AMENDED CLINICAL TRIAL PROTOCOL 04

Protocol title:	**A randomized, multicenter, double-blind Phase 3 study of amcenestrant (SAR439859) plus palbociclib versus letrozole plus palbociclib for the treatment of patients with ER (+), HER2 (-) breast cancer who have not received prior systemic anti-cancer treatment for advanced disease**
Protocol number:	**EFC15935**
Amendment number:	**04**
Compound number (INN/Trademark):	**SAR439859** **Amcenestrant/Not Applicable**
Brief title:	**Amcenestrant (SAR439859) plus palbociclib as first line therapy for patients with ER (+) HER2 (-) advanced breast cancer (AMEERA-5)**
Acronym:	**AMEERA-5**
Study phase:	**Phase 3**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
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Monitoring team's representative name and contact information	

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 04	*All*	*02 September 2021, version 1 (electronic 5.0)*
Amended Clinical Trial Protocol 03	*All*	*13 December 2020, version 1 (electronic 4.0)*
Amended Clinical Trial Protocol 02	*All*	*30 September 2020, version 1 (electronic 2.0)*
Amended Clinical Trial Protocol 01	*All*	*27 July 2020, version 1 (electronic 1.0)*
Original Protocol	*All*	*02 July 2020, version 1 (electronic 1.0)*

Amended protocol 04 (02 September 2021)

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 because it either significantly impacts the safety or physical/mental integrity of participants or the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

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

- To change the recommendations for amcenestrant 200 mg intake from with or without food to now to be taken only with food
- To remove the restriction to enroll male patients from Japan
- To add interstitial lung disease as an adverse event of special interest
- To detail the diagnostic testing in case of suspicion of ILD
- To update exclusion criteria and concomitant medication section with results from recent in vitro and clinical drug-drug interaction studies.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 (Synopsis); 1.3 (Schedule of Activities - Study Intervention Administration); 2.1 (Study rationale); 6.1 (Study interventions(s) administered); 6.1.1 ((Amcenestrant (SAR439859)/Amcenestrant (SAR439859)-matching placebo); 6.1.2 (Letrozole/ letrozole-matching placebo); 6.1.3 (Palbociclib)	Amcenestrant/amcenestrant-matching placebo, Letrozole/letrozole-matching placebo, and Palbociclib (regardless of the administered formulation) should be taken with food.	According to new data from a food effect study, when amcenestrant is given with food (high fat meal) the exposure to the compound increases. To ensure favorable exposure in patients who may have lower absorption, it is recommended to take amcenestrant/amcenestrant-matching placebo with food together with palbociclib, regardless of the palbociclib formulation (capsules/tablets). As the study intervention is blinded, the recommendation on 'to be taken with food' applies to letrozole/letrozole-matching placebo as well.
1.1 (Synopsis); 4.1.1 (Duration of the study period)	Expected duration of treatment for participants in control arm was updated.	Inconsistencies were corrected.
1.2 (Schema)	In Figure 1, number of patients in arm A and arm B has been updated from 354 patients to 533 patients.	For consistency.
1.3 (Schedule of activities),	"Hepatitis C antibody or quantitative hepatitis C (HCV) ribonucleic acid (RNA)" has been changed to "Hepatitis C antibody and quantitative hepatitis C (HCV) ribonucleic acid (RNA)."	Correction for clarity.
1.3 (Schedule of activities), 8.1 (Efficacy assessments)	Updated the disease assessment requirements in study participants without progressive disease per RECIST 1.1 on end-of-treatment visit and clarified the reference timepoint for disease assessment during the follow-up period.	To bring clarity and to ensure that the disease assessment is consistent (every 12 weeks ±7 days from randomization) throughout the study period.
3 (Objective, Endpoints, and estimands), 9.2 (Statistical analyses)	Primary estimands have been added, Table 2 - Summary of primary estimand for main endpoints has been added in Section 3.	To define primary estimands for primary and key secondary efficacy endpoints.
5.2 (Exclusion criteria, E 02)	Modified the exclusion criterion 02: Participants with known active hepatitis A (positive HA antigen or positive IgM); B (either positive HBs antigen or positive hepatitis B viral DNA test above the lower limit of detection of the assay); C (positive hepatitis C antibody result ~~or~~ **and** quantitative hepatitis C (HCV) ribonucleic acid (RNA) results greater than the lower limits of detection of the assay) infection	Previously reported incorrect information was corrected.

Section # and Name	Description of Change	Brief Rationale
5.2 (Exclusion criteria, E11),	Exclusion criterion 11 was adjusted to remove substrates of P-gp and BCRP and added substrates of OATP1B1/B3 substrates. 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.
6.8 (Concomitant therapy)	Substrates of P-gp and BCRP related information has been removed; substrates of OATP1B1/B3 related information has been added.	
5.2 (Exclusion criteria, E27),	Ethics considerations added as part of exclusion criteria E27.	Update as per latest One Document protocol template.
5.5. (Criteria for Temporarily Delaying administration of study intervention)	Updated the title of the subsection. The following text has been added " that results in travel restrictions, confinement, or restricted site access" after “During a regional or national emergency declared by a governmental agency.”.	To clarify that the temporary delay is related to administration of study intervention
6.2 (Preparation, handling, storage, and accountability)	Term “NIMP” was added to include all study treatment sourced centrally.	For consistency across protocol Section 6.1 and 6.2.
6.8 (Concomitant therapy)	Removed the special caution with regards to Proton Pump Inhibitors (PPI) (ie, omeprazole) and H2 blockers (ie, ranitidine).	A recent drug-drug interaction study showed that acid reducing agent had no clinically relevant effect on amcenestrant exposure given with food which is now the dosing recommendation in this study for both amcenestrant and palbociclib (whatever the formulation).
8.2.6 (Pregnancy testing)	Pregnancy testing guidance has been added into this newly created subsection	To be aligned with the latest One Document protocol template.
8.3.7 (Adverse events of special interest)	Added ILD/Pneumonitis as an adverse event of special interest	ILD/Pneumonitis is a common (with an incidence of 1.4% all grades from 3 palbociclib randomized trials) adverse drug reaction of palbociclib. Per recommendation of Data Monitoring Committee, ILD/pneumonitis will be monitored as an AESI, and recommendations for diagnostic testing in suspicion of ILD/pneumonitis has been detailed.
8.2.5.1 (Guideline for management of specific adverse events: Interstitial Lung Disease/Pneumonitis)	Detailed diagnostic testing in case of suspicion of ILD/Pneumonitis has been added.	
8.4 (Pharmacokinetics)	Pre-dose and post-dose PK samples should be collected even in case of IMP dose omission.	To bring clarity on PK blood sampling

Section # and Name	Description of Change	Brief Rationale
8.6 (Pharmacodynamics) in previous amended protocol 03	Section was removed per latest One Document template, considering pharmacodynamic assessments will not be included in this study.	To be aligned with latest One Document protocol template.
8.10 (Use of biological samples and data for future research)	Samples storage duration after the end of the study has been updated to 25 years.	To be aligned with latest One Document protocol template.
9.1 (Populations for analyses)	In Table 6, descriptions for population have been added. The following sentence has been removed "For any participant randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be reported separately."	For clarity.
9.2.1 (General considerations)	New texts have added as per latest One Document protocol template.	For clarity and to be aligned with latest One Document protocol template.
9.2.3 (Secondary endpoint(s) analyses	Previous Efficacy analyses table (Table 6) has been updated to Efficacy analyses for other secondary endpoints (Table 7) which includes the secondary endpoints only.	For clarity.
9.2.5 (Multiplicity adjustment)	A new section of multiplicity adjustment has been added.	To define hypothesis testing of the key secondary efficacy endpoint.
9.2.6.1 (Adverse events)	The following sentence has been added "Similarly, the deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment periods.". "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.
9.2.7.1 (Analyses of patient reported outcome endpoints)	The secondary paragraph of statistical analysis strategy for the 3 PROs has been updated.	For clarification of analyses that are planned for PRO data.
9.3.1 (Interim analyses for PFS)	In Table 9, PFS Final analysis has been updated from 49 to 40.	Typo correction.
10.2 (Appendix 2: Clinical laboratory tests)	In Table 11, viral serology tests have been added for other screening tests and pregnancy test has been added.	For consistency.
10.6 (Appendix 6: Country-specific requirements)	Removed the restriction to enroll male patients from Japan	Based on the feedback received from Japanese health authorities
10.8 (Appendix 8: Protocol amendment history)	Updated by including amendment history of amended protocol 03.	For consistency.

Section # and Name	Description of Change	Brief Rationale
Entire document	Editorial changes, updates as per latest One Document protocol template.	Correction of typographical errors and minor inconsistencies across different sections, and clarifications. To be aligned with latest One Document protocol template.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A randomized, multicenter, double-blind Phase 3 study of amcenestrant (SAR439859) plus palbociclib versus letrozole plus palbociclib for the treatment of patients with ER (+), HER2 (-) breast cancer who have not received prior systemic anti-cancer treatment for advanced disease

Brief title:

Amcenestrant (SAR439859) plus palbociclib as first line therapy for patients with ER (+) HER2 (-) advanced breast cancer (AMEERA-5)

Rationale:

The purpose of the proposed study is to demonstrate the superiority of a new oral selective estrogen receptor degrader (SERD), amcenestrant, in combination with palbociclib versus letrozole in combination with palbociclib in participants with estrogen receptor-positive [ER(+)], human epidermal growth factor receptor 2 negative [HER2(-)] advanced or metastatic breast cancer who have not received prior systemic anti-cancer treatment for advanced disease. Refer to Section 2.1.

Objectives and endpoints:

Objectives	Endpoints
Primary	
• To determine whether amcenestrant in combination with palbociclib improves progression free survival (PFS) when compared with letrozole in combination with palbociclib in participants with ER+, HER2- advanced breast cancer who have not received prior systemic anticancer therapies for advanced disease	• 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 local radiologist/investigator or death (due to any cause), whichever comes first.
Secondary	
• To compare the overall survival (OS) in both treatment arms [**Key Secondary Objective**]	• Overall survival is defined as the time interval from the date of randomization to the date of documented death (due to any cause). **[Key Secondary Endpoint**]
• To evaluate the objective response rate (ORR) in both treatment arms	• ORR is defined as the proportion of participants who have a complete response (CR) or partial response (PR), as best overall response determined as per RECIST 1.1, from the date of randomization until disease progression, death, cutoff date, initiation of post-treatment anti-cancer therapy, whichever occurs first.

• To evaluate the duration of response (DOR) in both treatment arms	• DOR is defined as the time from first documented evidence of CR or PR until progressive disease (PD) as determined as per RECIST 1.1 or death from any cause, whichever occurs first.
• To evaluate the clinical benefit rate (CBR) in both treatment arms	• CBR is defined as the proportion of participants who have a confirmed CR, PR, or stable disease (SD) for at least 24 weeks determined as per RECIST 1.1, from the date of randomization until disease progression, death, cutoff date, initiation of post treatment anti-cancer therapy, whichever occurs first.
• To evaluate progression-free survival on next line of therapy (PFS2)	• The PFS2 is defined as the time from the date of randomization to the date of first documentation of PD on the next systemic anti-cancer therapy according to investigator or death due to any cause in the absence of documented PD on the next systemic anti-cancer therapy, whichever occurs first.
• To evaluate the pharmacokinetics (PK) of amcenestrant, and palbociclib	• Plasma concentrations of amcenestrant, palbociclib
• To evaluate health-related quality of life (HRQL) in both treatment arms	• Symptoms and function related to HRQL as measured by EORTC QLQ-C30, breast cancer specific module (QLQ-BR23/BR45) and EQ-5D-5L Disease-specific and generic HRQL, disease and treatment-related symptoms, the impact of symptoms and treatment, health state utility, and health status will be evaluated using the European Organization for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30), the EORTC-QLQ breast cancer specific module (QLQ-BR23/BR45) 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 study treatment
• To evaluate the time to first chemotherapy in both treatment arms	• Time to chemotherapy is defined as the time interval from the date of randomization to the start date of the first chemotherapy after study treatment discontinuation
• To evaluate safety in both treatment arms	• Treatment emergent adverse events (TEAEs)/serious adverse events (SAEs) and laboratory abnormalities

Exploratory

• 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).	• Tumor ER, Ki67, Bcl-2, and PgR protein, and RNA gene expression profiles in paired biopsies at Cycle 1 Day 1 (pre-treatment) and optional at end of treatment for participants who discontinued treatment due to disease progression
• 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.	• The gene mutation profile of the tumor by cfDNA analysis over time (Cycle 1 Day 1 [pre-treatment], at Cycle 4 Day 1 predose (tumor assessment), and upon disease progression on treatment or EOT whichever comes first)

• To evaluate exposure/response relationship of amcenestrant and palbociclib • To evaluate the PK of goserelin • To evaluate PFS in participants expressing PIK3CA and ESR1 mutation in both treatment arms	• PK of amcenestrant will be correlated with safety and/or efficacy • Plasma concentrations of goserelin • 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 local radiologist/investigator or death (due to any cause), whichever comes first.

For China, please see Section 10.6 for details.

Overall design:

This is a prospective multicenter, international, randomized, double-blind, double-dummy, Phase 3 trial comparing the efficacy and safety of amcenestrant in combination with palbociclib versus letrozole in combination with palbociclib in men, pre/peri-menopausal women (with goserelin), and postmenopausal women, all with ER(+)/HER2(-) breast cancer who have not received prior systemic treatment for advanced disease.

Eligible participants should have histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of either loco-regional recurrent or metastatic disease not amenable to radiation therapy or surgery with curative intention, and for whom chemotherapy is not indicated.

Participants who progressed while on or within 12 months from completion of (neo)adjuvant endocrine therapy with any of the following agents: aromatase inhibitor (eg, letrozole, anastrozole, exemestane); selective estrogen receptor modulator - eg, tamoxifen, toremifene, raloxifene; CDK4/6 inhibitors (eg, palbociclib, ribociclib, abemaciclib) will not be eligible.

Participants should not have received prior systemic anti-cancer therapies for their advanced disease. Participants may have measurable disease as per RECIST v.1.1 or non-measurable bone only disease with at least one predominant lytic bone lesion or mixed lytic-blastic lesion.

All eligible participants will be randomly assigned using an Interactive Response Technology (IRT) to either amcenestrant plus palbociclib (experimental) arm or letrozole plus palbociclib (control) arm in a 1:1 ratio.

The population will be stratified by:

- De-novo metastatic disease (Yes or No)
- Postmenopausal women (Yes or No)
- Visceral metastasis defined by at least 1 liver, lung, brain metastasis, pleural, or peritoneal involvement (Yes or No).

Participants will continue to receive their assigned treatment until objective disease progression, unacceptable toxicity, participant's request to stop treatment, or investigator's decision, whichever

occurs first. However, participants may continue treatment as assigned at randomization beyond the time of RECIST defined disease progression at the discretion of the investigator, if that is considered to be in the best interest of the participant and as long as no new anticancer treatment is initiated. In these cases, the investigator must discuss the rationale with the sponsor before the decision to continue treatment on-study is made.

Tumor assessments will be performed within 4 weeks (ie, 28 days) prior to randomization, followed by every 12 weeks (±7 days) from the date of randomization. Participants with bone lesions identified at baseline will also have repeat bone scans performed every 24 weeks (±7 days) from the date of randomization for the first 18 months, and then every 12 weeks (±7 days). Each assessment will be performed as scheduled regardless of any dosing delay to prevent the introduction of bias into the assessment of efficacy. Tumor assessments will be performed until documented PD as per RECIST v.1.1, or final PFS analysis cut-off date (COD), and at EOT (to be performed if it falls within the regular disease assessment time window of 12 weeks ±7 days), whichever occurs first.

Participants discontinuing the active treatment phase will be followed until death or final study cut-off date, whichever comes first. Participants who discontinue the study treatment without documented PD as per RECIST v.1.1 will be followed every 12 weeks until disease progression.

In participants with documented disease progression as per RECIST v.1.1, follow-up visits will be performed every 24 weeks (±7 days) from the last dose of study intervention for overall survival status and collection of data on subsequent anticancer therapies, until death or until the OS cutoff date, whichever comes first.

A blinded Independent Review Committee (BIRC) assessment will be performed retrospectively on a sample of participants based on radiographic images and clinical information collected on-study.

An independent data monitoring committee (DMC) will monitor the safety data on a periodic basis. The DMC will make recommendations as to whether the trial should continue based on ongoing reviews of safety data. The DMC will also evaluate efficacy at the interim analyses and make a recommendation regarding study continuation based on observed results of the study. The DMC procedures will be detailed in the DMC charter and approved by the DMC members.

A Study Steering Committee will supervise the progress of the trial and review relevant information that may affect the study conduct as well as review DMC recommendations.

Brief summary:

This is a parallel, Phase 3, two-arm study for treatment that is blinded for Participant, Investigator, and Outcomes Assessor [Study sponsor (except bioanalysts assessing PK samples) and all stakeholders (except DMC and independent statistician) involved in study conduct].

Number of participants:

Approximately 1333 participants will be screened in the study, and 1066 participants will be randomly assigned to study intervention with a balanced randomization ratio (533 participants randomized per treatment arm).

Note: Enrolled participants are all participants from screened participants who have been allocated to an intervention regardless of whether the intervention was received or not.

Intervention groups and duration:

Participants will be randomly assigned (1:1) to either Arm A (experimental) or Arm B (control).

- Arm A: Amcenestrant (SAR439859) 200 mg + letrozole-matching placebo + palbociclib 125 mg
- Arm B: amcenestrant (SAR439859) -matching placebo + letrozole 2.5 mg + palbociclib 125 mg.

The treatments in both arms are given orally. During the treatment period, men and pre/perimenopausal women will receive goserelin subcutaneously.

No dose reductions for letrozole and amcenestrant (SAR439859) are permitted but dosing omissions are allowed in case of severe toxicity. In the event of significant treatment-related toxicity, palbociclib dosing may be omitted or delayed and/or reduced.

If palbociclib is prematurely permanently discontinued due to treatment-related toxicity, participants may continue as per investigator's discretion on the active treatment phase of the study receiving letrozole plus amcenestrant (SAR439859) -matching placebo or amcenestrant (SAR439859) plus letrozole-matching placebo.

Participants discontinuing treatment of either letrozole/letrozole-matching placebo treatment or amcenestrant (SAR439859) /amcenestrant (SAR439859) -matching placebo, due to treatment-related toxicity will be discontinued from the active treatment phase of the study and enter the follow-up phase.

Study intervention(s)

Investigational medicinal product(s)

Amcenestrant (SAR439859) and Amcenestrant (SAR439859) -matching placebo

- Dosage form and strength: 200 mg tablets
- Route(s) of administration: oral route
- Dose regimen: the recommended dose is 200 mg once daily, continuously, to be taken approximately at the same time each day, with food intake.
- amcenestrant (SAR439859)-matching placebo will be supplied as tablets identical to amcenestrant (SAR439859) 200 mg tablets in appearance.

Letrozole and letrozole-matching placebo

- Dosage form and strength: 2.5 mg tablets over-encapsulated
- Route(s) of administration: oral route
- Dose regimen: 1 capsule once daily, continuously, to be taken approximately at the same time each day, with food intake.
- Letrozole-matching placebo will be supplied as capsules identical to letrozole 2.5 mg capsules in appearance.

Palbociclib (Ibrance®)

- Dosage forms and strengths: 125 mg, 100 mg, 75 mg capsules or tablets.
- *Study to be initiated with the capsules and will be switched to tablets as commercially available.*
- Route(s) of administration: oral route
- Dose regimen: the recommended dose is 125 mg once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. To be taken at approximately the same time each day.
- Should be taken with food, regardless of the administered formulation.

When given the same day, amcenestrant (SAR439859) plus letrozole matching placebo plus palbociclib or letrozole plus amcenestrant (SAR439859) matching placebo plus palbociclib will be taken at the same time.

If a dose is vomited or omitted, the participant should not take the dose later or 2 doses at the next planned dose.

Non investigational medicinal product(s)

Goserelin

Additional treatment with goserelin is required for men and pre/perimenopausal participants.

- Dosage form and strength: 3.6 mg injection
- Route(s) of administration: subcutaneous
- Dose regimen: administered once every 28 days into the anterior abdominal wall below the navel line using an aseptic technique prior to study IMPs. While delay of a few days is permissible, every effort should be made to adhere to the 28-day schedule.

Duration of study intervention

The expected duration of treatment for participants who benefit from study intervention may vary, based on progression date; but median expected duration of study per participant is estimated as median 59 months in experimental arm (1 month for screening, 33 months for treatment, and

25 months for the EOT and follow-up visits) and 47 months in control arm (1 month for screening, 25 months for treatment, and 21 months for the EOT and follow-up visits).

Statistical considerations:

Sample size determination

A total of 516 PFS events assessed by local radiologist/investigator will be needed to reject the null hypothesis using a logrank test at the one-sided level of 2.5% and a 90% power under the assumption of a HR of 0.75. Assuming proportional hazards under an exponential model and based on an anticipated median PFS time of 24.8 months in the letrozole + palbociclib arm, this is expected to correspond to a median PFS of 33.1 months in the SAR439859 + palbociclib arm. Based on an expected accrual duration of 18 months (15% of total accrual in the first 4.5 months and 40% of total accrual in the first 9 months), a PFS analysis cut-off date (COD) 40 months after first participant in and an annual dropout rate of 5%, a total of 1066 participants are expected to be randomized in a 1:1 ratio into the SAR439859 + palbociclib and letrozole + palbociclib arms. The power calculation accounts for two interim analyses at 40% and 70% of the planned number of events (as described in the interim analysis part).

For OS, a total of 632 deaths will be needed to reject the null hypothesis using a logrank test at the one-sided level of 2.5% and an 80% power under the assumption of a HR of 0.80. Assuming proportional hazards under an exponential model and based on an anticipated median OS of 46 months in the letrozole + palbociclib arm, this is expected to correspond to a median OS of 57.5 months in the SAR439859 + palbociclib arm. OS COD is expected 80 months after the first participant randomized (assuming an annual dropout rate of 1%). The power calculation accounts for two interim analyses at the time of the PFS primary analysis and at 75% of the planned number of OS events.

Analysis populations:

- Enrolled population: All participants who sign the informed consent form (ICF).
- 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 take 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 one evaluable plasma concentration post-treatment.

Primary analysis:

Primary analysis will consist of PFS according to local radiologist's/investigator's assessment comparison between amcenestrant + palbociclib arm and letrozole + palbociclib arm through a logrank test procedure stratified by the stratification factors as entered in the IRT. An overall 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 PFS analysis COD, PFS will be censored at the date of the last evaluable tumor assessment with no evidence of a disease progression before the start of further anti-cancer therapy
- A participant without an event (death or disease progression) and without any evaluable postbaseline tumor assessments will be censored at the day of randomization (Day 1).
- Documented progression (or death) occurring after two or more non-evaluable tumor assessments will be censored at the date of the last evaluable tumor assessment documenting no progression.

Two interim analyses at 40% (206PFS events, non-binding futility only) and 70% (361PFS events, efficacy only) of the planned number of events (516PFS events) are planned. The primary PFS analysis corresponds either to a positive interim PFS analysis or the final PFS analysis.

The HR estimates and corresponding 95% two-sided confidence intervals (CI) will be provided using the Cox proportional hazard model stratified by the same stratification factors as those used for the log rank 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). Subgroup analyses of PFS will also be conducted.

A random sample-audit BIRC approach will be used as an auditing tool to evaluate the concordance between local radiologist's/investigator's assessment and BIRC on the PFS data. Approximately 50% of the randomized participants will be randomly selected and the BIRC will assess the tumor progression of these participants based on the review of tumor assessments. Participants selected for the sample-audit BIRC will not be known to the investigators. NCI (1) and PhRMA (2) methods will be used to provide assurance on the PFS treatment effect based on the local radiologist's/Investigator's assessment.

Analysis of key secondary efficacy endpoint:

Overall survival is defined as the time from date of randomization to date of death due to any cause. In the absence of observation of death, survival time will be censored at the last date the participant is known to be alive or at the OS cut-off date, whichever occurs first. Similar methods as for PFS will be used.

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.

Analysis of secondary efficacy endpoints:

Analysis of response-based endpoints (ie, ORR, CBR, and DOR) will be performed primarily on the ITT population and supported by the analyses based on the subset of measurable disease participants from the ITT population. Analysis of the time to first chemotherapy (TT1C) and progression-free survival on the next systemic anti-cancer therapy (PFS2) will be performed on the ITT population, using Cox proportional hazard model and Kaplan-Meier method. No formal statistical testing will be performed, and only descriptive statistics will be provided.

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 EORTC QLQ-C30, the breast cancer specific module (QLQ-BR23/QLQ-BR45), and the 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 subscales), QLQ-BR23/QLQ-BR45 (13 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 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/QLQ-BR45(13 subscales), 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 (MedDRA) primary system organ class (SOC) and preferred term (PT) 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, and premature discontinuation of palbociclib, 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:

Two interim analyses are planned based on the primary PFS endpoint at 40% (non-binding futility only) and 70% (efficacy only) of the planned total number of events expected. 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 efficacy will be derived based on the O'Brien and Fleming α- spending functions and depend on the actual number of PFS events observed at the time of the interim analysis.

In case of positive results at interim analysis, disease assessments data will be collected according to the protocol until the final analysis cut-off date (defined as the date when 516 PFS events assessed by radiologist/Investigator are observed) and PFS results will be updated (non-inferential analysis only).

Comparison between arms on the OS will be performed only if the primary analysis of the PFS is statistically significant. Therefore, a maximum of three analyses are planned for OS, at the time of the primary analysis of PFS, at the 75% of the planned number of OS events and at the final OS analysis.

A gamma error spending function ($\gamma = -10$) independent from the O'Brien and Fleming α-spending function for PFS will be used, along with the hierarchical testing strategy in order 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 (3).

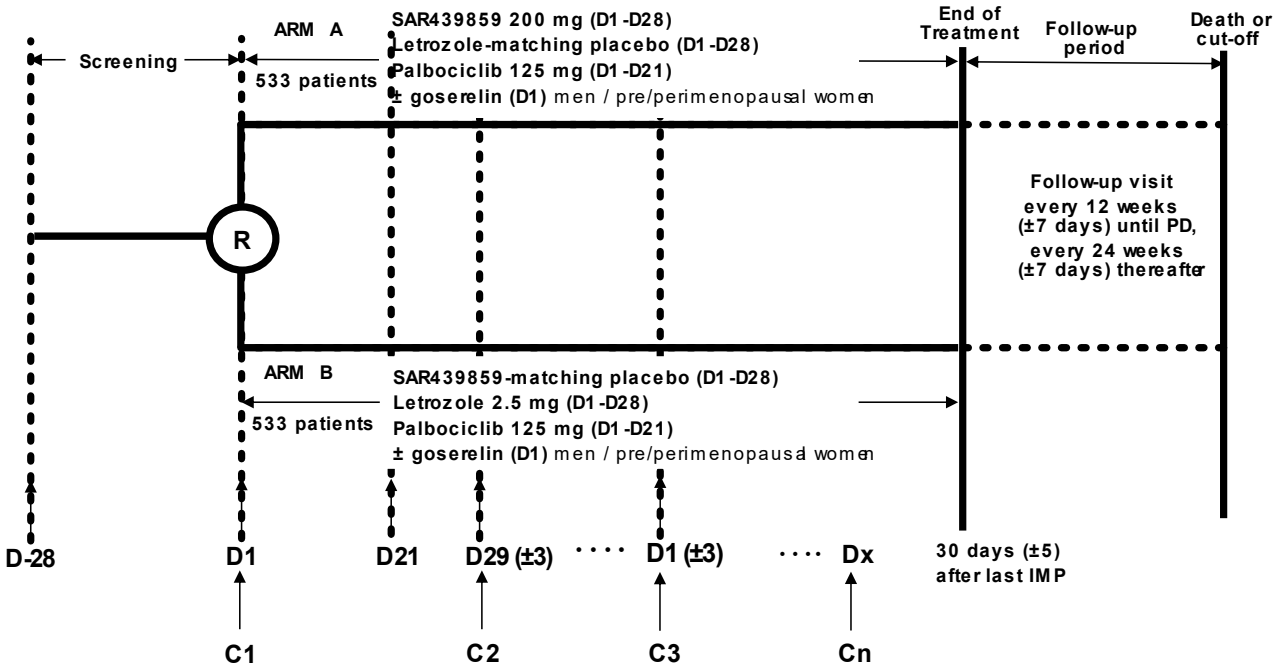
Planned database lock date:

Estimated COD will be approximately 19.5, 28, and 40 months after first randomized participant respectively for the first interim, second interim, and final PFS analysis. After final COD for PFS analysis, no more efficacy assessment will be performed except collection of survival status.

The final OS analysis COD will be the last COD, and it will fall approximately 80 months after the first patient randomized. If a participant treated continues to benefit from the treatment after the last COD, 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, all ongoing SAEs (related or not), all related non-serious AEs ongoing at the COD, and all new related AEs (serious or not) occurring post-COD will be followed until resolution or stabilization; as well as IMP administrations, and related concomitant medication, and reason for EOT will continue to be collected.

Data Monitoring/Other committee: Yes

1.2 SCHEMA



C = Cycle; D = day; IMP= investigational medicinal product; PD= progressive disease; R = randomization.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening up to 28 days before randomization	Treatment Period			EOT	Post Treatment Follow-up period		Notes
		Cycles 1 & 2		Subsequent Cycles	30 Days (±5 Days) after last study treatment administration	Every 12 weeks (±7D) until disease progression	Every 24 weeks (±7D) after disease progression	
		D1 (±3)	D15 (±1)	D1 (±3)				
IRT contact	X	X		X	X			
Inclusion/exclusion criteria and Informed consent	X							Informed consent (including genetic sampling) may be signed prior to D-28. Recheck clinical status before randomization and/or 1st dose of study medication.
Demography, medical/surgical and disease history, prior cancer therapies	X							
Height	X							
Vital signs, physical examination/signs and symptoms	X	X		X	X			
ECOG performance status, body weight	X	X		X	X			
Follicle-stimulating hormone	X	X		X	X			At screening for eligibility in all female study participants - local labs. On C1D1, then every 4th cycle during study treatment and EOT - only in pre/perimenopausal women - local labs

Procedure	Screening	Treatment Period			EOT	Post Treatment Follow-up period		Notes
		Cycles 1 & 2		Subsequent Cycles				
	up to 28 days before randomization	D1 (±3)	D15 (±1)	D1 (±3)	30 Days (±5 Days) after last study treatment administration	Every 12 weeks (±7D) until disease progression	Every 24 weeks (±7D) after disease progression	
Estradiol	X[a]	X[b]		X[c]				***a.*** At screening for eligibility in female study participants - local labs ***b.*** Estradiol sampling at predose C1D1 - central labs (all participants) ***c.*** Estradiol sampling at predose C3D1 - central labs (all participants)
Pregnancy test (WOCBP only) - Local labs	X[a]	(X[b])		X[b]	X[b]	X[c]		***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, at EOT, **c** Urine pregnancy test (dipstick) to be done every month, up to 12 weeks after last dose of any study intervention. Urine pregnancy test must have a sensitivity of at least 25 mIU/mL.
Triplicate 12-lead ECG	X				X			Screening, EOT and as clinically indicated - To be assessed locally. Triplicate ECGs are collected within about a five-minute window at a nominal time-point.

Procedure	Screening up to 28 days before randomization	Treatment Period			EOT	Post Treatment Follow-up period		Notes
		Cycles 1 & 2		Subsequent Cycles	30 Days (±5 Days) after last study treatment administration	Every 12 weeks (±7D) until disease progression	Every 24 weeks (±7D) after disease progression	
		D1 (±3)	D15 (±1)	D1 (±3)				
Laboratory assessments - Local labs	X	(X)	X	X	X			Hematology/biochemistry panels and coagulation to be performed at screening within 7 days of C1D1. -Complete blood counts and biochemistry: at the beginning of each cycle, as well as on D15 of the first 2 cycles, and as clinically indicated. Lipids assessments (total cholesterol, LDL-cholesterol, HDL-cholesterol): on D1 of each cycle until Cycle 6.
Urine dipstick testing (Local labs)	X	(X)		X	X			Urinalysis to be performed at screening within 7 days of C1D1.
Viral serology tests	X							Hepatitis A antigen or IgM hepatitis A antibody; HBs antigen or hepatitis B viral DNA; Hepatitis C antibody and quantitative hepatitis C (HCV) ribonucleic acid (RNA).
Randomization	X							Every effort should be made to start treatment within 3 working days of randomization.
Study Intervention Administration:								
Amcenestrant (SAR439859) or Amcenestrant (SAR439859)-matching placebo		Once daily ←→						To be taken with food.

Procedure	Screening up to 28 days before randomization	Treatment Period			EOT	Post Treatment Follow-up period		Notes
		Cycles 1 & 2		Subsequent Cycles	30 Days (±5 Days) after last study treatment administration	Every 12 weeks (±7D) until disease progression	Every 24 weeks (±7D) after disease progression	
		D1 (±3)	D15 (±1)	D1 (±3)				
Palbociclib		D1 to D21 (once daily) followed by 7 days off ←→						To be taken with food, regardless of the administered formulation
Letrozole or letrozole-matching placebo		Once daily ←→						To be taken with food
Goserelin		X		X				In pre/perimenopausal women and men
AE/SAE review	←==========					X (ongoing related AEs, ongoing SAEs at EOT and new related AE/SAEs)		
Concomitant medication review	X	←==========				X (related to AE/SAEs listed above)		From the date of informed consent form up to 30 days after the last dose of study treatment

Procedure	Screening up to 28 days before randomization	Treatment Period			EOT	Post Treatment Follow-up period		Notes
		Cycles 1 & 2		Subsequent Cycles	30 Days (±5 Days) after last study treatment administration	Every 12 weeks (±7D) until disease progression	Every 24 weeks (±7D) after disease progression	
		D1 (±3)	D15 (±1)	D1 (±3)				
Tumor assessments:								
CT/MRI Scans with contrast agent of Chest, Abdomen, Pelvis, any clinically indicated sites of disease, and of bone lesions; Clinical evaluation of superficial disease	X[a]	X[b]			X[c]	X[d]		***a.*** Screening: within 4 weeks (ie, 28 days) prior to randomization unless otherwise specified. ***b.*** Post baseline: every 12 weeks (±7 days) from randomization (until documented progressive disease as per RECIST v.1.1 or final PFS analysis cut-off date). ***c***. EOT: to be performed if it falls within the regular disease assessment time window of 12 weeks ±7 days (only in participants without PD as per RECIST 1.1). ***d***. If no PD as per RECIST 1.1 at EOT, disease assessment will continue to be performed every 12 weeks ±7 days from randomization up to documented PD as per RECIST v.1.1, or final PFS COD, whichever occurs first.

Procedure	Screening up to 28 days before randomization	Treatment Period			EOT	Post Treatment Follow-up period		Notes
		Cycles 1 & 2		Subsequent Cycles	30 Days (±5 Days) after last study treatment administration	Every 12 weeks (±7D) until disease progression	Every 24 weeks (±7D) after disease progression	
		D1 (±3)	D15 (±1)	D1 (±3)				
Radionuclide Bone Scan, Whole Body	X[a]	X[b]			X[c]	X[d]		***a.*** Screening: within 12 weeks prior to randomization ***b.*** Post baseline: • If bone lesions identified at baseline: to be repeated every 24 weeks (±7 days) from randomization for the first 18 months, and then every 12 weeks (±7 days). • If no bone lesions identified at baseline: to be repeated only if clinically indicated. ***c***. EOT: to be performed if it falls within the regular disease assessment time window of 12 weeks ±7 days (only in participants without PD as per RECIST 1.1 and no bone lesions identified at baseline). ***d***. If no PD as per RECIST 1.1 at EOT, disease assessment will continue to be performed from randomization date as reference in participants with bone lesions identified at baseline, up to documented PD as per RECIST v.1.1, or final PFS COD, whichever occurs first. During follow-up period, bone scan should be performed at the same frequency as described in note b.

Procedure	Screening up to 28 days before randomization	Treatment Period			EOT	Post Treatment Follow-up period		Notes
		Cycles 1 & 2		Subsequent Cycles	30 Days (±5 Days) after last study treatment administration	Every 12 weeks (±7D) until disease progression	Every 24 weeks (±7D) after disease progression	
		D1 (±3)	D15 (±1)	D1 (±3)				
Dual-energy x-ray absorptiometry (DXA) scan of anteroposterior spine and total hip	X[a]	X[b] (every 2 years from randomization or more frequently if clinically indicated)						***a.*** Screening: Only in study participants who are not on bone-targeted agents (eg, bisphosphonates, denosumab) prior to initiation of study IMPs (if not done during the previous 6 months prior to randomization) ***b.*** Post baseline: Only in study participants who had DXA scan at baseline, or if clinically indicated
Survival Follow-up						X		After discontinuation of study treatment, post-study survival status (including post-study anti-cancer therapies (start/stop date, date of PD), and their responses will be collected during on-site visits or by contacting the patient or family by telephone until death or OS cut-off date, whichever comes first.

Procedure	Screening up to 28 days before randomization	Treatment Period			EOT	Post Treatment Follow-up period		Notes
		Cycles 1 & 2		Subsequent Cycles	30 Days (±5 Days) after last study treatment administration	Every 12 weeks (±7D) until disease progression	Every 24 weeks (±7D) after disease progression	
		D1 (±3)	D15 (±1)	D1 (±3)				
Pharmacokinetics sampling - central labs		X[a]	X[b]	X[c]				Amcenestrant and palbociclib: ***a***. C1D1: Post dose T3h ±1h C2D1: Predose, Post dose T3h ±1h ***b***. C1D15 and C2D15: Predose ***c***. C3D1: Predose Cycles 4, 7, and 10: Predose at D1 No PK samples will be taken after Cycle 10 or PFS cut-off date, whichever comes first Goserelin (only in pre/perimenopausal women and men): ***a***. C1D1 and C2D1 predose ***c***. C3D1 predose
Electronic HRQL: QLQ-C30, QLQ-BR23/QLQ-BR45, EQ-5D-5L		X[a]		X[a]	X[a]	X[b]		***a.*** Every cycle from Cycle 1 to Cycle 4, then every 3 cycles from Cycle 6 and at EOT ***b.*** First follow-up visit only

Procedure	Screening up to 28 days before randomization	Treatment Period			EOT	Post Treatment Follow-up period		Notes
		Cycles 1 & 2		Subsequent Cycles	30 Days (±5 Days) after last study treatment administration	Every 12 weeks (±7D) until disease progression	Every 24 weeks (±7D) after disease progression	
		D1 (±3)	D15 (±1)	D1 (±3)				
Tumor specimen/Biopsy	X[a]				X[b]			***a.*** Most recent archived FFPE biopsied tumor tissue samples of metastatic/recurrent lesion. If archived tumor tissue is not available, then fresh tumor biopsy of metastatic/recurrent lesion should be collected from time of screening to Cycle 1 D1 pre-treatment. Original diagnostic tumor tissue sample will be used in absence of metastatic/recurrent tissue sample and whenever a fresh biopsy of the metastatic/recurrent lesion is not feasible. ***b.*** Fresh tumor biopsy (optional) collected at EOT, for study participants who discontinue treatment due to disease progression, if feasible. It is recommended that the second biopsy (optional) is collected at the same location as the baseline biopsy, whenever possible unless new lesion is identified.
Molecular profiling in cfDNA (plasma) - central labs		X		X (Cycle 4)	X			cfDNA sample should be collected at pre-treatment (Cycle 1 D1), at Cycle 4 Day 1 predose (at tumor assessment), and upon disease progression on treatment or EOT whichever comes first.
DMET genotyping and normal tissue reference DNA (whole blood) - central labs		X						To be collected pre-treatment Cycle 1 D1

All study visits performed during treatment period and follow-up period (in participants without progressive disease per RECIST 1.1 at EOT) are conducted on-site until disease progression. On-site visits could be substituted by remote visits in specific circumstances (see Section 10.15).

Screening: Routine baseline tests performed prior to ICF signature do not need to be repeated as long as they are within the screening defined timeframe. Informed consent should be signed

before any study specific procedures. It can be signed more than 28 days prior to randomization. Screening time indicates in which timeframe exams used to support eligibility have to be done prior to randomization.
In addition to lipid assessments, investigator should monitor bone mineral density using dual-energy x-ray absorptiometry (DXA) scan of anteroposterior spine and total hip in study participants who are not on bone-targeted agents (eg, bisphosphonates, denosumab) prior to initiation of study IMPs (if not done during the past 6 months) and then repeated every 2 years during the treatment (or more frequently, if clinically indicated).
Randomization: To take place once the consented patient 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 Interactive Response Technology (IRT). Every effort should be made to start treatment within 3 working days of randomization.
Cycle 1 D1 refers to the day the patient receives the initial dose of IMP. (**X): Optional assessments:** Repeated evaluation of pregnancy test, urine dipstick testing (ie, urinalysis), body weight, signs and symptoms, physical examination, hematology and blood chemistry labs is not necessary if performed within 7 days prior to1st IMP administration. If evaluation performed during screening was abnormal, repeated evaluation is recommended within 2 days prior to 1st IMP administration. Urine pregnancy test must have a sensitivity of at least 25 mIU/mL.
Treatment period: All the tests or procedures on D1 should be done prior to IMP administration unless otherwise stated. Men and pre/perimenopausal women will receive goserelin (NIMP) on D1 of each cycle.
End of treatment (EOT): should be performed within 30 days (±5 days) after the last IMP and prior to the initiation of any new anti-cancer therapy, whichever comes first.
Follow-up period:
-Participants with documented progressive disease (PD) at time of treatment discontinuation: follow-up visit will be done every 24 weeks ±7 days from the date of last study treatment administration until death or final OS analysis cut-off date, whichever comes first.
-Participants without documented PD at time of treatment discontinuation will be followed every 12 weeks ±7 days from randomization until documented progression. After PD participants will be followed every 24 weeks ±7 days as described above until death or final OS analysis cut-off date.
Tumor assessment: The schedule of assessments should be fixed according to the calendar, regardless of treatment delays/omissions. Imaging assessments are to be scheduled using the randomization date as the reference date for all time-points and are NOT to be scheduled based on the date of the previous imaging time-point. Imaging assessment delay to conform to treatment delay is not permitted. The same tumor assessment technique MUST be used throughout the study for a given lesion/patient.
Bone scans: Any suspicious abnormalities (ie, hotspots) identified on bone scans at baseline and on subsequent bone scans MUST be confirmed by X-ray, CT scan with bone windows or MRI.
Baseline brain scans (CT, MRI) only required within 6 weeks before randomization if signs and symptoms suggest presence of metastatic brain disease. Post-baseline repeat brain scans will only be required only if metastases are present at baseline.
Baseline scans performed before the signing of informed consent as routine procedures (but within the protocol defined timeframe) do not need to be repeated and may be used as baseline assessments provided tests were performed using the method requirements outlined in RECIST v.1.1.
Clinical assessment of superficial disease must be carried out on the same date as the imaging studies and will include color photographs including a metric ruler of all superficial metastatic lesions.
HRQL assessments: Study participants will complete electronic questionnaires prior to any study or medical procedures or discussion of their health status on D1 of Cycles 1, 2, 3, and 4 and then every 3 cycles starting from Cycle 6 D1 (ie, Cycle 6, 9, 12, etc), at end of treatment and at 1st follow-up visit. The time estimated to complete the EORTC QLQ-C30 and EORTC QLQ BR23/BR45 is approximately 15 to 20 minutes, and the time estimated to complete the EQ-5D-5L is approximately 5 to 10 minutes (for a total of 20 to 30 minutes to complete all three assessments). In countries where the translated and validated EORTC QLQ-BR45 questionnaire is not available, study participants can use EORTC QLQ-BR23 questionnaire until the availability of translated and validated EORTC QLQ-BR45 questionnaire. Paper format will be used in case of extreme circumstances eg, technical issue making the electronic format temporarily unusable.

AE = adverse event; C = cycle; cfDNA = cell free deoxyribonucleic acid; COD = cut-off date; 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; FFPE = formalin fixed paraffin embedded; FSH = follicle-stimulating hormone; HRQL = health-related quality of life; IRT = Interactive Response Technology; MRI = magnetic resonance imaging; PD = progressive disease; PFS = progression free survival; PK = pharmacokinetics; QLQ BR23 = EORTC QLQ breast cancer specific module-23 items; QLQ BR45 = EORTC QLQ breast cancer specific module-45 items; QLQ C30 = EORTC core quality of life questionnaire. RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

2 INTRODUCTION

Invasive breast cancer affects 1 in 8 women in the United States (12.4%) during their lifetime. In the United States, in 2020, an estimated 279,100 new cases of invasive breast cancer are expected to be diagnosed in United States (4). Breast cancer incidence in Europe in 2018 was estimated to be 522513 cases (5). Male breast cancer is uncommon, comprising <1% of all cases of breast cancers, but its treatment is based on the guidelines for female breast cancer. The incidence rate of breast cancer increases with age, from 1.5 cases per 100 000 in women 20 to 24 years of age to a peak of 421.3 cases per 100 000 in women 75 to 79 years of age; 95% of new cases occur in women aged 40 years or older. The median age of women at the time of breast cancer diagnosis is 61 years (6).

With early detection and significant advances in treatment, death rates from breast cancer have been decreasing over the past 25 years in North America and other parts of the World. However, breast cancer remains a serious condition since even an early detection leading to an immediate surgery followed by adjuvant therapy does not systematically prevent a potential recurrence of the disease, even many years after the diagnosis. Moreover, for patients presenting with advanced stages (stage II or III) in the early breast cancer setting, for those with immediate metastatic breast cancer and for those who become resistant after one or several lines of anticancer therapy, the probability of survival is limited and the medical need for more active agents in this clinical setting remains very high.

2.1 STUDY RATIONALE

Study rationale and purpose

The purpose of the proposed study is to demonstrate the superiority of a new oral SERD, amcenestrant, in combination with palbociclib versus letrozole in combination with palbociclib in patients with ER(+), HER2(-)advanced or metastatic breast cancer who have not received prior systemic anti-cancer treatment for advanced disease.

The standard of care for decades in first-line was endocrine therapy (ET) with a median PFS varying from 6 to 17 months (7, 8, 9, 10, 11, 12) with single hormonal agents such as tamoxifen and AIs.

Recently, targeted therapy such as CDK4/6 inhibitor was combined with ET in the first- and second-line of metastatic breast cancer. Multiple trials have evaluated these combinations, either with an AI or fulvestrant. Three first-line trials have studied an AI as an endocrine backbone in combination with a CDK4/6 inhibitor in postmenopausal women with HR-positive HER2-negative advanced or metastatic breast cancer: PALOMA-2, MONALEESA-2 and MONARCH 3 (mPFS: 24.8-28.2 months; HR: 0.54-0.58). These studies demonstrated almost a doubling of PFS when the CDK4/6 inhibitor was added to ET, with remarkably similar HR across trials. However, the initial first-line trials looking at CDK4/6 inhibitors excluded women who were premenopausal and taking chemical ovarian suppression agents (13, 14, 15). The

American Society of Clinical Oncology (ASCO) guidelines note that patients who are premenopausal and able to use ovarian suppression should receive the same treatment as postmenopausal women (16). MONALEESA-7 study focused on premenopausal women, showing almost similar PFS benefit and HR compared with the ones observed in postmenopausal mBC trials. An overall survival benefit from combination endocrine treatment with ribociclib demonstrated in MONALEESA-7 has provided an insightful rationale for the treatment of patients with premenopausal hormone receptor-positive, HER2-negative metastatic breast cancers (17, 18). More recently, data from a Phase 2 trial (YoungPEARL) comparing exemestane plus palbociclib with ovarian function suppression vs chemotherapy showed clinical benefit in terms of improved progression-free survival (20.1 months, HR 0.65) in premenopausal patients with hormone receptor-positive, HER2-negative mBC. This study provides further data to support the use of ET with palbociclib and ovarian suppression as first-line treatment for metastatic HR-positive breast cancer in premenopausal women (19).

Endocrine therapy is the backbone of any treatment in the ER+, HER2- advanced or metastatic breast cancer regardless of the line of therapy. Unfortunately, these treatments administered alone or in combination with targeted therapies, even if they in general significantly improve survival without progression, are unable to identify which patients can benefit from one treatment or the other, single agent or combination of therapies.

Fulvestrant, the only approved treatment in SERD class, has demonstrated a significant PFS improvement versus anastrozole in the first line setting (20) and in combination with ribociclib versus fulvestrant (21, 22).

SERDs are competitive ER antagonists that also induce conformational ER changes that lead to the degradation of ER via an ubiquitin proteasome system. The unique dual-function of SERDs (ER antagonism and depletion) may enable them to block ER signaling in cellular settings where other endocrine agents, such as tamoxifen or AIs have failed. Although fulvestrant has served as an important proof of concept for the SERD approach, this therapy is limited by its poor pharmaceutical properties which necessitate intramuscular administration and limits the applied dose, exposure and receptor engagement. The fulvestrant 500 mg regimen (500 mg on Days 1, 14, and 28; monthly thereafter) does not fully saturate ER binding in some patients as inhibition of ^{18}Fluoroestradiol Positron-emission tomography (FES-PET) scan uptake was incomplete in 38% (6/16) of patients (23). This incomplete receptor occupancy was associated with lack of clinical benefit.

Rationale for dose and regimen selection

The Phase 1/2 first-in-human (FIH) study with amcenestrant single agent, TED14856, started in November 2017 and designed in several parts, includes ER+, HER2-, postmenopausal women presenting with measurable advanced/metastatic breast cancer who progressed after several therapies.

Part A was a dose escalation Phase (3 + 3 design) evaluating amcenestrant single agent from 20 mg to 600 mg in a QD regimen, with the aim of assessing safety (including dose-limiting toxicities), pharmacokinetics, and pharmacodynamics and defining the recommended dose as

single agent. A total of 16 post-menopausal patients presenting with advanced/metastatic breast cancer were treated.

At the time of the analysis of the data to determine the recommended dose:

Safety was assessed in 16 patients, all of them presented with at least one treatment-emergent AE (TEAE). No DLT was observed during Cycle 1 at any tested dose levels. MTD was not reached. Most frequent TEAEs related to treatment were hot flushes (31.3%), diarrhea, nausea (both 25%), decreased appetite, constipation, night sweats, asthenia (all 18.8%), arthralgia and fatigue (both 12.5%); no event was Grade ≥3. Serious adverse events (SAEs) considered to be not associated with amcenestrant have been reported in 2 patients (24, 25).

Pharmacodynamics was assessed using ^{18}FES PET scans performed at baseline and between 11 and 15 days after the first administration of amcenestrant and close to the time of PK trough, prior to the next dose. High levels of inhibition of the signal were observed from the 150 mg dose level: 100% inhibition at this dose level, and more than 87% in all patients treated at further dose levels when C_{trough} was above 100 ng/mL.

Pharmacokinetic (PK) analysis obtained from a total of 16 patients shows that amcenestrant was generally well absorbed but showed a high within and total-subject variability of exposure. After multiple QD dosing in patients, a moderate accumulation is 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 (C_{max} and $AUC_{0\text{-}24h}$) 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 evaluation, amcenestrant exposure increased by 21-77% between 200 and 600 mg in a subset of patients, and up to 71% in heathy subjects at 400 mg with a high fat meal. Recommendation is done to give amcenestrant with food intake (when given at 200 mg once daily) for all amcenestrant clinical studies, including the current study to ensure favorable exposure in patients who may have lower absorption.

A strong PK/PD 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.

The best overall responses according to RECIST.1 criterion, were PR in 1 patient treated at 150 mg QD (6.3%), stable disease (SD) in 8 patients (50.0%), including 7 (43.8%) with long-term SD (≥24 weeks) and PD in 7 patients (43.8%).

Taking into account all these parameters, amcenestrant 400 mg dose level was established as the recommended dose for the Part B expansion cohort.

Part B was the expansion phase of amcenestrant single agent in similar population except a limitation to only one prior chemotherapy. A total of 49 heavily pretreated patients received amcenestrant 400 mg in this dose expansion. The analyses were conducted in 49 patients of Part B in addition to 13 patients of Part A who received amcenestrant 150 mg dose or more.

Safety was assessed in 62 patients. A total of 38 patients (61.3%) experienced TEAEs that are considered to be related to amcenestrant by the Investigator. The most frequently reported related

TEAEs by MedDRA PT were hot flushes (16.1%), constipation and arthralgia (9.7%), decrease appetite, nausea, diarrhea and vomiting (8.1%). Related TEAEs were Grade 1 and 2 and non-serious. None of the 22 SAEs observed in 13 patients (21%) were considered as related to amcenestrant. Eighty-two per cent of the events were of Grade ≤3 and were distributed among various SOCs.

Clinical activity was assessed in 59 evaluable patients as well as in a subset of patients naïve from targeted therapies and/or fulvestrant.

The best overall responses based on RECIST1.1 criteria for the 59 patients were: 4 confirmed PRs (6.8%), 25 SD (42.4%), and 30 PD (50.8%). More importantly, the CBR (= CR + PR + SD ≥24 weeks) was of 35.6% in the global population.

A comparison of the results observed in TED14856 study with those of fulvestrant in the literature was undertaken in order to place the results from amcenestrant in the context of historical control. A total of 5 comparative studies were selected with fulvestrant given as a single agent, in which selection criteria excluded patients with prior targeted therapies (mTOR and CDK 4/6 inhibitors) and fulvestrant. The results were consistent between studies with an ORR of 7 to 12% and a CBR of 31 to 37%; however, the results observed in the TED14856 were in heavily pre-treated population.

The ORR and CBR in TED14856 study in a similar population, ie, when considering the selected subset of 14 patients with neither prior targeted therapies (mTOR or CDK 4/6 inhibitor) nor fulvestrant, was of 21.3% and 64.3%, respectively.

The results of the activity observed with amcenestrant described above in a heavily pretreated population indicate a high rate of long stabilization (CBR). In addition, the safety and tolerability profiles of amcenestrant QD given as single agent are favorable with TEAEs of low grades.

Part C was a dose escalation of two dose levels of amcenestrant (200 and 400 mg) in combination with a 125 mg fixed dose of palbociclib followed by Part D, an expansion phase with this combination at the recommended dose.

A total of 6 patients were included in the dose escalation part, 3 at each dose level of amcenestrant. No DLT was reported. However, a signal of palbociclib exposure decrease was observed (compared to literature data), and additional patients were enrolled and treated.

When compared to amcenestrant monotherapy data after repeated QD dosing, palbociclib 125 mg had no effect on the PK of amcenestrant at 200 mg, and had minimal effect (28% decrease of amcenestrant exposure) at 400 mg. Conversely, amcenestrant administered QD decreased palbociclib exposure, with an increase of the effect when increasing effect from 200 to 400 mg. When compared to palbociclib PK historical published data of palbociclib given as single agent (or in combination with letrozole) (26, 27), exposure decreased on average by 23% when combined with 200 mg amcenestrant QD (N=8) and by 60% with 400 mg amcenestrant QD (N=5).

Palbociclib clearance is mainly metabolic and showed a 32% decrease of exposure when combined with a moderate CYP3A inducer (Modafinil) (28). This extent of decrease was not considered as clinically relevant according to palbociclib labelling.

Considering the facts that more than 90% of target engagement is shown by ^{18}FES-PET inhibition from 150 mg and above for amcenestrant, and that a decrease of palbociclib around 23% can be considered as not clinically significant, the dose of 200 mg of amcenestrant in combination with125 mg of palbociclib was established as the recommended dose.

The dose expansion part of amcenestrant 200 mg in combination with palbociclib 125 mg is ongoing in patients naïve from prior targeted therapies (CDK4/6, PI3K or mTOR inhibitors) who progressed during adjuvant therapy or after hormonal therapy for metastatic breast cancer.
An interim analysis was conducted to assess the safety of the combination in 36 patients treated at 200 mg (9 from Part C and 27 from Part D) and the activity based on RECIST1.1 criterion in 19 evaluable patients (6 from Part C who did not receive a prior targeted therapy and 13 from Part D). A total of 75% of these patients are still ongoing, 22.2% have 1 cycle or less of treatment and 44.4% at least 4 cycles. The median duration of treatment was of 10.4 weeks. The median relative dose intensity was about 100% for amcenestrant and 90% for palbociclib in line with what was observed in PALOMA-3 study (91.7%).

Among these 36 patients, 29 patients (80.6%) experienced at least one TEAE (all grades, excluding laboratory abnormalities), regardless the relationship to amcenestrant or Palbociclib: the most frequently reported TEAEs (>10%) by Medical dictionary for regulatory activities (MedDRA) preferred term (PT) were: nausea (22.2%); fatigue (19.4% each); constipation and diarrhea (13.9% each), asthenia, cough, dizziness, and dry skin.

Most of these TEAEs were of Grade 1 and 2. A total of 12/36 (33.3%) patients had at least one Grade ≥3 TEAE. Twenty-two patients (61.1%) had TEAEs related to amcenestrant and 25 patients (69.4%) had TEAE related to palbociclib by the investigator.

The most frequently reported TEAEs related to amcenestrant by MedDRA PT (≥5%) were mainly of Grade 1 with no Grade 3: nausea (16.7%), fatigue (11.1%), asthenia, diarrhea and hot flushes (8.3%, each), and dizziness, dry skin, malaise, stomatitis (5.6%, each).

The most frequently reported TEAEs related to palbociclib by MedDRA PT (≥5%) were the following: fatigue (19.4%), nausea and neutropenia (16.7%, each), neutrophil count decreased (11.1%), asthenia and dizziness (8.3%, each), diarrhea, dry skin, malaise, stomatitis, and ALT increased (5.6%, each). Grade 4 was observed for neutropenia (2.8%) and Grade 3 for neutropenia (8.3%), neutrophil count decreased (11.1%) and ALT increased (5.6%).

A total of 5 patients (13.9%) had at least one SAE. All of them were considered as not related to the amcenestrant or Palbociclib intake by the investigator. A total of 3 patients (8.3%) presented with SAEs of Grade ≥3: pneumonia and pleurisy in 1 patient, duodenal obstruction in 1 patient, gastritis and small intestinal obstruction in 1 patient.

The main hematological laboratory abnormality during the TEAE period was neutrophil count decrease in 87.9% of the patients; Grade 1, 2, 3 and 4 were observed in 6.1%, 39.4%, 39.4% and 3.0%, respectively. In a pooled analysis conducted in 1666 patients treated with palbociclib, 95.2% of patients had neutrophil count decrease; Grade 1, 2, 3 and 4 were observed in 4.4%, 23.8%, 56.4% and 10.5%, respectively (ref: Investigator's brochure, Palbociclib. June 2019, Table 6.2-13). Liver enzymes increased were very limited with no Grade ≥3 AST increased and 5.6% of Grade 3 ALT increased.

The preliminary activity was assessed in 19 evaluable patients naïve from targeted therapies based on RECIST1.1 criterion. The best overall responses are: 1 confirmed PR (5.3%), 17 SD (89.5%) including two patients who have achieved PR not yet confirmed, and 1 PD (5.3%). The disease control rate (CR+PR+SD) is 94.7% and the clinical benefit rate is not mature as most of the patients have not reached 24 weeks of treatment yet. Tumor shrinkage was observed in 57.9% (11/19) of the patients and tumor size remains stable in 26.3% (5/19) of the patients.

The preliminary analysis of the combination of amcenestrant with palbociclib indicate a favorable safety profile, the related TEAEs to amcenestrant in the combination were similar to the ones observed with amcenestrant single agent. The incidence of neutrophil count decreased related to palbociclib was in line with palbociclib combined with endocrine therapy literature. The preliminary antitumor activity of this combination observed so far in these 19 hormonal resistant patients is encouraging with a controlled disease for almost (94.7%) all patients.

Taken together, these observations suggest that the combination of amcenestrant, a selective ER down-regulator, and palbociclib can be an important therapeutic option for patients with ER+ metastatic breast cancer.

2.2 BACKGROUND

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 ER, PR, and HER2 receptor status into HER2-positive, ER-positive/HER2-negative, and triple negative clinical subtypes. About 75% of breast cancers express estrogen ERα which is a hormone regulator transcription factor (29).

There are several classical ET for the treatment of HR+/HER2- advanced breast cancer in postmenopausal women: selective ER modulators (SERMs) that act by blocking the ER (eg, tamoxifen), nonsteroidal and steroidal AIs which reduce estrogen levels by inhibiting the peripheral synthesis of estrogen, and the selective estrogen receptor degrader (SERD) fulvestrant (30, 31).

Amcenestrant is a potent, orally bioavailable, and selective ERα inhibitor that belongs to the SERD class of compounds. SERDs have the potential to block endocrine-dependent and endocrine-independent ERα signaling by ablation of ERα and have been recognized to offer a therapeutic approach to ERα positive breast cancer in both early stage and more advanced treatment resistant cases. Amcenestrant antagonizes the binding of estradiol to ER but also promotes the transition of ERα to an inactive conformation that leads to up to 98% receptor degradation at sub-nanomolar concentrations in cellular assays.

These dual properties of amcenestrant translate in a deeper inhibition of ERα pathways and a more effective anti-proliferative activity in ERα-dependent breast cancer cell lines driven by mutant or wild-type ERα compared to other ERα inhibitors.

A detailed description of the chemistry, pharmacology, pharmacokinetics, clinical safety, and preliminary efficacy of amcenestrant is provided in the Investigator's Brochure.

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.

2.3 BENEFIT/RISK ASSESSMENT

Amcenestrant (a new oral SERD) may represent a new therapeutic option with a better benefit/risk ratio than approved endocrine monotherapies, such as AIs, tamoxifen and fulvestrant. In the first-line setting, fulvestrant (Faslodex®) single agent, a SERD compound, demonstrated a significant superiority versus anastrozole and was recently approved in that indication. Combining amcenestrant with palbociclib in animal models led to further growth-inhibitory effects compared with monotherapy alone suggesting that the combination of amcenestrant with palbociclib could bring more therapeutic benefit to ERα positive breast cancer patients than SERD monotherapy. amcenestrant single agent offers a favorable safety profile according to the preliminary results obtained in FIH study with limited rate of related Grade 1/2 adverse events. With amcenestrant monotherapy, most frequently observed TEAEs regardless of relationship are constipation, nausea, vomiting, diarrhea, fatigues, arthralgia, and decreased appetite. With amcenestrant in combination with palbociclib. most frequently observed TEAEs regardless relationship are neutropenia, nausea, asthenia, diarrhea, cough, and fatigue. The most common AEs reported for letrozole monotherapy arm in PALOMA-2 were arthralgia, hot flushes, fatigue, headache, and nausea; 5.9% of the patients discontinued for toxicity (13). In addition, in the adjuvant setting, angina requiring surgery, new or worsening of angina, myocardial infarction, venous thromboembolic events have been reported (Letrozole EU SmPC). Prevention, monitoring and management of any cholesterol increase could help decrease risk of cardiac disease. In addition, awareness and early recognition of clinical signs of ischemic heart disease (chest pain, breathlessness etc) with timely medical assistance help reduce risk of developing life-threatening condition. In addition, healthy lifestyle changes can also help reduce the risk. Tendonitis and tendon rapture (rare) may occur. The patients who experienced tendon pain or swelling should be closely monitored and appropriate measures (eg, immobilization) must be initiated for the affected tendon. 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 well-being of the participants, the benefit-to-risk assessment is deemed acceptable within the context of the planned EFC15935 study. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of amcenestrant may be found in the Investigator's Brochure.

2.3.1 Risk assessment

2.3.1.1 Risks in the Context of COVID-19

The risks in the context of COVID-19 have been evaluated as follows.

2.3.1.1.1 Risks related to the patient population

The UK Coronavirus Cancer Monitoring Project (UKCCMP) has shown that the patients with breast cancer were at lower risk of contracting or dying from COVID-19, primarily because of patients being women rather than inherently lower risk associated with the tumor type (32). A cohort study from breast cancer patients from France showed that, breast cancer patients share the same risk factors for severe COVID-19 as the general population (33).

Testing for SARS-CoV-2 infection during the screening phase should be based on investigator discretion and should also follow local/international guidelines (eg, asymptomatic but high risk of infection patients, patients with symptoms that could be associated with SARS-CoV-2 infection). Patients known to have had SARS-CoV-2 infection prior to study entry must be fully clinically recovered in order to be eligible for participation in the study.

During the study, if a study participant is diagnosed with SARS-CoV-2, dose modification of study intervention should be based on the recommendations provided in Section 10.7. In addition, all investigators are instructed to consult official COVID-19 clinical research guidance from their local hospital/institution along with other relevant resources, such as:

- American society of clinical oncology (ASCO) (34)
- European Society for Medical Oncology (ESMO) (35).

2.3.1.1.2 Risks related to study related activity

It is important to minimize the risk of exposure of patients to COVID-19. In addition to the contingency measures described in Section 10.15 following prevention and mitigation plans could be implemented at clinical sites. Such plans may include:

- All participating sites should have implemented measures according to regional/local Health Authorities, European medicines agency (EMA), ESMO, ASCO guidelines including but not limited to restrictions of access to the hospitals for visitors, physical distancing and personal protective equipment (PPE).
- Study participants should be treated in a dedicated area that is separated from patients with COVID-19 infection.

2.3.1.1.3 Risks related to study treatment

Amcenestrant is a selective estrogen receptor degrader, and letrozole is a non-steroidal aromatase inhibitor. Both amcenestrant and letrozole belong to endocrine therapy, and they do not cause myelosuppression unlike other types of anti-cancer treatment (ie, chemotherapy, CDK4/6

inhibitor). Thus, the endocrine therapy does not pose additional risk for patients in the context of the current COVID-19 pandemic.

Palbociclib is a CDK4/6 inhibitor, and has myelosuppressive properties (very common - leukopenia, and neutropenia). It may predispose patients to infections, while it is unknown if palbociclib is known to be associated to viral infections. As described in Section 6.8, in patients with treatment-emergent neutropenia or in case of neutropenic complications, G-CSF may be given at the discretion of the investigator, if dose modification is not warranted.

As of 10 September 2020, one patient (67 years, Female, ECOG PS=0 at baseline) who received amcenestrant 200 mg QD in combination with palbociclib 100 mg QD in TED14856 study (36) experienced Grade 2 serious COVID-19 infection during Cycle 6. The patient was asymptomatic with oxygen saturation of 98%, while Chest CT showed subpleural opacities in lower lobes. amcenestrant was continued without dose modifications, while palbociclib administration was omitted until the recovery of event. Palbociclib was resumed later and currently, the study participant is ongoing study treatment with amcenestrant and palbociclib (Cycle 11).

2.3.2 Benefit assessment

2.3.2.1 Benefits in the context of COVID-19

The participants potentially eligible for this trial have locoregional recurrent or metastatic breast cancer. Based on the mechanism of action of amcenestrant and clinical data generated as monotherapy and in combination with palbociclib, there is the potential for benefit for these patients.

2.3.3 Overall benefit/risk conclusion

Overall, benefit-risk is deemed acceptable in patients with advanced breast cancer during COVID-19 pandemic. Sponsor will continue to evaluate benefit-risk during the study period.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine whether amcenestrant in combination with palbociclib improves progression free survival (PFS) when compared with letrozole in combination with palbociclib in participants with ER+, HER2- advanced breast cancer who have not received prior systemic anticancer therapies for advanced disease	• 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 local radiologist/investigator or death (due to any cause), whichever comes first.
Secondary	
• To compare the overall survival (OS) in both treatment arms [**Key Secondary Objective**]	• Overall survival is defined as the time interval from the date of randomization to the date of documented death (due to any cause). **[Key Secondary Endpoint**]
• To evaluate the objective response rate (ORR) in both treatment arms	• ORR is defined as the proportion of participants who have a complete response (CR) or partial response (PR), as best overall response determined as per RECIST 1.1, from the date of randomization until disease progression, death, cutoff date, initiation of post-treatment anti-cancer therapy, whichever occurs first.
• To evaluate the duration of response (DOR) in both treatment arms	• DOR is defined as the time from first documented evidence of CR or PR until progressive disease (PD) as determined as per RECIST 1.1 or death from any cause, whichever occurs first.
• To evaluate the clinical benefit rate (CBR) in both treatment arms	• CBR is defined as the proportion of participants who have a confirmed CR, PR, or stable disease (SD) for at least 24 weeks determined as per RECIST 1.1, from the date of randomization until disease progression, death, cutoff date, initiation of post treatment anti-cancer therapy, whichever occurs first.
• To evaluate progression-free survival on next line of therapy (PFS2)	• The PFS2 is defined as the time from the date of randomization to the date of first documentation of PD on the next systemic anti-cancer therapy according to investigator or death due to any cause in the absence of documented PD on the next systemic anti-cancer therapy, whichever occurs first.
• To evaluate the pharmacokinetics (PK) of amcenestrant, and Palbociclib	• Plasma concentrations of amcenestrant, palbociclib
• To evaluate health-related quality of life (HRQL) in both treatment arms	• Symptoms and function related to HRQL as measured by EORTC QLQ-C30, breast cancer specific module (QLQ-BR23/BR45) and EQ-5D-5L

	• Disease-specific and generic HRQL, disease and treatment-related symptoms, the impact of symptoms and treatment, health state utility, and health status will be evaluated using the European Organization for Research and Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30), the EORTC-QLQ breast cancer specific module (QLQ-BR23/BR45) 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 study treatment
• To evaluate the time to first chemotherapy in both treatment arms	• Time to chemotherapy is defined as the time interval from the date of randomization to the start date of the first chemotherapy after study treatment discontinuation
• To evaluate safety in both treatment arms	• Treatment emergent adverse events (TEAEs)/serious adverse events (SAEs) and laboratory abnormalities
Exploratory	
• 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).	• Tumor ER, Ki67, Bcl-2, and PgR protein, and RNA gene expression profiles in paired biopsies at Cycle 1 Day 1 (pre-treatment) and optional at end of treatment for participants who discontinued treatment due to disease progression
• 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.	• The gene mutation profile of the tumor by cfDNA analysis over time (Cycle 1 Day 1 [pre-treatment], at Cycle 4 Day 1 predose (tumor assessment), and upon disease progression on treatment or EOT whichever comes first)
• To evaluate exposure/response relationship of amcenestrant and palbociclib	• PK of amcenestrant will be correlated with safety and/or efficacy
• To evaluate the PK of goserelin	• Plasma concentrations of goserelin
• To evaluate PFS in participants expressing PIK3CA and ESR1 mutation in both treatment arms	• 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 local radiologist/investigator or death (due to any cause), whichever comes first.

For China, please see Section 10.6 for details.

Primary estimands defined for primary and key secondary efficacy endpoints are summarized in Table 2 below. More details are provided in Section 9.2.

For both estimands, the comparison of interest will be the comparison of amcenestrant in combination with palbociclib versus letrozole in combination with palbociclib. The analysis population corresponds to all participants from the intent-to-treat population.

Table 2 - Summary of primary estimand for main endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event(s) handling strategy	Population-level summary (Analysis and missing data handling)
Primary objective: to determine whether amcenestrant in combination with palbociclib improves the progression free survival (PFS) when compared to letrozole in combination with palbociclib.				
Primary endpoint (Estimand 1)	PFS	ITT	- Interruption/discontinuation of study intervention: PFS will be analyzed based on events irrespective of study intervention interruption/discontinuation (treatment policy strategy). - Start of new anti-cancer therapy prior to PFS event: PFS will be censored at the last evaluable tumor assessment prior to a new anti-cancer therapy is initiated (hypothetical strategy). - PFS event documented after two or more non-evaluable tumor assessments: PFS will be censored at the last evaluable tumor assessment prior to the event (hypothetical strategy).	One-sided log-rank test stratified by randomization stratification factors, as entered in the IRT system. Hazard ratio (HR) and corresponding 95% CI estimated using stratified Cox proportional hazard model. The Kaplan Meier estimate of PFS at specified time points, PFS quartiles and corresponding 95% CI from Kaplan Meier method.
Key secondary objective: to compare overall survival between two treatment arms.				
Key secondary endpoint (Estimand 2)	OS	ITT	- Interruption/discontinuation of study intervention: OS will be analyzed based on events irrespective of study intervention interruption/discontinuation (treatment policy strategy). - Start of new anti-cancer therapy prior to death: OS will be analyzed based on events irrespective of start of new anti-cancer therapy (treatment policy strategy).	One-sided log-rank test stratified by randomization stratification factors, as entered in the IRT system. Hazard ratio (HR) and corresponding 95% CI estimated using stratified Cox proportional hazard model. The Kaplan Meier estimate of OS at specified time points, OS quartiles and corresponding 95% CI from Kaplan Meier method.

3.1 APPROPRIATENESS OF MEASUREMENTS

Radiographic tumor assessments directly measure components of the disease, and tumor measures commonly trigger treatment decisions in clinical practice. Therefore, the tumor measure-based endpoint PFS is considered clinically relevant in our study. PALOMA-2 study showed a statistically significant PFS benefit in post-menopausal women with on ER+/HER2- breast cancer receiving palbociclib and letrozole when compared with letrozole alone.

Each of the secondary endpoints (efficacy, safety and QoL assessments) chosen for use in this study is considered well established and relevant in a breast cancer study setting.

In addition, suitable steps have been built into each of these assessments to ensure their reliability and accuracy.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a prospective, multicenter, international, randomized, double-blind, double-dummy, Phase 3 trial comparing the efficacy and safety of amcenestrant in combination with palbociclib versus letrozole in combination with palbociclib in men, pre/peri-menopausal women (with goserelin) and postmenopausal women with ER(+)/HER2(-) breast cancer who have not received prior systemic treatment for advanced disease.

Eligible participants should have histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of either loco-regional recurrent or metastatic disease not amenable to radiation therapy or surgery with curative intention, and for whom chemotherapy is not indicated.

The study will have 3 main periods: screening, active treatment, and follow up. After being screened, participants meeting the eligibility criteria will be randomly assigned using an IRT to either amcenestrant plus palbociclib (experimental) arm or letrozole plus palbociclib (control) arm in a 1:1 ratio.

- Arm A: Amcenestrant 200 mg + letrozole-matching placebo + palbociclib 125 mg
- Arm B: Amcenestrant-matching placebo + letrozole 2.5 mg + palbociclib 125 mg

The study population will be stratified by:

- De-novo metastatic disease (Yes or No)
- Postmenopausal women (Yes or No)
- Visceral metastasis defined by at least 1 liver, lung, brain metastasis, pleural, or peritoneal involvement (Yes or No).

A BIRC assessment will be performed retrospectively on a sample of participants based on radiographic images and clinical information collected on-study.

An independent DMC will monitor the safety data on a periodic basis. The DMC will also evaluate efficacy at the interim analyses and make a recommendation regarding study continuation based on observed results of the study.

A Study Steering Committee will supervise the progress of the trial, review relevant information that may affect the study conduct as well as review DMC recommendations.

4.1.1 Duration of the study period

The duration of the study for each participant will include screening period of up to 28 days and active treatment period, for which the duration varies based on the progression date, followed by a follow-up period. The cycle duration for both arms is 28 days.

Study participants will continue to receive their assigned treatment until objective disease progression, unacceptable toxicity, participant's request to stop treatment, or Investigator's decision, whichever occurs first.

After study treatment discontinuation, participants will return to the study site approximately 30 days (+/- 5 days) (for EOT assessments) after the last IMP administration or before the start of another anti-cancer therapy, whichever is earlier.

EOT visit will be followed by FU visits. During the FU visits, the participants will be monitored for all ongoing related AEs and all the SAEs (regardless of relationship) until resolution or stabilization (ie, an event ongoing without any change for at least 3 months).

In participants who discontinue the study treatment without documented PD, the FU visits will be performed every 12 weeks until disease progression. In participants with documented PD, FU visits will be performed every 24 weeks. All study participants will be followed until death or final study cut-off date, whichever comes first. For cycles completed after the final analysis for PFS cut-off date, all ongoing SAEs (related or not), all related non-serious AEs ongoing at the cut-off date, and all new related AEs (serious or not) occurring post cut-off date will be followed until resolution or stabilization; as well as IMP administration, related concomitant medication, and reason for EOT will continue to be collected.

The total estimated duration of enrollment will be approximately 18 months.

The expected duration of treatment for participants who benefit from study intervention may vary, based on progression date; but median expected duration of study per participant is estimated as median 59 months in experimental arm (1 month for screening, 33 months for treatment, and 25 months for the EOT and follow-up visits) and 47 months in control arm (1 month for screening, 25 months for treatment, and 21 months for the EOT and follow-up visits).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

See Section 2.1 Study Rationale.

4.2.1 Participant input into design

Not applicable.

4.3 JUSTIFICATION FOR DOSE

A total of 6 patients, enrolled in the Part C of TED14856 study, assessed the dose escalation of two dose levels of amcenestrant (200 and 400 mg) in combination with a 125-mg fixed dose of palbociclib.

Pharmacokinetics analysis did not show a major effect of palbociclib 125 mg on amcenestrant 200 mg or 400 mg exposure after single or repeated administration compared to monotherapy exposure. Conversely, amcenestrant administered QD had shown a decrease of palbociclib

exposure, with an increase of the effect when increasing amcenestrant dose. When compared to PK historical published data of palbociclib given as single agent (or in combination with letrozole) (26, 27), exposure decreased on average by 23% when combined with 200 mg amcenestrant QD (N=8) and by 60% with 400 mg amcenestrant QD (N=5). Palbociclib clearance is mainly metabolic and showed a 32% decrease of exposure when combined with a moderate CYP3A inducer (Modafinil) (28). This extent of decrease was not considered as clinically relevant according to palbociclib labelling. Considering the facts that more than 90% of target engagement is shown by 18FES-PET inhibition from 150 mg and above for amcenestrant, and that a decrease of palbociclib around 23% can be considered as not clinically relevant, the dose of 200 mg of amcenestrant is proposed to assess the efficacy of the combination of amcenestrant with 125 mg of palbociclib.

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 last scheduled procedure shown in the schedule of activities 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, or country's legal age of majority if the legal adult age is >18 years old at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Participants with histological or cytological proven diagnosis of adenocarcinoma of the breast with evidence of either loco-regional recurrent or metastatic disease not amenable to radiation therapy or surgery in a curative intent, and for whom chemotherapy is not indicated.

I 03. 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 04. Documentation on the most recently analyzed biopsy (either primary tumor or any metastatic site) of HER2 non over-expressing 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 (37).

- 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 05. Participants previously untreated with any systemic anti-cancer therapy for their loco-regional recurrent or metastatic disease.

I 06. Measurable disease ie, at least one measurable lesion evaluable per RECIST v.1.1, or non-measurable bone only disease with at least one predominant lytic bone lesion without a measurable soft tissue component or mixed lytic-blastic lesion without a measurable soft tissue component must be present (criterion modified by amendment 03).

I 07. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2 (criterion modified by amendment 02).

I 08. Willingness and ability to provide tumor tissues [ie, archived formalin fixed paraffin embedded (FFPE) tissues]. If tumor tissue is not available, then a fresh biopsy will be required for patient participation.

Weight (not applicable)

Sex, contraceptive/barrier method and pregnancy testing requirements

I 09. All Male, or Female of any menopausal status (pre-, peri- or post-menopausal) are eligible. Post-menopausal status is defined in Section 10.4 (Appendix 4). Pre/peri-menopausal women are those not meeting the criteria for being post-menopausal.

It is recommended that men with no prior bilateral orchiectomy and pre/perimenopausal women are on a GnRH agonist for at least 4 weeks prior to randomization. If participants have received an alternative GnRH agonist prior to study entry, they must switch to goserelin for the duration of the trial (criterion modified by amendment 03).

Informed Consent

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

Other inclusions

Not applicable.

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Participants with known active brain metastases (criterion modified by amendment 02).

Participants with treated/stable brain metastases are eligible if they:

- Have completed treatment (whole brain radiotherapy, radiosurgery, or combination)/ stable brain metastases for at least 4 weeks prior to start of study treatment, and
- Have recovered from the effects of this treatment, and
- Are neurologically stable
- If receiving corticosteroid for central nervous system adverse events, the dose should be stable or decreasing over ≥2 weeks prior to first IMP.

E 02. Medical history or ongoing gastrointestinal disorders potentially affecting the absorption of amcenestrant (SAR439859) and/or palbociclib. Participants with known active hepatitis A

(positive HA antigen or positive IgM); B (either positive HBs antigen or positive hepatitis B viral DNA test above the lower limit of detection of the assay); C (positive hepatitis C antibody result and quantitative hepatitis C (HCV) ribonucleic acid (RNA) results greater than the lower limits of detection of the assay) infection; hepatic cirrhosis. Participants unable to swallow normally and to take capsules or tablets. Predictable poor compliance to oral treatment. Active inflammatory bowel disease or chronic diarrhea, short bowel syndrome, or total gastric resection (criterion modified by amendment 03).

E 03. Diagnosis of any other malignancy within 3 years prior to randomization. Adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer are allowed.

E 04. Pregnant or nursing woman, or woman who intends to become pregnant during the study. Woman of childbearing potential (WOCBP) unwilling to prevent pregnancy using highly effective non-hormonal contraception during treatment, and for at least 12 weeks after discontinuation of any study intervention and/or WOCBP unwilling to be tested for pregnancy before study treatment, every 28 days during treatment, and for at least 12 weeks after the last dose of any study intervention.

Note: WOCBP is a woman who is considered fertile following menarche and until becoming post-menopausal, unless permanently sterile.

E 05. Male participants who disagree to practice true abstinence or disagree to use a condom during sexual contact with a pregnant woman or a WOCBP while participating in the study, and for at least 14 weeks after the last dose of any study intervention.

Note: True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.

E 06. Participants with unrecovered acute toxic effects of prior anti-cancer therapy or surgical procedures of NCI CTCAE version 5.0 Grade >1 (except alopecia or other toxicities not considered a safety risk for the participant at investigator's discretion, eg, 3-month stable Grade 2 peripheral neuropathy), or with Pneumonitis, and Interstitial Lung Disease (ILD).

E 07. Participants with advanced, symptomatic visceral spread, that are at risk of life-threatening complications in the short term (including participants with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, leptomeningeal carcinomatosis, and over 50% liver involvement).

E 08. 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 09. Participants with abnormal coagulation profiles, or any history of coagulopathy within 6 months prior to the first dose of IMP, including history of deep vein thrombosis (DVT) or pulmonary embolism. However, participants (except pre/perimenopausal women and male participants) with adequately treated catheter-related venous thrombosis occurring

more than one month prior to the first dose of IMP will be allowed to participate (criterion modified by amendment 02).

E 10. 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. However, participants (except pre/perimenopausal women and male participants) being treated with an anticoagulant for a stable and allowed medical condition (eg, well controlled atrial fibrillation), provided dose and coagulation parameters (as defined by local standard of care) are stable for at least one month prior to the first dose of study drug will be allowed to participate

Prior/concomitant therapy

E 11. Ongoing treatment with drugs that are sensitive substrates of OATP1B1/B3 (asunaprevir, atorvastatin, bosentan, danoprevir, fexofenadine, glyburide, nateglinide, pitavastatin, pravastatin, repaglinide, rosuvastatin and simvastatin acid) (criterion modified by amendment 04).

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*

E 12. Treatment with strong CYP3A inhibitors and strong CYP3A inducers within 2 weeks before first study treatment administration or 5 elimination half-lives whichever is longest and cannot be replaced (criterion modified by amendment 03).

E 13. Criterion removed in amendment 03.

E 14. Treatment with drugs that have the potential to inhibit UGT (uridine 5'-diphospho-glucuronosyltransferase), including, but not limited, to atazanavir and probenecid, within 2 weeks before study treatment administration or 5 elimination half-lives whichever is longest and which cannot be replaced.

E 15. Medical conditions requiring concomitant administration of medications with a narrow therapeutic window metabolized by CYP3A (and for which a dose reduction cannot be considered.

E 16. Disease recurrence while on, or within 12 months of completion of (neo)adjuvant endocrine therapy with any of the following agents: (criterion modified by amendment 03)

- Aromatase inhibitor - eg, letrozole, anastrozole, exemestane.
- Selective estrogen receptor modulator - eg, tamoxifen, toremifene, raloxifene
- CDK4/6 inhibitors - eg, palbociclib, ribociclib, abemaciclib.

E 17. Prior (neo)adjuvant treatment with another selective ER down-regulator (SERD).

E 18. Major surgery or radiotherapy within 4 weeks before randomization.

Participants who received prior radiotherapy to ≥25% of bone marrow are not eligible independent of when it was received.

E 19. Drugs that are known to prolong the QT interval (premenopausal and male participants

Prior/concurrent clinical study experience

E 20. Participation within 4 weeks before randomization in any other clinical study involving an investigational study treatment including anti-cancer agents or within 2 weeks before randomization for any other type of medical research.

Diagnostic assessments

E 21. Inadequate hematological function including:

- Neutrophils $<1.5 \times 10^9$/L
- Platelet count $<100 \times 10^9$/L

E 22. Inadequate renal function estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m² as estimated using the abbreviated Modification of Diet in Renal Disease formula (see Section 10.12).

E 23. Inadequate liver function defined as:

- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 × ULN (>5.0 × ULN if liver metastases present)
- Alkaline phosphatase (ALP) >2.5 × ULN (>5.0 × ULN if bone or liver metastases present)
- Total bilirubin >1.5 × ULN (>3.0 × ULN if Gilbert's disease).

Other exclusions

E 24. Known hypersensitivity/contraindicated to goserelin (men and pre/perimenopausal participants), palbociclib, letrozole, or any of their excipients, or to any amcenestrant (SAR439859) and placebo excipients.

E 25. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 26. Participant 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 study procedures.

E 27. Any specific situation during study implementation/course that may raise ethics considerations, including participants that are dependent on the Sponsor or Investigator (in conjunction with Section 1.61 of the ICH-GCP Ordinance E6) (criterion modified by amendment 04).

E 28. Participants are 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 29. Any country-related specific regulation that would prevent the participant from entering the study - see Appendix 6 (Section 10.6) (country specific requirements).

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

Participants are to refrain from consumption of grapefruit, grapefruit hybrids, or products containing the juice of each during the study treatment period.

5.3.2 Activity (Sun Protection)

Preclinical toxicity studies using amcenestrant indicate a potential risk for phototoxicity; in addition, 1 participant from Part A 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 amcenestrant (SAR439859)/amcenestrant (SAR439859)-matching placebo 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.

5.3.3 Osteoporosis

Due to anti-estrogenic properties of amcenestrant, and letrozole being a potent estrogen lowering agent, 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.

5.4 SCREEN FAILURES

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomized. 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 (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once only. Participants who are rescreened are required to sign a new informed consent form, and should be assigned a new study participant number, and all the screening procedures should be repeated and entered in the screening visit pages. In case the participant is a

temporary screen failure, there is no need to have participant reconsent (ie, new ICF signed) if the participant finally participates in the trial. However, if the reason for temporary screen failure is a reason that might have altered the initial given agreement of the participant to participate, the Investigator should ensure the willingness of the participant to continue or redo some screening procedures and his/her participation to the trial. This oral agreement should be documented in the participant's chart. All the tests out of protocol window should be repeated and entered to the additional pages.

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 10.15 (Appendix 15) should be considered.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1 STUDY INTERVENTION(S) ADMINISTERED

The study interventions (amcenestrant (SAR439859)/amcenestrant (SAR439859)-matching placebo, palbociclib, and letrozole/letrozole-matching placebo, goserelin) will be administered as a flat-fixed dose, and not by body weight or body surface area. All study IMPs must be taken with food, either together or 5 minutes apart, regardless of the order of intake, at approximately the same time each day, whenever possible (Table 3).

Participants will receive study drug diaries for amcenestrant (SAR439859)/amcenestrant (SAR439859)-matching placebo, palbociclib, and letrozole/letrozole-matching placebo to document study intervention intake, and the completed study drug diaries should be returned to the study site at the subsequent study visit.

Any doses of study intervention that are not taken within 6 hours of the intended time should be considered as missed dose. If the participant misses a dose of study intervention, a double dose should not be taken the next day to compensate the missed dose. If the participant vomits a dose of study intervention, an additional dose should not be taken, and this information has to be recorded in the study medication diary. The next prescribed dose should be taken at the usual time.

Table 3 - Overview of Study intervention(s) administered

Intervention label	Amcenestrant (SAR439859)	Amcenestrant (SAR439859) Placebo	Palbociclib	Letrozole	Letrozole Placebo	Goserelin
Intervention name	**Amcenestrant (SAR439859)**	**Amcenestrant (SAR439859)-matching Placebo**	**Palbociclib**	**Letrozole**	**Letrozole-matching Placebo**	**Goserelin**
Intervention description	200 mg Tablet PO OD	Placebo Tablet PO OD	75 mg, 100 mg, or 125 mg Tablet/Capsule PO OD	2.5 mg Capsule PO OD	Placebo Capsule PO OD	3.6 mg subq OD
Type	Drug	Drug	Drug	Drug	Drug	Drug
Dose formulation	Tablets	Tablets	Capsules then Tablets	Capsules	Capsules	In accordance with the approved label
Unit dose strength(s)	200 mg	-	75 mg, 100 mg, 125 mg	2.5 mg	-	3.6 mg
Dosage level(s)	200 mg once daily, continuously	-	75 mg, 100 mg, 125 mg D1-D21 every 28 days	2.5 mg once daily, continuously	-	3.6 mg once every 28 days
Route of administration	Oral	Oral	Oral	Oral	Oral	Subcutaneous
Use	Amcenestrant (SAR439859) active experimental	Amcenestrant (SAR439859) matching placebo	Palbociclib active comparator	Letrozole active comparator	Letrozole matching placebo	Goserelin active comparator
IMP and NIMP	IMP	IMP	IMP	IMP	IMP	NIMP
Packaging and labeling	Amcenestrant (SAR439859) active study intervention will be provided in blisters containing tablets. Labelling will be as required per country requirement	Amcenestrant (SAR439859) placebo study intervention will be provided in blisters containing tablets. Labelling will be as required per country requirement	Palbociclib active comparator will be provided in blisters containing caps and then switch during the trial to blisters containing tablets. Labelling will be as required per country requirement	Letrozole active comparator will be provided in blisters containing capsules. Labelling will be as required per country requirement	Letrozole matching placebo will be provided in blisters containing capsules. Labelling will be as required per country requirement	Goserelin active intervention for subcutaneous administration will be packaged in accordance with the approved label.
[Current/former name(s) or alias(es)]	Amcenestrant (SAR439859)	Amcenestrant (SAR439859)	Ibrance	Letrozole	Letrozole	Zoladex

Between the protocol-scheduled on-site visits, interim visits may be required for study intervention dispensing. As an alternative to these visits, study intervention may be supplied from the PI/site to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed up on by the participant.

6.1.1 Amcenestrant (SAR439859)/Amcenestrant (SAR439859)-matching placebo

Amcenestrant (SAR439859)/Amcenestrant (SAR439859)-matching placebo will be administered orally at a dose of 200 mg once daily continuously and at approximately the same time each day (±3 hours), together with palbociclib.

The assigned daily dose is to be taken once in the morning, with food, at approximately the same time each day (±3 hours), throughout treatment cycles. The daily dose of amcenestrant (SAR439859) tablets is to be swallowed whole with a glass of noncarbonated water and a second glass of water is to be used to rinse out the mouth (for a total of approximately 240 mL). Study participants should be instructed not to bite or chew on the tablets.

On days of PK assessment, amcenestrant (SAR439859)/ amcenestrant (SAR439859)-matching placebo and palbociclib will be taken together. On other days, they can be taken either together or 5 minutes apart, regardless of the order of intake.

6.1.2 Letrozole/Letrozole-matching placebo

Letrozole/Letrozole-matching placebo will be administered orally at a dose of 2.5 mg once daily continuously together with palbociclib.

Letrozole/Letrozole-matching placebo should be taken with food and should be swallowed whole with a glass of water or another liquid.

Letrozole/letrozole-matching-matching placebo and palbociclib can be taken either together or 5 minutes apart, regardless of the order of intake.

Refer to the Letrozole Summary of Product Characteristics for additional administration instructions.

6.1.3 Palbociclib

Palbociclib will be administered orally at a dose of 125 mg once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Palbociclib (regardless of the administered formulation) should be taken with food at approximately the same time each day. Only a single strength of palbociclib capsules/tablets will be dispensed to the patient prior to each cycle. In case of dose modification, participants should return the previously dispensed palbociclib before dispensing new capsules/tablets.

Palbociclib capsules/tablets should be swallowed whole (not chewed, crushed or opened prior to swallowing). Capsules/tablets should not be ingested if they are broken, cracked, or otherwise not intact. The capsules/tablets should be swallowed with a full glass of water (not fruit juices). Refer to the Palbociclib Summary of Product Characteristics for additional administration instructions.

Study will be initiated with palbociclib capsules and will be switched to palbociclib tablets as they become commercially available.

6.1.4 Goserelin

Goserelin will be administered as an injectable subcutaneous implant on Day 1 of every 28-day cycle at a dose of 3.6 mg in pre/peri-menopausal women and men. Refer to the Goserelin Summary of Product Characteristics for additional administration instructions.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

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. 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).

Partially used and used study treatments 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 study treatment 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/NIMP unless Sanofi provides written authorization. Further guidance and information for the final disposition of used and unused study medications are provided in the pharmacy manual and/or monitoring plan.

Any quality issue noticed with the receipt or use of an IMP/NIMP (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 8.3.8).

A potential defect in the quality of IMP/NIMP 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 IMP/NIMP and eliminate potential hazards. Under no circumstances will the Investigator supply IMP/NIMP to a third party, allow the

IMP/NIMP to be used other than as directed by this clinical trial protocol, or dispose of IMP/NIMP in any other manner except for DTP shipment, for which a courier company has been approved by the Sponsor.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

- The randomized intervention kit number list is generated centrally by Sanofi.
- The IMPs are packaged in accordance with this list.
- The randomization and IMP allocation are performed centrally by 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. Details of the IRT procedure will be provided in the IRT Site Manual.

  WARNING: Randomization will not be possible if study treatment is not available at site. Please consider up to 11 days between screening call and arrival of IMP on site.
- The randomization is stratified by De-novo metastatic disease (Yes or No), Postmenopausal women (Yes or No), and Visceral metastasis defined by at least 1 liver, lung, brain metastasis, pleural, or peritoneal involvement (Yes or No).
- A participant cannot be randomized more than once in the study.

Risk related to blinding

This is a double-blind, double dummy study. Participants will be randomly assigned in a [1:1] ratio to receive study intervention. Study participants, Investigators, Study sponsor (except bioanalysts assessing PK samples) and all stakeholders (except DMC and independent statistician) involved in study conduct will remain blinded to each participant's assigned study intervention throughout the course of the study.

Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted. In case of an AE/SAE, the code can be broken only in exceptional circumstances when knowledge of the study IMP is essential for treating the study participant. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. The IRT will be programmed with blind-breaking instructions. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

If the code is broken, the participant must withdraw from IMP administration.

Methods of blinding

- Blinding is done using the double-dummy method.
- IMPs (amcenestrant (SAR439859), Letrozole) and their matching-placebo will be supplied in indistinguishable boxes.

- During the study, an external independent statistician will perform unblinded safety and efficacy analyses for the data review of Data Monitoring Committee (DMC). Access to these data and analyses will be restricted to the DMC members.

6.4 STUDY INTERVENTION COMPLIANCE

Administration of the IMP/NIMP will be supervised by the Investigator or Sub-investigator.

The person responsible for drug dispensing is required to maintain adequate records of the IMP/NIMPs. These records (eg, drug movement form) include the date the IMP/NIMPs are received from the Sponsor, dispensed to the participant and destroyed or returned to the Sponsor. The packaging batch number (IP number) and the treatment number on the IMP/NIMP package must be recorded on the drug accountability form.

A record of the number of amcenestrant (SAR439859)/amcenestrant (SAR439859)-matching placebo, letrozole/letrozole-matching placebo, palbociclib capsules/tablets, and goserelin dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records.

On Day 1 of a given cycle, when participants are dispensed with study interventions at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. On days when there are no on-site visits, study participants will take the study IMP(s) at home. The study staff will demonstrate to the patient how to record information on study IMP(s) intake in study medication diary. Study participants will have to complete the study medication diary on days when study IMP(s) are omitted and on days prior to PK sampling (time of IMP(s) intake, fasting state, vomiting if any), and the completed study medication diary should be returned to study site at subsequent site visit. In case of an early vomiting event, the administered dose of study IMP(s) should not be repeated.

When participants take study medication(s) at home, compliance with study intervention will be assessed using study medication diaries and study medical record (study source documentation). Compliance will also be assessed either by direct questioning, or counting returned tablets/capsules, during the site visits and documented in the source documents and clinical database.

Study participants will be requested to return all unused study interventions to the study site at the end of the treatment period for each cycle for a full compliance assessment. Site staff will record the study intervention dosing information including start and stop dates, including dates for IMP omissions and/or dose reductions in the patient chart and then in to the clinical database.

6.5 DOSE MODIFICATION

Dose modifications are permitted in case of study-treatment related toxicity, and dose could be modified based on the following guidelines:

- Omission of one or more doses until the adequate recovery of toxicity. If a TEAE lead to dose omissions, restart of study IMP(s) could occur either within the same cycle or only up on the initiation of the subsequent cycle (see Section 10.7, Appendix 7). Doses omitted for toxicity should not be replaced.
- Dose reduction during the current cycle, or during subsequent cycle because of the toxicity experienced during previous cycle. This is applicable only to palbociclib, as dose adjustment for amcenestrant (SAR439859)/amcenestrant (SAR439859)-matching placebo and letrozole/letrozole-matching placebo is managed via dose omission instead of continuation at a reduced dose.
- Delay in the start of subsequent cycle (ie, none of the IMP taken) due to persisting toxicities attributed to all IMPs

Every effort should be made to administer the full planned dose in accordance with treatment schedule.

In case of treatment-related toxicity, dose modifications should be made according to the Appendix 7 (Section 10.7). Dose adjustments will be made according to the worst grade of adverse event observed within a cycle. If a participant experiences several adverse events and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed.

Administration of the study treatment will be discontinued in the event of a TEAE that persists despite appropriate dose modifications or any other AE that, in the opinion of the Investigator, warrants discontinuation. In case of recurrent adverse events with severity of Grade ≥3, dose modification of study IMP(s) is required. Please refer to Appendix 7 (Section 10.7) for details.

In case of more than 2 weeks without any IMP intake for reasons other than treatment-related toxicity, study intervention can be resumed only after discussions with study sponsor.

6.5.1 amcenestrant (SAR439859)/amcenestrant (SAR439859)-matching placebo

No dose reduction of amcenestrant (SAR439859)/amcenestrant (SAR439859)-matching placebo is permitted, dose adjustment in case of treatment-related toxicity is managed by dose omission of amcenestrant (SAR439859)/amcenestrant (SAR439859)-matching placebo.

In case of hematological toxicities, no dose adjustment of amcenestrant (SAR439859)/amcenestrant (SAR439859)-matching placebo is required. Dose modification guidelines for amcenestrant (SAR439859)/amcenestrant (SAR439859)-matching placebo in case of non-hematological toxicities could be found in Appendix 7 (Section 10.7).

Participants with definitive discontinuation of amcenestrant (SAR439859)/amcenestrant (SAR439859)-matching placebo due to treatment-related toxicity are not allowed to continue with

palbociclib alone, will be discontinued from the study treatment and will enter the follow-up phase.

6.5.2 Palbociclib

Dose modification (omissions/reduction) are allowed for palbociclib in case of treatment-related toxicity. In case of dose reduction, palbociclib will be administered as shown in Table 4.

Table 4 - Dose levels for palbociclib dose reduction

Starting dose	125 mg/day
Dose Level -1	100 mg/day
Dose Level -2	75 mg/day[a]

a If further dose reduction below 75 mg/day is required, palbociclib will be permanently discontinued.

Once palbociclib dose has been reduced, re-escalation back to the previous dose level is not allowed. Dose reduction could occur during the current cycle or during the initiation of the next cycle. Dose reduction occurring during the current cycle requires that participants should return to study site for new supply of palbociclib.

If palbociclib is definitively discontinued because of treatment-related toxicity, participants may continue as per investigator's discretion on the active treatment phase of the study receiving letrozole plus amcenestrant (SAR439859)-matching placebo or amcenestrant (SAR439859) plus letrozole-matching placebo.

Participants should be monitored for any new or worsening of respiratory symptoms and be advised to report such symptoms promptly. If participants show any signs or symptoms of suspecting interstitial lung disease (ILD)/Pneumonitis (eg, symptoms, such as hypoxia, cough, dyspnea), treatment with palbociclib should immediately be omitted, and appropriate diagnosis testing should be initiated as well as appropriate treatment if judged necessary by the investigator. If participants are diagnosed with ILD/pneumonitis, palbociclib should be permanently discontinued (see Section 10.7, Appendix 7).

6.5.3 Letrozole/Letrozole-matching Placebo

No dose reduction of letrozole/letrozole-matching placebo is permitted, dose adjustment in case of treatment-related toxicity is managed by dose omission of letrozole/letrozole-matching placebo.

In case of hematological toxicities, no dose adjustment of letrozole/letrozole -matching placebo is required. Dose modification guidelines for letrozole/letrozole-matching placebo in case of non-hematological toxicities could be found in Appendix 7 (Section 10.7).

Participants with definitive discontinuation of letrozole/letrozole-matching placebo due to treatment-related toxicity are not allowed to continue with palbociclib alone, will be discontinued from the study treatment and will enter the follow-up phase.

6.5.4 Retreatment criteria

Retreatment criteria after recovery of the toxicity are described below:

- Hematological toxicity (applicable only to Palbociclib): National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5 Grade ≤2 or to their baseline status.
- Non-hematological toxicity: NCI-CTCAE v5 Grade ≤1 or Grade ≤2 (if not considered a safety risk for the patient) or to their baseline status.

Start of new cycle or restart of study intervention after dose omission occurs only when the above criteria are met, and study intervention is administered.

If these criteria are not met on the scheduled Day 1, the start of the next cycle should be delayed until participants recover as defined above. If Day 1 delay is more than 3 days, the reason for delay (eg, adverse event) should be documented in eCRF. If retreatment criteria are not met, despite 2 weeks of cycle delay, permanent discontinuation of study treatment should be considered, unless there is strong evidence of clinical benefit (per investigator's decision) to justify continuation of study intervention.

If within a cycle, these criteria are not met after dose omission lasting more than 2 consecutive weeks, permanent discontinuation of the IMP and/or the study treatment should be considered, unless there is strong evidence of clinical benefit (per investigator's decision) to justify continuation of study intervention.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

There is no intervention following the end of the study. Additional care provided to participants after the completion of the study is based on routine clinical practice.

6.7 TREATMENT OF OVERDOSE

In the event of an overdose, the investigator should:

1. Contact the Sponsor or Sponsor representative(s)immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities.
3. Document appropriately in the e-CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Sponsor or Sponsor representative(s)based on the clinical evaluation of the participant.

6.8 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, 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

The Sponsor or Sponsor representative(s)should be contacted if there are any questions regarding concomitant or prior therapy.

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.

Any medication considered necessary for the patient's welfare and are unlikely to interfere with the IMP may be given at the discretion of the investigator and recorded in the e-CRF. Concomitant medication will be recorded in the eCRF from 28 days prior to the first study intervention administration, any time during the study treatment period, and for up to 30 days after the final dose of study intervention. Once the participant has withdrawn from study treatment, concomitant medication should only be recorded if used to treat new or unresolved study treatment-related adverse events.

The following therapies are prohibited throughout the active treatment phase:

- Concurrent radiotherapy (except palliative radiotherapy) or cancer-related surgery.
- Palliative radiotherapy in the only evaluable lesions. The irradiated area cannot be used as a parameter for response assessment. Participants requiring any of these procedures will be discontinued from the active treatment phase and will enter the follow-up phase. Participants should have a tumor assessment of the lesion(s) before receiving radiotherapy.
- Additional investigational or commercial anticancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy other than study medication.
- Herbal medications and food supplements including St John's Worth and genistein during treatment period since they could decrease amcenestrant (SAR439859) exposure.
- Drugs that are strong inducers of CYP3A since they may decrease amcenestrant (SAR439859) and/or palbociclib exposure. (See Section 10.10 [Appendix 10])
- Drugs that have UGT (uridine 5'-diphospho-glucuronosyltransferase) inhibition potential and are contra-indicated with UGT substrates, including but not limited to atazanavir and probenecid, since amcenestrant (SAR439859) is substrate of UGT1A1 and UGT1A4.

- 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.
- Strong CYP3A inhibitors, since they can increase palbociclib exposure (See Section 10.9 [Appendix 9]).
- Medications with narrow therapeutic window metabolized by CYP3A (See Section 10.16 [Appendix 16]) and for which a dose reduction cannot be considered, since their exposure can be increased by palbociclib.
- In premenopausal women and men, medications that are known to prolong the QT interval (see Section 10.14 [Appendix 14]).

Special caution should be taken with regards to the following therapies:

- The concomitant use of drugs that are sensitive substrates of CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or UGTs since it may result in loss of efficacy of these agents. Substitute for these medications or monitor study participants for loss of efficacy if use of these medications. (See Section 10.11 [Appendix 11]).

The following concomitant treatments are permitted during this study:

- Bisphosphonates and denosumab for the treatment of osteoporosis or management of existing bone metastases may be continued for participants who have been receiving them at a stable dose for at least 2 weeks prior to randomization. However, the need to initiate or increase the dose of these therapies during the study will be considered as indicative of disease progression leading to the discontinuation of participant from the active treatment phase unless disease progression can be completely ruled out and the exact reason for the use of these therapies clearly documented in the participant's source documentation.
- At study entry, bone-targeted agents such as bisphosphonates or denosumab is recommended in study participants with bone mineral density T score of <-2 or with ≥2 risk factors for fracture per ESMO clinical practice guidelines on bone health in cancer (38).
- Hematopoietic growth factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage colony stimulating factor [GM-CSF]): Primary prophylactic use of granulocyte-colony stimulating factors is not permitted but they may be used to treat treatment-emergent neutropenia as indicated by the current ASCO guideline. If neutropenic complications are observed in a cycle in which primary prophylaxis with CSFs was not received, secondary prophylaxis may be given at the discretion of the investigator, but only if dose reduction or delay are not considered a reasonable alternative.
- Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia.
- In case of severe anemia, blood transfusion is permitted as per investigator's judgment.

- Palliative radiotherapy may be given for control of bone pain or for lytic lesions at risk of fracture, provided that the lesions were present at study entry. 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. If palliative radiotherapy is initiated after start of study treatment, the reason for its use must be clearly documented and disease progression should be ruled out. Participants should have a tumor assessment of the lesion(s) before receiving radiotherapy.
- Standard therapies for pre-existing medical conditions, medical complications, and palliation. Any medications used for supportive care in routine clinical practice (eg, analgesics, antidiarrheals, antiemetics) may also be used at the investigator's discretion. All medications should be recorded.
- Live vaccines should be avoided. However, given the increased risk of infection with palbociclib, routine vaccinations are recommended for the patients and their contacts. 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.

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 10.1.9).

7.1 DISCONTINUATION OF STUDY INTERVENTION

Pregnancy of female participant will lead to definitive discontinuation of study intervention in all cases.

7.1.1 Permanent discontinuation

The study intervention should be continued until the objective progressive disease whenever possible. Participants can withdraw their participation at any time during the study. The investigator has the right to remove any participant (eg, Poor compliance to the protocol, intercurrent illness that prevents further administration of study treatment) from study. Any study intervention discontinuation must be fully documented in the e-CRF.

Study intervention should be discontinued in below circumstances:

- disease progression,
- unacceptable adverse event (refer to Section 10.7 [Appendix 7] for some of the adverse events leading to definitive/premature discontinuation of study intervention),
- poor compliance to the study protocol
- other such as concurrent illness, that prevents further administration of study intervention.

If participants are clinically stable, and possibly deriving clinical benefit from therapy with minimal toxicity, they can continue the study intervention until disease progression, unacceptable toxicity, participant's request to stop treatment, or investigator's decision. However, participants may continue treatment as assigned at randomization beyond the time of RECIST-defined disease progression at the discretion of the investigator if that is in the best interest of the participant and as long as no new anticancer treatment is initiated. In these cases, the Investigator must discuss the rationale with the Sponsor before the decision to continue treatment on-study is made.

If study intervention is permanently discontinued because of reasons other than documented PD, the participant will remain in the study for tumor assessment until documented progressive disease or final PFS analysis cut-off date and will be followed for survival status until OS cut-off date. In case of documented PD being the reason for definitive treatment discontinuation, participants will be followed for survival status until OS cut-off date.

See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

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.

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

7.1.2 Temporary discontinuation

Not applicable.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

The following describes the criteria for withdrawal of participants 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. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an end of treatment visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant who withdraws from the study will be permanently discontinued both from the study intervention and from the study at that time.
- 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.

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

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 e-CRF 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 non-participant 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, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether 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.
- 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, imaging) and obtained before signing of the ICF may be utilized for screening purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1 EFFICACY ASSESSMENTS

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

Primary criteria

The primary endpoint is Progression-free survival (PFS) 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 local radiologist/investigator or death (due to any cause), whichever comes first.

Secondary criteria

The key secondary endpoint is Overall survival (OS), defined as the time interval from the date of randomization to the date of documented death (due to any cause).

The other secondary endpoints related to efficacy are objective response rate (ORR), clinical benefit rate (CBR), and the duration of response (DoR).

Assessments

Participants may have measurable disease as per RECIST v.1.1, or non-measurable bone only disease with at least one predominant lytic bone lesion or mixed lytic-blastic lesion.

The schedule of tumor assessments should be fixed according to the calendar, regardless of treatment delays/interruptions. Imaging assessments are to be scheduled using the randomization date as the reference date for all time-points and are NOT to be scheduled based on the date of the previous imaging time-point. Imaging assessment delay to conform to treatment delay is not permitted. The same tumor assessment technique MUST be used throughout the study for a given lesion/patient.

Baseline scans performed before the signing of informed consent as routine procedures (but within the protocol defined timeframe) do not need to be repeated and may be used as baseline assessments as long as tests were performed using the method requirements outlined in RECIST v.1.1.

Tumor assessments using CT/MRI Scans (with contrast agent) of chest, abdomen, pelvis, any clinically indicated sites of disease, bone lesions, and clinical evaluation of superficial disease will be performed within 4 weeks (ie, 28 days) prior to randomization, followed by every 12 weeks (±7 days) from the date of randomization until documented progressive disease or final PFS analysis cut-off date, and at EOT (to be done if it falls within the 12 weeks ±7 days time window from randomization, and only in participants without PD as per RECIST 1.1). If no PD as per RECIST 1.1 at EOT, disease assessment will continue to be performed every 12 weeks ±7 days up to documented PD as per RECIST v.1.1, or final PFS COD, whichever occurs first.

If signs and symptoms suggest presence of metastatic brain disease, brain scans (CT/MRI) are required at baseline (within 6 weeks prior to randomization). Post-baseline, brain scans are to be repeated only if metastases are present at baseline.

Whole body radionuclide bone scans should be performed at baseline (within 12 weeks prior to randomization). Any suspicious abnormalities (ie, hotspots) identified on bone scans at baseline and on subsequent bone scans MUST be confirmed either by X-ray, CT scan with bone windows or MRI. If bone lesions are identified at baseline, radionuclide bone scans should be repeated every 24 weeks (±7 days) from the date of randomization for the first 18 months, and then every 12 weeks (±7 days) until documented progressive disease or final PFS analysis cut-off date, and at EOT (to be done if it falls within the 12 weeks ±7 days time window from randomization, only in participants without documented PD as per RECIST 1.1 and no bone lesions identified at baseline). If no PD as per RECIST 1.1 at EOT, disease assessment will continue to be performed from randomization date as reference in participants with bone lesions identified at baseline, up to documented PD as per RECIST v.1.1, or final PFS COD, whichever occurs first. During follow-up period, radionuclide whole body bone scan should be performed at the same frequency as done during treatment period.

In addition to the investigators' tumor assessment, radiographic (and photographical when applicable) images and clinical information collected on-study will also be reviewed by a blinded independent review committee, in order to verify investigator-reported tumor assessments. For this purpose, the tumor assessment images should be transferred to the blinded independent review committee for tumor response evaluation.

Participants who discontinue the study treatment without documented PD will be followed every 12 weeks (±7 days) from randomization until progressive disease as per RECIST 1.1 or final PFS analysis cut-off date (COD), whichever occurs first.

In participants with documented disease progression, follow-up visits will be performed every 24 weeks (±7 days) from the last dose of study intervention for survival status and collection of data on post-study anti-cancer therapies (start/stop dates, date of PD) and their responses, until death or until the OS cutoff date, whichever comes first.

8.2 SAFETY ASSESSMENTS

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

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

8.2.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of skin, head & neck, eyes, ear, nose, throat, thyroid, breast & regional lymph nodes, and organ systems such as cardiovascular, respiratory, gastrointestinal, musculoskeletal and neurological systems. Height (only at screening) and weight will also be measured and recorded.
- Clinical evaluation of superficial disease at the time of tumor assessments which will include color photography of all superficial metastatic 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 metric ruler to estimate the size of the lesion is suggested. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study. All lesion measurements must be recorded in the eCRF.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any new finding or worsening of previous finding should be reported as a new adverse event

8.2.2 Vital signs

- Temperature, pulse rate, and blood pressure will be assessed. Blood pressure and pulse measurements will be assessed with a completely automated device, and those measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones). Manual techniques will be used only if an automated device is not available.
- Vital signs abnormalities are to be recorded as adverse events only if they are symptomatic and/or requiring corrective treatment and/or leading to treatment discontinuation and/or dose modification and/or fulfilling a seriousness criterion (see Section 10.3 [Appendix 3]).

8.2.3 Electrocardiograms

- Triplicate12-lead electrocardiogram (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. Triplicate ECGs are collected within about a five-minute window at a nominal time-point.

- ECG abnormalities are to be recorded as adverse events only if they are symptomatic and/or requiring corrective treatment and/or leading to treatment discontinuation and/or dose modification and/or fulfilling a seriousness criterion (see Section 10.3 [Appendix 3]).

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 (see Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. Laboratory abnormalities are to be recorded as adverse events only if they lead to treatment discontinuation and/or dose modification and/or fulfill a seriousness criterion and/or are defined as an AESI (see Section 10.3 [Appendix 3])
- All laboratory tests with values considered clinically significantly abnormal (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 or are no longer considered clinically significant by the Investigator or Sponsor or Sponsor representative(s).
  - 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.
  - 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 (Section 1.3).
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the e-CRF.

8.2.5 Guideline for management of specific adverse events

8.2.5.1 Interstitial Lung Disease/Pneumonitis

Study participants should be monitored for any new or worsening of respiratory symptoms and be advised to report such symptoms promptly. If participants show any signs or symptoms of suspecting interstitial lung disease (ILD)/Pneumonitis (eg, hypoxia, cough, dyspnea), treatment with palbociclib should immediately be omitted, and appropriate diagnosis testing should be initiated as well as appropriate treatment if judged necessary by the investigator.

Whenever appropriate, diagnostic testing in study participants with suspected ILD/Pneumonitis may include (but not be limited to) the following tests/procedures.

- clinical evaluation: assessment of comorbidities, medications, potential exposure to occupational and environmental agents, and concurrent adverse events
- laboratory tests: hematology, biochemistry, and serum markers (such as Kerbs von Lungren [KL]-6, Surfactant protein [SP]-A, SP-D, etc.) suggestive of ILD
- pulmonary function testing: measurement of lung function, resting and exercise pulse oximetry
- imaging: high-resolution computed tomography of the chest

Bronchoalveolar lavage with sequential lavages should be considered in study participants presenting with hemoptysis and radiographic ILD that is acute or rapidly progressive.

Lung biopsy should be considered in study participants with atypical or progressive signs and symptoms, atypical radiographic features, unexplained extrapulmonary manifestations, rapid clinical deterioration, or sudden change in radiographic appearance.

If participants are diagnosed with ILD/Pneumonitis, palbociclib should be discontinued. (see Section 10.7 [Appendix 7]).

For specific AE related to palbociclib intake, refer to the prescribing information or Summary of Product Characteristics.

8.2.5.2 Amcenestrant-related Adverse Events

Based on preclinical data and clinical data from amcenestrant, it is anticipated that amcenestrant-related AEs could be managed by standard medical treatment/practice, which will also include but not limited to the provision of corrective treatment or medications, supportive care and dose omission. Investigators are encouraged to exercise their medical judgment in the management of the toxicities.

Management of the AE related to amcenestrant and palbociclib is also summarized in Section 10.7 (Appendix 7).

8.2.6 Pregnancy testing

Serum pregnancy test (β-hCG) will be done in WOCBP before starting study intervention.

Urine pregnancy test (dipstick) will be done on Day 1 of each cycle, at EOT, then monthly until 12 weeks after last dose of any study intervention, whichever comes last.

Urine pregnancy test must have a sensitivity of at least 25 mIU/mL.

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

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.3.7.

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 study.(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 and SAEs will be collected from the signing of the informed consent form (ICF) at the time points specified in the SoA (Section 1.3) and until at least 30 days after administration of the last study intervention. After this period, all ongoing related AEs, all ongoing SAEs regardless of relationship with study treatment, and all new related AEs (serious or nonserious), are to be reported and followed up until resolution or stabilization.

All SAEs and AESI will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 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.

8.3.2 Method of detecting AEs and SAEs

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).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading 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 pre-specified study end-date, all SAEs and AEs of special interest (AESI) (as defined in Section 8.3.8), 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 provided 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 (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Serious adverse events that are considered expected will be specified in the reference safety information (IB for amcenestrant, SmPC or package insert for other IMP/NIMPs).
- 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.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure 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 while participating in the study and, female partners of male participants while the male participant is in this study will be collected. Pregnancy 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.
- In order to avoid pregnancy in women of childbearing potential (WOCBP) and female partners of male participants, including effects on male fertility and known potential genotoxicity with the study IMP,
  - WOCBP, should use highly effective non-hormonal methods of contraception (see Appendix 4, Section 10.4) during the study, and for at least 12 weeks after last dose of any study intervention.
- Male participants and male partners of female participants must wear a male condom with spermicide, in combination with a highly effective method of contraception (see Appendix 4, Section 10.4) during the study, and for at least 14 weeks after last dose of any study intervention. 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 intervention 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 Adverse events of special interest

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/NIMP;**
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 4 [Section 10.4]).
  - In the event of pregnancy in a female participant, study intervention should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Appendix 4 [Section 10.4]).
- **Symptomatic overdose (serious or nonserious) with IMP/non-investigational medicinal product (NIMP)**
  - An overdose (accidental or intentional) with the IMP/NIMP 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.
    Of note, asymptomatic overdose has to be reported as a standard AE.
- **Increase in alanine transaminase (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 increase of ALT. (Appendix 7 [Section 10.7]).

- 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 of liver, 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, considering 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 10.7 [Appendix 7] for treatment-related dose modification for non-hematological toxicities). 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.
- **Interstitial Lung Disease (ILD)/Pneumonitis, any grade**
  - Severe, life-threatening, or fatal ILD/pneumonitis can occur in patients treated with palbociclib. Study participants should be monitored for pulmonary symptoms indicative of ILD/pneumonitis (e.g., hypoxia, cough, dyspnea). Palbociclib should be omitted immediately in study participants who have new or worsening respiratory symptoms and are suspected to have developed ILD/pneumonitis. Please refer to Section 8.2.5.1 for recommendations on diagnostic testing of ILD/pneumonitis. Palbociclib should be permanently discontinued if ILD/pneumonitis is diagnosed (refer to Section 10.7 [Appendix 7] for dose modification guidelines for management of ILD/pneumonitis).

8.3.8 Guidelines for reporting product complaints

Any defect in the IMP or NIMP must be reported as soon as possible by the Investigator to the monitoring team that will complete 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 PHARMACOKINETICS

Collection and analysis of pharmacokinetic (PK) samples are described as follows:

- Whole blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of amcenestrant and palbociclib and approximately 4 mL of whole blood for plasma concentration of goserelin, when relevant (see Table 5). Pre-dose and post-dose PK samples should be collected even in case of IMP dose omission. Sampling time are specified in the SoA (Section 1.3).

Table 5 - PK samples collection for amcenestrant, palbociclib and goserelin

Analytes	Population	Sample and Visits
Amcenestrant (SAR439859)	All participants	Cycle 1: Day 1 post-dose T3h, Day 15 pre-dose Cycle 2: Day 1 pre-dose and post-dose T3h; Day 15 pre-dose Cycle 3: Day 1 pre-dose Cycle 4: Day 1 pre-dose Cycle 7: Day 1 pre-dose Cycle 10: Day 1 pre-dose
Palbociclib		
Goserelin	Men, pre/peri-menopausal women	Cycle 1: Day 1 pre-dose Cycle 2: Day 1 pre-dose Cycle 3: Day 1 pre-dose

- The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of amcenestrant, palbociclib, and goserelin. Samples collected for analyses of amcenestrant, palbociclib and goserelin concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- A population PK analysis will be performed on amcenestrant and/or palbociclib data and reported in a standalone report.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel.

The bioanalysts responsible for the sample analysis will be unblinded. They will, however, agree not to disclose the randomization schedule or the individual unblinded analytical results before the official opening of the randomization schedule.

For China, please see Section 10.6 for details.

8.5 GENETICS

8.5.1 cfDNA tumor and germline mutation analysis

A 20-mL per time point blood sample for CfDNA isolation will be collected from participants for genetic analysis.

Cancer gene mutations present in the tumor prior to treatment might influence the response to amcenestrant. The presence of gene mutations in tumor DNA may be assessed through mutation analysis of cfDNA isolated from plasma.

cfDNA samples will be collected pre-treatment and post treatment. These analyses will focus on genes that may increase understanding of disease subtypes, the biology of cancer and related conditions, how the body handles amcenestrant, and drug response and toxicity, and possibly to identify new drug targets or biomarkers.

An additional blood sample (6ml) will be used as source of normal reference DNA for comparison with the tumor-derived DNA data. Sequencing may be performed on the DNA from blood sample. The same blood sample will be used for DMET genotyping (see Section 8.5.2)

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

Samples may be stored for a maximum of 25 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable additional analysis of DNA biomarkers to increase understanding of amcenestrant and/or cancer or related diseases, and potentially to identify new drug targets or biomarkers.

Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.5.2 Drug metabolizing enzymes and related genes DNA samples

A whole blood sample will be collected pre-dose to obtain deoxyribonucleic acid (DNA) in case investigations of allelic variants of UGT were needed to further explore influence on PK, efficacy and/or safety profile of amcenestrant.

The blood sample, and the DNA that is isolated from it, will remain labelled with the same identifiers used during the study (ie, Participant ID). The Sponsor has included safeguards for protecting participant confidentiality and personal data. The DNA, and any remaining whole blood, will be destroyed after the Drug Metabolism Enzyme and Transporter (DMET) related analysis and the main clinical study report have been completed, or as per local regulations.

Special procedures for storage and shipping of DMET DNA samples will be described in the study laboratory manual.

8.6 BIOMARKERS

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

Samples may be stored for a maximum of 25 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarkers related to amcenestrant and/or cancer or related diseases, or to develop methods, assays, prognostics and/or companion diagnostics, and potentially to identify new drug targets or biomarkers.

8.6.1 Protein expression

The expression of several proteins in the tumor will be assessed by IHC of biopsy tissue collected pre-treatment (or archival) and at EOT/progression. These proteins will include the ER, the progesterone receptor (PgR), B-Cell Lymphoma 2 (BCL2), and potentially other proteins related to cancer or the activity of amcenestrant. These studies will be conducted by a central IHC lab.

These studies will increase the understanding of the activity of amcenestrant and may increase our knowledge of cancer or related conditions.

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).

8.6.3 RNA transcriptome research

Genome-wide transcriptome studies of ribonucleic acid (RNA) isolated from tumor biopsies are planned in this study by measuring the relative abundances of the RNA transcripts. This will enable the evaluation of changes in transcriptome profiles that may increase understanding of the pathogenesis of cancer and related conditions, the participant's response to amcenestrant, and disease subtypes, and possibly to identify new drug targets or biomarkers. The samples may be analyzed by RNAseq or similar technologies.

For China, please see Section 10.6 for details.

8.7 IMMUNOGENICITY ASSESSMENTS

Immunogenicity is not evaluated in this study.

8.8 HEALTH ECONOMICS

Not applicable.

8.9 PATIENT REPORTED OUTCOMES

Patient-reported outcomes (PROs) will be measured in both study arms using completion of the following questionnaires in electronic format. Paper format will be used in case of extreme circumstances eg, technical issue making the electronic format temporarily unusable. Process of handling the data captured in paper format will be detailed in the Electronic Clinical Outcome Assessment manual. Please refer to Appendix 17 (Section 10.17) for the PROs questionnaires.

8.9.1 EORTC QLQ-C30

- Cancer-specific health-related quality of life (HRQL), and disease- and treatment-related symptoms and the impact of symptoms will be assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC) core quality of life questionnaire with 30 items (QLQ-C30) (C30). The C30 provides a multi-dimensional assessment of HRQL domains identified as relevant by cancer patients. The validity and reliability of the EORTC QLQ-C30 has been established in various types of cancers. The C30 consists of 2-item scale evaluating global health status/quality of life scale (GHS/QoL), 5 functional scales (Physical, Role, Cognitive, Emotional, and Social functioning). There are also 3 symptom scales (Fatigue, Pain, and Nausea/Vomiting), 5 single symptom items (Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea), and an item on the perceived financial impact of the disease as measured by the Financial Difficulties item. For the GHS/QoL and functional scales, a higher score indicates better global health status/better function, while for the symptom scales/items and financial difficulties item, lower scores indicate fewer symptoms/difficulties.

8.9.2 EORTC QLQ-BR23

The EORTC Breast Cancer Module (QLQ-BR23)

The EORTC QLQ-BR23 (BR23) is meant for use among patients with breast cancer and comprised of 23 questions with three symptom subscales (arm/hand, breast, and systemic side effects), two functional scales (body image and sexuality), and single items covering sexual enjoyment, distress at hair loss, and future perspective).

8.9.3 EORTC QLQ-BR45

The EORTC Breast Cancer Module (QLQ-BR45)

- The EORTC QLQ-BR45 (BR45) is meant for use among patients with breast cancer and comprised of 45 questions to assess body image, future perspective, sexual functioning/ enjoyment/symptoms; breast-related symptoms/satisfaction, arm symptoms, hair loss, skin mucosis, systemic side effects, endocrine specific symptoms, ie, sexual and any additional symptoms).
- In countries where the translated and validated EORTC QLQ-BR45 questionnaire is not available, study participants can use EORTC QLQ-BR23 questionnaire until the availability of translated and validated EORTC QLQ-BR45 questionnaire.

8.9.4 EUROQoL EQ-5D-5L

The EUROQoL EQ-5D-5L

- EuroQoL Group measure with 5 dimensions and 5 levels per dimension (EQ-5D-5L) addressing mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.
- The EQ-5D-5L incorporates the EQ-5D-5L descriptive system to generate a health state utility value and the EQ-5D VAS to generate health status (VAS) scores.

All three questionnaires have been designed for self-completion. Study participants will complete the questionnaires prior to any study or medical procedures or discussion of their health status on Day 1 of Cycles 1, 2, 3 and 4 and then every 3 cycles starting from Cycle 6 Day 1 (ie, Cycle 6, 9, 12, etc), at end of treatment and at 1st follow-up visit.

The time estimated to complete the EORTC QLQ-C30 and EORTC QLQ-BR23/BR45 is approximately 15 to 20 minutes, and the time estimated to complete the EQ-5D-5L is approximately 5 to 10 minutes (for a total of 20 to 30 minutes to complete all three assessments).

8.10 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, mechanism of action, or possible toxicity, and can help identify new drug targets or biomarkers that predict participant response to treatment. Therefore, data and biological samples will be stored and used for future research when consented to by participants (see Section 10.1.3) unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF).

For participants who consent to the storage and use of their data and remaining (leftover) and/or extra (additional) clinical samples, data and samples may be used for future research related either to the drug, the mechanism of action, and the disease or its associated conditions. Such research may include, but is not limited to, performing assessments on DNA, RNA, proteins or metabolites. If future research on genetic material is performed, this will also be limited to the

purpose of addressing research questions related to the drug, the mechanism of action, the disease or its associated conditions.

Remaining leftover samples will be used only after the study ends, ie end of study as defined in the study protocol. Additional/extra samples can be collected and used during the study conduct at a given timepoint (eg, at randomization visit) as defined in the study protocol.

In the event future research is conducted for other purposes, the study participants will be informed of those purposes and will be given means to object to those research projects. Data and samples will be used in alignment with the information provided to participants in the ICF Part 2 (future research). For future research projects, all biological samples and relating data to be used will be coded such that no participant direct identifiers will be linked to them. These coded data and samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

Relating data and biological samples for future research will be stored for up to 25 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

Participant's coded datasets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

9 STATISTICAL CONSIDERATIONS

9.1 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined (Table 6):

Table 6 - Population for Analyses

Population	Description
Screened	All participants who signed the ICF
Randomized	All participants from screened population who have been allocated to a randomized intervention by IRT regardless of whether the intervention was received.
Intent-to-treat (ITT)	All randomized participants. Participants will be analyzed according to the treatment arm assigned at randomization.
Safety	All randomized participants and who took at least 1 dose of study intervention. Participants will be analyzed according to the treatment arm they actually received.
Pharmacokinetic (amcenestrant)	All participants from the safety population who receive at least 1 dose of amcenestrant and with at least 1 evaluable plasma concentration of amcenestrant posttreatment.
Pharmacokinetic (palbociclib)	All participants from the safety population who receive at least 1 dose of palbociclib and with at least 1 evaluable plasma concentration of palbociclib posttreatment.
Pharmacokinetic (goserelin)	All participants from the safety population who receive at least 1 dose of goserelin and with at least 1 evaluable plasma concentration of goserelin posttreatment.
Population without trial impact (disruption) due to Covid-19	All randomized participants: • without any critical or major deviation related to Covid-19 • and who did not permanently discontinue full treatment due to Covid-19 • and who did not permanently discontinue study due to Covid-19.

Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as randomized.

9.2 STATISTICAL ANALYSES

The statistical analysis plan will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

Planned date for analysis cut-off:

Estimated COD will be approximately 40 months after the first randomized participant for the PFS final analysis. The COD for final analysis of OS will be approximately 80 months after the first randomized participant.

9.2.1 General Considerations

The baseline value is defined as the last value or measurement taken up to the date of randomization. This definition applies for all variables unless otherwise specified.

Unless otherwise specified, analyses will be performed by intervention group (and overall for baseline and demographics characteristics).

The observation period will be divided into 3 segments:

- The **pre-treatment period** is defined as the period up to first IMP administration.
- The **on-treatment period** (ie, treatment-emergent (TE) period) is defined as the period from the first IMP administration to the last IMP administration + 30 days.
- The **post-treatment period** is defined as the period from the end of the on-treatment period.

9.2.2 Primary endpoint(s) analyses

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 according to local radiologist's/investigator's assessment comparison between the amcenestrant + palbociclib arm and the letrozole + palbociclib 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 primary analysis of PFS will be based on the following censoring rules:

- If progression and death are not observed before the PFS analysis COD, PFS will be censored at the date of the last evaluable tumor assessment with no evidence of a disease progression before the start of further anti-cancer therapy.
- A participant without an event (death or disease progression) and without any evaluable post-baseline tumor assessments will be censored at the day of randomization (Day 1).
- Documented progression (or death) occurring after two or more non-evaluable tumor assessments will be censored at the date of the last evaluable tumor assessment documenting no progression.

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. The PFS quantiles 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 (eg, different censoring rules and PFS assessed by the BIRC) and subgroup analyses of PFS will be performed as specified in the SAP.

Two interim analyses at 40% (206 PFS events, non-binding futility only) and 70% (361 PFS events, efficacy only) of the target number of events (516 PFS events) are planned. The primary PFS analysis corresponds either to a positive interim PFS analysis or the final PFS analysis. Detail of the interim analyses are provided in Section 9.3.

A summary of the primary estimand associated with the primary endpoint is provided in Table 2.

Random sample-audit Blinded Independent Review Committee (BIRC)

A random sample-audit BIRC approach will be used as an auditing tool to evaluate the concordance between local radiologist's/investigator's assessment and BIRC on the PFS. Approximately 50% of the randomized participants will be randomly selected and the BIRC will assess the tumor progression of these participants based on the review of tumor assessments. Participants selected for the sample-audit BIRC will not be known to the investigators. The audit size calculation approach will be based on the method proposed by Dodd, et al (1). Assuming local radiologist's/investigator's and BIRC assessments are similar, and the estimated log of investigator-based HR is -0.2877 (ie, HR=0.75), the audit size of 50% will ensure that the upper bound of a one-sided 95% CI for BIRC-based log-hazard ratio has 83% probability of being below 0 (ie, HR <1) if the correlation between local radiologist's/investigator's assessment and BIRC assessment is 0.65.

Two methods will be used to summarize the data from the sample-based BIRC assessment of PFS.

- The NCI (National Cancer Institute) method (1), uses an auxiliary variable estimator of the log-hazard ratio that combines information from participant level local radiologist's/investigator's assessment from all participants and the BIRC assessment of participants randomly selected for central review. The auxiliary variable estimates and its one-sided 95% CI will be provided.
- The Pharmaceutical Research and Manufacturers of America (PhRMA) method (2) estimates the early discrepancy rate (EDR) and late discrepancy rate (LDR) differences between the two treatment arms. The EDR and LDR results will also be summarized by treatment arm.

Detail of the two methods will be provided in the SAP.

Assurance regarding the PFS treatment effect based on local radiologist's/investigator's assessment will be based on the NCI method. If the upper bound of the one-sided 95% CI of the true BIRC log-hazard ratio calculated using the NCI method is below 0, assurance will be considered and the full BIRC will not be triggered; otherwise, a full BIRC may be triggered.

All efficacy analyses will be performed on the ITT population unless stated otherwise. All primary and secondary efficacy endpoints based on radiological assessments of tumor burden (ie, PFS, BOR, ORR, CBR, and DOR) will be primarily derived using the local radiologist's/Investigator's assessment tumor assessment.

9.2.3 Secondary endpoint(s) analyses

The secondary endpoints detailed in this section are efficacy secondary endpoints.

Other secondary endpoints analyses are defined in Section 9.2.6.1 (AE, SAE), Section 9.2.6.2 (laboratory abnormalities), Section 9.2.7 (PRO, PK, immunogenicity).

Analysis of response-based endpoints (ie, ORR, CBR, and DOR) will be performed primarily on the ITT population and supported by the analyses based on the subset of measurable participant from the ITT population. Except for OS, PFS2, and TT1C, secondary endpoints will be analyzed at the time of the PFS analyses only. Of note, the BOR for each participant will also be summarized by treatment arm. BOR is the best overall response observed from the date of the randomization until disease progression, death, cutoff date, initiation of post-treatment anti-cancer therapy, whichever occurs first.

Key secondary endpoint:

Overall Survival

Overall survival is defined as the time from date of randomization to date of death due to any cause. In the absence of observation of death, survival time will be censored at the last date the participant is known to be alive or at the OS cut-off date, whichever occurs first.

Primary efficacy analysis of OS will consist of comparison between the amcenestrant + palbociclib arm and the letrozole + palbociclib arm through a logrank test procedure stratified by the stratification factors as entered in the IRT. 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. Therefore, a maximum of two analyses are planned for OS (see Section 9.3.2).

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. The OS quantiles and probabilities of being alive 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 OS curves will also be provided.

Sensitivity analyses (eg, different censoring rules, dealing with informative censoring) and subgroup analyses of OS will be performed as specified in the SAP.

A summary of the estimands associated with the key secondary endpoint is provided in Table 2.

Other secondary endpoints:

A summary of efficacy analyses for other secondary endpoints is provided in Table 7. No statistical testing will be performed for other secondary endpoints.

Table 7 - Efficacy analyses for other secondary endpoints

Endpoint	Statistical Analysis Methods
ORR, CBR	Descriptive statistics by treatment arm and Clopper-Pearson method for CI calculation.
DOR, TT1C, PFS2	Kaplan-Meier method for quantiles and probabilities of being event free at different time points.
Exploratory	Will be described in the SAP.

CBR = clinical benefit rate; CI = confidence interval; DOR = duration of response; HR = hazard ratio; ORR = objective response rate; PFS2: progression-free survival on next line of therapy, SAP = statistical analysis plan; TT1C = time to first chemotherapy.

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.

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 two treatment arms will be summarized using Kaplan-Meier methods and displayed graphically, if appropriate. The DOR quantiles and associated 95% CI will be provided.

Time to first chemotherapy

The TT1C is defined as the time from the date of randomization to the start date of the first chemotherapy after study treatment discontinuation. Study participants alive without further treatment with chemotherapy will be censored at the last date the participant is known to be alive

or at the cut-off date, whichever occurs first. Participants who died without further treatment with chemotherapy will be censored at the date of death or at the cut-off date, whichever occurs first.

The HR estimates and corresponding 95% two-sided CIs will be provided using the Cox proportional hazard model stratified by the stratification factors as entered in the IRT. The TT1C quantiles and probabilities of being chemotherapy-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 TT1C curves will also be provided.

Sensitivity analyses (eg, different censoring rules) and subgroup analyses of TT1C will be performed as specified in the SAP.

Progression-free survival on the next systemic anti-cancer therapy (PFS2)

The PFS2 is defined as the time from the date of randomization to the date of first documentation of PD on the next systemic anti-cancer therapy according to investigator or death due to any cause in the absence of documented PD on the next systemic anti-cancer therapy, whichever occurs first. Next systemic anti-cancer therapy is defined as the first further anti-cancer therapy initiated after discontinuation of study intervention regardless of the discontinuation reason. Study participants on their next systemic anti-cancer therapy without PFS2 events will be censored at the last date the participant is known to be alive without a first documentation of PD on the next systemic anti-cancer therapy or at the cut-off date, whichever occurs first. Study participants who discontinued their next systemic anti-cancer therapy without PFS2 events will be censored at the end of their next systemic anti-cancer therapy or at the cut-off date, whichever occurs first. Detailed event/censoring scheme will be provided in the SAP.

The HR estimates and corresponding 95% two-sided CIs will be provided using the Cox proportional hazard model stratified by the stratification factors as entered in the IRT. The PFS2 quantiles 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 TT1C curves will also be provided.

Sensitivity analyses (eg, different censoring rules) and subgroup analyses of PFS2 may be performed as specified in the SAP.

9.2.4 Tertiary/exploratory endpoint(s) analyses

Tertiary/exploratory endpoints analyses will be described in the SAP.

9.2.5 Multiplicity adjustment

Hypothesis testing of the key secondary efficacy endpoint will be carried out. 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.

9.2.6 Safety analyses

All safety analyses will be performed on the Safety Population. A summary of safety analyses is provided in Table 8.

Table 8 - 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

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

9.2.6.1 Adverse events

General common rules for adverse events

The AEs will be analyzed in the following 3 categories:

- Pretreatment AEs are defined as any AE occurring during the pretreatment period.
- Treatment-emergent AEs (TEAEs) 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.

Similarly, the deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment periods.

The primary focus of AE reporting will be on TEAEs. Pretreatment 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-emergent AEs leading to premature treatment discontinuation

- Treatment-related TEAEs
- Treatment-related TEAEs Grade ≥3
- Serious treatment-related TEAEs.
- AESIs

Number and percentage of participants experiencing TEAEs by primary SOC 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, and premature discontinuation of palbociclib, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, AESIs, and AEs/SAEs occurring during the post-treatment period.

9.2.6.2 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.

9.2.7 Other analyses

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.15 (Appendix 15: Contingency measures for a regional or national emergency that is declared by a governmental agency).

9.2.7.1 Analyses of patient reported outcome endpoints

Analyses of the 3 selected PRO instruments (EORTC C30, QLQ-BR23/BR45, and EQ-5D-5L) will be analyzed in participants from the safety population.

For each questionnaire the compliance profile over time will be summarized on the safety population (number and percentage of forms received versus expected). For the C30 (15 total scales), QLQ-BR23/BR45 (13 total scales), and EQ-5D-5L (health state utility index and visual analogue scale) instruments, descriptive statistics for the absolute value at each time point, for the change from baseline for each treatment arm at each time point, until EOT and 90 days after the last study administration (follow-up) will be presented on the safety population. Between treatment comparisons for the change from baseline over time will be provided for each scale of each questionnaire on the safety population who have completed the baseline and at least one post-baseline PRO assessment using a MMRM. No formal statistical hypothesis will be tested.

A more detailed statistical analysis strategy for the 3 PROs will be detailed in the study SAP.

9.2.7.2 Analyses of other endpoints

Pharmacokinetics, genetics, and biomarker exploratory analyses will be described in the SAP. The population PK analysis and/or population PK/PD analyses will be presented separately from the main clinical study report (CSR).

9.3 INTERIM ANALYSES

9.3.1 Interim analyses for PFS

Two interim analyses are planned based on the primary PFS endpoint at 40% (non-binding futility only) and 70% (efficacy only) of the planned total number of events expected. 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 efficacy will be derived based on the O'Brien and Fleming α-spending function and depend on the actual number of PFS events observed at the time of the interim analysis.

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

Table 9 - PFS analyses

Analysis	Months after FPI (approx. under PFS HR=0.75)	Planned accrual	Number of events	Information fraction	Cumulative Power (under PFS HR=0.75)	Futility boundary	Efficacy boundary
PFS IA 1 (futility only)	19.5	1066	206	40%		HR >1.1	NA
PFS IA 2 (efficacy)	28	1066	361	70%	62%	NA	p ≤0.0074 (HR[a] ≤0.7736)
PFS Final analysis	40	1066	516	100%	90%	p >0.0228 (HR[a] >0.8386)	p ≤0.0228 (HR[a] ≤0.8386)

a 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.
FPI = first participant in; HR = hazard ratio; IA = interim analysis; NA = not applicable; PFS = progression-free survival

In case of positive results at interim analysis, disease assessments data will be collected according to the protocol until the final PFS analysis cut-off date (defined as the date when 516 PFS events assessed by radiologist/investigator are observed) and PFS results will be updated (non-inferential analysis only).

The Statistical Analysis Plan will describe the planned interim analyses in greater detail.

9.3.2 Interim analyses for OS

Comparison between arms on the OS will be performed only if the primary analysis of the PFS is statistically significant. Therefore, a maximum of three analyses are planned for OS, at the time of the primary analysis of PFS, at 75% of the planned number of OS events and at the final OS analysis.

A gamma error spending function (γ=-10) independent from the O'Brien and Fleming α-spending function for PFS will be used, along with the hierarchical testing strategy in order 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 (3).

A summary of the OS analyses is provided in Table 10.

Table 10 - OS analyses

Analysis	Months after FPI (approx.)	Planned accrual	Number of deaths (approx.)	Information fraction	Cumulative Power[a] (under HR=0.80)	Futility boundary	Efficacy boundary
Scenario 1: PFS is statistically significant at the PFS IA 2							
OS IA 1 (at PFS IA 2)	28	1066	228	36.1%	1.2%	NA	$p \leq 4.07\times10^{-5}$ (HR[b] ≤0.5934)
OS IA 2	55	1066	474	75%	32.9%	NA	p ≤0.0020 (HR[b] ≤0.7680)
Final analysis	80	1066	632	100%	80%	p >0.0248 (HR[b] >0.8554)	p ≤0.0248 (HR[b] ≤0.8554)
Scenario 2: PFS is statistically significant at the PFS final analysis							
OS IA 1 (at PFS final analysis)	40	1066	348	55.1%	8.5%	NA	$p \leq 2.78\times10^{-4}$ (HR[b] ≤0.6408)
OS IA 2	55	1066	474	75%	32.7%	NA	p ≤0.0020 (HR[b] ≤0.7673)
Final analysis	80	1066	632	100%	80%	p >0.0248 (HR[b] >0.8554)	p ≤0.0248 (HR[b] ≤0.8554)

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 an annual dropout rate of 1%.

FPI = first participant in; HR = hazard ratio; IA = interim analysis; NA = not applicable; OS = overall survival.

9.3.3 Data Monitoring Committee (DMC)

This study will use an independent DMC. The first DMC meeting will be set up to review early safety results (eg, after approximately 50 participants have completed at least 2 cycles, or after 6 months after first participant randomized), and then periodically. In addition to review of safety results, DMC will also evaluate efficacy at the interim analyses and make a recommendation regarding study continuation based on observed results of the study. 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.

9.4 SAMPLE SIZE DETERMINATION

For PFS, a total of 516 PFS events assessed by local radiologist/investigator will be needed to reject the null hypothesis using a logrank test at the one-sided level of 2.5% and a 90% power under the assumption of a HR of 0.75. Assuming proportional hazards under an exponential model and based on an anticipated median PFS of 24.8 months in the letrozole + palbociclib arm, this is expected to correspond to a median PFS of 33.1 months in the SAR439859 + palbociclib arm. Based on an expected accrual duration of 18 months (15% of total accrual in the first 4.5 months and 40% of total accrual in the first 9 months), a PFS analysis cut-off date (COD) 40 months after the first participant randomized and an annual dropout rate of 5%, a total of 1066 participants are expected to be randomized in a 1:1 ratio into the SAR439859 + palbociclib and letrozole + palbociclib arms. The power calculation accounts for two interim analyses at 40% and 70% of the planned number of events.

For OS, a total of 632 deaths will be needed to reject the null hypothesis using a logrank test at the one-sided level of 2.5% and a 80% power under the assumption of a HR of 0.80. Assuming proportional hazards under an exponential model and based on an anticipated median OS of 46 months in the letrozole + palbociclib arm, this is expected to correspond to a median OS of 57.5 months in the SAR439859 + palbociclib arm. OS COD is expected 80 months after the first participant randomized (assuming an annual dropout rate of 1%). The power calculation accounts for two interim analyses at the time of the PFS primary analysis and at 75% of the planned number of OS events.

Calculations were made using East 6.5 software.

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 (CIOMS) international ethical guidelines
  - Applicable ICH Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - GDPR)
- The protocol, protocol amendments, ICF, Investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
  - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
  - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.

- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IRB/IEC of 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 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.

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant, and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for the study).
- Participants must be informed that their participation is voluntary. Participants 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.

- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s). Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc).
- A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF (see Section 5.4).

The ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future 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.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.15: Contingency measures for a regional or national emergency that is declared by a governmental agency.

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant data

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 they are expected to modify the drug response/because they are required by regulatory agencies (eg, on African American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices

Agency in Japan). They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- 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.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an

adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:

- The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
- Sanofi's Binding Corporate Rules for intra-group transfers.

- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees structure

10.1.5.1 Steering committee

The Steering Committee will include a Chairman, Investigators and Sponsor's representatives. The Steering Committee will be responsible for:

- Supervising the progress of the trial towards its overall objectives.
- Reviewing at regular intervals relevant information that may affect the study conduct.
- Discussing the implementation of the recommendations of the independent DMC.

10.1.5.2 Independent Data Monitoring Committee

An independent DMC, consisting of 3 external independent members (2 physicians with breast cancer expertise and 1 statistician), not associated with the conduct of the study or other study committees will meet regularly to, as specified in the DMC charter:

- Review the progress of the trial.

- Review the safety data.
- Advise the Sponsor on potential modifications or communications that may be necessary to ensure the patient safety or protect the scientific integrity of the trial. The Sponsor will make the final decision(s).

The DMC will also be in charge of evaluating efficacy at the interim analyses and make a recommendation regarding study continuation based on observed results of the study.

10.1.5.3 Blinded Independent Review Committee

In addition to investigators' tumor assessments, a Blinded Independent Review Committee (BIRC) will assess the radiographic (and photographical when applicable) images and clinical information collected on-study per RECIST 1.1 criteria. For this purpose, the tumor assessment images should be transferred to the blinded independent review committee for tumor response evaluation. No BIRC review will be performed after the final PFS analysis cut-off date.

10.1.6 Dissemination of clinical study data

Study participants

Sanofi shares information about clinical trials and results on publicly 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 clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in participants 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.

Professionals involved in the study or in the drug development program

Sanofi undertakes the legal obligation to disclose the full name of the Investigator and his/her affiliated institute/hospital's name and location on the China Trial Disclosure website as required by the National Medical Products Administration (NMPA) in its guidance "Implementation of Drug Clinical Trial Information Registration and Disclosure" ("Notification No. 28"), requesting name disclosure of Chinese and foreign investigational sites and Investigators in any eligible clinical trial.

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations".

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on e-CRF 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 physically or electronically signing the e-CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the e-CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- 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.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations)
- Study monitors will perform ongoing source data verification to confirm that data entered into the e-CRF 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 signature of the final study report 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.

10.1.8 Source documents

- Every data point recorded in the CRF must have a source document. The investigator/delegated site staff will report all the original data in the participant's medical chart or in a study specific source document created by him/her. If such document is used,

the template should be reviewed by the CRA. A list of SD and their location will be filed in the Investigator Study File.

- 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 reported on the e-CRF or entered in the e-CRF 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.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF 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.

10.1.9 Study and site start and 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 study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio
  - Discontinuation of further study intervention development
- For site termination:
  - 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 or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
  - Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate therapy and/or follow-up for that participant.

10.1.10 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 laboratory tests detailed in Table 11 will be performed by the local laboratory and the results must be entered in the e-CRF.
- 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
- Serum pregnancy test (β-hCG) will be done in WOCBP before starting study treatment. Urine pregnancy test (dipstick) will be done on Day 1 of each cycle at EOT, then monthly until 12 weeks after last dose of any study intervention, whichever comes last. Urine pregnancy test must have a sensitivity of at least 25 mIU/mL.

Table 11 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Hematology	Platelet count
	Hemoglobin
	Red blood cell
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry[a]	Blood urea nitrogen (BUN) or Urea
	Creatinine
	Estimated Glomerular Filtration Rate
	Glucose (nonfasting)
	Potassium
	Sodium
	Phosphate
	Lactate dehydrogenase (LDH)
	Magnesium
	Calcium
	Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT)
	Alkaline phosphatase
	Total and direct bilirubin, Gamma-glutamyl transferase (GGT)
	Albumin
Coagulation	INR, Prothrombin time
Lipid Profile	Total cholesterol
	LDL-cholesterol
	HDL-cholesterol
Urinalysis (semi-quantitative test)	• pH, glucose, protein, blood, ketones by dipstick
Other screening tests	• Follicle-stimulating hormone[b]
	• Estradiol
	• Viral serology tests: Hepatitis A antigen or IgM hepatitis A antibody; HBs antigen or hepatitis B viral DNA; Hepatitis C antibody and quantitative hepatitis C (HCV) ribonucleic acid (RNA).
Pregnancy tests	Serum pregnancy test (β-hCG), Urine pregnancy test (dipstick)
	The results of each test must be entered into the e-CRF.

a Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 1. All events of Grade ≥3 ALT increase should be reported as adverse events of special interest (AESI).

b During treatment period FSH will be done on C1D1, then every 4th cycle during study treatment and EOT-local labs in pre/perimenopausal women only.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE 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

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg,:
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI
- 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.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other 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. Laboratory abnormalities should be reported as AEs only in case they lead to an action on study treatment or if they fulfil the criteria for seriousness or AESI.

- 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

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an 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.
- Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
  - Intensive treatment in an emergency room or at home for
    - Allergic bronchospasm
    - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
    - Convulsions (seizures, epilepsy, epileptic fit, absence, etc)
  - Development of drug dependency or drug abuse
  - Suicide attempt or any event suggestive of suicidality,
  - Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
  - Bullous cutaneous eruptions
  - Invasive or malignant cancers.

10.3.3 Recording and follow-up of AE and/or SAE

AE 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 e-CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to monitoring team in lieu of completion of the Sanofi/AE/SAE e-CRF page.
- There may be instances when copies of medical records for certain cases are requested by Sanofi. In such case, care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the study are properly mentioned on any copy of a source document provided to the Company. For laboratory results, include the laboratory normal ranges.
- 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. (39)

An event is defined as “serious” when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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 (IB) 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 e-CRF. 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 monitoring team.**
- The Investigator may change his/her opinion of causality in light of the 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 monitoring team 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 e-CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to Sanofi via an electronic data collection tool

- The primary mechanism for reporting an SAE to Sanofi will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- 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 telephone.
- Contacts for SAE reporting can be found in Investigator Study File.

SAE reporting to Sanofi via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the monitoring team
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in Investigator Study File.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

Woman of childbearing potential (WOCBP)

A woman, who is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Postmenopausal women as defined by one of the following:

A) With spontaneous cessation of menses >12 months prior to randomization in the absence of physiological or medical cause.

B) Or with cessation of menses of duration ≤12 months or secondary to hysterectomy AND have FSH and estradiol level in the postmenopausal range according to institutional standards (or >34.4 IU/L for FSH and <10 pg/mL for estradiol if institutional range is not available) prior to randomization,

C) Or who have received hormonal replacement therapy but have discontinued this treatment AND have FSH and estradiol level in the postmenopausal range according to institutional standards (or >34.4 IU/L for FSH and <10 pg/mL for estradiol if institutional range is not available) prior to randomization,

D) Or with status post bilateral surgical oophorectomy,

E) Or post bilateral ovarian ablation through pelvic radiotherapy.

NOTE: As per local regulations, to demonstrate postmenopausal status, serial measurements of FSH may be required in participants who are not using hormonal contraception or hormonal replacement therapy, and in the absence of amenorrhea for at least 12 months.

10.4.2 Contraception guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

Male Participants:

- 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 14 weeks 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.

Male participants and male partners of female participants must wear a male condom with spermicide, in combination with a highly effective method of contraception.

Male participants should consider sperm preservation prior to beginning therapy with study IMPs. Because exposure to SAR439859, has the potential risk of testicular injury with partial or permanent infertility. Also, exposure to palbociclib may compromise male fertility.

Women of Childbearing Potential:

Highly Effective Methods[b] That Have Low User Dependency

Intrauterine device (IUD)

Bilateral tubal occlusion

Vasectomized partner

(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days).

Highly Effective Methods[b] That Are User Dependent

Sexual abstinence

(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)

a *Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.*
b *Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.*

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

COLLECTION OF PREGNANCY INFORMATION:

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.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial 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 for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study 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 study intervention or be withdrawn from the study.

10.5 APPENDIX 5: MODIFIED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS VERSION (RECIST 1.1)

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable 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:
  - 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
  - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
  - 20 mm 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). 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 non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam 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 a particular comment:

Bone lesions:

- Bone scan, 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 MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) 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 non-cystic lesions are present in the same patient, 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 exam. 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 exam 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.

- *CT, 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. MRI 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 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 patient to be considered in complete response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 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 PR and CR in rare cases if required by protocol (for example, 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 in order to differentiate between response (or stable disease) and progressive disease.

Baseline documentation of "target" and "non-target" lesions

When more than 1 measurable lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as "present", "absent", or "unequivocal progression". In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Special notes on the assessment of target lesions

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become "too small to measure": All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as

target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure". When this occurs, it is important that a value be recorded on the CRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

When non-nodal lesions "fragment", the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

Evaluation of non-target lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease: Unequivocal progression of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

The concept of progression of non-target disease requires additional explanation as follows: When the participant also has measurable disease; in this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

When the participant has only non-measurable disease; to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from localized to widespread, or may be

described in protocols as “sufficient to require a change in therapy”. If “unequivocal progression” is seen, the patient should be considered to have had overall PD at that point.

New lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some “new” bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the participant’s baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a “new” cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The participant’s brain metastases are considered to be constitute PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents new disease. If repeat scans confirm that there is a new lesion, then progression should be declared using the date of the initial scan.

While fluorodeoxyglucose-positron emission tomography (FDG-PET) response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible “new” disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b) No FDG-PET at baseline and a positive FDG-PET at follow-up:

If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

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.
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).
Non-CR/non-PD:	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 "non target" 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. The following table provides a summary of the overall response status calculation at each time point for participants who have measurable disease at baseline.

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
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

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

Overall response First time point	Overall response Subsequent time point	BEST overall response
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 patient 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; PD = progressive disease; PR = partial response; SD = stable disease

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

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (ie, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient 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 patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of complete or partial response IS required: 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 described above.

Missing assessments and inevaluable designation: When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.

If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based

on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

In trials where confirmation of response is required, repeated "NE" time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

The objective response status of such patients is to be determined by evaluation of target and non-target disease. For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

[Reproduced from: Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.]

10.6 APPENDIX 6: COUNTRY-SPECIFIC REQUIREMENTS

CHINA

CHINA EXTENSION STUDY

It is planned to enroll approximately 160 Chinese patients in EFC15935, equivalent to 15% of the global population. If enrollment of 160 Chinese patients is not achieved at the time of completion

of global enrollment (1066 patients), enrollment in China will continue until the target number of patients is reached.

Patients enrolled from sites in China for Global part and extension part shall not fulfill the inclusion criterion I 08, as no archived FFPE or fresh tumor sample will not be collected from participants enrolled in China.

For study participants enrolled from clinical sites in China, biological samples related to secondary (Pharmacokinetics - except palbociclib and amcenestrant), and exploratory (genetic analyses and biomarkers) endpoints will not be collected or analyzed. The impacted biological samples are,

- Collection of blood sample for pharmacokinetics of goserelin in pre/perimenopausal women and men on Cycle 1 D1, Cycle 2 D1, and Cycle 3 D1.
- Collection of archived FFPE or fresh tumor sample during screening, and EOT (optional) in all study participants.
- Collection of plasma sample for Molecular profiling in cfCNA in all study participants on Cycle 1 D1, at Cycle 4 Day 1 predose (at tumor assessment), and EOT.
- Collection of blood sample for DMET genotyping and normal tissue reference DNA in all study participants on Cycle 1 D1.
- Collection of blood sample for estradiol assessment in all study participants on Cycle 1 D1, and Cycle 3 D1.

10.7 APPENDIX 7: Recommended Dose Modification Guidelines For Study Treatment-Related Adverse Events

Recommended dose modifications of endocrine therapy (**amcenestrant/amcenestrant-matching placebo**, **Letrozole/Letrozole-matching placebo)** and Palbociclib are presented in Table 12.

Table 12 - Recommended dose modification or discontinuation

NCI CTCAE v5 grade[a]	Management of endocrine therapy (Amcenestrant/amcenestrant-matching placebo, Letrozole/Letrozole-matching (placebo)	Management of Palbociclib
Hematological toxicities		
Grade 1 or 2	No dose adjustment is required.	
Grade 3*	No dose adjustment is required - continue endocrine therapies without any dose omission.	**Day 1 of cycle**: Omit palbociclib administration and repeat complete blood count monitoring within 1 week. When recovered to Grade ≤2, start palbociclib at the same dose within the cycle if recovery occurs before Day 21 of the cycle or at Day 1 of the next planned cycle if there is a strong evidence of clinical benefit in case of omission >2 weeks. **Day 15 of first 2 cycles**: continue palbociclib at current dose to complete cycle. Repeat complete blood count on Day 22. Consider palbociclib dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia in Day 1 of subsequent cycles and maintain endocrine therapies at the same dose.
Grade 3 neutropenia[b] with fever ≥38.5ºC and/or infection or Grade 4* hematological toxicity	No dose adjustment is required - continue endocrine therapy without any dose omission	Omit palbociclib administration, repeat complete blood count monitoring within 1 week. When recovered to Grade ≤2, administer palbociclib at the next lower dose if recovery occurs before Day 21 of the cycle or at Day 1 of the next planned cycle if there is a strong evidence of clinical benefit in case of omission >2 weeks.

NCI CTCAE v5 grade[a]	Management of endocrine therapy (Amcenestrant/amcenestrant-matching placebo, Letrozole/Letrozole-matching (placebo)	Management of Palbociclib
Non-hematological toxicities		
Grade 1 or 2	No dose adjustment is required.	
Grade ≥3 (if persisting despite optimal medical treatment)	**Day 1 of cycle**: 1. Administer cycle as planned if toxicity is not attributed to any of IMPs. 2. If toxicity attributable to both endocrine therapy and palbociclib, delay cycle (ie, delay of all IMPs) until symptoms resolve to Grade ≤1 or Grade ≤2 (if not considered a safety risk for the patient). When resolved to Grade ≤1 or Grade ≤2 (if not considered a safety risk for the patient), administer a. endocrine therapy at the same dose b. and palbociclib at the next lower dose. 3. If toxicity attributable to palbociclib, omit it while continuing the endocrine therapy without changes until symptoms resolve to Grade ≤1 or Grade ≤2 (if not considered a safety risk for the patient). Resume the omitted palbociclib at the next lower dose within cycle if recovery occurs before Day 21 of the current cycle or at or at Day 1 of the next planned cycle providing omission lasts no more than 2 weeks unless there is a strong evidence of clinical benefit. In case of first recurrence of the same Grade ≥3 event attributable to palbociclib, a dose reduction of it to next dose level is recommended when symptoms resolve to ≤1 or Grade ≤2 (if not considered a safety risk for the patient). If further dose reduction below 75 mg/day is required, palbociclib should be permanently discontinued. In case of second recurrence of the same Grade ≥3 event, palbociclib should be permanently discontinued. 4. If toxicity attributable to endocrine therapy, omit them while continuing palbociclib without changes until symptoms resolve to Grade ≤1 or Grade ≤2 (if not considered a safety risk for the patient). Resume the omitted endocrine therapy at the same dose within cycle or at subsequent cycle providing omission lasts no more than 2 weeks unless there is a strong evidence of clinical benefit. In case of first recurrence of the same Grade ≥3 event attributable to endocrine therapy, omit them until symptoms resolve to Grade ≤1 or Grade ≤2 (if not considered a safety risk for the patient), and restart at the same dose. In case of second recurrence of the same Grade ≥3 event, all study IMPs should be permanently discontinued	
	Within cycle: continue endocrine therapy if toxicity is not attributed to these IMPs. If attributable, omit endocrine therapy until symptoms resolve to: Grade ≤1 or Grade ≤2 (if not considered a safety risk for the patient). 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 therapy.	**Within cycle**: omit palbociclib until symptoms resolve to: Grade ≤1 or Grade ≤2 (if not considered a safety risk for the patient) and administer palbociclib at the next lower dose within cycle if recovery occurs before Day 21 of the current cycle, or at Day 1 of the next planned cycle. In case of first recurrence of the same Grade ≥3 event: administer at the next lower dose level if restart is possible. If further dose reduction below 75 mg/day is required, palbociclib should be permanently discontinued. In case of second recurrence of the same Grade ≥3 event: permanently discontinue palbociclib.

NCI CTCAE v5 grade[a]	Management of endocrine therapy (Amcenestrant/amcenestrant-matching placebo, Letrozole/Letrozole-matching (placebo)	Management of Palbociclib
Interstitial Lung Disease/Pneumonitis		
Grade 1 (asymptomatic or suspected pneumonitis) or Grade 2 (symptomatic new or worsening respiratory symptoms)	No dose adjustment is required - continue endocrine therapy without any dose omission	Omit palbociclib, if applicable (ie, within D1 to D21 period of a given cycle); evaluate the patient until pneumonitis is diagnosed. - If pneumonitis is diagnosed, palbociclib must be permanently discontinued. - If pneumonitis is not diagnosed, restart palbociclib at the next lower dose when symptoms recover to the baseline level. Restart could be either within current cycle if recovery occurs before 21 days (and up to D21 of the cycle) or at the next planned cycle Day 1.
Grade 3 & 4 attributed to palbociclib	No dose adjustment is required - continue endocrine therapy without any dose omission	Permanently discontinue palbociclib
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 endocrine therapies 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.	No dose adjustment is required.
Grade 3	Omit endocrine therapies 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.	Omit palbociclib 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) and administer palbociclib at the next lower dose within cycle if recovery occurs before Day 21 of the current cycle, or at Day 1 of the next planned cycle. In case of first recurrence of the same Grade ≥3 event: administer at the next lower dose level if restart is possible. If further dose reduction below 75 mg/day is required, palbociclib should be permanently discontinued. In case of second recurrence of the same Grade ≥3 event: permanently discontinue palbociclib.
Grade 4	Permanently discontinue study treatment	

a Table applies to all hematologic abnormalities except lymphopenia (unless associated with clinical events, eg, opportunistic infections.

b Absolute neutrophil count (ANC): Grade 1: ANC <LLN -1500/mm^3; Grade 2: ANC 1000 -<1500/mm3; Grade 3: ANC 500 -<1000/mm3; Grade 4: ANC 500/mm^3

* Except lymphopenia (unless associated with clinical events, eg, opportunistic infections)

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).

Grading according to CTCAE v5.0.

NCI CTCAE v5 = National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; LLN = lower limit of normal.

10.8 APPENDIX 8: PROTOCOL AMENDMENT HISTORY

Amendment 01 dated 27-Jul-2020

Section # and Name	Description of Change	Brief Rationale
Title page (Protocol title); 1.1 (Synopsis); 2.1 (Study rationale); 3 (Objectives and Endpoints); 4.1 (Overall Design);	Updated the protocol title from "A randomized, multicenter, double-blind Phase 3 study of SAR439859 plus palbociclib versus letrozole plus palbociclib for the treatment of patients with ER (+), HER2 (-) breast cancer who have not received any prior systemic anti-cancer treatment for advanced disease" to "A randomized, multicenter, double-blind Phase 3 study of SAR439859 plus palbociclib versus letrozole plus palbociclib for the treatment of patients with ER (+), HER2 (-) breast cancer who have not received prior systemic anti-cancer treatment for advanced disease"	"Any" before "prior therapy" is a duplicate.
Title page	Removed the field "Study Name"	Removed as it was not part of the study protocol template
1.1 (Synopsis);. 1.3 (Schedule of Activities); 3 (objectives and Endpoints); 8.11.2 (EORTC QLQ-BR23); 8.11.3 (EORTC QLQ-BR45); 8.11.4 (EuroQoL EQ-5D-5L); 9.4.3.1 (Analyses of patient reported outcome endpoints)	Added the option to use EORTC QLQ-BR23 questionnaire until the availability of translated and validated EORTC QLQ-BR45 questionnaire. And added the description of EORTC QLQ-BR23 questionnaire in patient reported outcomes section.	EORTC QLQ-BR45 is a relatively new questionnaire, and its translation and validation in various languages are still ongoing.
1.3 (Schedule of Activities)	During study treatment period, Follicle-stimulating hormone will be performed in pre/peri-menopausal women every 4th cylce. Estradiol (local labs) will not be performed anymore.	There exists structural similarity between selective estrogen receptor degraders (SERD) and estradiol. SERD may interfere with estradiol immunoassays and may result in falsely increased levels of estradiol.
	Urine pregnancy test to be done at 12 weeks after last dose of any study intervention.	Correction of inconsistency between schedule of activities and main protocol.
	Removed the IRT contact on C1D14 and C2D14 visits	No IRT contacts are planned during these visits.

Section # and Name	Description of Change	Brief Rationale
1.3 (Schedule of Activities); 8.5 (Pharmacokinetics)	Changed the on-site study visit days planned Day 14 of Cycles 1 and 2 to Day 15 of Cycles 1 and 2. Subsequently PK samples will be collected on C1D15 and C2D15	To ensure that visits falls on the same day of the weeks.
	Pharmacokinetics sampling time were updated.	Changes were made in order to easier interpret the data.
2.1 (Study rationale); 4.3 (Justification for Dose)	Added the preliminary safety and efficacy results from dose escalation and expansion cohort of SAR439859 in combination with palbociclib from TED14856 study. Updated the inconsistent numbers in provided in “Justification for Dose” section.	Availability of encouraging preliminary safety and antitumor activity results of SAR439859 + palbociclib combination.
1.1 (Synopsis);	Patients who progress while on or within 12 months from completion of (neo)adjuvant therapy with tamoxifen could be allowed for enrollment into the study.	Patients progressing while on or within 12 months on tamoxifen could still benefit from SAR439859 or letrozole in combination with palbociclib.
5.2 (Exclusion criteria “E19”)	Patients who are involved in any type of medical research (except investigational study treatment) for at least 2 weeks prior to randomization are allowed for enrollment into the study.	Patients who are participating in any medical research not related to investigational study treatment (eg, molecular research of tumor samples) does not need to wait for 4 weeks duration to get enrolled into the study.
5.5 (Criteria for temporarily delaying); 10.15 (Appendix 15: Contingency measures for a regional or national emergency that is declared by a governmental agency)	New sections were added describing the contingency measures for a regional or national emergency, that is declared by a government agency.	These measures have been added to help manage the study conduct during an emergency (eg, COVID).
6.4 (study intervention compliance)	Information related to vomiting will not be collected in study drug diary	As vomiting related information are necessary only during the days of PK sampling, and the patient is on site during PK sampling, there exists no necessity to collect this information in the study drug diary.
8.3.6 (Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs)	The information provided in this section has been removed.	The prior information listed under this section was not relevant for oncology studies.
8.7 (Genetics); 8.7.1 (cfDNA tumor and germline mutation analysis); 8.8.2 (Tumor Protein Biomarkers)	Blood sample volume collected for genetic analysis has been updated. A new subsection title has been added for cfDNA and tumor protein biomarkers.	Availability of new specifications. For clarity purposes, these sections have been added.

Section # and Name	Description of Change	Brief Rationale
8.7.2 (Drug metabolizing enzymes and related genes DNA samples)	The title of the section has been updated (word "transporters" has been deleted from the section name), and information on optional blood sample has been removed, as it will be part of mandatory study procedures. This section has been updated to remove inconsistent text on analyses that may be performed with DMET genotyping sample.	Previously reported incorrect information were corrected.
8.8.1 (Estradiol)	Section Estradiol was moved to Biomarkers section and the further section numbers were updated.	This section was initially Incorrectly reported under Pharmacodynamics section.
9.4.3.2 (Analyses of other endpoints)	Pharmacodynamics analyses were removed, and genetics analyses were added	Pharmacodynamics analyses are not planned in study, and genetic analyses were missing.
10.2 (Appendix 2: Clinical laboratory tests)	FSH (local labs) and Estradiol (local labs) levels should be assessed in all study participants for eligibility during screening.	Inconsistency in information between schedule of activities and appendix 2 has been corrected.
10.6 (Appendix 6: Country-specific requirements)	Information on Chinese extension part has been added.	In order to fulfill the regulatory requirements in China, additional number of patients will be enrolled in an extension of the Global part of the study.
	In participants enrolled from clinical sites in China (in both Global part and extension part) biological samples related to secondary (except PK assessment of SAR439859 and palbociclib), exploratory (genetic analyses and biomarkers) endpoints will neither be collected nor analyzed.	As per HGRAC regulation, sites in China will not participate in the several secondary and exploratory endpoints assessment.
10.7 (Appendix 7: Recommended Dose Modification Guidelines for Study Treatment-Related Adverse Events)	The dose modification guidelines for endocrine therapy (SAR439859/ SAR439859-matching placebo, Letrozole/Letrozole-matching placebo) has been updated.	As it is a double blind, double dummy study, neither patients nor investigators would know, whether the patient is receiving SAR439859/ SAR439859-matching placebo or Letrozole/Letrozole-matching placebo. Therefore, in case of adverse events requiring dose modification of the endocrine therapy, both IMPs (Arm A: SAR439859 + letrozole-matching placebo; Arm B: SAR439859-matching placebo + letrozole) should have the same action (dose omission or dose delay).
Entire document	Editorial changes	Correction of typographical errors and minor inconsistencies across different sections, and clarifications.

Amendment 02 dated 30-Sep-2020

Section # and Name	Description of Change	Brief Rationale
1.1 (Synopsis); 9.4.1.1 (Analysis of primary efficacy endpoint)	Updated the censoring rules for PFS analysis	The censoring rules have been detailed based on feedback from regulatory authorities.
9.4.1.1 (Analysis of primary efficacy endpoint)	PFS assessed by the BIRC will be considered as supportive analysis of the primary PFS analysis even if a full BIRC is triggered	The strategy has been updated based on the feedback from regulatory authorities.
2.3.1 (Benefit and Risks assessment in context of COVID-19 pandemic); 2.3.1.1 (Benefits in the context of COVID-19); 2.3.1.2 (Risks in the context of COVID-19); 2.3.1.2.1 (Risks related to the patient population); 2.3.1.2.2 (Risks related to study related activity); 2.3.1.2.3 (Risks related to study treatment);	Added benefits risks assessment in the context of COVID-19 pandemic based on feedback from regulatory authorities	
5.1 (Inclusion criteria, I 09)	For clarity, the inclusion criterion 09 has been reworded.	
5.1 (Inclusion criteria, I 07)	Modified the inclusion criterion 07 - participants with ECOG performance status 2 are eligible for enrollment	The eligibility criterion on performance status has been updated for greater generalizability of real-life oncology population.
5.2 (Exclusion criteria, E 01)	Modified the exclusion criterion 01 to exclude participants with active brain metastases. Participants with treated/stable brain metastases will be eligible	The eligibility criterion on brain metastases has been updated based on recommendations from American Society of Clinical Oncology (ASCO)-Friends of Cancer Research Brain Metastases Working Group (40).
5.2 (Exclusion criteria, E 09, E 10)	Modified the exclusion criterion 09 to exclude enrolling pre/perimenopausal women and men receiving goserelin, who are fully anticoagulated for a past thromboembolic event. For clarity, the exclusion criterion 09 has been split to E 09 and E 10. Consequently, the numbering order of exclusion criteria has been changed.	Goserelin is not recommended in patients who are fully anticoagulated (INR >2) due to the risk of vascular injury and subsequent bleeding during administration (Product Monograph ZOLADEX; Goserelin. Dec 21, 2017).
6.3 (Measures to minimize bias: randomization and blinding)	Updated the unblinding rules to allow investigators to unblind participant's intervention assignment in case of emergency without the requirement for consultation with the Sponsor prior to unblinding.	The previous unblinding rules requested mandatory consultation with sponsor prior to unblinding participant's intervention assignment, which could have delayed the unblinding in case of emergency situations.

Section # and Name	Description of Change	Brief Rationale
6.6 (Dose Modification); 10.7 (Appendix 7: Recommended dose modification guidelines for study treatment-related adverse events)	Added the dose modification guidelines for recurrent adverse events with a severity of Grade ≥3.	This was previously missing.
7.1 (Discontinuation of study intervention); 8.3.7 (Adverse Event of special interest)	Pregnancy of female participant will lead to definitive discontinuation of study intervention (IMP and NIMP)	This was previously missing in the discontinuation of study intervention section.
8.3.5 (Pregnancy); 10.4 (Appendix 4: Contraceptive guidance and collection of pregnancy Information)	Contraception guidelines for male participants and male partners of female participants were updated.	Given the contraindication of pregnancy with all the study drugs, including effects on male fertility and known genotoxicity with the IMP, contraception guidelines for men have been updated.
1.3 (Schedule of Activities); 8.5 (Pharmacokinetics, Table 4)	Additional blood samples for PK assessment will be collected beyond Cycle 3	Additional blood samples for PK of SAR439859 and palbociclib will be collected based on feedback from regulatory authorities
1.3 (Schedule of Activities); 10.2 (Clinical laboratory tests)	Pregnancy tests to be performed monthly until 12 weeks after the last dose of any study intervention	The monthly pregnancy tests after the last dose of any study intervention were missing
Entire document	Editorial changes	Correction of typographical errors and minor inconsistencies across different sections, and clarifications.

Amendment 03 dated 13-Dec-2020

Section # and Name	Description of Change	Brief Rationale
1.1 (Synopsis); 9.2 (Sample size determination); 4.1.1 Duration of the Study Period; 9.5.1 (Interim analyses for PFS)	Modification of statistical assumptions; modification of the study sample size from 708 to 1066 patients; addition of second interim analysis for OS; and change in study duration & estimated cut-off dates for PFS and OS analyses.	Revised PFS HR assumption used to power this endpoint, revised futility analysis strategy at interim analyses and revised dropout assumption due to change in PFS censoring scheme. Revised OS HR assumption used to power this endpoint.
1.1 (Synopsis); 3 (objectives and Endpoints, other secondary objectives and endpoints); 9.4.1 (Efficacy analyses); 9.4.1.2 (Analysis of secondary efficacy endpoints)	Addition of PFS2 as secondary endpoint and description of how the PFS2 will be assessed.	To assess the PFS after next line of therapy. PFS2 is a useful endpoint to assess any benefit beyond initial disease progression.

Section # and Name	Description of Change	Brief Rationale
1.1 (Synopsis); 3 (objectives and Endpoints, Tertiary/exploratory objectives and endpoints)	Change of PK assessment from secondary objective to exploratory objective. The exposure/response relationship of palbociclib will be evaluated as exploratory objective.	The potential effect of amcenestrant on goserelin C_{trough} assessed through PK of goserelin bears exploratory nature. Thus, it has been moved to exploratory objective. As palbociclib will be assessed in both arms with possibly different exposure.
1.1 (Synopsis, Disclosure statement);	Updated the list of stakeholders for whom the study is blinded	To have consistent information between synopsis and Section 6.5 (measures to minimize bias: randomization and blinding)
1.1 (Synopsis, Number of participants);	Added the total number of patients that will be screened in the current study.	For clarity purposes.
1.1 (Synopsis, study interventions);	The dose regimen of Letrozole and letrozole-matching placebo was changed from “1 tablet once daily” has been changed to “1 capsule once daily”.	Corrected the incorrect description.
1.1 (Synopsis); 1.3 (Schedule of Activities); 3 (objectives and Endpoints, Tertiary/exploratory endpoint); 10.6 (Appendix 6: Country-specific requirements)	Modified the cfDNA timepoint from “end of Cycle 3” to “Cycle 4 Day 1 predose”.	For clarity purposes.
1.1 (Synopsis); 1.3 (Schedule of Activities); 8.1 (Efficacy Assessments)	Clarified the disease assessment to be performed at EOT visit and during follow-up period.	During follow-up period, tumor assessment is required only in study participants without documented PD as per RECIST 1.1.
1.3 (Schedule of Activities);	All study visits conducted during treatment period and follow-up period (in participants without progressive disease per RECIST 1.1 at EOT) are conducted on-site until disease progression. On-site visits could be substituted by remote visits in specific circumstances.	For clarity purposes.
1.3 (Schedule of Activities); 8.2.3 (Electrocardiograms)	Added the five-minute window at a nominal time-point for triplicate ECGs.	This information was missing.
1.3 (Schedule of Activities); 8.5 (Pharmacokinetics)	Modified the PK sampling time points in schedule of activities, and table 4 (PK samples collection for amcenestrant, palbociclib and goserelin) has been updated accordingly. PK sample IDs were removed, as they are available in laboratory manual; Updated the incorrect volume of blood to be collected (from 2 mL to 4 mL) for goserelin PK assessment.	Optimized the PK sample collection time points in such a way that those time points fall on study visits when there are additional on-site assessments (eg, disease assessments).

Section # and Name	Description of Change	Brief Rationale
1.3 (Schedule of Activities); 8.11 (Patient reported outcomes)	PROs (Patient-reported outcomes) will be reported in electronic format". Paper format of PROs questionnaires will be used in case of extreme circumstances eg, technical issue making the electronic format temporarily unusable.	To avoid missing PROs data, which is a secondary endpoint of the study.
1.3 (Schedule of Activities); 10.2 (Appendix 2: Clinical laboratory tests)	Added the requirement for highly sensitive (at least 25mIU/mL) urine pregnancy test	With higher sensitivity, the chances of not detecting pregnancies decreases.
1.3 (Schedule of Activities);	Goserelin administration on EOT visit has been removed	Administration of goserelin is done every 28 days, and its subsequent administration shall not necessarily fall at the date of EOT.
1.3 (Schedule of Activities);	Dual-energy x-ray absorptiometry (DXA) scan of anteroposterior spine and total hip will be performed in study participants who are not on bone-targeted agents at baseline (unless not performed within 6 months prior and during treatment period	Endocrine therapies used in EFC15935 study have a risk of osteoporosis because of their anti-estrogenic properties. The implemented changes are added as part of risk minimization strategy
5.1 (INCLUSION CRITERIA - I06); 1.1 (Synopsis); 8.1 (Efficacy assessments)	Inclusion criterion I06 has been updated as: Measurable disease ie, at least one measurable lesion evaluable per RECIST v.1.1 or non-measurable bone only disease with at least one predominant lytic bone lesion or mixed lytic-blastic lesion without a measurable soft tissue component must be present (criterion modified by amendment 03). Updated the non-measurable disease criteria in various sections.	In addition to measurable disease per RECIST 1.1, patients with non-measurable bone-only disease are enrolled. In order to avoid confusion on interpretation of non-measurable disease and for clarity, the inclusion criterion I06 has been updated.
5.1 (INCLUSION CRITERIA - I09)	Modified the inclusion criterion I09 to remove the mandatory use of GnRH agonist at least 4 weeks prior to randomization in men with no prior bilateral orchiectomy and pre/perimenopausal women. GnRH agonist initiation up to 4 weeks before starting the study is permitted, but not required.	With the current protocol requirements, pre/premenopausal women and men with no prior orchiectomy are waiting for the 4-weeks duration (under GnRH agonist) to get elapsed prior to getting randomized into the study, which is creating a delay in the initiation of the study treatment. In MONALEESA-7 Phase III study (Lancet Oncol 2018; 19: 904-15), goserelin was initiated on the same day as other study drugs so that patients could begin the full treatment regimen without delay, and simultaneous initiation did not cause any negative effects.
5.2 (EXCLUSION CRITERIA - E02); 1.3 (Schedule of Activities);	Updated the exclusion criterion E 02 to exclude participants with known active hepatitis A/B/C, or hepatic cirrhosis. Added the viral serology tests in the schedule of activities.	As the study IMPs have a potential to induce hepatic toxicity, the implemented changes are added as part of risk minimization strategy.
5.2 (EXCLUSION CRITERIA - E12)	Updated the exclusion criterion E12 to remove treatment with moderate CYP3A inducers.	Availability of new data showing that there is a modest decrease (30%) of amcenestrant with strong CYP3A inducers.

Section # and Name	Description of Change	Brief Rationale
5.2 (Exclusion criteria - E13); 6.5 (Concomitant therapy); 10.10 (Appendix 10: List of Strong CYP3A Inducers);	Removed exclusion criterion E13 - "Treatment with strong or moderate CYP2C8 inducers within 2 weeks before first study treatment administration or 5 elimination half-lives whichever is longest and cannot be replaced" and adapted the list of prohibited concomitant therapies with regards to CYP2C8 inducers.	Availability of new data showing that there is Availability of new data showing that there is a modest decrease (30%) of amcenestrant with strong CYP3A inducers and considering that there is no known strong CYP2C8.
5.2 (EXCLUSION CRITERIA - E16)	Updated the exclusion criterion E 16 to exclude participants with recurrent disease, who have primary or secondary resistance to prior (neo)adjuvant endocrine therapy	To ensure that the enrolled study population with recurrent disease is homogenous with endocrine sensitive disease.
5.3.1 (Sun protection)	Added recommendations for using broad spectrum sunscreens filtering both UVA and UVB light exposure	To ensure that the recommendations provided for sun protection are adequate.
5.3.3 (Osteoporosis)	A new subsection "Osteoporosis" has been added under "Life-style considerations", to reduce the risk of osteoporosis	Endocrine therapies used in EFC15935 study have a risk of osteoporosis because of their anti-estrogenic properties. The implemented changes are added as part of risk minimization strategy.
5.4 (Screen failures)	Added information on management of temporary screen failures	The signed informed consent form is valid beyond 28 days. In case of temporary screen failures, there is no necessity to have participant reconsented with new ICF signed, if participant finally participates in the study. The process of handling such cases are described.
6.1 (Study interventions administered); 10.15 (Appendix 15: Contingency measures for a regional or national emergency that is declared by a governmental agency)	Removed sponsor from the list of entities for direct to patient IMP dispensation service.	With direct to patient IMP dispensation service, IMPs could be supplied only from the PI or study site to the study participant.
6.4 (Study intervention compliance)	Updated the rules for completion of study medication diary; updated the term from "study drug diary" to "study medication diary;	Patients do not complete the study medication diary every day, but only on days when doses are omitted and on days prior to PK sampling.

Section # and Name	Description of Change	Brief Rationale
6.5 (Concomitant therapy)	Added recommendations for study participants with bone mineral density T score of < -2 or with ≥2 risk factors for fracture per ESMO clinical practice guidelines on bone health in cancer.	Endocrine therapies used in EFC15935 study have a risk of osteoporosis because of their anti-estrogenic properties. The implemented changes are added as part of risk minimization strategy.
	Provided guidance on the administration of vaccines during the study.	With the increased rate of infections associated with palbociclib, and with availability of vaccines to SARS-COV-2, this guidance has been added.
	Added the description for prohibited medications that could prolong QT interval in premenopausal women and men, as they are contraindicated when co-administered with goserelin.	To be aligned with exclusion criterion E 19
6.5 (Concomitant therapy); 8.2.4 (Clinical safety laboratory assessments); 8.4 (Treatment of Overdose)	Replaced “medical monitor” by “Sponsor or Sponsor representative(s)”.	Change in terminology.
7.1.1 (Definitive discontinuation)	Provided the reference to adverse events leading to definitive/premature discontinuation of study intervention.	For clarity purposes.
8.2.3 (Vital signs)	Removed the AE reporting guidance for vital signs abnormalities, when they are defined as AESI	Vital signs abnormalities are not AESI per current study protocol
8.3.4 (Regulatory reporting requirements for SAEs)	Updated the suspected unexpected serious adverse reactions (SUSARs) reporting timelines	In order to be aligned with the pharmacovigilance (PV) guidelines.
8.3.5 (Pregnancy); 10.4 (Appendix 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.
8.3.7 (Adverse event of special interest)	Added “Photosensitivity” as a new adverse event of special interest (AESI)	Preclinical studies using SAR439859 indicate a potential risk for phototoxicity. Photosensitivity events has been added as an AESI in order to collect relevant information.
8.3.7 (Adverse event of special interest)	Added guidance on the management of Increase in alanine transaminase (ALT) ≥ Grade 3	As the study IMPs have a potential to induce hepatic toxicity, the implemented changes are added as part of risk minimization strategy.
8.7.1 (cfDNA tumor and germline mutation analysis)	Removed the requirement of replacement genetic blood sample.	Considering the exploratory nature of the analyses, replacement genetic blood sample will not be requested in case of DNA extraction failure.
8.8 (Biomarkers); 8.8.1 (Protein expression); 8.8.3 (RNA transcriptome research)	Rearranged the text related to samples storage under the main section biomarkers.	For clarity purposes.

Section # and Name	Description of Change	Brief Rationale
8.8.1 (Protein expression)	A new subsection title has been added "Protein expression"	For clarity purposes.
8.8.4 (Future use of samples); 8.9 (Use of biological samples and data for future research)	Section 8.8.4 "Future use of samples" has been removed and substituted with a new Section 8.9 "Use of biological samples and data for future research".	The new section provides information on streamlined process for accessing clinical data/samples for secondary use.
9.2 (Sample size determination); 10.6 (Appendix 6: Country-Specific Requirements)	Removed descriptions for China extension study including objective, population and sample size consideration.	In Nov 2020, an enrollment plan for China was adopted that targeted the completion of enrollment at the same time as global population. It is possible that an extension study is no longer needed. Therefore, relevant descriptions for sub-study are removed and flexible statement regarding the enrollment plan has been added. Consideration on patient number was also removed as all study participants from China may be treated within the global study. Specific sample size consideration will be provided in separate regulatory packages submitted to China National Medical Products Administration - Center for Drug Evaluation (NMPA-CDE).
10.1.3 (Informed consent process)	Updated the informed consent process	To provide a clear description on the ICF process, especially in case of amendments.
10.1.4 (Data protection)	Updated data protection of participants and professionals involved in study	GDPR compliance related to Investigators and staff data, as well as service providers, experts, Ethics Committee members.
10.1.5 (Committees structure)	Information about Blinded Independent Review Committee (BIRC) has been added.	Information on BIRC was missing within the relevant "committees structure" section, where description on all study committees are provided.
10.1.6 (Dissemination of clinical study data)	Added the study disclosure information in China and added information on what could be publicly disclosed and communicated to relevant authorities by sponsor.	GDPR compliance related to Investigators and staff data, as well as service providers, experts, Ethics Committee members.
10.3.2 (Definition of SAE)	Added a list of medically important events.	Guideline for the investigator for SAE reporting.
10.4 (Appendix 4: Contraceptive guidance and collection of pregnancy Information)	Added the reason for sperm preservation prior to beginning therapy with study IMPs.	Per request from health authorities.
10.7(Appendix 7: Recommended Dose Modification Guidelines For Study Treatment-Related Adverse Events)	Added dose modification guidelines for study IMPs in case of increase in ALT levels, and updated the palbociclib dose modification guidelines for Grade 3 hematological toxicity in order to be aligned with palbociclib SmPC.	As the study IMPs have a potential to induce hepatic toxicity, the implemented changes are added as part of risk minimization strategy.
10.8 (Appendix 8: Protocol amendment history)	Updated by including amendment history of amended protocol 02.	

Section # and Name	Description of Change	Brief Rationale
10.9 (Appendix 9: List of CYP3A Inhibitors); 10.10 (Appendix 10: List of Strong CYP3A Inducers); 10.11 (Appendix 11: List of CYP Sensitive Substrates)	The list of strong CYP3A inhibitors/inducers, CYP sensitive substrates has been updated.	With the availability of updated data from October 2020 extraction - from the DDI database of University of Washington.
10.16 (Appendix 16: Drugs with a narrow therapeutic window metabolized by CYP3A)	Added the list of drugs with a narrow therapeutic window metabolized by CYP3A	For clarity purposes.
10.17 (Appendix 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); EORTC BR-45 (for female and male participants); EQ-5D-5L.	As paper questionnaires are allowed in extreme circumstances, these sample questionnaires are added for use by study sites.
Several sections of protocol have been impacted	Changed the name of “SAR439859” IMP to “Amcenestrant’	Availability of amcenestrant INN for SAR439859
Entire document	Editorial changes	Correction of typographical errors and minor inconsistencies across different sections, and clarifications.

10.9 APPENDIX 9: LIST OF CYP3A INHIBITORS

Concomitant administration of medications that are strong CYP3A inhibitors 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 INHIBITORS			
CYP3A inhibitors	**Precipitant Therapeutic Class**	**Victim (oral, unless otherwise specified)**	**AUC Ratio**
Potent CYP3A Inhibitors (yielding substrate AUCratio >5)			
Telaprevir	Antivirals	midazolam	13,5
Indinavir/RIT	Protease inhibitors	alfentanil	36,50
Tipranavir/RIT	Protease inhibitors	midazolam	26,91
Ritonavir	Protease inhibitors	midazolam	26,41
Cobicistat (GS-9350)	None	midazolam	19,03
Indinavir	Protease inhibitors	midazolam	9.67
Ketoconazole	Antifungals	midazolam	17.08
Troleandomycin	Antibiotics	midazolam	14,80
Saquinavir/RIT	Protease inhibitors	midazolam	12,48
Itraconazole	Antifungals	midazolam	10,80

STRONG CYP3A INHIBITORS			
CYP3A inhibitors	**Precipitant Therapeutic Class**	**Victim (oral, unless otherwise specified)**	**AUC Ratio**
Potent CYP3A Inhibitors (yielding substrate AUCratio >5)			
Voriconazole	Antifungals	midazolam	9,63
Mibefradil	Calcium Channel Blockers	midazolam	8,86
Clarithromycin	Antibiotics	midazolam	8,39
Danoprevir/RIT	Antivirals	midazolam	13,42
Lopinavir/RIT	Protease inhibitors	alfentanil	11,47
Elvitegravir/RIT	Treatments of AIDS	midazolam	12,80
Posaconazole	Antifungals	midazolam	6,23
Telithromycin	Antibiotics	midazolam	6,2
Grapefruit Juice DS	Food Products	midazolam	5,95
Conivaptan	Diuretics	midazolam	5,76
Nefazodone	Antidepressants	midazolam	5,44
Nelfinavir	Protease inhibitors	midazolam	5,29
Saquinavir	Protease inhibitors	midazolam	5,18
Boceprevir	Antivirals	midazolam	5,05
Idelalisib	Kinase inhibitors	midazolam	5,15
LCL161	Cancer treatments	midazolam	8,80
VIEKIRA PAK	Antivirals	tacrolimus	55,76
Mifepristone	Antiprogestins	simvastatin	estimated 9.55
Ceretinib	Kinase inhibitors	midazolam	5.84 (PBPK)
Ribociclib	Kinase inhibitors	midazolam	5.17
Tucatinib	Kinase inhibitors	midazolam	5.74
Josamycin	Antibiotics	ivabradine	7.70

10.10 APPENDIX 10: LIST OF STRONG CYP3A INDUCERS

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

The following tables were 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)

10.11 APPENDIX 11: 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 or matching placebo 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

Drug (oral)	**Therapeutic Class**
eplerenone	Diuretics
everolimus	Immunosuppressants
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

Drug (oral)	**Therapeutic Class**
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
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.

In vitro, letrozole inhibits the cytochrome P450 isoenzymes 2A6 and, moderately, 2C19, but the clinical relevance is unknown. Caution is therefore indicated when giving letrozole/letrozole-matching placebo concomitantly with medicinal products whose elimination is mainly dependent on these isoenzymes and whose therapeutic index is narrow.

10.12 APPENDIX 12: ABBREVIATED MODIFICATION OF DIET IN RENAL DISEASE FORMULA

Glomerular Filtration Rate (GFR) (mL/min/1.73 m^2) = 175 × $(SCr)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if Female) × (1.212 if African-American).

Abbreviation: SCr = Serum creatinine in mg/dL; Age in years

10.13 APPENDIX 13: EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS SCALE

Performance	Status Description
0	Fully active, able to carry on all pre-disease 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 house work, 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.

10.14 APPENDIX 14: LIST OF DRUGS THAT CAN CAUSE QT PROLONGATION

Anti-arrhythmic drugs

- Amiodarone, disopyramide, dronedarone, flecainide, sotalol

Other cardiac drugs

- Ranolazine

Antibiotics

- macrolides (eg, erythromycin, clarithromycin, azithromycin), quinolones (eg, levofloxacin, moxifloxacin)

Antifungals

- Fluconazole, ketoconazole

Antimotility and antiemetic agents

- Domperidone, granisetron, ondansetron

Antimalarials

- Quinine, chloroquine

Antihistamines

- Hydroxyzine

Antipsychotics

- Chlorpromazine, clozapine droperidol, fluphenazine, haloperidol, olanzapine, pimozide, paliperidone, quetiapine, risperidone

Antidepressants

- Amitriptyline, citalopram, escitalopram, dosulepin doxepin, fluoxetine, imipramine, lofepramine

Miscellaneous

- Methadone, antiretrovirals (eg, foscarnet)

[Source: BMJ 2016;353:i2732; BMJ 2016;354:i4331]

The list is not exhaustive.

10.15 APPENDIX 15: 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). 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, mobile applications, 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 PI/site where allowed by local regulations and agreed upon by participant. (Section 6.1).

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.

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).

10.16 APPENDIX 16: DRUGS WITH A NARROW THERAPEUTIC WINDOW METABOLIZED BY CYP3A

Alfentanil

Cyclosporine

Dihydroergotamine

Ergotamine

Everolimus

Fentanyl

Pimozide

Quinidine

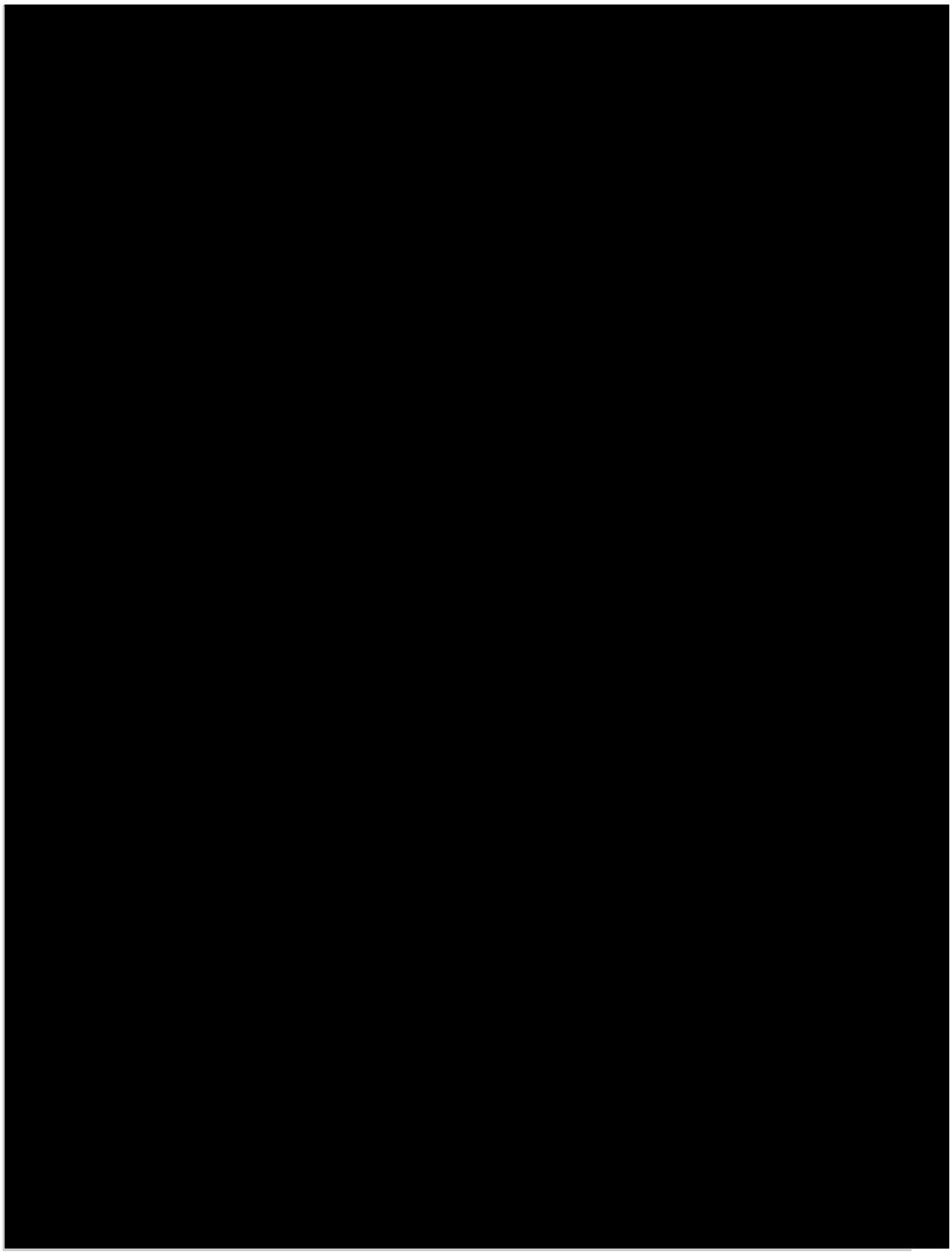
Sirolimus

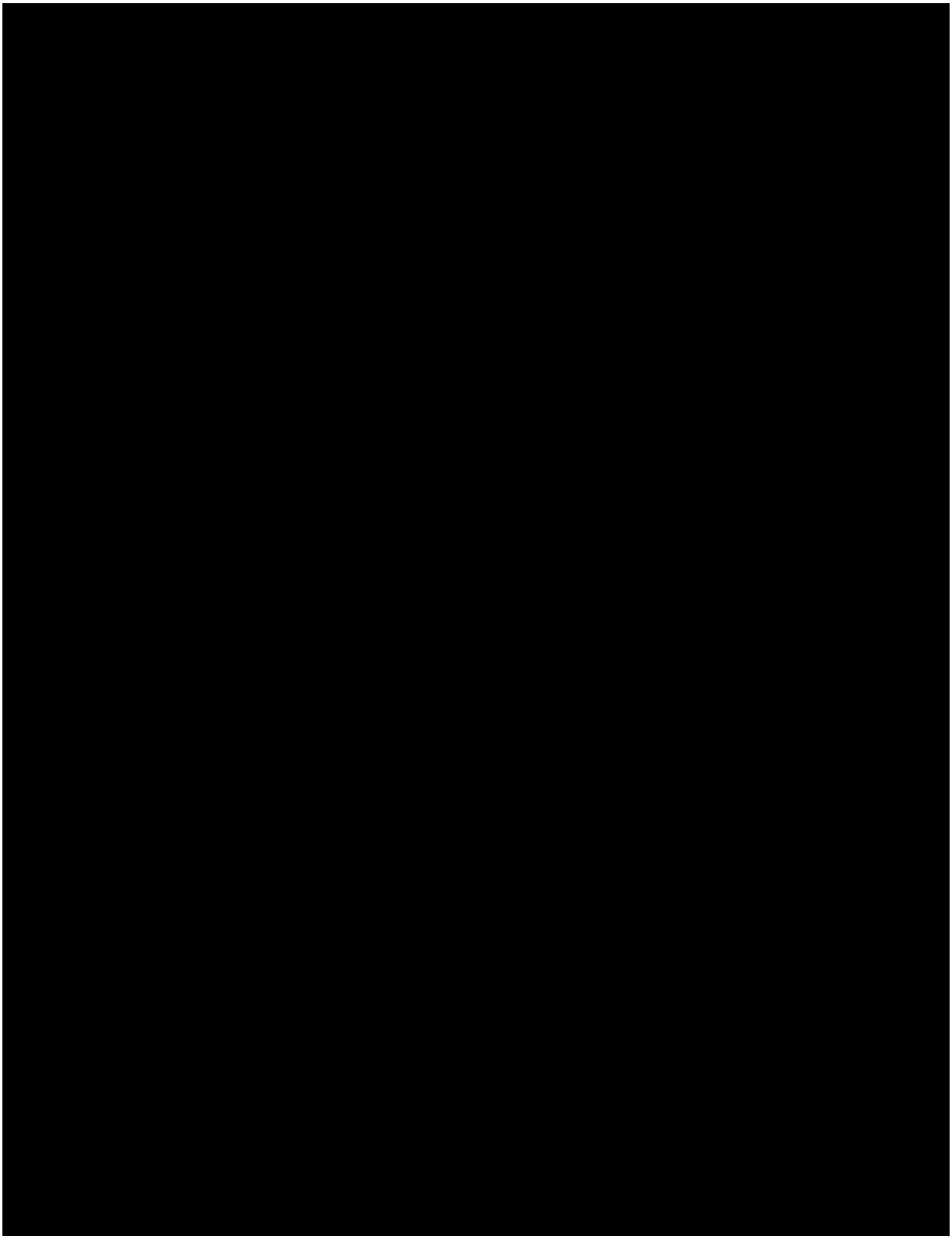
Tacrolimus

The list is not exhaustive.

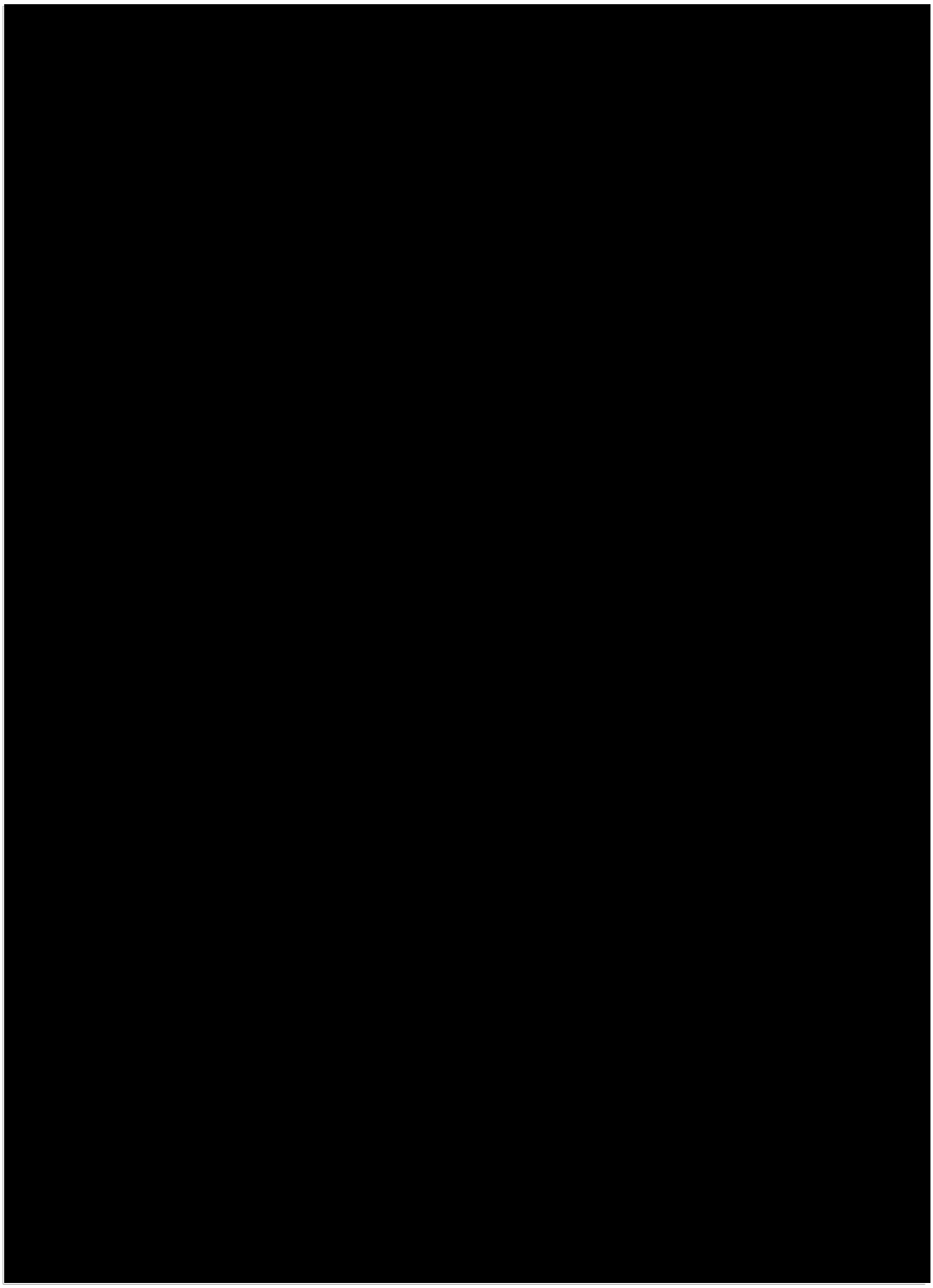
10.17 APPENDIX 17: PATIENT-REPORTED OUTCOMES

10.17.1 EORTC QLQ-C30 questionnaire

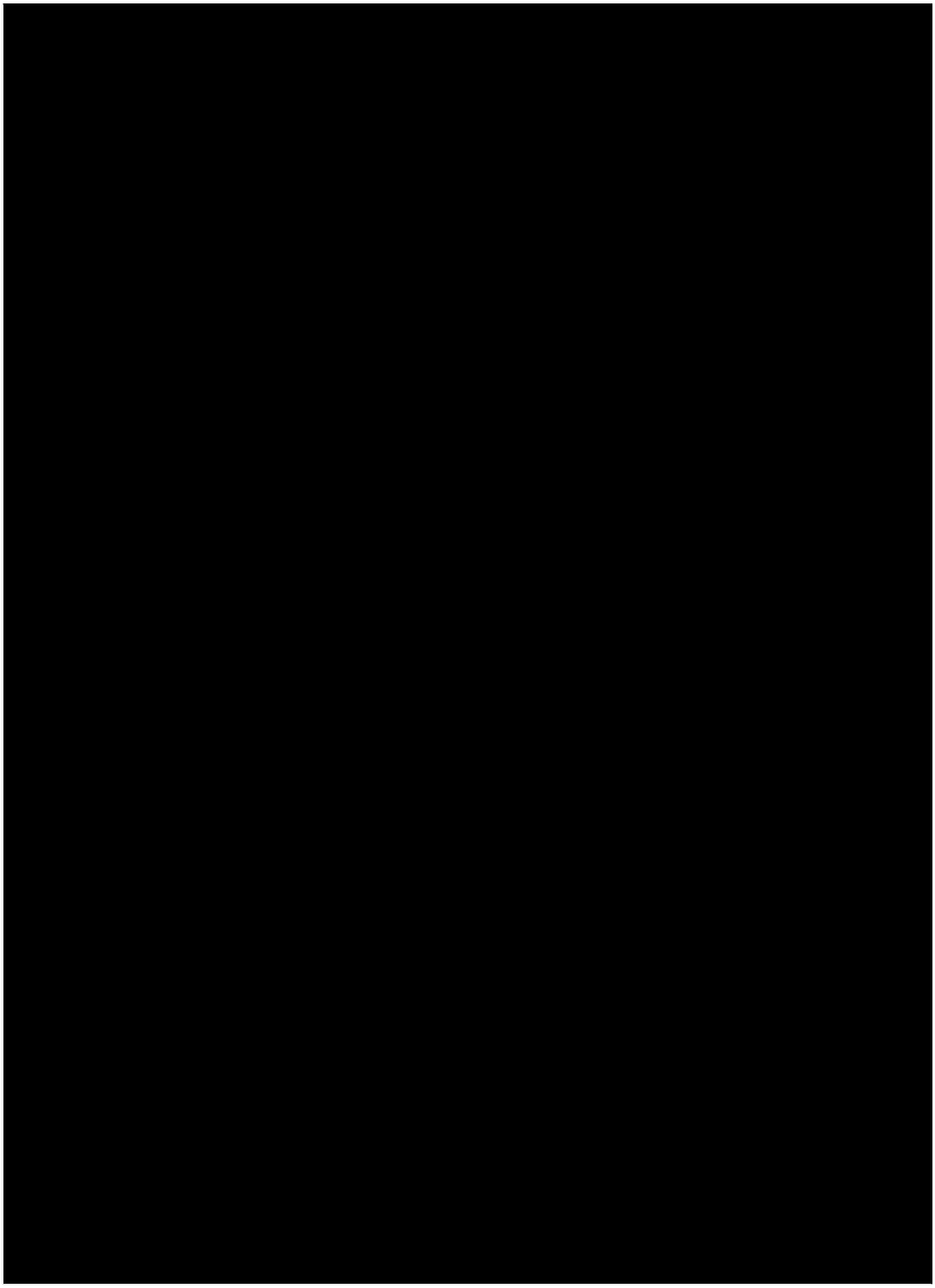




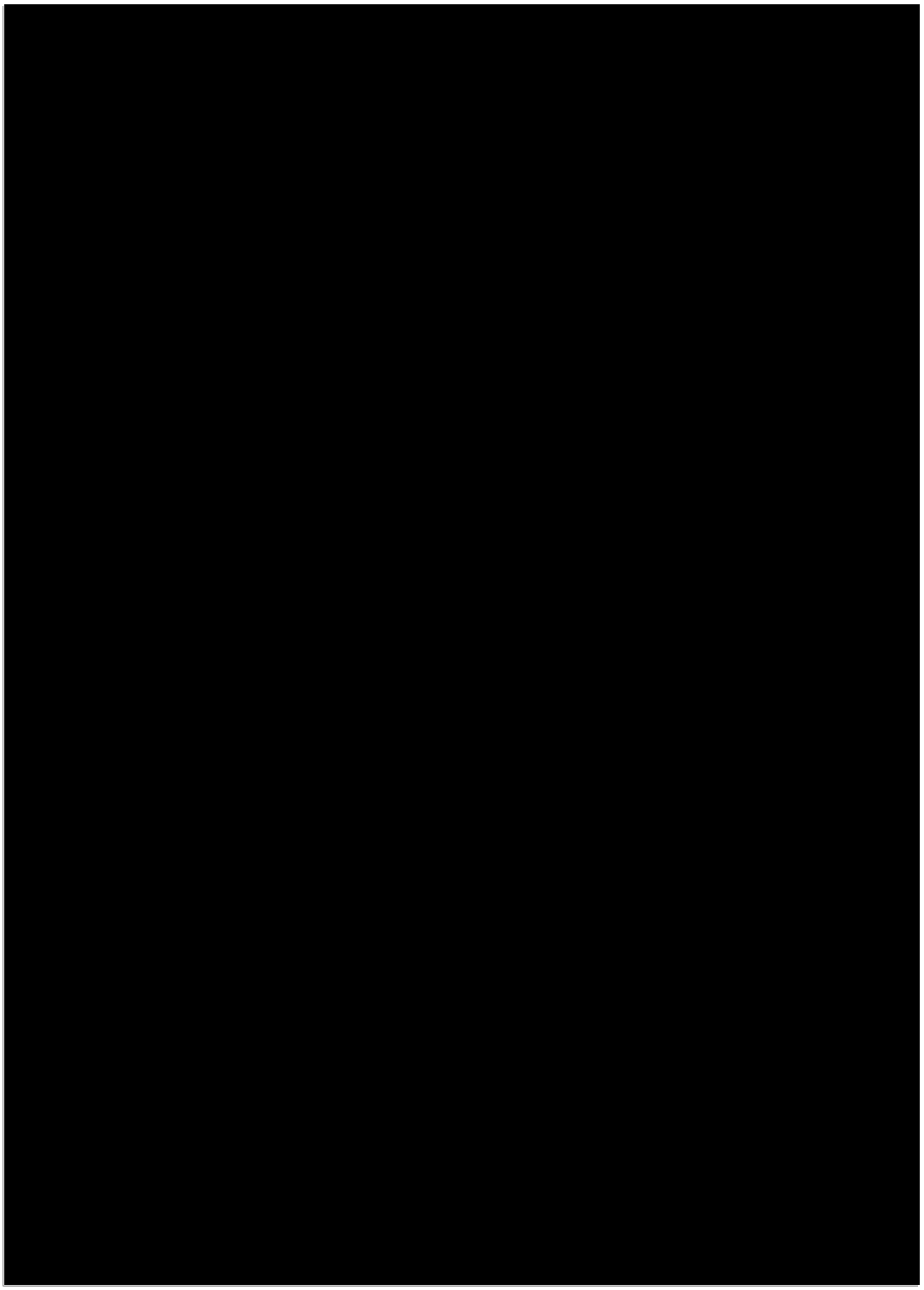
10.17.2 EORTC QLQ-BR23 questionnaire (for female participants)

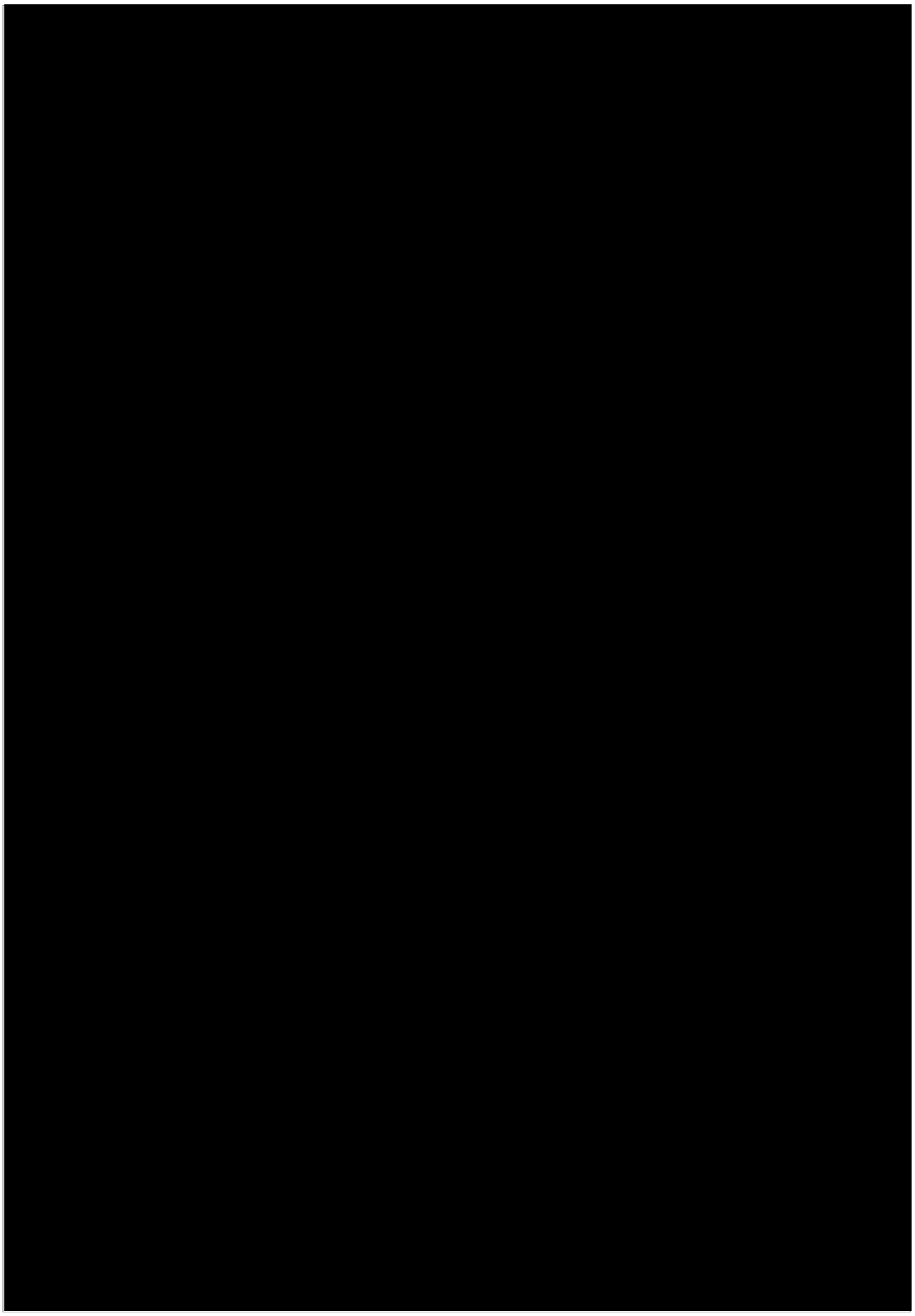


10.17.3 EORTC QLQ-BR23 questionnaire (for male participants)

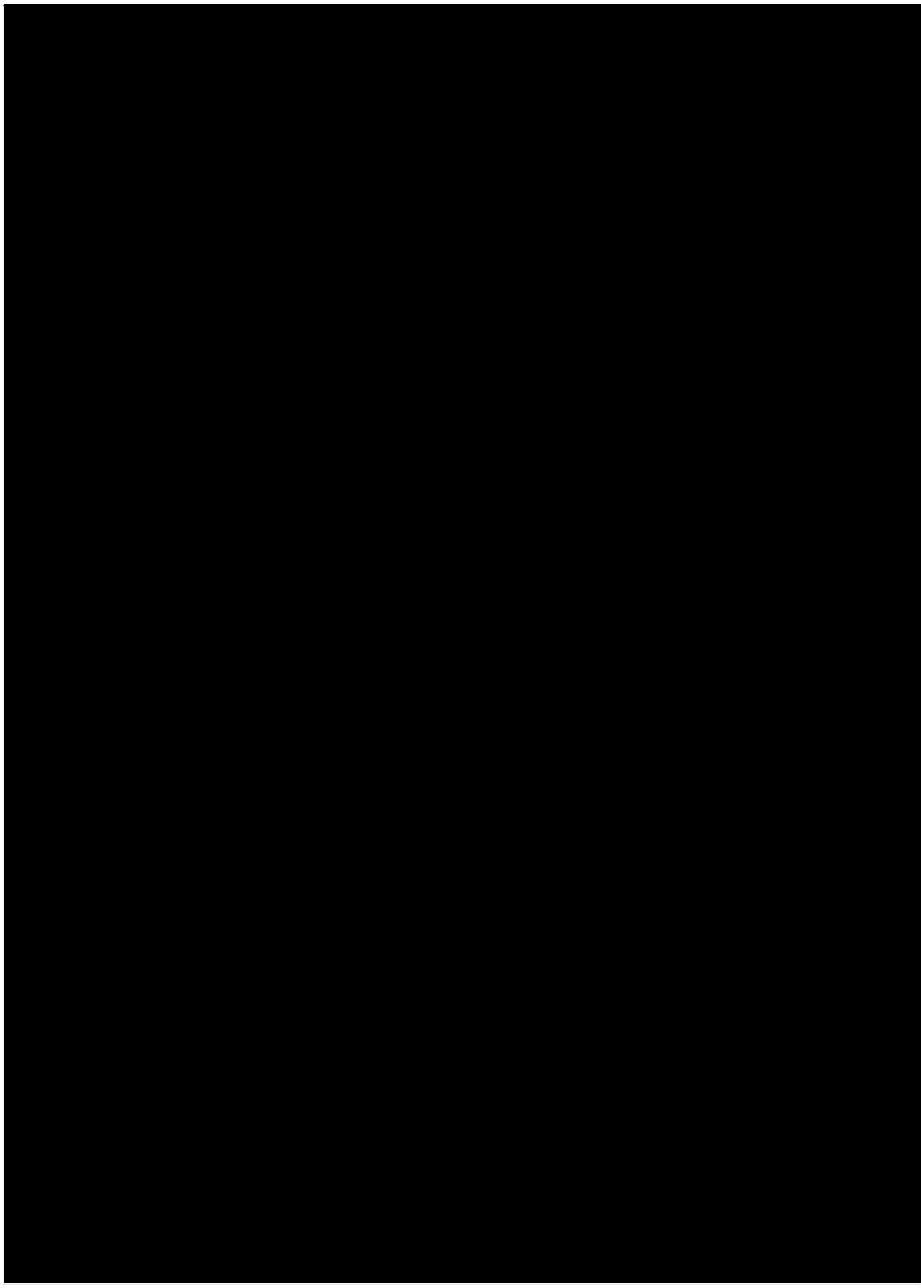


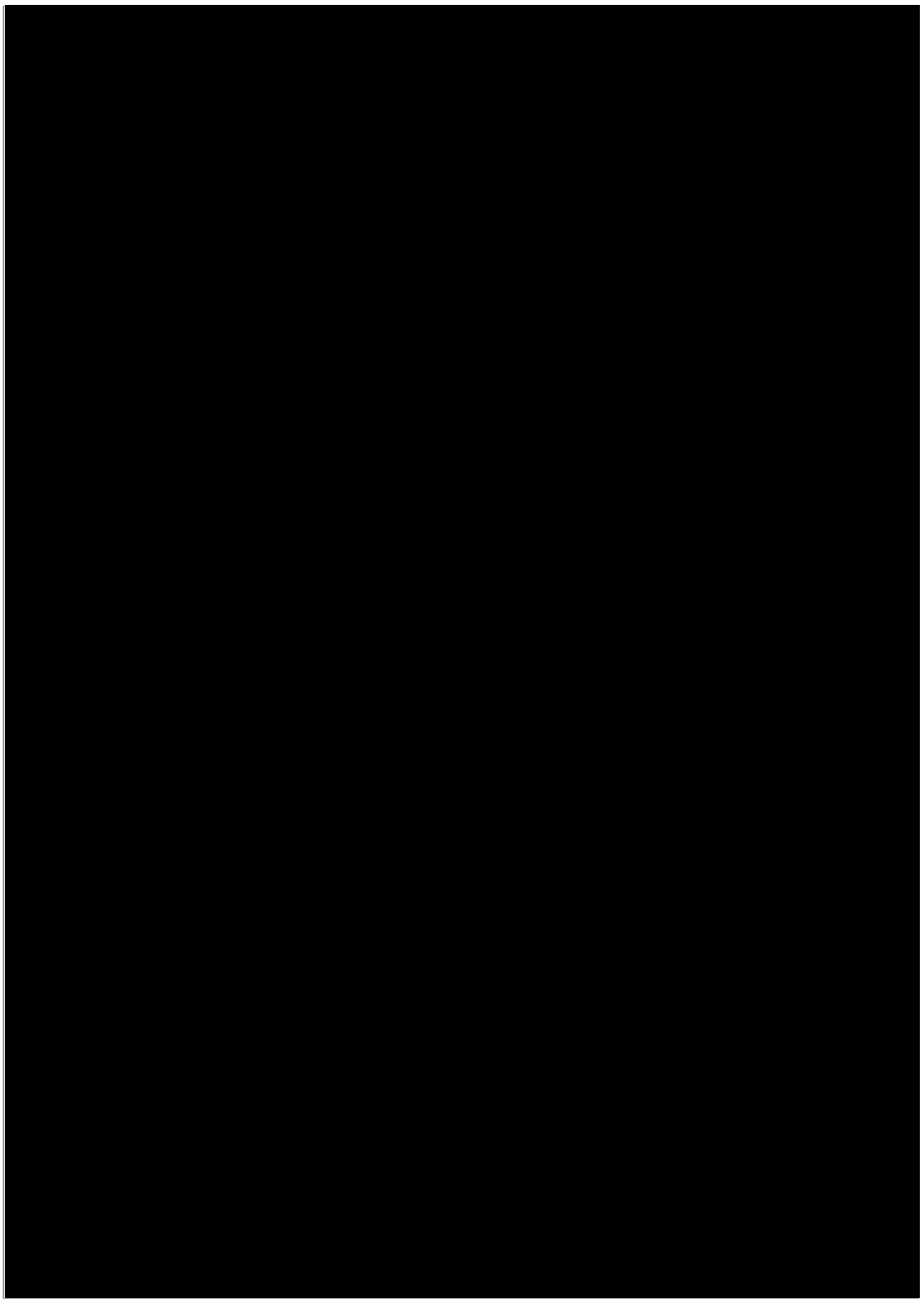
10.17.4 EORTC QLQ-BR45 questionnaire (for female participants)



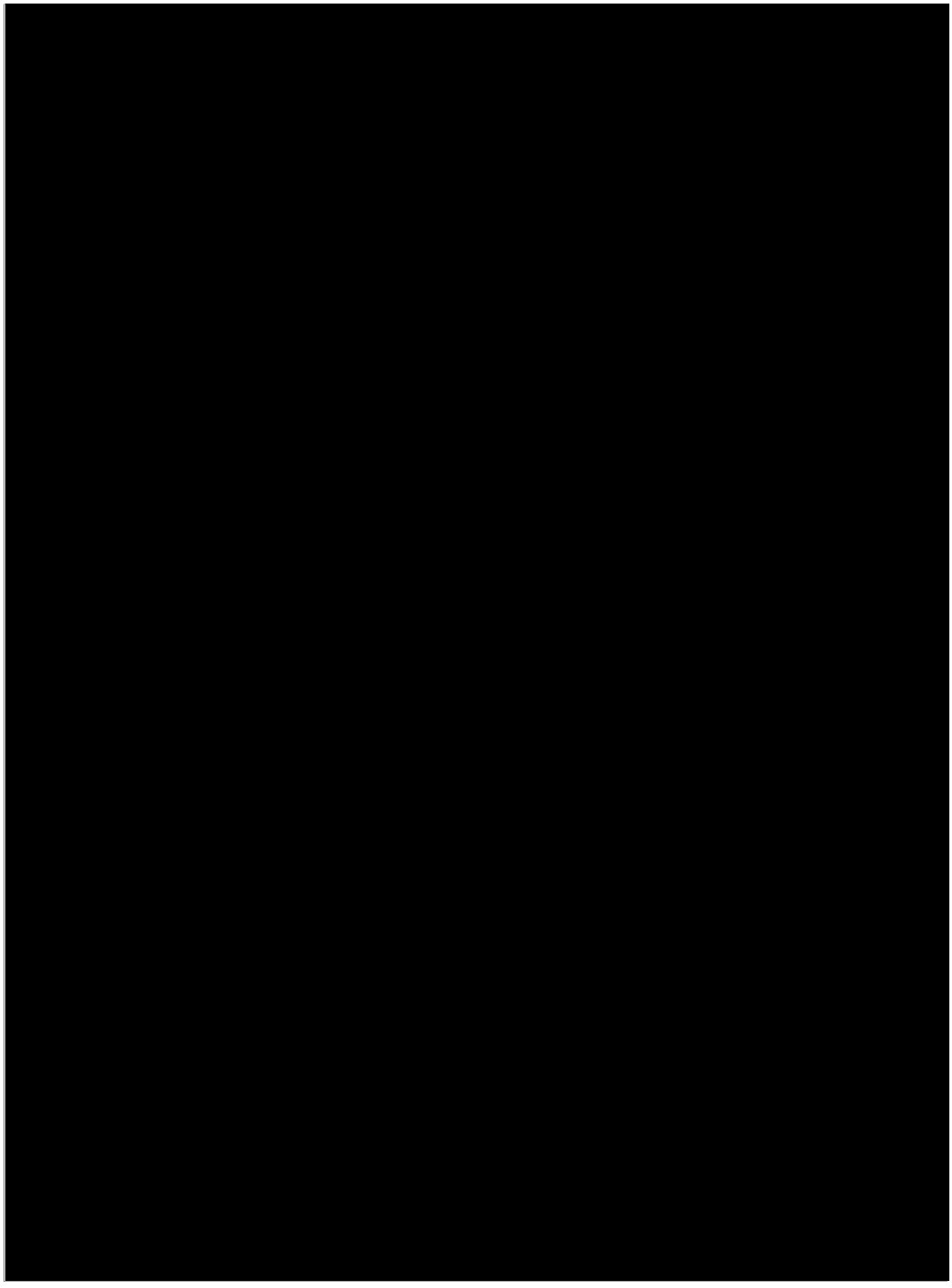


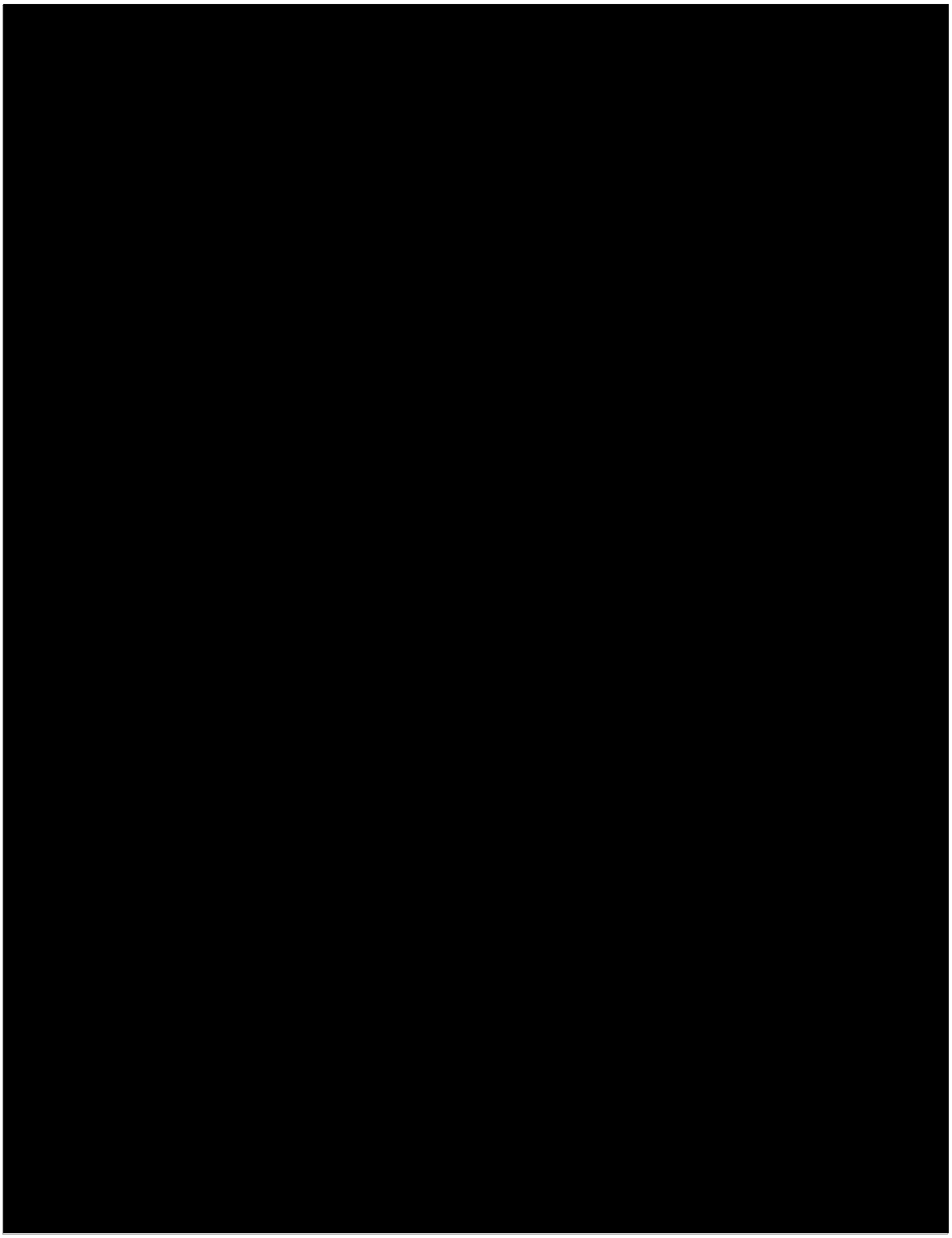
10.17.5 EORTC QLQ-BR45 questionnaire (for male participants)





10.17.6 EQ-5D-5L Health Questionnaire





10.18 ABBREVIATIONS

AESI:	adverse event of special interest
AI:	aromatase inhibitor
ALT:	alanine aminotransferase
ASCO:	American Society of Clinical Oncology
AST:	aspartate aminotransferase
BIRC:	blinded independent review committee
BOR:	best overall response
CBR:	clinical benefit rate
CEP17:	centrometric probe for chromosome 17
cfDNA:	cell free deoxyribonucleiic acid
CI:	confidence interval
COD:	cut-off date
CT:	computed tomography
CYP:	cytochrome P450
DMC:	Data Monitoring Committee
DMET:	drug metabolizing enzymes and transporters
DOR:	duration of response
DXA:	dual-energy x-ray absorbtiometry
ECG:	electrocardiogram
ECOG:	Eastern Cooperative Oncology Group
EDR:	early discrepancy rate
EHA:	European hematology association
EMA:	European Medicines Agency
EOT:	end of treatment
EQ-5D-5L:	EuroQoL questionnaire with 5 dimensions and 5 levels per dimension
ESMO:	European society for medical oncology
ET:	endocrine therapy
FES-PET:	Fluoroestradiol Positron-emission tomography
FFPE:	formalin fixed paraffin embedded
FWER:	family wise error rate
GCP:	good clinical practice
HR:	hazard ratio
HR+:	hormone receptor positive
HRQL:	health-related quality of life
IHC:	immunohistochemistry
IMP:	investigational medicinal product
IMP:	investigational medicinal product
IRT:	interactive response technology
ITT:	intent-to-treat
LDR:	late discrepancy rate
MRI:	magnetic resonance imaging
NCI-CTCAE:	National Cancer Institute Common Terminology Criteria for Adverse Events
NIMP:	noninvestigational medicinal product

OS:	overall survival
PPE:	personal protective equipment
PRO:	patient reported outcomes
PS:	performance status
QLQ-BR23:	EORTC QLQ breast cancer specific module
QLQ-C30:	EORTC core quality of life questionnaire
RECIST:	Response Evaluation Criteria in Solid Tumors
SD:	stable disease
SERD:	selective estrogen receptor degrader, selective estrogen receptor degrader
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reaction
TE:	treatment-emergent
TEAE:	treatment-emergent adverse event
UGT:	uridine 5'-diphospho-glucuronosyltransferase

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