appendix 1]), and every effort will be made to protect participant confidentiality. In case the results are published, they will be done so anonymously.

9.3 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

This study, the ICFs for this study, and any advertisement for participant recruitment will be submitted for review and approval to the IRB/IEC charged with this responsibility.

9.4 RECORDS RETENTION

Investigators must retain records pertaining to this extension as described in the global study protocol (see Section 10.1 [Appendix 1]).

10.9 APPENDIX 9: ABBREVIATIONS

^{18}FES:	^{18}fluoroestradiol
AE:	adverse event
AESI:	adverse event of special interest
AI:	aromatase inhibitor
ALT:	alanine aminotransferase
ANC:	absolute neutrophil count
AST:	aspartate aminotransferase
AUC:	area under the curve
AUC_{0-24h}:	area under the plasma concentration curve within 0 to 24 hours
BOR:	best overall response
CBR:	clinical benefit rate
cfDNA:	cell-free deoxyribonucleic acid
CFR:	Code of Federal Regulations
CI:	confidence interval
COD:	cut-off date
CR:	complete response
CT:	computed tomography
C_{trough}:	plasma concentration observed before treatment administration
CYP:	cytochrome P450
DCR:	disease control rate
DMC:	Data Monitoring Committee
DNA:	deoxyribonucleic acid
DOR:	duration of response
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
eCRF:	electronic case report form
EORTC:	European Organisation for Research and Treatment of Cancer
EOT:	end of treatment
EQ-5D-5L:	EuroQoL questionnaire with 5 dimensions and 5 levels per dimension
ER:	estrogen receptor
ESR1:	estrogen receptor 1 gene
FIH:	first in human
FSH:	follicle-stimulating hormone
FWER:	family-wise error rate
GCP:	Good Clinical Practice
GHS:	Global Health Status
GnRH:	gonadotropin-releasing hormone
HER2:	human epidermal growth factor receptor 2
HR:	hazard ratio
HRQL:	health-related quality of life
IB:	Investigator's Brochure
ICF:	informed consent form
ICH:	International Council for Harmonisation

ICR:	independent central review
IEC:	Independent Ethics Committee
IHC:	immunohistochemistry
IM:	intramuscular
IMP:	investigational medicinal product
INR:	international normalized ratio
IRB:	Institutional Review Board
IRT:	Interactive Response Technology
ITT:	intent-to-treat
LFT:	liver function test
MedDRA:	Medical Dictionary for Regulatory Activities
MRI:	magnetic resonance imaging
NCI-CTCAE:	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR:	objective response rate
OS:	overall survival
PD:	progressive disease
PDy:	pharmacodynamic(s)
PET:	positron emission tomography
PFS:	progression-free survival
P-gp:	P-glycoprotein
PgR:	progesterone receptor
PK:	pharmacokinetic(s)
PO:	per os
PR:	partial response
PRO:	patient reported outcome
PT:	preferred term
QD:	once daily
QLQ-BR23:	EORTC QLQ breast cancer specific module
QLQ-C30:	EORTC core quality of life questionnaire
RECIST:	Response Evaluation Criteria in Solid Tumors
RNA:	ribonucleic acid
SAE:	serious adverse event
SAP:	statistical analysis plan
SD:	stable disease
SDF:	survival distribution functions
SERD:	selective estrogen receptor degrader
SERM:	selective estrogen receptor modulator
SoA:	Schedule of Activities
SUSARs:	Suspected unexpected serious advarse reactions
TEAE:	treatment-emergent adverse event
TTP:	time to progression
UGT:	Uridine 5'-diphospho-glucuronosyltransferase
ULN:	upper limit of normal
VAS:	visual analogue scale

10.10 APPENDIX 10: EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Table 16 - Eastern Cooperative Oncology Group performance status scale

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55. (35)

10.11 APPENDIX 11: LIST OF STRONG CYP3A4 INDUCERS

Concomitant administration of medications that are strong CYP3A inducers are not permitted throughout the active treatment phase.

The following table was extracted in October 2020 from the Drug- Drug Interaction Database from the University of Washington (www.druginteractioninfo.org).

STRONG CYP3A INDUCERS				
Inducers	**Therapeutic Class**	**Victim (oral unless otherwise specified)**	**Max AUCR**	**Precipitant dose (oral)**
Strong Inducers (AUCR ≤ 0.2 or CL Ratio ≥ 5)				
Rifampin	Antibiotics	Budesoinide	0.003	600 mg QD (7 days)
Mitotane	Other Antineoplastics	Midazolam	0.06	Maximum of 3.5g TID (chronic therapy)
Avasimibe	Other Antilipemics	Midazolam	0.07	750 mg/day (7 days)
Rifapentine	Antibiotics	Midazolam	0.07	20 mg/kg QD (14days)
Apalutamide	Antiandrogens	Midazolam	0.08	240 mg QD (29 days)
Ivosidenib	Cancer Treatments	Midazolam	0.10 (PBPK)	1200 mg QD (19 days; PBPK modeling)
Phenytoin	Anticonvulsants	Nisoldipine	0.11	200-450 mg/day (chronic treatment)
Carbamazepine	Anticonvulsants	Quetiapine	0.13	200 mg TID (26 days)
Enzalutamide	Antiandrogens	Midazolam	0.14	160 mg QD (85±3 days)
St John's Wort extract	Herbal Medicines	Midazolam	0.20	300 mg TID (14 days)
Lumacaftor	Cystic Fibrosis Treatments	Ivacaftor	0.20	Not provided
Phenobarbital	Anticonvulsants	Verapamil	0.23	100 mg QD (21 days)

10.12 APPENDIX 12: LIST OF CYP SENSITIVE SUBSTRATES

In vivo, amcenestrant is a weak to moderate CYP3A inducer, and in vitro a potential inducer of CYP2B6 and CYP2Cs family. Therefore, study participants receiving amcenestrant and treated or intended to be treated with the following drugs presented as CYP sensitive substrates should be carefully monitored since it may result in loss of efficacy of these agents.

The tables for CYP sensitive substrates were extracted in October 2020 from the Drug- Drug Interaction Database from the University of Washington (www.druginteractioninfo.org). Some known substrates of the enzymes may not be listed because they do not have changes in exposure reaching sufficient level or may not have DDI studies with AUC/CL changes available.

In vivo CYP3A Sensitive Substrate

Drug (oral)	**Therapeutic Class**
alfentanil	Opioids
alisporivir	Antivirals
almorexant	Hypnotics - Sedatives
alpha-dihydroergocryptine	Dopaminergic Agonists
aplaviroc	CCR5 Receptor Antagonists
aprepitant	Neurokinin-1 Receptor Antagonists
asunaprevir	Antivirals
atazanavir	Protease Inhibitors
atorvastatin	HMG CoA Reductase Inhibitors (Statins)
avanafil	Erectile Dysfunction Treatments
blonanserin	Antipsychotics
brecanavir	Protease Inhibitors
brotizolam	Benzodiazepines
budesonide	Corticosteroids
buspirone	Anxiolytics
capravirine	Antivirals
casopitant	Neurokinin-1 Receptor Antagonists
conivaptan	Vasopressin Antagonists
danoprevir	Antivirals
darifenacin	Muscarinic Antagonists
darunavir	Protease Inhibitors
dronedarone	Antiarrhythmics
ebastine	H1 Receptor Antagonists
eletriptan	Triptans
eliglustat (in subjects CYP2D6 PMs)	Glucosylceramide Synthase Inhibitors
elvitegravir	HIV-Integrase Strand Transfer Inhibitors
eplerenone	Diuretics
everolimus	Immunosuppressants

Drug (oral)	**Therapeutic Class**
felodipine	Calcium Channel Blockers
indinavir	Protease Inhibitors
isavuconazole	Antifungals
itacitinib	Kinase Inhibitors
ivabradine	Cardiovascular Drugs
ivacaftor	Miscellaneous Agents
levomethadyl (LAAM)	Drug Addiction Treatments
lomitapide	Other Antilipemics
lopinavir	Protease Inhibitors
lovastatin	HMG CoA Reductase Inhibitors (Statins)
lumefantrine	Antimalarials
lurasidone	Antipsychotics
maraviroc	CCR5 Receptor Antagonists
midazolam	Benzodiazepines
morphothiadin	Antivirals
naloxegol	Gastrointestinal Agents
nisoldipine	Calcium Channel Blockers
paritaprevir	Antivirals
perospirone	Antipsychotics
quetiapine	Antipsychotics
saquinavir	Protease Inhibitors
sildenafil	Erectile Dysfunction Treatments
simeprevir	Protease Inhibitors
simvastatin	HMG CoA Reductase Inhibitors (Statins)
sirolimus	Immunosuppressants
tacrolimus	Immunosuppressants
terfenadine	H1 Receptor Antagonists
ticagrelor	Anticoagulants and Antiplatelets
tilidine	Treatments of Pain and Inflammation
tipranavir	Protease Inhibitors
tolvaptan	Vasopressin Antagonists
triazolam	Benzodiazepines
ubrogepant	Migraine Treatments
ulipristal	Hormones
vardenafil	Erectile Dysfunction Treatments
vicriviroc	CCR5 Receptor Antagonists
vilaprisan	Progesterone Receptor Modulator
voclosporin	Immunosuppressants

NOTES: The present list includes CYP3A substrates with AUC Ratio of at least 5 when coadministrated with strong CYP3 inhibitor

In vivo CYP2B6 Sensitive substrate

Substrate (oral)	**Therapeutic Class**
bupropion	Anticoagulants and Antiplatelets
efavirenz	Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

NOTE: There are no CYP2B6 substrates with AUC Ratio of at least 5, or decrease in oral CL of 80% or more. However, bupropion and efavirenz are considered the most sensitive substrates studied.

In vivo CYP2C8 Sensitive substrate

Substrate (oral)	**Therapeutic Class**
daprodustat	Other
dasabuvir	Antivirals
repaglinide	Meglitinides

NOTE: The present list includes CYP2C8 substrates with AUC Ratios ≥5 or CL Ratios ≤0.20.

In vivo CYP2C9 Sensitive substrate

Substrate (oral)	**Therapeutic Class**
tolbutamide	Sulfonylureas
(S)-warfarin	Anticoagulants and Antiplatelets
benzbromarone	Anticoagulants and Antiplatelets
celecoxib	NSAIDS
ibuprofen	NSAIDS
glimepiride	Sulfonylureas
glipizide	Sulfonylureas
lornoxicam	NSAIDS
meloxicam	NSAIDS
piroxicam	NSAIDS

NOTE: The present list includes CYP2C9 substrates with AUCR ≥ 5 or CL Ratio ≤ 0.20

In vivo CYP2C9 Sensitive substrate

Substrate (oral)	**Therapeutic Class**
lansoprazole (dexlansoprazol)	Proton Pump Inhibitors
(S)-mephenytoin	Anticonvulsants
omeprazole	Proton Pump Inhibitors
tilidine	Treatments of Pain and Inflammation
(R)-(-)-hexobarbital	Hypnotics - Sedatives
(R)-mephobarbital	Anticonvulsants
clobazam (parent drug)	Benzodiazepines
diazepam	Benzodiazepines
gliclazide	Sulfonylureas

Substrate (oral)	**Therapeutic Class**
pantoprazole	Proton Pump Inhibitors
proguanil (prodrug)	Antimalarials
rabeprazole	Proton Pump Inhibitors

NOTE: The present list includes CYP2C19 substrates with an AUCR ≥5, or CL ratio ≤0.20.

10.13 APPENDIX 13: ABBREVIATED MODIFICATION OF DIET IN RENAL DISEASE FORMULA

$$GFR\ (mL/min/1.73\ m^2) = 175 \times (Scr) - 1.154 \times (Age) - 0.203 \times (0.742 \text{ if female}) \times (1.212 \text{ if African American}) \text{ (conventional units)}$$

GFR = glomerular filtration rate; Scr = serum creatinine.
Source: https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators/mdrd-adults-conventional-units

10.14 APPENDIX 14: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST 1.1)

Details provided in bibliographic reference (36).

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or nonmeasurable as follows:

Measurable

- Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - Ten millimeters by computed tomography (CT) scan (CT scan slice thickness no greater than 5 mm).
  - Ten-millimeter caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as nonmeasurable).
  - Twenty millimeters by chest X-ray.
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed (see Special Issue 15 [36]). See also notes below on “Baseline documentation of target and nontarget lesions” for information on lymph node measurement.

Non-measurable

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis) as well as truly nonmeasurable lesions. Lesions

considered truly nonmeasurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, positron emission tomography (PET) scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or magnetic resonance imaging (MRI) can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are nonmeasurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same participant, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Methods of measurement

- Measurement of lesions:

  All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

- Method of assessment:

  The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based

evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination. Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and 10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- Computed tomography, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. Magnetic resonance imaging is also acceptable in certain situations (eg, for body scans).
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.
- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.
- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a participant to be considered in CR. Specific guidelines for both cancer antigen 125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed cancer antigen 125 progression criteria which are to be integrated with objective tumor assessment for use in first line trials in ovarian cancer.
- Cytology, histology: These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (eg, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease.

Tumor response evaluation

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only participants with measurable disease at baseline should be included in protocols where objective tumor

response is the primary endpoint. Measurable disease is defined by the presence of at least 1 measurable lesion. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether participants having non measurable disease only are also eligible.

Response criteria

Table 17 - Response criteria, evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Table 18 - Response criteria, evaluation of nontarget lesions

Complete Response (CR):	Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis).
Incomplete Response/Stable Disease (SD):	Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression (see comments below)[a] of existing nontarget lesions. (Note: the appearance of one or more new lesions is also considered progression).

a Although a clear progression of "nontarget" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 19 provides a summary of the overall response status calculation at each time point for participants who have measurable disease at baseline. If participants have non-measurable (therefore non-target) disease only, Table 20 is to be used.

Table 19 - A summary of overall response status

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR

Target lesions	Non-target lesions	New lesions	Overall response
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

Table 20 - A summary of overall response status for non-measurable disease

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; SD = stable disease.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials, so to assign this category when no lesions can be measured is not advised.

Table 21 - Evaluation of best overall response

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the participant had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

The best overall response is determined once all the data for the participant is known.

When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline (defined as 42 days). If the minimum time is not met when SD is otherwise the best time point response, the participant's best response depends on the subsequent assessments. For eg, a participant who has SD at first assessment, PD at second and does not meet minimum

duration for SD, will have a best response of PD. The same participant lost to follow-up after the first SD assessment would be considered inevaluable. Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 21.

10.15 APPENDIX 15: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

10.15.1 Amended protocol 01: 08 August 2019

This amended protocol (amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The objective of this amendment is to clarify and improve the feasibility of study procedures, as well as to clarify inclusion/exclusion criteria. An extension to the study in China has been added to enable the enrollment of sufficient Chinese participants to support analysis of the data for participants in China alone.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.2 Schema	The text in Figure 1 was updated: "OS [overall survival] follow-up Every ~~3~~ **2** months until 18 months after PFS [progression-free survival] cut-off date."	To correct error in the text.
1.3 Schedule of activities	The tumor assessment schedule has been updated: c "If no radiological PD [progressive disease] at ~~EOT~~ **last tumor assessment during the treatment period**, disease assessment will **continue to** be performed every 8 weeks **±7 days (projected from last tumor assessment)** up to PD"	To clarify the tumor assessment schedule.

Section # and Name	Description of Change	Brief Rationale
	The bone scan schedule has been updated: *a* "If at screening, lesions are detected in the bone scan but not in the CT/MRI [computed tomography/magnetic resonance imaging] (RECIST [Response Evaluation Criteria in Solid Tumors] 1.1) scan, further bone scans should be conducted every 8 weeks ±7 days. If the lesions seen in the bone scan are no longer visible, these assessments can be conducted every 16 weeks **±7 days**. If lesions are detected in the bone scan and CT/MRI (RECIST 1.1) scan**,** further bone scan assessments will be conducted every 16 weeks **±7 days.**"	To clarify the bone scan schedule.
	amcenestrant pharmacokinetic assessment schedule has been updated: "Cycle**s** ~~2 to 6~~ **3, 4, and 6**: ~~On the day of tumor assessment: 1 sample~~ **Day 1: predose.**"	To accommodate the pharmacokinetic assessments with participant visits to the site.
	Tumor specimen/biopsy schedule updated: "~~To be done~~ **Cycle 3 Day 1 (allowed up to Cycle 3 Day 15** or within 14 days after first radiological tumor assessment after baseline**).**"	To clarify tumor specimen/biopsy schedule on Cycle 3.
	Clarified that estrogen receptor 1 gene (ESR1) analysis of cell-free deoxyribonucleic acid (cfDNA) will be performed on Cycle 1 Day 1 and Cycle 3 Day 1.	To clarify ESR1 analysis on Cycle 3.
2 Introduction	The following indication has been added for letrozole: "Neoadjuvant treatment of postmenopausal women with hormone receptor-positive, HER2 [human epidermal growth factor receptor 2]-negative breast cancer where chemotherapy is not suitable and immediate surgery not indicated (European Union only)."	To complete all approved indications for letrozole.
2.1 Study rationale	Cut-off date for the presentation of TED14856 results updated from 22 October 2018 to 29 May 2019.	To align with the updated Investigator's Brochure.
	Details on study TED14856 updated: Number of participants in Part B updated from 4 to 48 Part C started in January 2019, with 6 participants recruited so far.	To align with the updated Investigator's Brochure.
2.2 Background	Breast cancer statistics updated: "In the United States, in ~~2015, it was estimated that 231 840~~ **2019, a total of 268 600** new cases of invasive breast cancer as well as ~~60 290~~ **62 930** additional cases of in situ breast cancer ~~would be reported~~ **are estimated**. **From 2006 to 2015, invasive female breast cancer incidence rates increased slightly, by 0.4% per year.** Approximately ~~40 290~~ **41 760** women ~~were~~ **are** expected to die from breast cancer in ~~the same year~~ **2019.**"	To provide updated statistics.

Section # and Name	Description of Change	Brief Rationale
2.3.1.1 amcenestrant	amcenestrant benefit information updated: Number of participants with stable disease updated from 7 to 8 Number of participants with long-term stable disease updated from 3 to 7 Clinical benefit observed in 8 participants so far.	To align with the updated Investigator's Brochure.
2.3.2.1 amcenestrant	amcenestrant safety information updated: Updated treatment-emergent adverse event results from TED14856 study Part A included Remaining information removed and referred to the Investigator's Brochure.	To align with the updated Investigator's Brochure.
3 Objectives and endpoints	The following exploratory endpoint has been updated: "The gene mutation profile of the tumor over time (Cycle 1 Day 1 [pre-treatment] and end of treatment) by cfDNA analysis, and ESR1 mutation analysis by cfDNA analysis pre-treatment and ~~within 14 days after first radiological tumor assessment after baseline~~ **at Cycle 3 Day 1.**"	To align with the updated schedule for ESR1 analysis.
	The following exploratory endpoint has been updated: "Tumor ER [estrogen receptor], Ki67, Bcl-2, and PgR [progesterone receptor] protein, and RNA [ribonucleic acid] gene expression profiles in paired biopsies at Cycle 1 Day 1 (pre-treatment) and **at Cycle 3, Day 1 (allowed up to Day 15;** or within 14 days after first radiological tumor assessment after baseline**).**"	To align with the updated tumor specimen/biopsy schedule.
4.3 Justification for dose	Updated pharmacokinetic information related to amcenestrant obtained from healthy volunteers and patients has been included.	To align with the updated Investigator's Brochure.
5.1 Inclusion criteria	In I 01, it was added that participants should be of the country's legal age of majority if the legal age is >18 years.	To comply with applicable local requirements.
	In I 07, the following text was removed: "Participants who received both prior chemotherapy and targeted therapy are not allowed."	To allow patients receiving chemotherapy and targeted therapy concomitantly.
	In I 07, the following text was added: "For countries where CDK4/6 inhibitors are available (ie, approved and can be reimbursed), prior treatment with a CDK4/6 inhibitor in combination with fulvestrant or an AI [aromatase inhibitor] is mandatory."	For clarity and in response to request from French Health Authority.
	In I 08, the following text was updated: "Participants must have progressed after at least 6 months of a continuous prior endocrine therapy for advanced breast cancer (single agent or in combination, the number of hormonal lines ~~is not limited~~ **will be limited to 2**), or have progressed within 12 months of completion of adjuvant endocrine therapy."	Number of prior endocrine therapies limited updated in line with the National Comprehensive Cancer Network guidelines (Version 2, 2019), which recommends treating metastatic breast cancer with no more than 3 lines of hormonal therapy before switching to chemotherapy.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion criteria	A new exclusion criterion (related to medical conditions) has been included: "E 08. Participants with abnormal coagulation profiles or any history of coagulopathy within the 6 months prior to the first dose of IMP [investigational medicinal product], including history of deep vein thrombosis or pulmonary embolism. However, participants with the following conditions will be allowed to participate: Participants with adequately treated catheter-related venous thrombosis that occurred more than 1 month prior to the first dose of IMP. Participants being treated with an anticoagulant (eg, warfarin or heparin) for a thrombotic event that occurred more than 6 months before enrollment, or for an otherwise stable and allowed medical condition (eg, well-controlled atrial fibrillation), provided that dose and coagulation parameters (as defined by local standard of care) are stable for at least 1 month prior to the first dose of IMP."	To exclude participants with high thromboembolic risk, in accordance with potential thromboembolic risks associated with the IMPs.
	In E 13, the following text was updated: "Prior treatment with **mammalian target of rapamycin inhibitors or** any other SERD [selective estrogen receptor degrader] compound, except fulvestrant if stopped for at least 3 months before randomization."	To align with current literature, which shows poor efficacy of SERD therapies in patients who received prior therapy with mammalian target of rapamycin inhibitors.
5.3 Lifestyle considerations	It was clarified that direct exposure to natural or artificial sunlight should be avoided for at least 30 days after last IMP dose.	For clarity.
	The following text was added: "… in addition, 1 participant from Part 1 of the TED14856 study experienced Grade 1 sunburn while exposed to the sun without protection, an event considered related to amcenestrant…"	To align with the updated Investigator's Brochure.
5.4 Screen failures	The text was updated as follows: "Participants who do not meet the criteria for participation in this study may be retested during the screening period (≤28 days) and included, providing they meet at that time all inclusion and exclusion criteria. **These participants are not considered screen failures.**"	To clarify screen failure criteria.
6.1 Study intervention(s) administered	The following text was added: "Between the protocol-scheduled on-site visits, interim visits may be required for IMP dispensing. As an alternative to these visits, IMPs may be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations and approved by the participant."	To clarify dispensing and shipping procedures for the IMP in case of Direct to Patient shipment of IMPs.
6.2.1 General rules	Potential defects in the quality of amcenestrant or any comparator supplied globally may be subject to initiation of a recall procedure by the Sponsor, as opposed to only amcenestrant, as previously stated.	To clarify recall procedures.

Section # and Name	Description of Change	Brief Rationale
	The Investigator must not supply any IMP to a third party nor dispose of IMP in any manner, as opposed to only amcenestrant, as previously stated.	To clarify procedures for IMP supply and disposal.
6.5 Concomitant therapy	The following sentence has been added: "Special caution should be taken with regards to protein pump inhibitors (ie, omeprazole): when prescribed concomitantly, amcenestrant should preferably be taken with food."	The absorption of amcenestrant may be decreased if the participant is treated with protein pump inhibitors. Taking amcenestrant with food in this case could help normalizing the absorption.
6.6 Dose modification	In Table 3, dose modifications and management of amcenestrant toxicities were updated to describe the management of Grade 3 and 4 adverse events separately.	To clarify dose modifications and management of amcenestrant toxicities.
8.1.2 Bone scans	If at screening, lesions are not detected in the bone scan nor in the CT/MRI (RECIST 1.1) scan, further bone scans are not required unless clinically indicated.	To clarify bone scan procedures when no lesions are detected at screening.
8.3 Adverse events and serious adverse events	The following text has been added as an adverse event of special interest (AESI): "Increase of ALT [alanine transaminase] Grade ≥3. In this case, this test will be repeated."	Increase of liver enzymes has been reported in a recent preclinical toxicity study and found in the participants who received amcenestrant in clinical trials. The Sponsor committed to closely monitor participants with an increase of liver enzymes.
8.3.1 Time period and frequency for collecting AE and SAE information	Text updated as follows: "All AEs [adverse events] ~~and SAEs [serious AEs]~~ **(regardless of seriousness or relationship with IMP)** will be collected from the signing of the ICF [informed consent form] until ~~the last follow-up visit at the time points specified in the SoA~~ **30 days after the last dose of the IMP** (Section 1.3)."	To clarify AE collection procedures.
8.3.4 Regulatory reporting requirements for SAEs	A statement was added clarifying that the Investigator is obligated to assess the relationship between the IMP and occurrence of AEs and SAEs.	For clarity.
8.3.7 Guidelines for reporting product complaints	Text updated as follows: "Any defect in the IMP **supplied centrally by Clinical Supplies (amcenestrant and control arm treatments in the United States and Poland)** must be reported as soon as possible by the Investigator to the monitoring team ~~that will complete~~ **responsible for completing** a product complaint form~~, for amcenestrant~~ within required timelines."	To clarify the applicable IMP supplying procedures.
8.8 Biomarkers	Samples collected for biomarker analyses and their derivatives will be stored from a period of up to 5 years after last participant last visit, instead of after completion of the final study report. Likewise, samples for future use will be stored for 15 years after last participant last visit, instead of after completion of the final study report.	Text updated to comply with the Sponsor standard procedures.

Section # and Name	Description of Change	Brief Rationale
8.8.1 Future use of samples	Text updated as follows: "For participants who have consented to it, the samples that are unused or left over after testing may be used for other research purposes (~~excluding~~ **including** genetic analysis ~~providing~~ **that may provide** information on the likelihood of developing **cancer and related** diseases) related to oncology than those defined in the present protocol."	For clarity.
9.1 Statistical hypotheses	Null hypothesis updated: survival distribution functions (SDF) for the PFS of the amcenestrant arm is lower than or equal to the SDF of the control arm. Alternative hypothesis updated: SDF for the PFS of the amcenestrant arm is superior to the SDF of the control arm.	To clarify the statistical hypotheses
9.4.1.1 Analysis of primary efficacy endpoint	Text updated as follows: "If progression and death are not observed before the PFS analysis COD [cut-off date], PFS will be censored at the date of the last valid disease assessment with no evidence of a disease progression ~~or the PFS analysis COD, whichever occurs first~~"	To clarify the PFS censoring procedures.
9.4.1.2 Analysis of secondary efficacy endpoints	Text updated as follows: "For participants with ongoing response at the time of the analysis, DOR [duration of response] will be censored at the date of the last valid disease assessment not showing disease progression performed before the initiation of a new anticancer treatment (if any)**.** ~~or the analysis COD, whichever occurs first.~~"	To clarify the DOR censoring procedures.
10.1.2 Informed consent process	Text updated as follows: "~~A separate signature will be required to document a participant's agreement~~ **Participant agreement will be required** to allow any remaining specimens to be used for exploratory research."	To clarify consenting procedures.
Appendix 2	Gamma-glutamyltransferase added as part of the laboratory assessments.	Added to help determine if abnormal liver function tests are associated with liver metastases.
	The following procedures were clarified for hematology analyses: To be repeated after screening within 2 or 3 days before randomization, in case of abnormal evaluations on parameters such as body weight, signs and symptoms, physical examination, electrocardiogram, hematology, coagulation tests, blood chemistry, and urinalysis. To be repeated at Cycle 1 Day 1 if screening test >7 days of Day 1 Cycle 1.	To clarify hematology analysis prior to Cycle 1 Day 1.

Section # and Name	Description of Change	Brief Rationale
Appendix 3	A definition for unexpected adverse drug reaction has been included "An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved investigational medicinal product)."	For clarity.
Appendix 5	Samples collected for genetic analyses and their derivatives will be stored from a period of up to 5 years after last participant last visit, instead of after completion of the final study report. Likewise, samples for future use will be stored for 15 years after last participant last visit, instead of after completion of the final study report.	Text updated to comply with the Sponsor standard procedures.
Appendix 8	Inclusion of a China extension study.	Added to enable a separate analysis of efficacy, safety, and pharmacokinetic data for participants in China.
Appendix 14	A table with overall response status for nonmeasurable disease was added.	To clarify response status attribution for nonmeasurable disease.
	The following text has been updated: "When SD [stable disease] is believed to be best response, it must also meet the protocol specified minimum time from baseline **(defined as 42 days)**."	To clarify the minimum time from baseline needed to be met when SD is determined as the best response.

10.15.2 Amended protocol 02: 13 February 2020

This amended protocol (Amendment 02) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The objective of this amendment is to update the protocol on the following topics:

- Study population and inclusion/exclusion criteria:
  - Allow the inclusion of male participants in the study.
  - Clarify that single-agent endocrine therapy must be considered appropriate for the participant.
  - Clarify that participants with bone-only metastases are allowed in the study.
- Inclusion of a formal interim analysis for futility with oversight from the Data Monitoring Committee.
- Limit the number of participants naïve to CDK4/6 inhibitors to a maximum of 20% of the overall sample size.
- Include overall survival as the key secondary endpoint.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor formatting and editorial updates.	For clarity and accuracy.
Title page	Protocol title updated as follows: "An open label randomized Phase 2 trial of amcenestrant, versus endocrine monotherapy as per physician's choice in ~~premenopausal and postmenopausal~~ patients with estrogen receptor-positive, HER2-negative locally advanced or metastatic breast cancer with prior exposure to hormonal therapies" Short title updated as follows: "Phase 2 study of amcenestrant versus physician's choice in ~~premenopausal and postmenopausal~~ **patients with** locally advanced or metastatic ER-positive breast cancer."	The protocol title has been updated in alignment with the inclusion of male participants in this study.
	The NCT number has been included: NCT04059484.	The NCT number is now available.
Synopsis	The text below has been updated as follows: "The treatment of ~~non-visceral~~ metastatic/advanced breast cancer **without visceral crisis** is based on hormonal therapies given as monotherapy (tamoxifen, aromatase inhibitors [AI], fulvestrant) and in combination with targeted agents such as everolimus + exemestane and AI or fulvestrant + CDK4/6 inhibitors."	Updated for clarity.
	The synopsis text has been updated to keep consistency with the changes in the remaining sections.	Updated for consistency with the remaining sections of the protocol.
1.2 Schema	The text below from Figure 1 has been updated as follows: "OS [overall survival] follow-up ~~Every 2 months until 18 months after PFS [progression-free survival] cut-off date~~**.**"	Updated for clarity and to simplify the schema.
1.3 Schedule of Activities	A screening assessment for follicle-stimulating hormone and estradiol assessment for premenopausal women has been added.	This assessment has been added to confirm that premenopausal women treated with gonadotropin-releasing hormone have the same follicle-stimulating and estradiol levels as postmenopausal women.
	New assessments have been added to the Schedule of Activities: • Estradiol. • Genetic sampling for drug metabolizing enzymes and transporters (amcenestrant treatment arm only).	Estradiol assessments will be performed to explore the possible influence of circulating levels of estradiol on the efficacy of amcenestrant. Drug metabolism enzyme genotyping has been included to assess the possibility of drug metabolism enzyme variants (eg, uridine 5' diphospho-glucuronosyltransferase [UGT] 1A1 and UGT1A4) as potential intrinsic factors associated with pharmacokinetic/dynamic variability of amcenestrant.

Section # and Name	Description of Change	Brief Rationale
2 Introduction	The following text has been removed: "amcenestrant showed superior and broader ER [estrogen receptor] degrading activity compared to all known SERD [selective estrogen receptor degrader] competitors."	Sentence removed to keep consistency with the amcenestrant Investigator's Brochure and bibliographic references.
2.2 Background	The following text has been updated: " In the United States, in 2019, a total of 268 600 new cases of invasive breast cancer as well as 62 930 additional cases of in situ breast cancer are estimated. From 2006 to 2015, invasive female breast cancer incidence rates increased slightly, by 0.4% per year. Approximately 41 760 women are expected to die from breast cancer in 2019. **In men, breast cancer is relatively uncommon, with 2670 new cases of invasive breast and 500 deaths estimated in the United States, in 2019** (10). […] According to the National Comprehensive Cancer Network guidelines (~~Version 2, 2018~~ **Version 1, 2020**), sequential hormonal therapy (alone or in combination) is the standard of care in the metastatic breast cancer setting for ER positive and HER2 negative participants without rapidly progressing visceral or symptomatic metastases. Common classes of drugs used after progression of hormonal treatment for this purpose include SERMs [selective estrogen receptor modulator] (eg, tamoxifen), AIs (eg, letrozole, anastrozole, or exemestane), and SERDs (fulvestrant). **Because few men have been historically included in breast cancer clinical trials, recommendations regarding management of breast cancer in men are generally extrapolated from findings in clinical trials focusing on breast cancer in women**. […] These data demonstrate that SERDs have the potential to provide effective and well-tolerated therapy for postmenopausal women with advanced breast cancer and highlight the need for the development of new SERD compounds with optimized characteristics: improved route of administration (PO [per os] versus IM [intramuscular]), bioavailability, and long-term maintenance of ER receptor blockade combined with a strong antitumor activity. **It would also be important to further understand the potential benefit and safety of SERDs in men with breast cancer, in alignment with the Food and Drug Administration draft guidance "Male Breast Cancer: Developing Drugs for Treatment", which recommends the inclusion of both men and women in breast cancer clinical trials**."	To provide some background information on male breast cancer and a rationale for the inclusion of men in this study.

Section # and Name	Description of Change	Brief Rationale
2.3.1.1 amcenestrant	The text below has been updated as follows: "amcenestrant has been administered to humans since November 2017, in the FIH [first in human] TED14856 study. Efficacy was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria in ~~14~~ **16** participants ~~(2 participants at 600 mg have not yet reached Cycle 2)~~; the best overall responses (BOR) have been partial response (PR) in 1 participant treated at 150 mg, stable disease (SD) in 8 participants**,** and PD in ~~6~~ **7** participants. Long-term SD (24 weeks or more) was seen in 7 participants so far. Clinical benefit (PR + SD ≥24 weeks) was therefore observed in 8 participants (29 May 2019)."	Updated in alignment with the current version of the Investigator's Brochure.
2.3.2.1 amcenestrant	The following text was included regarding potential amcenestrant risks anticipated in humans: "Based on the nonclinical data available for amcenestrant and the safety profile observed in compounds of the same class approved and in development, the following are potential side effects and risks anticipated in humans: • Gastrointestinal toxicities, including anorexia, nausea, vomiting, diarrhea (and possibly dehydration and electrolyte imbalance in severe cases), and upper and/or lower abdominal pain. • Changes in liver function, including elevated liver enzymes and bilirubin. • Hematological toxicities potentially presenting with laboratory abnormalities (leukopenia, neutropenia, thrombocytopenia, anemia), infections, and neutropenic fever. • Effects in the female reproductive system (ovary, uterus, cervix, vagina, mammary glands). • Risk of photosensitivity. • Theoretical risk of osteoporosis, due to the mechanism of action of SAR439849, in case of long-term exposure. • Risk of drug drug interaction: in vitro, amcenestrant is mainly metabolized by uridine 5' diphospho-glucuronosyltransferase (UGT) 1A1 and UGT1A4, and to a lesser extent by CYP [cytochrome P450] enzymes (<20%) CYP2C8 and/or CYP3A. Therefore, drugs that are potential inhibitors of UGTs (ie, atazanavir and probenecid) should not be administered with amcenestrant, as well as drugs that are strong or moderate inducers of CYP3A and CYP2C8 • , since they may also induce UGTs. In vitro studies results showed that amcenestrant has the potential to induce CYP3A4, and to a lesser extent CYP2B6, CYP2Cs, and UGTs." In consequence, the following text has been removed: "No potential and identified risks have yet been reported for amcenestrant."	Updated to include the most up to date information on potential amcenestrant risks anticipated in humans.

Section # and Name	Description of Change	Brief Rationale
	The text below has been updated as follows: "**Preliminary safety results in humans from the FIH TED14856 study are as follows:** ~~As~~ **as** of 29 May 2019, 16 participants have been treated in the dose escalation part **at doses from 20 to 600 mg (Part A)** of TED14856 study, and 48 participants have been treated in the dose expansion part **at the recommended dose of 400 mg (Part B)**. The safety was assessed in 16 participants in the dose escalation part of study. No dose limiting toxicities were observed during Cycle 1 at any tested dose levels. All of them presented with at least 1 treatment emergent AE (TEAE)~~. In Part A of the ongoing TED14856 study, as of 29 May 2019, all 16 participants (100.0%) experienced at least 1 TEAE~~**,** regardless of relationship."	Updated to clarify the dose levels used in the TED14856 study.
	The following text was included regarding amcenestrant updated liver toxicity tests in humans: "Updated safety information from July 2019 shows the following results regarding liver function tests (LFTs). Two of 16 participants from Part A of the TED14856 study developed treatment-emergent LFT abnormalities Grade ≥3. One participant (treated with amcenestrant 200 mg) developed Grade 3 aspartate aminotransferase (AST) and alkaline phosphatase increase with Grade 1 alanine aminotransferase (ALT) increase and normal total bilirubin. Another participant (treated with amcenestrant 600 mg) developed Grade 4 AST and total bilirubin increase with Grade 3 ALT and alkaline phosphatase increase. Both participants had liver metastasis and Grade 1 AST increase at baseline. These LFT abnormalities were observed concomitantly with disease progression in the liver."	Section updated to include up to date information related with liver safety.
3 Objectives and endpoints	Overall survival has been relocated as the first secondary objective.	Overall survival has been considered the key secondary endpoint, in response to the Food and Drug Administration recommendations.
	The objective response rate (ORR) endpoint has been updated as follows: "Objective response rate is defined as the proportion of participants who have a confirmed complete response (CR) or partial response (PR), as best overall response **derived from overall response** determined by ICR [independent central review] as per RECIST 1.1, from the date of randomization to the date of end of treatment."	Updated for accuracy, as the best overall response will be derived from overall response determined by ICR
4.1 Overall design	The text below has been updated as follows: "This is an international, prospective, open-label, Phase 2 randomized study comparing the efficacy and safety of amcenestrant versus a single endocrine therapy of the choice of the physician in **men,** postmenopausal women or premenopausal women on a gonadotropin-releasing hormone (GnRH) analog with ER positive and HER2 negative advanced and/or metastatic breast cancer."	To clarify that men will be included in this study

Section # and Name	Description of Change	Brief Rationale
	The text below has been updated as follows: • "Selective ER modulator (PO, QD [once daily] **or two times a day**): - Tamoxifen 20 mg/day to be taken approximately at the same time every day, regardless of food status."	To align with the possible dosing regimens for tamoxifen, as per label.
	The text below was updated as follows: "For the global study, estimated COD [cut-off date] **for final PFS** will be approximately ~~17~~ **18** months after first randomized participant in ~~for the PFS analysis~~. No PK [pharmacokinetic] sample will be taken after Cycle 6 or ~~PFS~~ COD **for final PFS**, whichever comes first. After **the** COD for **final** PFS analysis, no more efficacy assessment will be performed except collection of survival status. For all participants alive at the COD for **final** PFS analysis, the first follow-up visit will be conducted at the site and subsequent telephone follow-up assessments will be conducted every 2 months to record survival data and further therapies, which will be collected until COD for OS analysis, or participant death, or upon participant's request, whichever occurs first. If a participant treated continues to benefit from the treatment after the ~~last~~ COD **for OS analysis**, the participant may continue until treatment is precluded by toxicity, progression, upon participant's request to stop treatment, or Investigator decision. For cycles completed after the ~~last~~ COD **for OS analysis**, all ongoing SAEs [serious AEs] (related or not), all related nonserious AEs ongoing at the COD, and all new related AEs (serious or not) occurring post COD and associated concomitant medication, as well as IMP [investigational medicinal product] administrations and reason for EOT [end of treatment] will continue to be collected."	The COD projections have been updated following the newly added futility interim analysis for PFS and the inclusion of OS as the key secondary endpoint. The COD definitions have also been updated for clarity.
	The text below has been updated as follows: "For the China extension, assuming that the first Chinese participant is planned to be enrolled 11 months after the first randomized participant of the global part and a ~~9.5~~ **17**-month enrollment period for the Chinese participants, the estimated China COD will be approximately 5 months after last Chinese participant enrolled, ie, approximately ~~9~~ **18** months after the PFS analysis of the global study."	Recruitment period for the Chinese population has been extended after the sample size has been revised for this population. After consultation with the Chinese Center for Drug Evaluation, as no prior Asian population exposure data were provided, the sample size of the Chinese extension should not be lower than 20% of the sample size of the global study and the Chinese extension should be powered to observe a hazard ratio (HR) lower than 0.8. To meet with these requirements, the number of participants in the China extension study has been increased from 42 to 90.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion criteria	In I 07, the following statement has been added: "Note: The number of participants naïve to CDK4/6 inhibitors should not be higher than 20% of the overall sample size."	The proportion of participants naïve to CDK4/6 inhibitors has been restricted to ensure that the study conclusions based on the intent-to-treat population can be extrapolated for the population previously treated with CDK4/6 inhibitors.
	In I 08, the following text has been updated: "Participants must have progressed after at least 6 months of a continuous prior endocrine therapy for advanced breast cancer (single agent or in combination, the number of hormonal lines will be limited to 2), or have ~~progressed within 12 months of completion of adjuvant endocrine therapy~~ **relapsed while on adjuvant endocrine therapy but after the first 2 years, or have relapsed within 12 months of completing adjuvant endocrine therapy**."	The definition of secondary endocrine resistance has been updated to align with the 3rd European School of Oncology- European Society for Medical Oncology International Consensus Guidelines for Advanced Breast Cancer.
	In I 09, the following text has been updated: "**Male or** Female."	Male participants have been considered eligible for participation in this study, in alignment with the Food and Drug Administration draft guidance "Male Breast Cancer: Developing Drugs for Treatment", which recommends the inclusion of both men and women in breast cancer clinical trials.
	In I 09, the following text has been added: "Sexually active males should be on a GnRH analog for at least 4 weeks (to be continued during study treatment)."	Because male participants have been considered eligible for this study, contraceptive guidance for male participants was included.
	The following inclusion criterion (I 11) was added: "Participants must be considered clinically eligible by the Investigator to receive single agent endocrine therapy."	Included to confirm that participants must be deemed appropriate to receive treatment with single endocrine agent.
5.2 Exclusion criteria	E 10 has been removed, and the text updated as follows: "~~Participants with bone-only metastasis (bone-only metastasis was defined as bone metastasis without evidence of involvement of any other organ)~~ **E 10 deleted in amended protocol 02**."	Participants with bone-only metastasis will be allowed in this study.
	In E 14, the following text has been updated: "Treatment with ~~atazanavir, lopinavir (antiviral agents), ketoconazole (antifungal), and quercetin (antioxidant)~~ **drugs that have the potential to inhibit UGT, including, but not limited, to atazanavir and probenecid, for** less than 2 weeks before randomization or 5 elimination half-lives whichever is longer."	Exclusion criteria clarified to include all potential UGT inhibitors.

Section # and Name	Description of Change	Brief Rationale
	In E 15, the following text has been updated: "Treatment with strong or moderate CYP3A **and CYP2C8** inducers within 2 weeks before randomization or 5 elimination half-lives**,** whichever is longer (Section 10.11 [Appendix 11])."	Concomitant administration of moderate CYP2C8 inducers will not be permitted in participants receiving amcenestrant, since they may decrease amcenestrant exposure.
6.1 Study intervention(s) administered	The following text has been updated in Table 2, in the amcenestrant dosing instructions section: "4 capsules once a day given in the morning with or without food**, at approximately the same time every day (±3 hours)**."	To include a time window for amcenestrant dosing.
	The following text has been updated in Table 2, in the tamoxifen dosing instructions section: "20 mg once daily **or 10 mg twice a day**, approximately at the same time every day, regardless of food status."	To align with the possible dosing regimens for tamoxifen, as per label.
	The following text has been updated in the Table 2 footnotes: "a In study visit days, participants should only be dosed after the ~~scheduled study assessments (Section 1.3) are performed~~ **predosing pharmacokinetic sampling collection**."	Updated to clarify dosing procedures.
6.3 Measures to minimize bias: randomization and blinding	The following text has been updated: "Randomization will be stratified according to the presence of visceral metastasis (defined by at least 1 liver or lung metastasis) (Yes or No), prior treatment with CDK4/6 inhibitors (Yes or No), and ECOG [Eastern Cooperative Oncology Group] status (0 or 1) **(Note: The number of participants naïve to CDK4/6 inhibitors should not be higher than 20% of the overall sample size).**"	The proportion of participants naïve to CDK4/6 inhibitors was restricted to ensure that the study conclusions based on the intent-to-treat population can be extrapolated for the population previously treated with CDK4/6 inhibitors.
6.4 Study intervention compliance	The following text has been updated: "In case of oral dosing omission or IM injection delay greater than 2 weeks, the participant will be withdrawn from the study treatment**, unless a clear benefit is identified and after discussion with the Medical Monitor** (Section 6.6)."	To allow participants that are benefiting from the medication to continue treatment after a delay longer than 2 weeks.
6.5 Concomitant therapy	The following text has been added: "Bisphosphonates and receptor activator of nuclear factor kappa B ligand inhibitors are allowed."	Updated for clarity and in agreement with the inclusion of participants with bone-only metastasis.
	The text in this section has been reorganized as follows, for clarity: "Special caution should be taken regarding the following therapies: • No additional investigational or commercial anticancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy other than amcenestrant or the selected control will be permitted during the active treatment phase. In general, any drugs containing "for the treatment of	Concomitant administration of strong and moderate CYP3A4 inducers and moderate CYP2C8 inducers will not be permitted in participants receiving amcenestrant, since they may decrease amcenestrant exposure. As amcenestrant is a substrate of UGT1A1 and UGT1A4, UGT inhibitors may increase amcenestrant exposure. The remaining medications were included in the previous version of the

Section # and Name	Description of Change	Brief Rationale
	breast cancer" on the product label are not permitted on study. • Palliative radiotherapy may be given for control of pain for palliative intents. The Sponsor team should be notified to obtain agreement prior to treatment if palliative radiotherapy is being considered, and prior to resuming therapy on the study. The irradiated area should be as small as possible and should never involve more than 20% of the bone marrow in any given 3-week period. In all such cases, the possibility of tumor progression should be ruled out by physical and radiological assessments of the tumor. If the only evaluable lesions are to be irradiated, the participant will stop the study treatment. The irradiated area cannot be used as a parameter for response assessment. ~~• Among herbal medications and food products, it is recommended to avoid consumption of St John's Wort and genistein during treatment period since they could decrease amcenestrant exposure.~~ ~~• The following therapies since they may increase amcenestrant exposure by more than 2-fold and are prohibited in this study:~~ ~~antiviral agents: atazanavir, lopinavir;~~ ~~antifungal: ketoconazole;~~ ~~antioxidant: quercetin.~~ • ~~Strong and moderate CYP3A4 inducers (see full list in Section 10.11 [Appendix 11]) since they may decrease amcenestrant exposure and are prohibited in this study.~~ • Drugs which are ~~mainly metabolized by~~ **sensitive substrates of** CYP3A, CYP2B6, CYP2Cs, and/or UGT should be closely monitored (see list Section 10.12 [Appendix 12]) since ~~the~~ **there may be loss of** efficacy of these drugs ~~may be decreased~~ by concomitant use of amcenestrant due to a potential induction effect of amcenestrant. ~~• Drugs that are substrate of P-gp [P-glycoprotein] should be avoided (dabigatran, digoxin, fexofenadine) since amcenestrant may increase their absorption.~~ • Special caution should be taken with regards to the proton pump inhibitors (ie, omeprazole): when prescribed concomitantly, amcenestrant should preferably be taken with food. **The following therapies/medications are prohibited throughout the active treatment phase for the amcenestrant treatment arm:** • **Drugs that are strong and moderate inducers of CYP3A and CYP2C8, since they may decrease**	protocol, but were reworded to clarify which medications were not allowed in participants receiving amcenestrant.

Section # and Name	Description of Change	Brief Rationale
	amcenestrant exposure (see full list in Section 10.11 [Appendix 11]). • **Herbal medications and food supplements including St John's Wort and genistein during treatment period, since they could decrease amcenestrant exposure.** • **Drugs that are sensitive substrates of P-gp including dabigatran, digoxin, and fexofenadine, since amcenestrant is a potential inhibitor of P-gp and may increase their absorption.** • **Drugs that have UGT inhibition potential and are contraindicated with UGT substrates, including, but not limited to, atazanavir and probenecid, since amcenestrant is substrate of UGT1A1 and UGT1A4."**	
6.6 Dose modification	The following text has been updated: "In case of oral dosing omission or IM injection delay greater than 2 weeks, the participant will be withdrawn from the study treatment**, unless a clear benefit is identified and after discussion with the Medical Monitor**."	To allow participants that are benefiting from the medication to continue treatment after a delay longer than 2 weeks.
8.1.1 Criteria for response (antitumor activity)	The text below has been updated as follows: "Participants who discontinue the study treatment without documented PD will be followed every 8 weeks (projected from last tumor assessment) until PD is documented or ~~primary analysis~~ COD **for final PFS**, whichever occurs first."	Updated for clarity.
8.1.2 Bone scans	The text below has been updated as follows: "If at Cycle 1 Day 1, lesions are detected in the bone scan but not in the CT [computed tomography]/MRI [magnetic resonance imaging] (RECIST 1.1) scan, further bone scans should be conducted every 8 weeks ±7 days until disease progression documented or ~~PFS~~ COD **for final PFS**, whichever occurs first. If the lesions seen in the bone scan are no longer visible, these assessments can be conducted every 16 weeks ±7 days until disease progression documented or ~~PFS~~ COD **for final PFS**, whichever occurs first. If bone lesions are detected in the bone scan and in CT/MRI (RECIST 1.1) scan at Cycle 1 Day 1, further bone scans will be conducted every 16 weeks ±7 days until disease progression documented or ~~PFS~~ COD **for final PFS**, whichever occurs first."	Updated for clarity.
8.2.2 Vital signs	The text below has been updated as follows: "~~Oral temperature~~ **Temperature**, pulse rate, respiratory rate, and blood pressure will be assessed."	Updated for improved feasibility.

Section # and Name	Description of Change	Brief Rationale
8.3 Adverse events and serious adverse events	The following text has been updated, regarding adverse events of special interest (AESI): • Pregnancy of a female participant entered in a study, **as well as pregnancy occurring in a female partner of a male participant entered in a study** with IMP: - Pregnancy occurring in a female participant **or female partner of a male participant** entered in the clinical study will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).”	Updated in alignment with the inclusion of men in this study, to consider pregnancy events of female partners of male participants.
8.3.5 Pregnancy	The text below has been updated as follows: “Details of all pregnancies in female participants **or female partners of male participants** will be collected after the start of study intervention and until 30 days after the last dose.”	Updated in alignment with the inclusion of men in this study, to consider pregnancy events of female partners of male participants.
	The text below has been updated as follows: “If a pregnancy is reported **in female participants or female partners of male participants**, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).”	Updated in alignment with the inclusion of men in this study, to consider pregnancy events of female partners of male participants.
8.5 Pharmacokinetics	The text below has been updated as follows: “Pharmacokinetic samplings will be stopped at the end of Cycle 6 or at the ~~primary analysis~~ COD **for final PFS**, depending which one comes first.”	Updated for clarity.
8.6.2 Estradiol	A new section has been included for estradiol assessments, which have been added in this amendment.	Estradiol assessments have been included to explore the possible influence of circulating levels of estradiol on the efficacy of amcenestrant.
8.7.4 Drug metabolizing enzymes and transporters DNA sample	A new section has been included for investigation of allelic variants of drug metabolizing enzymes and/or drug transporters.	Included to assess the possibility of drug metabolism enzyme variants (eg, UGT1A1 and UGT1A4) as intrinsic factors associated with pharmacokinetic/dynamic variability of amcenestrant.
9.1 Statistical hypotheses	Clarified that the statistical hypotheses defined for the primary endpoint will also be tested for the OS key secondary endpoint.	To clarify the statistical hypotheses for the key secondary endpoint (OS).
9.2 Sample size determination	The following text has been updated regarding the global sample size calculation rationale: “The sample size for the global part of this study is determined based on following assumptions: the median PFS for the control arm is assumed to be 4.5 months (2, 3, 4, 5, 6, 7) and an improvement of ~~35~~ **53**% to a median PFS of 6.9 months (corresponding to a HR = 0.65) would be considered clinically meaningful.	The sample size calculation has been updated in accordance with the newly added futility interim analysis for PFS. The improvement in median PFS was corrected from 35 to 53%.

Section # and Name	Description of Change	Brief Rationale
	A total of ~~195~~ **201** ICR assessed PFS events will be required in the 2 treatment arms for the global part of the study to have ~~an~~ **approximately** 85% power to detect an increase in PFS, assuming a true HR [hazard ratio] of 0.65 (representing a ~~35~~ **53**% increase in median PFS from 4.5 to 6.9 months**, under exponential model**), tested at a one-sided significance level of alpha = 0.025. For the global part of the study, assuming a uniform accrual **rate of 23.5 participants per month** accomplished over a period of about 12 months~~, a duration of approximately 17 months from the start of study randomization to final PFS analysis,~~ and an annual dropout rate of 10%, a total sample size of approximately 282 participants (randomized in a 1:1 ratio) is required. **The sample size calculation considers 1 futility interim analysis at 50% of the planned number of events. Under this current assumption, the COD for final PFS is approximately 18 months after first participant randomized.**"	
	The power calculations for OS analysis have been included in this section. The following will be applied for this endpoint: • The interim analysis of OS is planned at the time of PFS analysis, ie, approximately 18 months from the start of study randomization. • The final OS analysis is planned to be performed when 196 randomized participants have died (ie, at approximately 70% OS data maturity). • The COD for OS is approximately 64 months after the first randomized participant.	The power calculations for OS analysis have been added in accordance with the inclusion of OS analysis as key secondary endpoint.
9.3 Populations for analyses	In Table 5, the response-evaluable population has been removed.	This population has been removed from the study in consistency with the other studies from the same program. The analyses that were to be performed in this population will be performed in the intent-to-treat (ITT) participants with measurable disease at study entry, regardless of postbaseline assessment availability. This ITT analysis will provide a more accurate estimation of the ORR.
9.4 Statistical analyses	The text below has been updated as follows: "Estimated COD **for the final PFS analysis** will be approximately ~~17~~ **18** months after first randomized participant. The COD for **final** analysis of OS will be ~~18~~ **approximately 64** months after the ~~PFS analysis~~ **first randomized participant**."	The COD projections have been updated following the newly added futility interim analysis for PFS and the inclusion of OS as the key secondary endpoint.
9.4.1 Efficacy analyses	The analysis methods for OS have been updated to include a formal comparison between the 2 treatment arms (stratified logrank for statistical testing).	To clarify the statistical method used for the formal comparison between the 2 treatment arms on OS.

Section # and Name	Description of Change	Brief Rationale
9.4.1.1 Analysis of primary efficacy endpoint	The text below has been updated as follows "If progression and death are not observed before the ~~PFS analysis~~ COD **for final PFS**, PFS will be censored at the date of the last valid disease assessment with no evidence of a disease progression."	Updated for clarity
9.4.1.2 Analysis of secondary efficacy endpoints	The text below has been updated as follows: "Analysis of response-based endpoints (ie, ORR, DCR [disease control rate], CBR [clinical benefit rate], and DOR [duration of response]) will be performed for the global part primarily on the ITT population and supported by the analyses based on the ~~response-evaluable~~ **ITT** population **with measurable disease at study entry**."	This population has been removed from the study in consistency with the other studies from the same program. The analyses that were to be performed in this population will be performed in the ITT participants with measurable disease at study entry, regardless of postbaseline assessment availability. This ITT analysis will provide a more accurate estimation of the ORR.
	Overall survival was relocated as the key secondary objective in place of ORR and the analysis methods for OS have been updated to include a formal comparison between the 2 treatment arms.	Overall survival has been considered the key secondary endpoint, in response to the Food and Drug Administration recommendations.
9.5 Interim analyses	An interim analysis for futility has been planned to be carried out at 50% of the planned total number of PFS events. An interim analysis on OS is also planned at the time of final PFS analysis, if PFS is statistically significant. Interim analyses will be overseen by the Data Monitoring Committee (DMC). The details of these analyses have been included in 2 new sections: • "9.5.1 Interim analysis for progression-free survival" • "9.5.2 Interim analysis for overall survival"	To clarify the methodology used for the interim analyses.
9.5.3 Data Monitoring Committee	The following text has been added: "The DMC will also oversee the interim analyses detailed in Section 9.5.1 and Section 9.5.2."	To clarify that the DMC will be overseeing the interim analyses planned for this study.
Appendix 1	In Section 10.1.1, the following text has been updated: • "Any amendments to the protocol will require **national Health Authority and** Institutional Review Board [IRB]/Independent Ethics Committee [IEC] approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants."	Updated after requested by the Health Authorities.
	In Section 10.1.4, the following text has been updated: "The DMC will be in charge of reviewing **the safety data and** the progress of the study **(including overseeing interim analyses)** and ~~the safety data and~~ advising the Sponsor on potential modifications or communications that may be necessary to ensure the participant safety or protect the scientific integrity of the study."	To clarify that the DMC will be overseeing the interim analyses planned for this study.

Section # and Name	Description of Change	Brief Rationale
Appendix 3	In Section 10.3, the following text has been removed from "Follow-up of AEs and SAEs": "If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Sponsor with a copy of any postmortem findings including histopathology."	The text has been updated to reflect the procedures that will be carried out for the follow-up of AEs and SAEs.
Appendix 4	The following text has been added: "**Male participants** • Male participants with heterosexual partners of reproductive potential are eligible to participate if they agree to use the following during the protocol defined timeline: - Refrain from donating sperm **and** - At least 1 of the following condition applies: - Are and agree to remain abstinent from penile vaginal intercourse on a long-term and persistent basis, when this is their preferred and usual lifestyle **or** - Agree to be on a gonadotropin releasing hormone analog for at least 4 weeks (to be continued during study treatment) as per label and use a male condom during intercourse during study treatment until 1 week after stopping the study treatment and should not father a child in this period. A condom is required to be used also by vasectomized men, as well as during intercourse with a male partner, in order to prevent delivery of the drug via seminal fluid. • Men with a pregnant or breast-feeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom for the time defined in the protocol."	Because male participants have been considered eligible for this study, contraceptive guidance for male participants was included.
	The following text has been updated: "Non hormonal methods of contraception should be employed during the study in premenopausal women on a gonadotropin releasing hormone analog as per label. **These include: intrauterine device, bilateral tubal occlusion, vasectomy partner, male or female condom with or without spermicide, cap, diaphragm, or sponge with spermicide.**"	Updated to clarify allowed contraceptive methods for women of childbearing potential.
Appendix 5	The following text has been updated: "Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or	To accommodate the new assessments on drug metabolizing enzymes and transporters added to this amendment.

Section # and Name	Description of Change	Brief Rationale
	molecular subtype of the disease being treated. Therefore, where local regulations and Institutional Review Boards/Independent Ethics Committees allow, **a blood and** a saliva sample will be collected for DNA analysis from consenting participants."	
Appendix 8	The following text has been included in Section 2 of this Appendix (Study design): "At the time of Amended Clinical Protocol 02 submission, there was no experience of amcenestrant in Chinese patients. However, based on available data, no ethnic difference in amcenestrant safety profile is expected between Chinese and non-Chinese patients. For the ACT16105 study, a safety observation period will be set for Chinese participants to secure safety. A safety run in step will consist in the sequential treatment of 6 participants with amcenestrant (ie, approximately 12 randomized participants). None of the first 3 participants of amcenestrant arm will be treated for first dose on the same day. The safety review will occur when 6 Chinese participants have been exposed to amcenestrant and completed a minimum of 1 cycle duration (approximately 4 weeks) of treatment. If 0 to 1 out of 6 evaluated participants had a treatment related adverse event of special interest (AESI) or treatment related AE leading to the treatment discontinuation, enrollment will continue in China. If at least 2 out of 6 evaluated amcenestrant treated participants have a treatment related AESI, or a treatment related AE leading to treatment discontinuation, enrollment will be on hold in China and further safety and pharmacokinetic (PK) assessment will be performed."	This section has been updated after a request has been made by the Chinese Center for Drug Evaluation, in order to account for a possible higher PK variability in this population.
	In Section 4 of this Appendix (Study population), the text below has been updated as follows: "A dedicated cohort of up to approximately ~~42~~ **90** participants will be included."	After consultation with the Chinese Center for Drug Evaluation, as no prior Asian population exposure data were provided, the sample size of the Chinese extension should not be lower than 20% of the sample size of the global study and the Chinese extension should be powered to observe a HR lower than 0.8. To meet with these requirements, the number of participants in the China extension study has been increased from 42 to 90.
	In Section 6 of this Appendix (Study procedures) the text on pharmacodynamic evaluation specific to the China extension study has been updated as follows: "For ~~patients~~ **participants** enrolled in China, samples for ~~mutation profiling in~~ **estrogen receptor 1 gene (ESR1) analysis of** cell free deoxyribonucleic acid (cfDNA) will be collected at ~~baseline, Cycle 3 Day 1, and end of treatment visit~~ **Cycle 1 Day 1 (predose)**. ~~Separate~~ **The other** samples for ~~estrogen receptor 1 gene~~ **ESR1** analysis of cfDNA will not be collected **and exploratory pharmacodynamic endpoints will not be assessed in this extension study**."	In the China extension study, the only biomarker to be collected from participants will be the estrogen receptor 1 gene mutation status, for evaluation of PFS according to ESR1 mutation status (secondary objective). Biomarkers for exploratory objectives will not be collected from these participants.

Section # and Name	Description of Change	Brief Rationale
	In Section 7.1 of this Appendix (Sample size determination) the text below has been updated as follows: "Assuming the hazard ratio (HR) of progression free survival (PFS) in the amcenestrant arm relative to the control arm is 0.65, a total of ~~25~~ **65** PFS events in the Chinese population would provide an ~~86~~ **80**% probability of observing a HR inferior to ~~1~~ **0.80** in both the Chinese and non-Chinese populations, given that the primary analysis of PFS is statistically significant in the global study. Approximately ~~42~~ **90** Chinese participants would need to be enrolled to reach ~~25~~ **65** PFS events~~,~~. ~~assuming~~ **Assuming** the first Chinese participant enrolls 11 months after the first randomized participant of the global study and Chinese participants have a ~~9.5~~ **17**-month enrollment period~~.~~**, the cut-off date (COD) for PFS analysis is estimated to occur 5 months after the last Chinese participant is enrolled. This number of events would provide a 79% probability of observing a HR inferior to 0.80 in Chinese population, given that the primary analysis of PFS is statistically significant in the global study**"	After consultation with the Chinese Center for Drug Evaluation, as no prior Asian population exposure data were provided, the sample size of the Chinese extension should not be lower than 20% of the sample size of the global study and the Chinese extension should be powered to observe a HR lower than 0.8. To meet with these requirements, the number of participants in the China extension study has been increased from 42 to 90.
	In Section 7.3 of this Appendix (Statistical analysis), the following text has been added: "The decision to continue or not with the recruitment of Chinese patients will be based on the results of the statistical analyses performed in the global population."	To clarify the impact of global population interim analysis on the China expansion cohort.
Appendix 11	Concomitant administration of moderate CYP2C8 inducers will not be permitted in this study. For this reason, a list of moderate CYP2C8 inducers has been included in this Appendix.	Concomitant administration of moderate CYP2C8 inducers will not be permitted in participants receiving amcenestrant, since they may decrease amcenestrant exposure.

10.15.3 Amended protocol 03: 30 June 2020

This amended protocol (Amendment 03) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The objective of this amendment is to update the protocol on the following topics:

- Study population and inclusion/exclusion criteria:
  - Define the paired biopsies planned in the study as optional procedures (I 06),
  - Clarification on inclusion criteria regarding sex (I 09).
- Introduction of study name AMEERA 3.
- Contingency measures for a regional or national emergency information have been added in Section 5.5 Criteria for temporary delaying, Section 6.1 Study intervention(s) administered, Section 9.4 Statistical analysis, and Section 10.1.2 Informed consent process.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor formatting and editorial updates.	For clarity and accuracy.
Title page	Protocol title updated as follows: An open label randomized Phase 2 trial of amcenestrant, versus endocrine monotherapy as per physician's choice in patients with estrogen receptor-positive, HER2-negative locally advanced or metastatic breast cancer with prior exposure to hormonal therapies **(AMEERA 3).** Short title updated as follows: "Phase 2 study of amcenestrant versus physician's choice in patients with locally advanced or metastatic ER-positive breast cancer **(AMEERA 3)**."	The study name is now available.
Synopsis	Protocol title updated as follows: An open label randomized Phase 2 trial of amcenestrant, versus endocrine monotherapy as per physician's choice in patients with estrogen receptor-positive, HER2-negative locally advanced or metastatic breast cancer with prior exposure to hormonal therapies **(AMEERA 3).** Short title updated as follows: "Phase 2 study of amcenestrant versus physician's choice in patients with locally advanced or metastatic ER-positive breast cancer **(AMEERA 3)**."	The study name is now available.
1.3 Schedule of Activities	Vitals signs information has been updated: For Vitals signs *a* In C1D1, vital signs will also be assessed **approximately** 2 hours after dosing.	Updated to allow some flexibility in the assessment of the vital signs following the first intake of the IMP.
	Tumor specimen/ biopsy information has been updated: For Tumor specimen/ biopsy **(optional procedures)** *a* Most recent archived biopsied tumor within past 3 months prior to initiation of study treatment, or fresh tumor biopsy collected from time of inclusion to C1D1 pre-treatment **(optional).** *b* Cycle 3 Day 1 (allowed up to Cycle 3 Day 15 or within 14 days after first radiological tumor assessment after baseline). Tumor biopsy should be performed only after radiological assessment **(optional).**	The status of this procedure has been updated as "optional", to limit the burden of the participants in the study, and to promote their recruitment.
	Removed follow-up visit mark "~~X~~" for "Follicle-stimulating hormone and estradiol (premenopausal women only)".	The GnRH agonist treatment for pre/perimenopausal participants will not be administered during the follow-up period: the ovarian function suppression will not be monitored after the end-of-treatment.
	Created a new footnote "a Predose Cycle 1 Day 1" for cross-referred to "Estradiol (serum) for Cycle 1, Day 1 Visit".	To specify Estradiol sampling at predose.
	The following text has been updated for footnote for Normal tissue reference DNA (Saliva) • Section 8.7.2 and **Section 10.16.**	To implement the instructions related to a regional or national emergency in the protocol.

Section # and Name	Description of Change	Brief Rationale
Section 2.3.2.1 Amcenestrant	Added the following text: • Risk of severe rash.	This potential risk related to amcenestrant has been added, as 2 Japanese participants have presented an episode of maculopapular rash in the TED15954 Phase I study. These 2 events (Grade 2 and Grade 3) led to study drug discontinuation.
Section 3 Objectives and endpoints Table 1 Objectives and endpoints Tertiary/exploratory	The following tertiary/exploratory objective and endpoint have been updated: Objective: To evaluate in participants tumor biomarkers over time such as estrogen receptor (ER), Ki67, Bcl 2, and progesterone receptor (PgR) protein, and ribonucleic acid (RNA) gene expression profiles (for participants with tumor sites accessible for biopsy who accept biopsies at study entry and on treatment). Endpoint: Tumor ER, Ki67, Bcl 2, and PgR protein, and RNA gene expression profiles in **optional** paired biopsies at Cycle 1 Day 1 (pre-treatment) and at Cycle 3, Day 1 (allowed up to Day 15; or within 14 days after first radiological tumor assessment after baseline).	Updated to indicate that the biopsies are optional.
Section 5.1 Inclusion criteria	In I 05, the following statement has been updated: ~~"Either the primary tumor or any metastatic site must be~~ **Documentation of** HER2 non over-expressing **based on most recent tumor sample** by IHC (0, 1+), or in situ hybridization-negative based on single-probe average HER2 copy number <6.0 signals/cell or dual-probe HER2/centromeric probe for chromosome 17 (CEP17) ratio <2 with an average HER2 copy number <6.0 signals/cell as per American Society of Clinical Oncology guidelines (28). Note that if the primary tumor is HER2-negative and any further metastatic lesion is HER2-positive, the participant cannot be selected for inclusion."	To clarify and harmonize the definition of HER non over-expressing tumors.
5.1 Inclusion criteria	In I 06, the following text has been updated: **"I 06 deleted in amended protocol 03**. ~~For participants with tumor accessible for paired biopsy at study entry: baseline samples, formalin fixed paraffin embedded (FFPE) archived biopsy samples (within 3 months prior initiation of study treatment) can be used, but preferably fresh biopsies from primary tumor or recurrence or metastasis, will be collected. It is recommended that the second biopsy is collected at the same location as the baseline biopsy, whenever possible."~~	Deleted as the biopsy procedures has been categorized as "optional", to limit the burden of the participants in the study, and to promote their recruitment.
	In I 07, the following text has been updated: "For ~~countries where~~ **participants for whom** CDK4/6 inhibitors are available (ie, approved **in their region** and can be reimbursed), prior treatment with a CDK4/6 inhibitor in combination with fulvestrant or an AI is mandatory."	Approval and reimbursement may vary according to participant's region or situation within the same country.

Section # and Name	Description of Change	Brief Rationale
	In I 08, the following text has been updated: "Participants must have **received** ~~progressed after~~ at least 6 months of a continuous prior endocrine therapy for advanced breast cancer and **have progressed while on** endocrine therapy **(in** single agent or in combination**). T**he number of **prior** hormonal lines will be limited to 2"**.** **"Participants with a relapse** ~~or have relapsed~~ while on adjuvant endocrine therapy but after the first 2 years**,** or ~~have relapsed~~ **with a relapse** within 12 months of completing adjuvant endocrine therapy **are also eligible**."	To align with the definition of secondary endocrine resistance as defined in the 3rd European School of Oncology European Society for Medical Oncology International Consensus Guidelines for Advanced Breast Cancer.
	In I 09, the following text has been updated: "**Male or** Female." **"A) Postmenopausal women** ~~Female participants must be postmenopausal,~~ as defined by one of the following: ~~Or participants are premenopausal women on a GnRH analog for at least 4 weeks (to be continued during study treatment).~~ ~~Sexually active males should be on a GnRH analog for at least 4 weeks (to be continued during study treatment).~~ **B) Pre/perimenopausal women, ie, not meeting the criteria for being postmenopausal.** **C) Male participants.** **Note: Male with no prior bilateral orchiectomy and pre/perimenopausal women should be on a GnRH agonist for at least 4 weeks prior to randomization (to be continued during study treatment)."**	The definition of a "sexually active male" has been clarified, as required by regulatory agency request.
Section 5.3 Lifestyle considerations	The following text has been updated: For this reason, participants should avoid direct exposure to natural or artificial sunlight during study treatment and for at least ~~30~~ **5** days after last IMP dose.	To update the duration of avoiding the natural or artificial sunlight exposure to 5 days, as it is 5 times the half-life of the IMP (24 hours).
Section 5.5 Criteria for temporarily delaying	Added a new section to the protocol and the following text has been updated: **"Section 5.5 Criteria for temporarily delaying** **During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures proposed in Section 10.16 (Appendix 16) should be considered".**	To implement the instructions related to a regional or national emergency in the protocol.
Section 6.1 Study intervention(s) administered	The following text has been updated: Between the protocol-scheduled on site visits, interim visits may be required for IMP dispensing. As an alternative to these visits, IMPs may be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations and approved by the participant **(Section 10.16 [Appendix 16])**.	To implement the instructions related to a regional or national emergency in the protocol.

Section # and Name	Description of Change	Brief Rationale
Section 8.6.1 Tumor biopsy to assess estrogen receptor degradation (optional procedures)	The following text has been updated: 8.6.1 Tumor biopsy to assess estrogen receptor degradation **(optional procedures)** Participants with an accessible tumor **who consented to the optional paired biopsy** will be asked to contribute the most recent archived biopsied tumor (within past 3 months prior to initiation of study treatment) or preferably a fresh tumor biopsy that can be collected between the time of ICF signature and Cycle 1 Day 1 prior to treatment.	To clarify the assessment of the estrogen receptor degradation with the biopsies, defined as “optional”.
Section 8.7.2 Mutation profiling in cell-free DNA	The following text has been added: **“For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.16 (Appendix 10.16)”.**	To implement the instructions related to a regional or national emergency in the protocol.
Section 8.7.3 RNA transcriptome analysis	The following text has been updated: Transcriptome studies of the **optional** tumor biopsy may be conducted using microarray, sequencing, and/or alternative similar techniques, which facilitates the simultaneous measurement of the relative abundances and sequences of thousands of RNAs, resulting in a transcriptome profile for each biopsy sample. The **optional** tumor biopsy taken for the assessments referred in Section 8.6.1 can be used for these analyses.	To clarify the transcriptome studies of the biopsies, defined as “optional”.
Section 8.8 Biomarkers	The following text has been updated: Samples may be stored for a maximum of ~~5 years, or~~ 15 years, if future use of samples is consented to, or according to local regulations, following the last participant last visit at a facility selected by the Sponsor to enable further analysis of biomarker responses to the IMP.	To harmonize the wording of the samples’ storage with the informed consent form.
Section 9.4 Statistical analysis	The following text has been added: **“For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.16 (Appendix 16)”.**	To implement the instructions related to a regional or national emergency in the protocol.
Section 9.5.3 Data Monitoring Committee	The following text has been updated: The DMC will also oversee the interim analyses **on PFS** detailed in Section 9.5.1 ~~and Section 9.5.2~~.	To clarify the scope of Data Monitoring Committee (DMC) responsibility - as the interim analyses on Overall Survival will happen at the time of final Progression Free Survival, treatment will be unblinded and thus there is no need for DMC at that time.
Section 10.1.2 Informed consent process	The following text has been added: **“For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.16 (Appendix 16)”.**	To implement the instructions related to a regional or national emergency in the protocol.
Section 10.5 Appendix 5: Genetics	The following text has been updated: RNA may be isolated from the **optional** tumor biopsy in order to assess effects of IMP on the tumor. Analyses may include	Updated to indicate that the biopsies are optional.

Section # and Name	Description of Change	Brief Rationale
	microarray, sequencing, and/or alternative similar techniques, resulting in a transcriptome profile. The analyses may include RNA of selected genes or all of the genome.	
Section 10.8 Appendix 8: Country-specific requirements	The following text has been updated: 4 STUDY POPULATION Participants will be selected based on the study inclusion and exclusion criteria as defined in Section 5 of the global study protocol and will have agreed to participate in this extension study. A dedicated cohort of up to approximately 90 participants will be included. **Note: In this extension cohort, previous treatment with a CDK 4/6 inhibitor will not be mandatory, and there will be no limitation to the number of participants naïve to CDK4/6 inhibitors.**	To specify that the previous treatment with a CDK 4/6 inhibitor and the limitation to the number of participants naïve to CDK4/6 inhibitors does not apply to the participants of the extension study.
Section 10.16 Appendix 16: Contingency Measures for a regional or national emergency that is declared by a governmental agency	New section 10.16 has been inserted in the protocol and added the following text: "**APPENDIX 16: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY** **Continuation of the study in the event of a regional or national emergency declared by a governmental agency:** **A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, and terrorist attack) may prevent access to the clinical trial site.** **Contingency procedures are suggested for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with GCP in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.** **The decision for each individual participant to remain and/or start in the study should be made on a case by case basis based on best Investigator medical judgment. The clinical judgment of the treating physician should guide the management plan of each participant based on individual benefit/risk assessment and the evolving situation at the site (Section 5.5). However, in case new participant eligible for the trial, the PI/site should assess the capacity to maintain these patients into the trial before any screening procedures will start. If the site cannot guarantee an accurate follow-up in the context of the trial, alternative treatment outside the clinical trial should be proposed.** **When participants are already randomized and/or treated, attempts should be made to perform all assessments in accordance with the protocol to the extent possible.**	To implement the instructions related to a regional or national emergency in the protocol.

Section # and Name	Description of Change	Brief Rationale
	When possible, the focus should be on Investigational Medicinal Product (IMP) administration and safety blood collection (eg, biochemistry and hematology). However, all efforts should be made to perform the measurements of key parameters for efficacy endpoints (eg, tumor assessments at every other cycle). The deviations from the study protocol (eg, treatment delay, omission, tests not performed…) should be documented in the source document and collected in the appropriate pages of the eCRF. **Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:** • **If onsite visits are not possible, remote visits (eg, with home nurses, home health vendor, etc) may be planned for the collection of possible safety and/or efficacy data (eg safety assessments, efficacy assessments especially the tumor assessment, PRO)** • **If onsite visits are not possible visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely** • **Use of local clinic or laboratory locations may be allowed** • **The Direct-to-Patient (DTP) supply of the IMP from the site/sponsor where allowed by local regulations and agreed upon by participant. (Section 6.1)** • **When collection of saliva sample is not feasible, the procedure will not be done. In that case, extraction of the DNA from the blood sample for genotyping and drug metabolizing enzyme and transporters may be considered.** **Contingencies implemented due to emergency will be documented.** **The impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP. (Section 9.4)** **For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local labs). (Section 10.1.2).”**	

10.15.4 Amended protocol 04: 17 December 2020

This amended protocol 04 (Amendment 04) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The objective of this amendment is to update the protocol on the following topics:

- To update exclusion criteria E15 and E16 with new data available on drug interactions (BCRP substrates, CYP3A and CYP2C8 inducers)
- To revise the futility analysis
- To add the risk of male fertility
- To add risk minimization strategies for pregnancy, osteoporosis induced by endocrine therapies, hepatic toxicity, and photosensitivity

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Throughout	• Minor formatting and editorial updates. • Changed the name of SAR439859 IMP to "Amcenestrant".	• For clarity and accuracy. • Availability of amcenestrant INN for SAR439859.
Synopsis (Objective and Endpoints); Section 3 Objective and endpoints (Table 1); 9.4.1 Efficacy analyses	The definitions of Disease Control Rate (DCR) and Clinical Benefit Rate (BCR) have been updated to add the "Non-Complete Response/Non-Progressive Disease" in the endpoint's descriptions.	To take in account the participants with only non-measurable disease in the definitions of DCR and CBR.
1.3 Schedule of Activities; Section 8 Study assessments and procedures,	A specification has been added to local "Follicle stimulating hormone and estradiol" samples: "**a. For patients receiving Fulvestrant as IMP, the local estradiol sample will not be required".**	Section updated to take in account that Estradiol levels can be high due to Fulvestrant intake.
	A pregnancy test has been added for WOCBP in screening, at D1 of each cycle and at EOT.	Pregnancy test added to follow the CTFG guidelines "Recommendations related to contraception and pregnancy testing in clinical trials" Version 1.1, taking in account the suspected risk of fetotoxicity of amcenestrant.
1.3 Schedule of Activities; 8.1.2 Bone scans	The section has been updated as follow: *a* "If at screening, lesions are detected in the bone scan but not in the CT/MRI (RECIST 1.1) scan, further bone scans should be conducted every 8 weeks ±7 days **after randomization**. If the lesions seen in the bone scan are no longer visible, these assessments ~~can~~ **should** be conducted every 16 weeks ±7 days **after randomization**. If lesions are detected in the bone scan and CT/MRI (RECIST 1.1) scan, further bone scan assessments will be conducted every 16 weeks ±7 days **after randomization**."	To add clarification on bone scans schedule.
2.3.2 Potential and identified risks	For amcenestrant, risk of male infertility has been added.	Amcenestrant has the potential to impair reproductive function and fertility in male humans based on clinical findings in dogs, attributed to the pharmacology of Amcenestrant in the testes. The reference to the label for safety information has been omitted in previous version for the IMP fulvestrant
2.3.2 Potential and identified risks; 5.2 Exclusion criteria; 6.5 Concomitant therapy; 10.12 List of CYP inducers	Updated data on amcenestrant allows the moderate inducers of CYP3A and CYP2C8 to be administered with amcenestrant. The Exclusion Criteria E 15. has been updated as follow: "Treatment with strong ~~**or moderate**~~ CYP3A ~~**and CYP2C8**~~ inducers within 2 weeks before randomization or 5 elimination half-lives whichever is longer" "Potential and identified risks", "Concomitant therapy" sections and Appendix 11 have also been updated accordingly.	To update the protocol with available data showing that there is a modest decrease (30%) of amcenestrant with strong CYP3A inducers.
5.2 Exclusion Criteria; 6.5 Concomitant therapy	The Exclusion Criteria E 16. has been updated as follow: "Ongoing treatment with drugs that are **sensitive** substrate of P-glycoprotein (P-gp) (dabigatran, digoxin, fexofenadine**), and of Breast Cancer Resistance Protein (BCRP) (rosuvastatin, sulfasalazine)** since amcenestrant is a potential inhibitor of P-gp **and BCRP".** "Concomitant therapy" section has also been updated accordingly.	Amcenestrant has a potential inhibitory effect on BCRP substrates, leading to increase their absorption: exclusion criteria and concomitant medication section has been updated accordingly.

Section # and Name	Description of Change	Brief Rationale
5.3 Lifestyle considerations	5.3.1 Sun protection section has been updated: "It is recommended to advise to wear protective clothing, lip balm, **and broad spectrum** sunscreen with a high sun protection factor (eg, ≥30) **to cover UVA and UVB light exposure** when outdoors **with frequent re-application as necessary."**	To ensure that the recommendations provided for sun protection are adequate.
	5.3.2 Osteoporosis section has been added: **"Due to anti-estrogenic properties of amcenestrant, fulvestrant, and aromatase inhibitors being potent estrogen lowering agents, there exists potential risk of osteoporosis. Lifestyle changes that preserve bone mineral density (eg, stopping or reducing smoking and drinking, and increasing physical activity, especially weight-bearing exercises), and adequate nutrition (protein, calcium, and supplementary vitamin D3) are recommended."**	Amcenestrant, fulvestrant and aromatase inhibitors have a risk of osteoporosis because of their anti-estrogenic properties. The implemented changes are added as part of risk minimization strategy.
6.5 Concomitant therapy	Following statement has been added: **Prophylactic vaccination is recommended for influenza A and B virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; ie COVID-19), Pneumococci, and Haemophilus influenza.**	To recommend some prophylactic vaccinations for the study participants.
6.6 Dose modification	The table 3 "Recommended dose modification and management of Amcenestrant related toxicities" has been updated to specify guidance on the management of isolated increase in alanine transaminase (ALT) Grade 3.	The dose modification table has been updated to provide guidance in case of isolated ALT increase.
Section 8 Adverse events and serious adverse events	For AESI ALT increase Grade ≥3: the following text has been added: • **"Omit study-treatment study-intervention administration, and repeat LFTs within 2-3 days. If not recovered, monitor LFTs weekly until recovery to Grade ⩽1 (or baseline grade). Confounding factors such as, liver metastasis, hepato-biliary disorders, concomitant medications, etc should be excluded prior to dose modifications. Please refer to the dose modification guidelines for management of isolated increase of ALT (Table 3 Section 6.6).** • **Close monitoring of study participants is recommended in cases of increase of Grade ≥3 ALT. LFTs should be performed in patients with onset of otherwise unexplained nausea, jaundice, right upper abdominal pain, fever, or rash.** • **LFTs include AST, ALT, ALP (isoenzymes if Grade >2), total bilirubin (fractionated if >2 x ULN direct), GGT, and INR (if total bilirubin >2.5 ULN).** • **An ultrasound, or other imaging, should be considered based on the clinical presentation.** • **A consultation with a hepatologist should be undertaken if there is,** - **Unexplained or persistent Grade ≥3 ALT despite dose omissions** - **ALT >3 ULN and concomitant jaundice (total bilirubin >2.5 ULN), in patients with normal ALT and total bilirubin at baseline.** **to exclude hepato-biliary disorders (eg, hepatotropic virus infections, autoimmune or alcoholic hepatitis, Non-Alcoholic Steatohepatitis, etc) or drug induced liver injury.** • **Further hepatic virology will be undertaken as per the site's local guidelines for the treatment of cancer**	The AESI section has been updated to provide guidance in case of an ALT increase.

Section # and Name	Description of Change	Brief Rationale
	patients, taking into account the local and national recommendations".	
	"Photosensitivity" has been added as an AESI: **"If photosensitivity is suspected in study participants, consider dermatologist consultation. Confounding factors such as other dermatological disorders, drug eruptions resulting from concomitant medication use, etc should be excluded prior to any dose modification (refer to Section 6.6 Dose modification). In case of study intervention discontinuation because of photosensitivity reaction, study participant should be followed for possibility of development of other manifestations of photosensitivity such as photo-onycholysis, lichenoid reaction or actinic granuloma."**	Preclinical studies using amcenestrant indicate a potential risk for phototoxicity. Photosensitivity events has been added as an AESI in order to collect relevant information.
8.3.5 Pregnancy; Section 10.4 Contraceptive guidance and collection of pregnancy information	The contraception guidance has been updated: • to specify that male participants contraceptive guidance does not apply for men with prior bilateral orchiectomy • to keep consistency in the protocol that all male participants without prior bilateral orchiectomy must be on a GnRH analog • to add a recommendation for male participants: **"Male participants should consider sperm preservation prior to beginning therapy with study IMPs because exposure to amcenestrant has the potential risk of testicular injury with partial or permanent infertility. Because exposure to amcenestrant, has the potential risk of testicular injury with partial or permanent infertility."** • to update the list of methods of contraception to present only "highly-effective" contraceptive measures • to clarify the duration of the contraception following the last IMP intake • Non-hormonal methods of contraception should be employed during the study in premenopausal participants and in male participants without prior orchiectomy on a GnRH analog as per label (please see Section 10.4 for details).	To clarify and update the section to follow the CTFG guidelines "Recommendations related to contraception and pregnancy testing in clinical trials" Version 1.1, taking in account the suspected risk of fetotoxicity of IMPs, and the risk of male fertility with amcenestrant per request from health authorities.
8.3.6 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs	This section has been deleted.	To delete a section which could be misunderstood in the AEs/SAEs reporting process.
9.4.3.1 Analyses of patient reported outcome endpoints	The following text has been updated: "Reasons for non-completion will be summarized on the safety population. For the QLQ-C30 (15 total scales), QLQ-BR23 (8 scales), and EQ-5D-5L (health index and VAS) instruments, descriptive statistics on the absolute value and changes from baseline will be done for each treatment arm at each time point, at EOT and **60 to** 90 days after the last study administration (follow-up)."	Clarification on PROs schedule, to take in account that EOT visit can be performed before 30 days following last IMP (if further therapy is started).

Section # and Name	Description of Change	Brief Rationale
9.5.1 Interim analysis for progression-free survival; 1.1 Synopsis	The following text has been updated: "**The stopping boundary for futility is based on the observed HR based on Cox proportional hazard model, ie, an HR>1.1**. ~~The stopping boundary for non-binding futility will be derived based on the O'Brien and Fleming β-spending function. If the value of the test-statistic exceeds the O'Brien and Fleming non-binding futility boundary (z >-0.435, p >0.332), the study may be stopped for futility~~." The same statement in the section 1.1 Synopsis has also been updated accordingly.	To revise the futility analysis strategy in order to recommend stopping the study only in case of observed increase risk of PFS events in the experimental arm compared to the control arm.
10.1.6 Data quality assurance	The following section has been added: "**Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents."**	To allow remote-monitoring when allowed by local regulations, if on-site monitoring is not possible
10.2, Clinical Laboratory Test	Table 10 was updated with the addition of GFR assessment	To clarify that renal function calculation is needed on top of the creatinine level for all patients.
10.4 Contraceptive guidance and collection of pregnancy information	Pregnancy outcome follow-up duration has been updated to up to one year.	As requirements of Health Authorities vary across countries, pregnancy outcome follow-up may last up to one year.
	The following text has been added: **"Male participants with partners who become pregnant** • **The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.** • **After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date but may last up to one year. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure."**	To mention in the "collection of pregnancy information" section the pregnant partners of male participants on top of the pregnant participants.
10.13 List of CYP sensitive substrates	List of CYP sensitive substrates has been updated.	To help investigators to monitor efficacy of CYP sensitive substrate drugs, for participants receiving amcenestrant.
10.17 Patient reported outcomes	Added a copy of the following PROs English-language questionnaires: EORTC QLQ-C30, EORTC BR-23 (for female and male participants) and EQ-5D-5L.	As required by Health Authority.

10.15.5 Amended protocol 05: 23 September 2021

Amended protocol 05 (23 September 2021)

This amended protocol 05 (Amendment 05) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for the amendment

The objective of the amendment is to update the protocol with the following key changes:

- To update exclusion criteria and concomitant medication section with results from recent in vitro and clinical drug-drug interaction studies.
- To update some safety guidance regarding osteoporosis risk following Belgium Health Authority commitment.
- To update in the Chinese extension cohort the procedures required in the full-PK sampling population, and to clarify how the cut-off date for PFS analysis is determined.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis and 4.1 Overall design	For planned cutoff date (previously database lock date) for the global study, the following sentence “For cycles completed after the COD for OS analysis, all ongoing SAEs (related or not), …” has been changed to “For cycles completed after the COD for final PFS analysis for the main cohort, only all ongoing SAEs (related or not), …”	To clarify that after COD for final PFS analysis, data collected will be limited to exposure data, reason of EOT, and safety events and its related information when adverse event is serious or related to IMP.
1.1 Synopsis and 4.1 Overall design	For planned cutoff date (previously database lock date) for the Chinese participants, the following sentence has been removed “ie, approximately 18 months after the PFS analysis of the global study”.	Both global and China study are event-driven, the cut-off dates are independent of each other. Therefore, removed the dependency on timing of global analysis, to bring more clarity.
5.2 Exclusion criteria	Exclusion criterion 16 was adjusted to remove sensitive substrates of P-gp and BCRP and add sensitive substrates of OATP1B1/B3. And a note was added under this exclusion criteria to refer to FDA website.	A recent clinical drug-drug interaction study showed that amcenestrant given at a higher dose of 400 mg has no clinically relevant effect on P-gp sensitive substrate (Dabigatran). Since inhibitory potential on BCRP is lower, no effect is anticipated either. In addition, it was identified in vitro that amcenestrant is a potential inhibitor of OATP1B1/1B3.
6.5 Concomitant therapy	Sensitive substrates of P-gp and BCRP related information has been removed; sensitive substrates of OATP1B1/B3 related information has been added.	
	Caution to be taken with the proton pump inhibitors has been removed.	To update recommendation following the most recent available data of drug-drug interaction studies.

Section # and Name	Description of Change	Brief Rationale
5.3.2 Osteoporosis	The following sentence was added "Investigators will monitor Bone Mineral Density if clinically indicated, taking into account full medical history of patients, all confounding factors, previous anti-cancer treatments and considering the anti-estrogenic properties of the study drugs."	To clarify the responsibilities for the monitoring, as a commitment to Belgium HA requirement.
6.6 Dose modification	In Table 3, "Omit endocrine therapies administration" has been updated to "Omit amcenestrant administration" for Grade 2 and Grade 3 for isolated increase of ALT part of the table.	To clarify that only amcenestrant is in scope of this 'recommended dose modification' table.
9.4.2.1 Analyses of adverse events	"AESIs" have been added as a bullet under the "The number and percentage of participants who experience any of the following will be provided".	For clarity and consistency.
10.8 Country-specific requirements (China extension study)	In Section 6, under pharmacokinetic evaluation, some flexibility has been added to the required samples in the "full-PK sampling" population in the extension cohort of China: samples on top of Cycle 1 Day 1/2 and Cycle 2 Day 1 may be omitted based on investigator decision.	To lighten the required PK samples of the "full-PK" population in China, when sampling is difficult for patients.
	In the section 6. "Procedures": • The following sentence has been modified: "Biopsy samples and blood samples will be taken in accordance with local regulations **for all participants from China (global and extension part)**. • The following sentence has been added: "Note: These specificities apply also for participants from China enrolled in the global part of the study."	To clarify that specificities regarding exploratory endpoints in China per local regulations apply also for participants from China enrolled in the global part of the study.
	• In the sample size determination section, the following sentence has been removed "This number of events would provide a 79% probability of observing a HR inferior to 0.80 in the Chinese population, given that the primary analysis of PFS is statistically significant in the global study". • The following sentence "It is anticipated to occur 5 months after the last Chinese participant is enrolled" has been changed to "The actual COD of the Chinese cohort will be the date with approximately 65 PFS events in Chinese population".	To clarify the sample size determination section, and to clarify the current definition of the COD rule for the Chinese population.
	In the informed consent section, "A separate informed consent (ICF) shall be obtained... will sign a separate informed consent for this aspect of the study" has been changed to "An informed consent (ICF) shall be obtained ... will sign a separate section in the informed consent for this aspect of the study".	To clarify that participants who agree to have samples taken for the full PK assessments will have to sign a separate section of the ICF rather than a separate ICF.
Entire document	Editorial changes, updates as per latest One Document protocol template (OneDocument Version 6.0).	Correction of typographical errors and minor inconsistencies across different sections, and clarifications.

Section # and Name	Description of Change	Brief Rationale
		To be aligned with latest One Document protocol template.

10.16 APPENDIX 16: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Continuation of the study in the event of a regional or national emergency declared by a governmental agency:

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, and terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with GCP in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

The decision for each individual participant to remain and/or start in the study should be made on a case by case basis based on best Investigator medical judgment. The clinical judgment of the treating physician should guide the management plan of each participant based on individual benefit/risk assessment and the evolving situation at the site (Section 5.5). However, in case new participant eligible for the trial, the PI/site should assess the capacity to maintain these patients into the trial before any screening procedures will start. If the site cannot guarantee an accurate follow-up in the context of the trial, alternative treatment outside the clinical trial should be proposed.

When participants are already randomized and/or treated, attempts should be made to perform all assessments in accordance with the protocol to the extent possible.

When possible, the focus should be on Investigational Medicinal Product (IMP) administration and safety blood collection (eg, biochemistry and hematology). However, all efforts should be made to perform the measurements of key parameters for efficacy endpoints (eg, tumor assessments at every other cycle). The deviations from the study protocol (eg, treatment delay, omission, tests not performed…) should be documented in the source document and collected in the appropriate pages of the eCRF.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If onsite visits are not possible, remote visits (eg, with home nurses, home health vendor, etc) may be planned for the collection of possible safety and/or efficacy data (eg safety assessments, efficacy assessments especially the tumor assessment, PRO).

- If onsite visits are not possible visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely.
- Use of local clinic or laboratory locations may be allowed.
- The Direct-to-Patient (DTP) supply of the IMP from the site/sponsor where allowed by local regulations and agreed upon by participant. (Section 6.1).
- When collection of saliva sample is not feasible, the procedure will not be done. In that case, extraction of the DNA from the blood sample for genotyping and drug metabolizing enzyme and transporters may be considered.

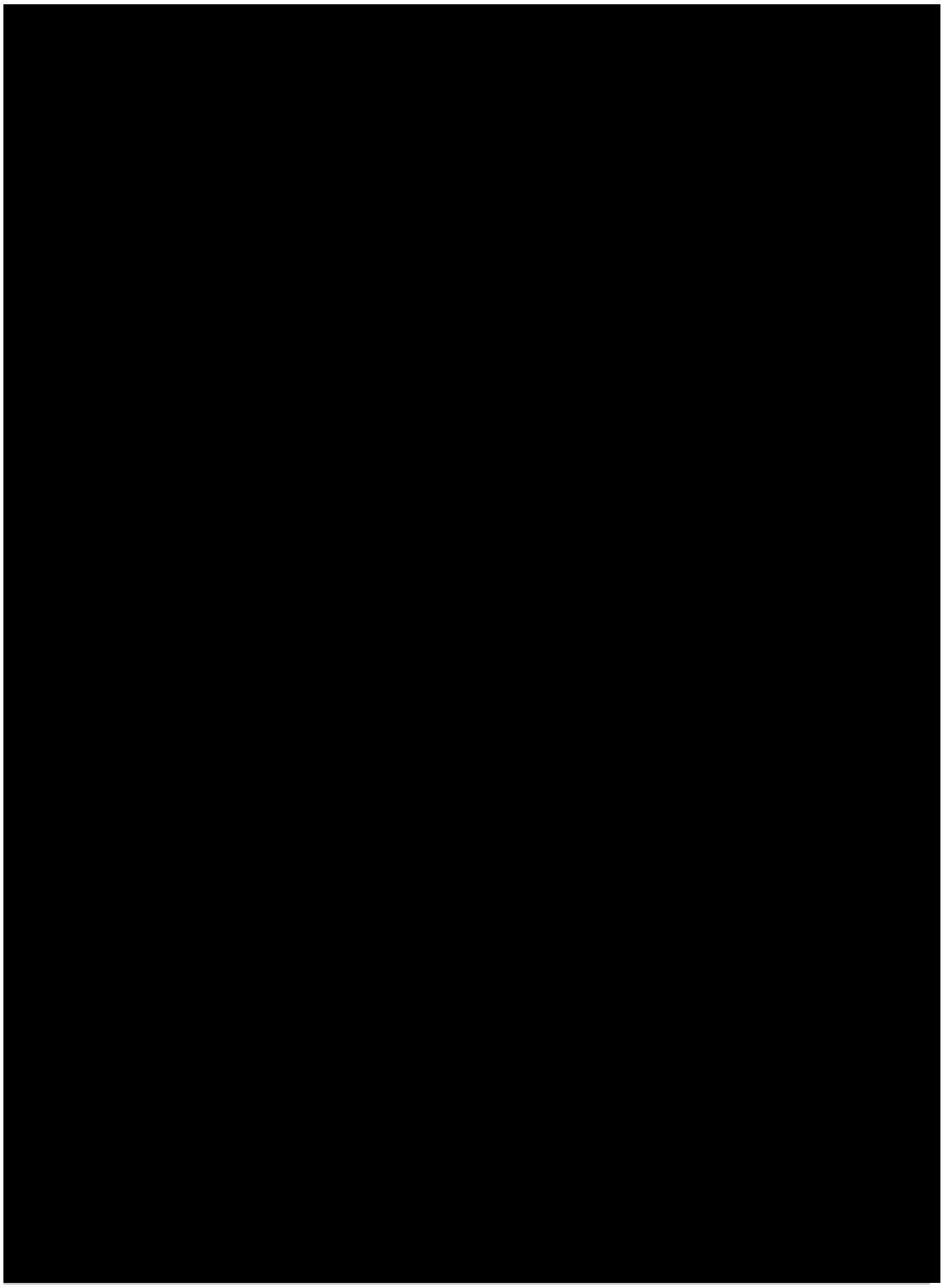
Contingencies implemented due to emergency will be documented.

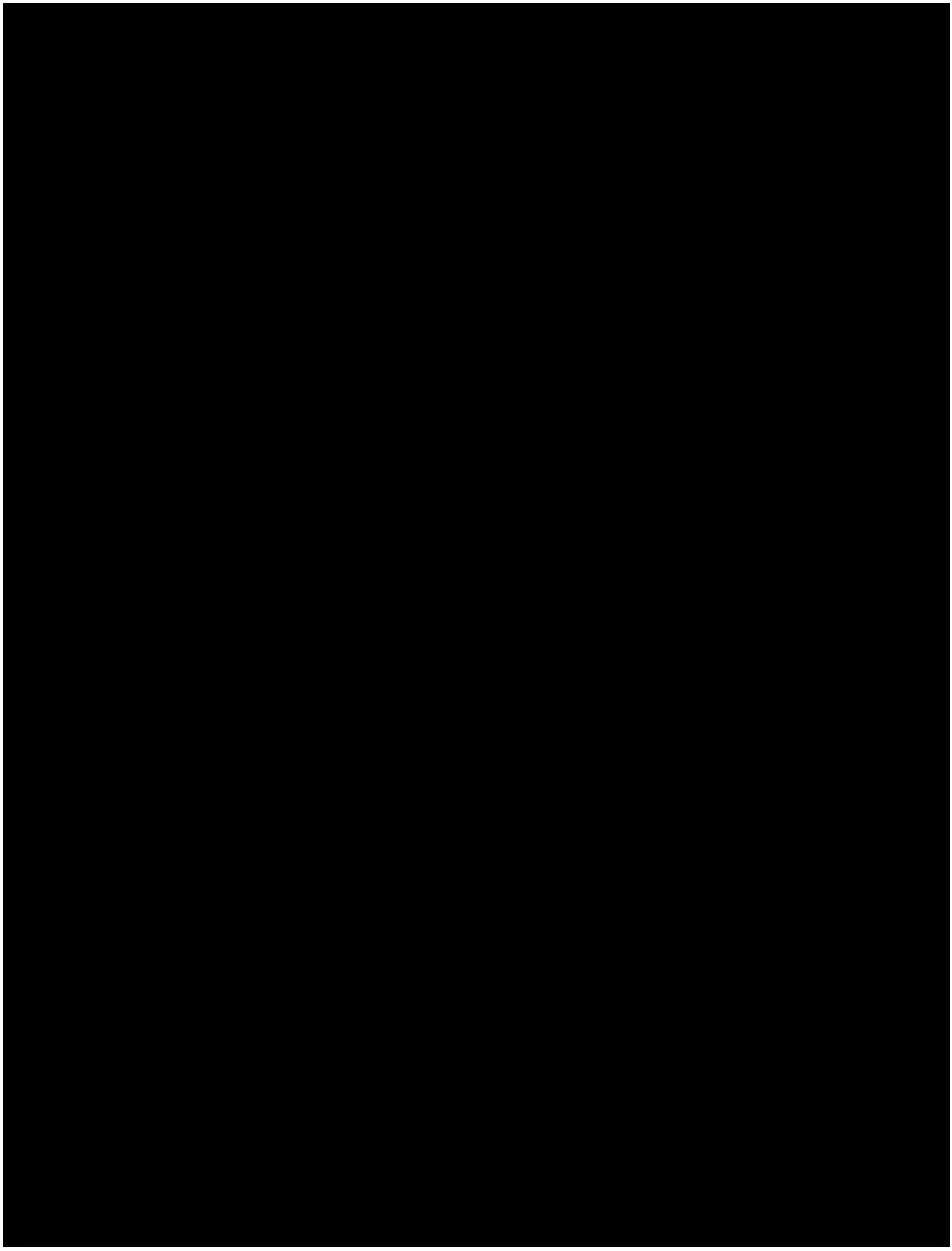
The impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP (Section 9.4).

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension, use of local labs) (Section 10.1.2 [Appendix 1]).

10.17 APPENDIX 17: PATIENT REPORTED OUTCOMES

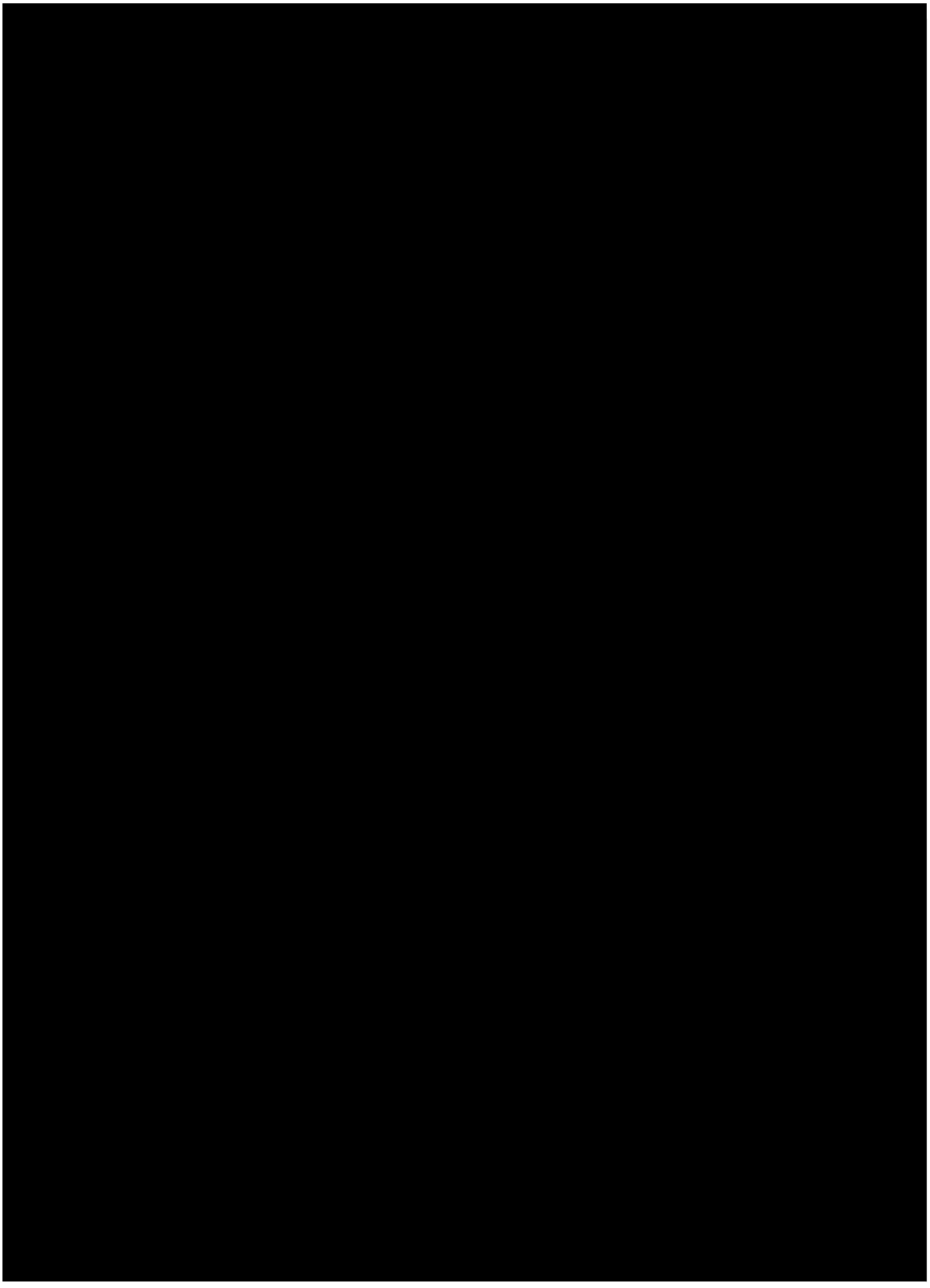
10.17.1 EORTC QLQ-C30



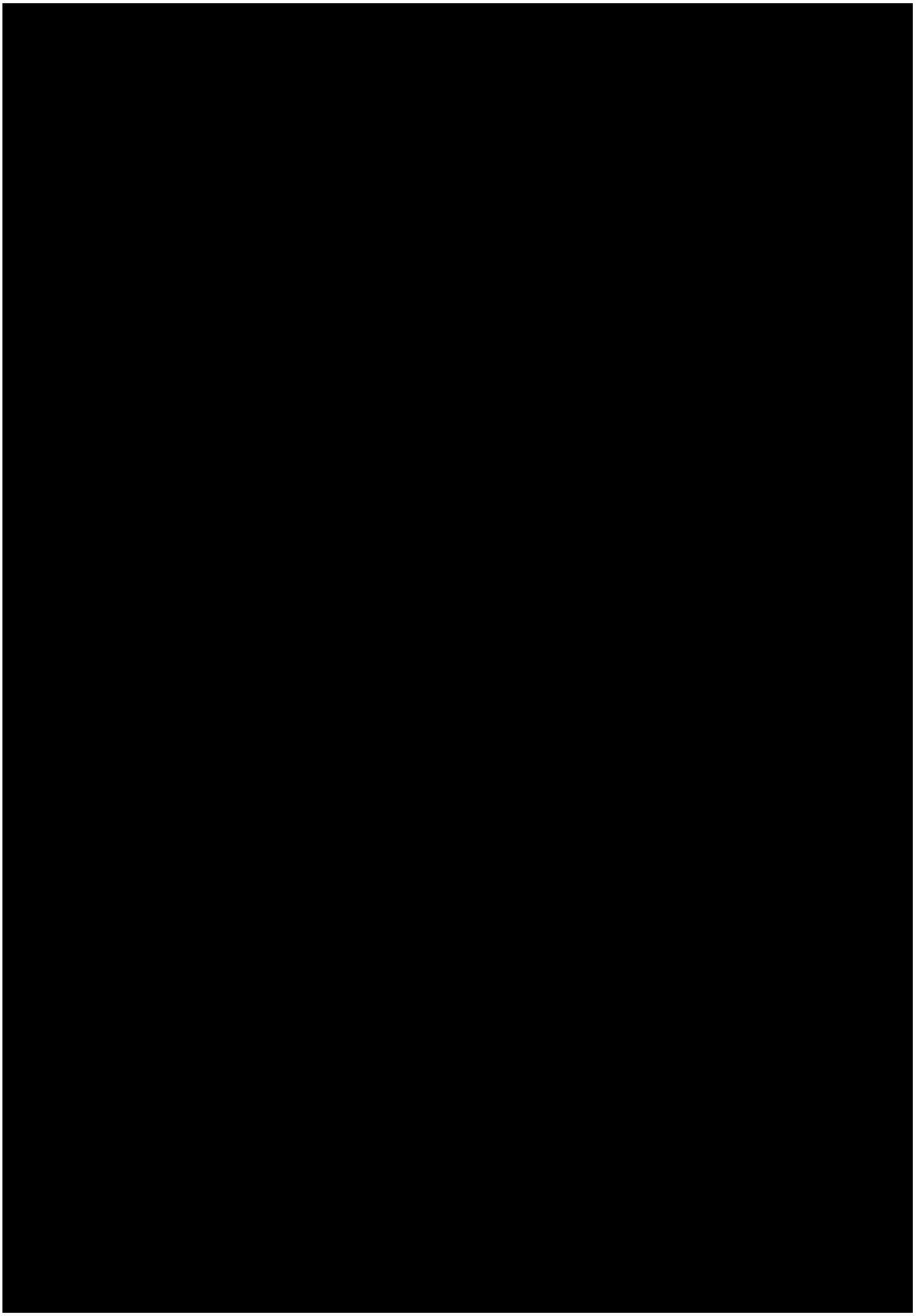


10.17.2 EORTC QLQ-B23

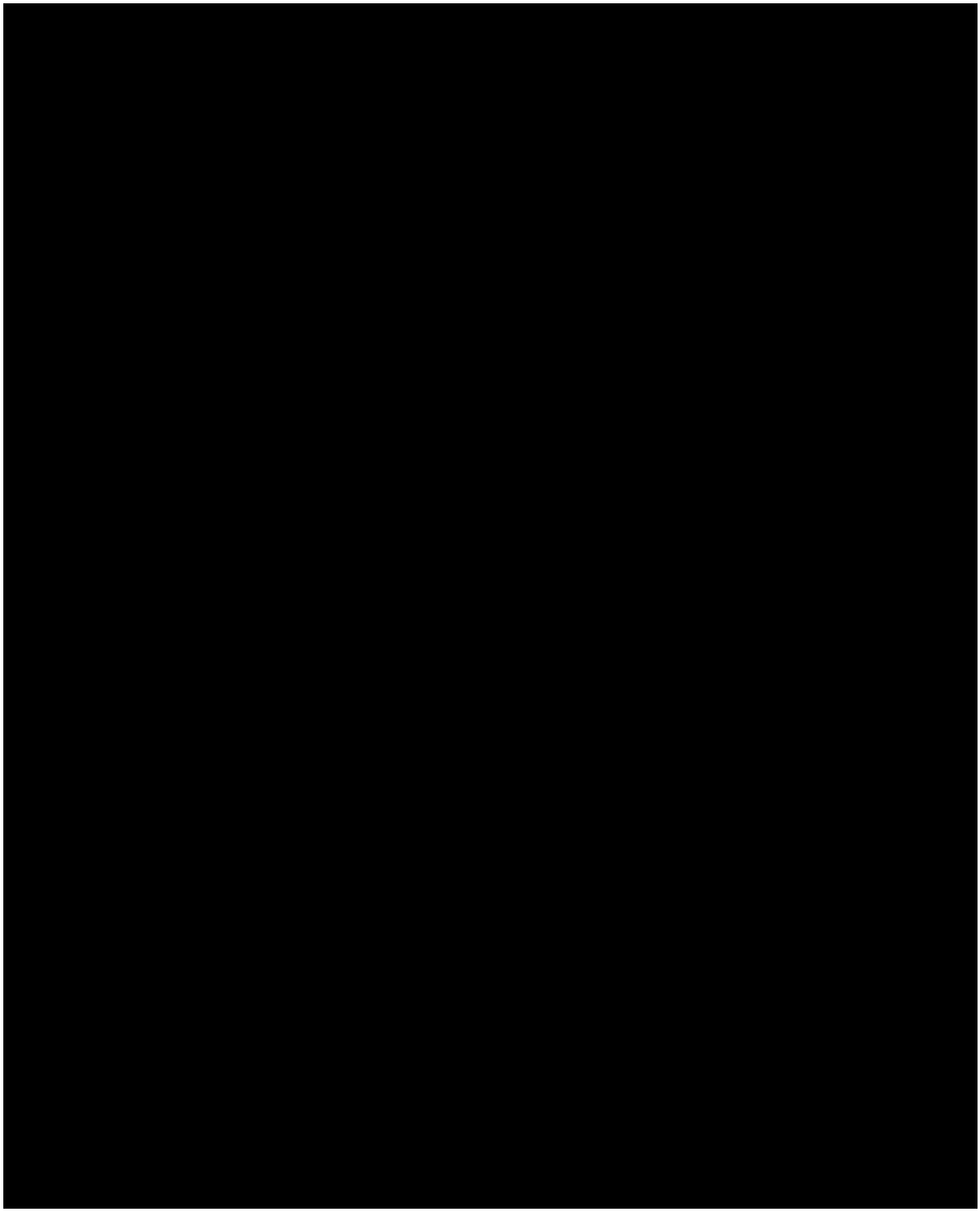
- For male participants:



- For female participants:



10.17.3 EQ-5D-5L



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