1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A randomized, multicenter, double-blind Phase 3 study of Study drug 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:

Study drug plus palbociclib as first line therapy for patients with ER (+)HER2 (-) advanced breast cancer

Rationale:

The purpose of the proposed study is to demonstrate the superiority of a new oral selective estrogen receptor degrader (SERD), study drug, 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.

Overall design:

This is a prospective multicenter, international, randomized, double-blind, double-dummy, Phase 3 trial comparing the efficacy and safety of study drug in combination with palbociclibversus 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 diseasenot 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)adjuvantendocrine 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 boneonly 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 study drug 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 peritonealinvolvement (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 beyondthe 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 treatmentis initiated. In these cases, the investigator must discuss the rationale with the sponsor before thedecision to continue treatment on-study is made.

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 participantsrandomized per treatment arm).

Note: Enrolled participants are all participants from screened participants who have been allocatedto 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: Study drug 200 mg + letrozole-matching placebo + palbociclib125 mg
- Arm B: Placebo + letrozole 2.5 mg + palbociclib125 mg.

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

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

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		D1 (±3)	D15 (±1)	D1 (±3)				
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.

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		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:								
[redacted] matching placebo		Once daily ←→						To be taken with food.

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		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

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		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.

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		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