PROTOCOL

TITLE:	**A PHASE IB/III STUDY OF IPATASERTIB PLUS PALBOCICLIB AND FULVESTRANT VERSUS PLACEBO PLUS PALBOCICLIB AND FULVESTRANT IN HORMONE RECEPTOR POSITIVE AND HER2 NEGATIVE LOCALLY ADVANCED UNRESECTABLE OR METASTATIC BREAST CANCER**
PROTOCOL NUMBER:	CO41012
VERSION NUMBER:	3
EUDRACT NUMBER:	2019-001072-11
IND NUMBER:	133823
NCT NUMBER:	*NCT04060862*
TEST PRODUCT:	Ipatasertib (RO5532961, GDC-0068), palbociclib, fulvestrant
MEDICAL MONITOR:	[redacted] M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	14 March 2019
DATES AMENDED:	Version 2: 14 October 2019 Version 3: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
12-Feb-2020 18:07:25	Company Signatory	[redacted]

PROTOCOL AMENDMENT, VERSION 3:
RATIONALE

Protocol CO41012 has been amended primarily to revise some eligibility criteria especially for the patients in the Phase III portion to ensure a more homogeneous study population, as well as to update the patient-reported outcome (PRO) measures administered in the Phase III portion. Overall changes to the protocol, along with a rationale for each change, are summarized below:

- Relevant clinical data for the combination of an AKT inhibitor with endocrine therapy was added based on the randomized Phase II study FAKTION that investigated the AKT inhibitor capivasertib in combination with fulvestrant (Section 1.1 and Section 3.3.5).
- The Steering Committee (a group of trial investigators who provide scientific and medical guidance for Study CO41012) advised that the specific 5-year timeframe for relapse during endocrine therapy was unnecessary and considered patients with relapse at any time during adjuvant endocrine therapy a relevant study population for this trial with similar poor prognosis. Based on this recommendation, the restriction of relapse specifically during the initial 5 years was removed throughout the protocol (Sections 1.5, 2, 3.1, 4.1.1, and Figure 3).
- For completeness and consistency with other sections, pneumonitis was added to the list of potentially overlapping toxicities that may be exacerbated when combining ipatasertib and palbociclib (Section 1.5).
- The PRO measures and associated endpoints were updated, resulting in changes to the PRO-related secondary and exploratory objectives. The “worst pain” item from the Brief Pain Inventory-Short Form (BPI-SF) was added to better understand the impact of treatment on pain based on regulatory feedback on hormone receptor−positive (HR+) breast cancer studies, while the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Breast Cancer Module 23 (EORTC QLQ-BR23) was added to align with other HR+ Breast Cancer studies (Sections 2.1.2, 2.1.3, 3.3.9, 4.5.10 [and associated subsections], 6.4.2.5, and 6.4.3.3, and Appendices 1, 10, and 12).
- Text in Section 3.1.1 was simplified for consistency with other sections given the updates to the eligibility criteria described below.
- The manufacturer is switching palbociclib from a capsule to a tablet formulation; therefore, drug supply for palbociclib will transition from capsule to tablet during the course of this study and thus the tablet formulation was added in multiple sections (Sections 3.1.1, 3.1.2, 4.3.1.2, and 4.3.2.2). Palbociclib tablets, in contrast to capsules, can be taken with or without food (Section 4.3.2.2).
- Figure 3 was updated to align the key eligibility portion of the study schema with the updated inclusion and exclusion criteria.
- The timeframe of at least 14 days for goserelin or alternative luteinizing hormone releasing hormone (LHRH) agonist therapy in combination with fulvestrant was deemed sufficient by the Steering Committee and thus recommended to facilitate

initiation of study treatment. A recommendation for men to be treated with goserelin or alternative LHRH was added (Sections 3.1.3, 4.1.1, 4.3.2.4, 4.4.1, Appendices 1 and 3).

- Clarification of central laboratory next-generation sequencing (NGS) testing was provided in Sections 3.1.4, 4.1.1, and 4.5.8, and Appendices 1 and 3. Text in the rationale for collection of tissue samples was updated and simplified for consistency with the description of NGS testing in Section 4.5.8 (Section 3.3.7.2).
- The tumor assessment schedule for patients who discontinue study treatment for reasons other than radiographic disease progression was aligned with that prior to study treatment discontinuation based on regulatory feedback (Sections 3.1.5, 4.5.6, and 4.6.1). In addition, the allowed window for tumor assessments and bone scans has been widened to ± 7 days from ± 5 days to facilitate scheduling (Section 4.5.6 and Appendix 1).
- The specific eligibility requirements for HER2 negativity were updated to be more complete within the text of the inclusion criterion and to provide additional clarity and facilitate eligibility determination (Section 4.1.1).
- The requirements for contraceptive methods for men were clarified, distinguishing the requirements if they are surgically sterile and whether the female partner of childbearing potential is pregnant or non-pregnant (Section 4.1.1).
- The eligibility criteria for the Phase III portion were updated to no longer allow prior CDK4/6 inhibitor for locally advanced unresectable or metastatic breast cancer. This update was made to keep the patient population more homogeneous, since efficacy has not been established for sequential CDK4/6 inhibitor therapy (Sections 4.1.1, 4.1.2, and Figure 3).
- The cap of prior CDK4/6 inhibitor for Phase III patients treated in the adjuvant setting remains at 20%, but further clarifications were added to include neoadjuvant treatment and a disease-free interval of at least 12 months after the CDK4/6 inhibitor portion, since sequential treatment with CDK4/6 inhibitors has not been established (Sections 4.1.1 and 4.1.2).
- In the Phase Ib portion, patients who received prior CDK4/6 inhibitor treatment will be allowed based on consultation with the Steering Committee given the pharmacokinetic (PK) and safety objectives but such a patient should have been on the 125-mg dose at the end of their treatment period to ensure that they can tolerate the starting dose given the scope of the Phase Ib (Sections 4.1.1 and 4.1.2).
- An additional exclusion criterion of no more than 1 prior line of endocrine-based therapy for Phase III patients was added for clarity and to maintain a more homogeneous patient population (Section 4.1.2 and Figure 3).
- The HBV-related testing requirements were clarified (Section 4.1.2).
- The exclusion criterion related to hypersensitivity to study treatment was updated for clarification and completeness (Section 4.1.2).
- The stratification factor “prior CDK4/6 inhibitor” was removed given new restrictions on prior CDK4/6 inhibitor in the eligibility criteria. In consultation with the Steering

Committee, it was deemed less meaningful relative to the stratification factor "baseline liver metastasis," which was selected to replace it (Section 4.2).

- Text describing the pharmacy manual was added for completeness (Section 4.3 and associated subsections).
- Clarification was added on taking the dose of ipatasertib/placebo (Section 4.3.2.1) and palbociclib (Section 4.3.2.2) at home on non-clinic visit days based on the 21/7 dose schedule.
- Text related to the medication diary was updated for consistency with other sections in the protocol and for clarification (Sections 4.5.2 and 4.3.2.5).
- Text was added that primary prophylactic use of hematopoietic growth factors is not permitted, but may be considered for treating treatment-emergent events and for secondary prophylaxis (Sections 4.4.1 and 4.4.3).
- Text was added to clarify use of live vaccines (Section 4.4.2).
- Fasting requirements were updated to require fasting also beyond the Cycle 6 Day 1 visit to allow for more consistent characterization in particular of hyperglycemia throughout the entire treatment period given that hyperglycemia is an identified risk with ipatasertib and that laboratory values are regularly analyzed independently of AE terms by health authorities (Section 4.5.8, Appendices 1 and 3).
- Text was added to clarify that re-escalation of palbociclib is not permitted, regardless of the dose level (Section 5.1.4.2).
- Text was updated to clarify that palbociclib local prescribing information may require more rigorous dose adjustments than provided in the corresponding adverse event management guideline tables (Section 5.1.4.5 and associated subsections).
- It was clarified that management guidelines for elevated glucose values $>$ 250 mg/dL apply regardless of fasting status (Section 5.1.4.5.2) and that guidelines for glucose values $>$ 500 mg/dL also apply to patients with life-threatening consequences (Table 4).
- A clarifying footnote was added to the rash management guidance in Table 6 that the Sponsor will monitor the incidence of rash and may advise investigators to consider antihistamine prophylaxis (Section 5.1.4.5.4).
- Guidance for resuming palbociclib for Grade 1 interstitial lung disease/pneumonitis was provided for completeness in Table 7 (Section 5.1.4.5.5).
- In the hematologic toxicity management guidance (Table 9), text related to dose modifications for ipatasertib/placebo and palbociclib was revised to better reflect the safety profile of the 2 study treatments given that neutropenia is included under the Warnings and Precautions for palbociclib (IBRANCE® U.S. Package Insert) and thus palbociclib is considered the primary cause for neutropenia. An additional footnote referencing Sections 5.1.4.1 and 5.1.4.2 (dose modifications for ipatasertib/placebo and palbociclib) was added in Table 9 for clarification (Section 5.1.4.5.7).
- The two back-up Medical Monitors were replaced (Section 5.4.1).

- A clarification was added that after the end of the adverse event reporting period, only patients in the Phase III portion of the study will be followed for long-term survival (Section 5.6).
- A new section was added to describe the implementation of a system to manage the quality of the study (Section 9.3).
- Text was modified to clarify that Roche's global policy on data sharing does not have requirements that must be met before study results can be made available (Section 9.6).
- Text was added throughout the schedules of assessments for clarification and to align with other sections of the protocol (Appendices 1 and 3).
- The schedule of the PRO measures collected for Phase III patients was updated to better reflect the schedule of each of the PRO assessments (Appendix 1).
- The sampling window for post-dose PK samples for Phase III patients on Cycle 1, Day 1 and Cycle 1, Day 15 were updated and aligned with that on Cycle 2, Day 15 so that PK can be compared between cycles more easily (Appendix 2).
- The screening windows for patients in Phase Ib were updated for consistency with the remainder of the protocol (Appendix 3).
- The sampling window for pre-dose PK samples was clarified, and the footnote was updated to provide clarification on the PK sampling timepoints (Appendix 4).
- Samples of the new PRO measures, Brief Pain Inventory-Short Form “worst pain” item (BPI-SF) and the EORTC QLQ-BR23, were added as Appendix 10 and Appendix 12, respectively.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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MEDICAL MONITOR:	[redacted] M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by the Sponsor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE IB/III STUDY OF IPATASERTIB PLUS PALBOCICLIB AND FULVESTRANT VERSUS PLACEBO PLUS PALBOCICLIB AND FULVESTRANT IN HORMONE RECEPTOR POSITIVE AND HER2 NEGATIVE LOCALLY ADVANCED UNRESECTABLE OR METASTATIC BREAST CANCER**
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EUDRACT NUMBER:	2019-001072-11
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TEST PRODUCT:	Ipatasertib (RO5532961, GDC-0068), palbociclib, fulvestrant
PHASE:	III
INDICATION:	HR-positive/HER2-negative locally advanced unresectable or metastatic breast cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

The open-label Phase Ib portion of this study will evaluate the safety and pharmacokinetics of ipatasertib in combination with palbociclib and fulvestrant to identify a dose of ipatasertib that can be combined with palbociclib and fulvestrant in the Phase III portion.

The randomized Phase III portion of this study will evaluate the efficacy, safety, and patient-reported outcome (PRO) objectives of ipatasertib + palbociclib + fulvestrant compared with placebo + palbociclib + fulvestrant in patients with hormone receptor–positive (HR+) human epidermal growth factor receptor 2 negative (HER2-), locally advanced unresectable or metastatic breast cancer who had relapsed during adjuvant endocrine therapy or progressed during the initial 12 months of first-line endocrine therapy in locally advanced unresectable or metastatic breast cancer.

In this protocol, the term "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., ipatasertib/placebo, palbociclib, and fulvestrant). Treatment with placebo only applies to the Phase III portion of this study.

In this study, when describing the different analysis populations and endpoints, Tri-AKT positive (Tri-AKT+) corresponds to the presence of *PIK3CA/AKT1/PTEN* alterations.

Efficacy objectives are applicable for only the randomized Phase III portion of this study as described below.

Primary Efficacy Objective

The primary efficacy objective for the randomized Phase III portion of this study is to evaluate the efficacy of ipatasertib + palbociclib + fulvestrant compared with placebo + palbociclib + fulvestrant on the basis of the following co-primary endpoints:

- Progression-free survival (PFS) in intent-to-treat (ITT) patients, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), or death from any cause, whichever occurs first

- Progression-free survival (PFS) in patients with Tri-AKT+ tumors, as defined by baseline ctDNA, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first

Secondary Efficacy Objective

The secondary efficacy objective for the randomized Phase III portion of this study is to evaluate the efficacy of ipatasertib + palbociclib + fulvestrant compared with placebo + palbociclib + fulvestrant on the basis of the following endpoints both in the ITT population and in patients with Tri-AKT+ tumors, as defined by baseline ctDNA:

- Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1
- Duration of objective response (DOR), defined as the time from the first occurrence of a documented objective response to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first
- Clinical benefit rate (CBR), defined as the proportion of patients who have a CR or PR, or stable disease for at least 24 weeks, as determined by the investigator according to RECIST v1.1
- Overall survival (OS), defined as the time from randomization to death from any cause
- Time to deterioration (TTD) in *severity of* pain, defined as the time from randomization to the first documentation of a 2-point or more increase from baseline *on the "worst pain" item from the Brief Pain Inventory-Short Form (BPI-SF)*
- *TTD in presence and interference of pain, defined as the time from randomization to the first documentation of a 10-point or more increase from baseline in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) pain scale (items 9 and 19)*
- TTD in physical functioning (PF), role functioning (RF), and Global Health *Status* (GHS)/Quality of Life (QoL) defined as the time from randomization to the first documentation of a 10-point or more decrease from baseline in the following scales of the EORTC QLQ-C30: PF, RF, and GHS/QoL

Exploratory Efficacy Objective

The exploratory efficacy objective for the randomized Phase III portion of this study is to evaluate the efficacy of ipatasertib + palbociclib + fulvestrant compared with placebo + palbociclib + fulvestrant on the basis of the following endpoints both in the ITT patients and patients with Tri-AKT+ tumors, as defined by baseline ctDNA:

- Mean and mean changes from baseline scores in all functions (physical, role, cognitive, emotional, and social), GHS/QoL, and disease/ treatment-related symptoms, as measured by the scales of the EORTC QLQ-C30 *and the EORTC Breast Cancer Module 23 Questionnaire (QLQ-BR23)*
- Health utility and visual analog score (VAS) of the European Quality of Life 5-Dimension 5-Level (EQ-5D-5L) questionnaire for pharmacoeconomic modeling
- PFS2, defined as the time from randomization to second occurrence of objective disease progression through the use of RECIST v1.1, or death from any cause, whichever occurs first
- Time to first skeletal–related event (SRE), defined as the time from randomization to the first occurrence of an SRE (an SRE is a pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression)

In addition, this study will evaluate the efficacy of ipatasertib + palbociclib + fulvestrant compared with placebo + palbociclib + fulvestrant on the basis of the following endpoints in patients with Tri-AKT+ tumor tissue and PTEN loss in tumor tissue:

- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first

Safety Objectives

Safety objectives are applicable for both the Phase Ib portion and the randomized Phase III portion of this study. The same endpoints as described below will be used for both portions.

Safety Objective

The safety objective for the Phase Ib portion of this study is to characterize the safety of combining ipatasertib with palbociclib + fulvestrant using endpoints listed below for the Phase III portion.

The safety objective for the randomized Phase III portion of this study is to evaluate the safety of ipatasertib + palbociclib + fulvestrant compared with placebo + palbociclib + fulvestrant in all randomized patients as well as patients with Tri-AKT+ tumors, as defined by baseline circulating tumor DNA (ctDNA), who received at least one dose of study treatment on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

Exploratory Safety Objective

The exploratory safety objective for the randomized Phase III portion of this study is to evaluate patient-reported symptomatic adverse events of ipatasertib + palbociclib + fulvestrant compared with placebo + palbociclib + fulvestrant in all randomized patients who received at least one dose of study treatment, on the basis of the following endpoints:

- Presence, frequency of occurrence, severity, and/or degree of interference with daily function of selected symptomatic treatment toxicities (i.e., diarrhea, nausea, vomiting, decreased appetite, fatigue, mouth sores, and rash symptoms and an additional item regarding the overall bother experienced due to side effects of treatment), as measured by the NCI Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) instrument
- Change from baseline in symptomatic treatment toxicities, as measured by the PRO-CTCAE

Pharmacokinetic Objectives

The pharmacokinetic (PK) objectives are applicable for both the open-label Phase Ib portion and the randomized Phase III portion of this study, unless otherwise specified below. The same endpoints, as described below, will be used for both portions, unless otherwise specified.

The PK objective for the open-label Phase Ib portion is to evaluate the effect of palbociclib, a weak time-dependent inhibitor of CYP3A, on the PK profile of ipatasertib.

The PK objective for the Phase III portion is to characterize the PK profiles of ipatasertib and its metabolite (G-037720) in combination with palbociclib and fulvestrant on the basis of the following endpoint:

- Plasma concentration of ipatasertib and its metabolite, G-037720, at specified timepoints for analysis using population PK methodology

The exploratory PK objectives for this study are as follows:

- To evaluate palbociclib trough concentrations and the effect of ipatasertib on palbociclib exposures in the open-label Phase Ib portion

- To evaluate potential relationships between drug exposure and the efficacy and safety of ipatasertib + palbociclib + fulvestrant in the randomized Phase III portion based on the following endpoints:
  - Relationship between plasma concentration or PK parameters for ipatasertib and efficacy endpoints
  - Relationship between plasma concentration or PK parameters for ipatasertib and safety endpoints

Biomarker Objective

The exploratory biomarker objective for the open-label Phase Ib portion is to evaluate changes in plasma ctDNA levels.

The exploratory biomarker objectives for the randomized Phase III portion of this study are as follows:

- Evaluate the effect of Tri-AKT status in tissue or plasma on treatment benefit to ipatasertib + palbociclib + fulvestrant compared with placebo + palbociclib + fulvestrant
- Identify and evaluate predictive or prognostic biomarkers associated with disease activity status or response to treatment with ipatasertib + palbociclib + fulvestrant
- Identify possible mechanisms of resistance to ipatasertib + palbociclib + fulvestrant through the comparative analysis of potential biomarkers in pretreatment and post-progression biopsy tissue samples and in blood
- Evaluate safety and pharmacodynamics biomarkers that may lead to improved monitoring and to provide evidence of activity of ipatasertib + palbociclib + fulvestrant, respectively
- Evaluate the relationship between tissue-based and blood-based biomarkers and patient clinical features (e.g., baseline features) and outcome (e.g., duration of PFS)
- To increase the knowledge and understanding of disease biology and drug safety on the basis of the following endpoint:
  - Relationship between biomarkers in blood and tumor tissue and efficacy, safety, PK, or other biomarker endpoints including biomarker relevant therapies in development

Study Design

Description of Study

Study CO41012 is a Phase III, randomized, multicenter, international, double-blind, placebo-controlled clinical study with an initial open-label, Phase Ib, safety portion. The open-label Phase Ib portion is intended to evaluate the safety of the triplet combination and to further characterize the potential drug-drug interaction between ipatasertib and palbociclib and to determine the ipatasertib dose to be combined with palbociclib and fulvestrant. The randomized Phase III portion is designed to compare the efficacy, as measured by PFS, and safety of ipatasertib + palbociclib + fulvestrant with that of placebo + palbociclib + fulvestrant in patients with HR+ HER2- locally advanced unresectable or metastatic breast cancer who relapsed during adjuvant endocrine therapy or progressed during the initial 12 months of first-line endocrine therapy in locally advanced unresectable or metastatic breast cancer.

Open-label Phase Ib Portion

Patients in the open-label Phase Ib portion are required to fulfill the same eligibility criteria as those in the randomized Phase III portion *unless otherwise specified.* Approximately 10 patients will initially be treated with a starting dose of 300 mg ipatasertib for 5-7 days as a single agent before palbociclib and fulvestrant will be started on Cycle 1, Day 1 (see additional details on the dose schedule below). All patients will be followed to at least Cycle 2, Day 15 before the initial safety review will be triggered. PK samples will be collected up to Cycle 3, Day 15 and results will be included where available at the time of the safety review. If multiple patients come off prior to Cycle 2, Day 15 for reasons other than toxicity, the Sponsor may elect to replace the patients. The internal safety review will be conducted by the Sponsor and will include members of the study team including, but not limited to, the study Medical Monitor, Safety Scientist, and Clinical Pharmacologist. Further enrollment will be halted until after the internal safety review has been completed and a recommendation has been made to either

expand the original cohort or explore an alternative ipatasertib dose, if warranted. In particular, if based on internal safety review, the 300 mg ipatasertib dose is comparable to the target 400-mg dose based on PK data and provides acceptable tolerability relative to historical data in ipatasertib clinical studies taking into consideration the palbociclib safety profile, the 300-mg dose cohort will be expanded further by approximately 5–10 patients. These additional patients may be able to start all three study drugs on Cycle 1, Day 1 if warranted by the initial PK data. On the other hand, if the 300-mg dose results in unacceptable toxicity, and if ipatasertib exposure is considerably above the target 400-mg dose equivalent, a lower dose will be explored. Depending on the safety and PK data, the Sponsor may also further explore the 400 mg starting dose used in other ipatasertib studies. For the second dose level, safety and PK data for up to 10 patients is expected to be sufficient to support the dose decision; however, the Sponsor may expand enrollment by approximately 5–10 patients if deemed necessary based on internal safety review.

Patients will start with a 5–7 day run-in of single-agent ipatasertib (300-mg tablet dose once daily [QD]) prior to Cycle 1, Day 1. The single-agent run-in will allow ipatasertib to reach steady-state on Cycle 1, Day 1 and enable characterization of the potential drug-drug interaction between ipatasertib and palbociclib. For the first cycle, ipatasertib will be administered continuously for 26–28 days given the Day -7 to Day -5 window for the initial single-agent ipatasertib run-in; however, starting with Cycle 2, Day 1 ipatasertib will be taken orally (PO) QD on Days 1–21 of each 28-day cycle.

Starting on Cycle 1, Day 1, palbociclib 125 mg (capsule*/tablet*) will be taken PO QD on Days 1–21 of each 28-day cycle. Fulvestrant 500 mg will be administered by intramuscular (IM) injection on Cycle 1, Days 1 and 15 and then on Day 1 of each subsequent 28-day cycle.

Randomized Phase III Portion

Enrollment to the randomized Phase III portion will be initiated only after the Sponsor has confirmed a dose of ipatasertib that can be combined with palbociclib and fulvestrant based on the internal safety review of the Phase Ib data. If no appropriate dose can be identified, for example if the combination is associated with high discontinuation rates due to unacceptable toxicity, the Phase III portion will not be initiated.

In the Phase III portion, approximately 340 patients will be randomized in a 1:1 ratio to either ipatasertib + palbociclib + fulvestrant or placebo + palbociclib + fulvestrant.

- **Ipatasertib Arm**: Ipatasertib tablet dose taken PO QD on Days 1–21 of each 28-day cycle beginning at Cycle 1, Day 1 and palbociclib 125-mg capsule*/tablet* dose taken PO QD on Days 1–21 of each 28-day cycle beginning at Cycle 1, Day 1 and fulvestrant 500 mg administered by IM injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28-day cycle. The ipatasertib dose will be established in the Phase Ib portion.
- **Control Arm**: Placebo taken PO QD on Days 1–21 of each 28-day cycle beginning at Cycle 1, Day 1 and palbociclib 125-mg capsule*/tablet* dose taken PO QD on Days 1–21 of each 28-day cycle beginning at Cycle 1, Day 1 and fulvestrant 500 mg administered by IM injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28-day cycle

Goserelin Treatment in Pre- and Peri-menopausal Women *and Men*

In both portions of the trial, pre- or peri-menopausal women must have started treatment with goserelin or an alternative luteinizing hormone releasing hormone (LHRH) agonist at least *14* days prior to first dose of study treatment. If patients have received an alternative LHRH agonist prior to study entry, it is recommended that they switch to goserelin for the duration of the trial, whenever possible. *For men, treatment with goserelin or alternative LHRH agonist therapy is recommended beginning at least 14 days prior to first dose of study treatment and continuing for the duration of study treatment.*

Key Study Parameters

Prior to enrollment but after signing the informed consent form, patients enrolled in the Phase III portion will have the Tri-AKT ctDNA test done by the central laboratory next *generation* sequencing (NGS) assay within 6 weeks of first dose of study treatment. For patients enrolled in the Phase Ib portion, the test may be performed after enrollment. A valid result (Phase III only) will be required for patient stratification and therefore patients whose ctDNA samples have invalid test results will not be permitted to enroll in the Phase III portion of the study.

Patients must have measurable disease per RECIST v1.1. Primary endpoint is investigator-assessed PFS *(Phase III). Tumor assessments will be conducted as outlined in the schedule of assessments.*

Number of Patients

Approximately 370 patients with HR+ HER2- locally advanced unresectable or metastatic breast cancer will be enrolled overall in this study in both the Phase Ib and the global enrollment portion of the Phase III. After completion of the global enrollment phase, additional patients may be enrolled in an extended China enrollment phase.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Histologically documented HR+ HER2- adenocarcinoma of the breast that is locally advanced or metastatic and is not amenable to surgical or local therapy with curative intent
- Documented *estrogen receptor* and/or progesterone receptor positivity defined as ≥ 1% of tumor cell nuclei immunoreactive to the respective hormonal receptor based on most recent evaluable tumor biopsy as assessed locally
- Documented HER2- as assessed locally based on most recent evaluable tumor biopsy defined as immunohistochemistry *(IHC)* score 0/1+ or *an IHC score of 2+ accompanied* by *a* negative *fluorescence, chromogenic, or silver* in situ hybridization (FISH/CISH/SISH) *indicating the absence of HER2 gene amplification, or a HER2/CEP17 ratio of < 2.0*
- Either male

  OR
- Postmenopausal, defined as:
  - Age ≥ 60 years -OR-
  - Age < 60 years AND have undergone bilateral oophorectomy, medically confirmed ovarian failure -OR-
  - Age < 60 years AND have had cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have serum levels of estradiol and follicle-stimulating hormone within the laboratory's reference range for postmenopausal females

  OR
- Pre- or peri-menopausal and amenable to being treated with the LHRH agonist goserelin

  Patients must have started treatment with goserelin or an alternative LHRH agonist at least *14* days prior to first dose of study treatment. If patients have received an alternative LHRH agonist prior to study entry, it is recommended that they switch to goserelin for the duration of the trial, whenever possible.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs as defined below:

  Women must remain abstinent or use non-hormonal contraceptive methods with a failure rate of < 1% per year during the treatment period and for 90 days after the final dose of study treatment (or longer if required per the local prescribing information).

  Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery

(i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

Examples of non-hormonal contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, and copper intrauterine devices.

Hormonal contraceptive methods may be used in accordance with specific country and local requirements for patients with breast cancer.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a *contraceptive methods*, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential *who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of* < *1% per year during the treatment period and for 6 months after the final dose of study treatment (or longer if required per the local prescribing information). Men must refrain from donating sperm during this same period.*

  With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for *90 days* after the final dose of study treatment *(or longer if required per the local prescribing information)* to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure. If required per local guidelines or regulations, *locally recognized adequate methods of contraception and* information about the reliability of abstinence will be described in the local Informed Consent Form.

- Patients must have experienced radiologic/objective relapse <u>during</u> adjuvant endocrine therapy or radiologic/objective disease progression <u>during</u> the initial 12 months of first-line (1L) endocrine therapy in locally advanced unresectable or metastatic breast cancer

  Up to 20% of patients enrolled in the Phase III portion may have received a CDK4/6 inhibitor as part of their *neoadjuvant/*adjuvant endocrine therapy.

  If a CDK4/6 inhibitor *was included* as part of *a neoadjuvant/adjuvant* therapy*, relapse must be ≥ 12 months since completion of the CDK4/6 inhibitor portion of the neoadjuvant/adjuvant therapy.*

  <u>Phase III portion only</u>: Prior CDK4/6 inhibitor is not permitted for locally advanced unresectable or metastatic breast cancer.

  <u>Phase Ib portion only</u>: Prior CDK4/6 inhibitor is permitted and if previously treated with palbociclib, patient should have been on the 125-mg dose at the end of their palbociclib treatment period.

- Radiologic/objective evidence of recurrence or progression to the most recent systemic therapy for breast cancer
- Patients for whom endocrine-based therapy (e.g., palbociclib and fulvestrant) is recommended and treatment with cytotoxic chemotherapy is not indicated at time of entry into the study, as per national or local treatment guidelines.
- At least one measurable lesion via RECIST v1.1

  Patients with <u>bone only</u> disease are <u>not</u> eligible even if a bone lesion qualifies as a measurable lesion.

Bone lesions are generally followed as non-target lesions. However, lytic bone lesions or mixed lytic–blastic lesions (unless previously irradiated), with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) may be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions, however, are non-measurable.

Previously irradiated lesions (other than bone) may be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.

- Have adequate organ and marrow function as defined below:
  - ANC $\geq$ 1500 cells/μL
  - Hemoglobin $\geq$ 9 g/dL
  - Platelet count $\geq$ 100,000/μL
  - AST and ALT $\leq$ 2.5 $\times$ upper limit of normal (ULN); with the following exception:

    Patients with liver or bone metastases may have AST and ALT $\leq$ 5 $\times$ ULN.
  - Alkaline phosphatase $\leq$ 2 $\times$ ULN ($\leq$ 5 $\times$ ULN if liver metastases present; $\leq$ 7 $\times$ ULN if bone metastases present)
  - Total bilirubin $\leq$ 1.5 $\times$ ULN ($\leq$ 3 x ULN if hyperbilirubinemia is due to Gilbert's syndrome)
  - Serum albumin $\geq$ 3.0 g/dL
  - Serum creatinine $\leq$ 1.5 $\times$ ULN or creatinine clearance $\geq$ 50 mL/min as calculated using the method standard for the institution
  - Fasting glucose $\leq$ 150 mg/dL and hemoglobin A1c (HbA1c) $\leq$ 7.5%
  - PTT (or aPTT) and INR $\leq$ 1.5 $\times$ ULN (except for patients receiving anticoagulation therapy)

    Patients receiving heparin treatment should have a PTT (or aPTT) between 1.5 and 2.5 $\times$ ULN (or patient value before starting heparin treatment). Patients receiving coumarin derivatives should have an INR between 2.0 and 3.0 assessed in two consecutive measurements 1 to 4 days apart.
- Life expectancy $>$ 6 months
- Resolved or stabilized toxicities resulting from previous therapy to grade 1

  An ongoing Grade 2 non-hematologic toxicity related to the most recent treatment regimen may be permitted with approval from the Sponsor based on consultation with the Medical Monitor (ongoing toxicities alopecia, neuropathy, and hot flashes do not require Sponsor approval)
- Phase III portion only: Consent to provide tumor specimen from the most recently collected, available tumor tissue (formalin-fixed, paraffin-embedded [FFPE] block [preferred] or a minimum of 12 slides containing unstained, freshly cut, serial sections)

  Cytologic or fine-needle aspiration samples and tumor tissue from bone metastases are not acceptable. Alternatively, a newly collected tumor tissue sample may be provided.
- Phase III portion only: Valid Tri-AKT ctDNA test result by *the central laboratory* NGS assay within 6 weeks prior to enrollment
- For patients enrolled in the China extension portion (if opened) of the Phase III: current resident of mainland China, Hong Kong, or Taiwan, and of Chinese ancestry

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 90 days after the final dose of study treatment (or longer if required per the local prescribing information).

Women of childbearing potential must have a negative serum pregnancy test result within 96 hours of first dose of study treatment. Alternatively, if a negative serum pregnancy test was obtained within 7 days of first dose of study treatment, it needs to be confirmed by a negative urine pregnancy test on the day of the first administration of study treatment prior to dosing.

- Prior treatment with fulvestrant or other SERDs, regardless of treatment setting
- Prior treatment with PI3K inhibitor (such as alpelisib, taselisib, or buparlisib), mTOR inhibitor (such as everolimus) or AKT inhibitor (such as ipatasertib or capivasertib), regardless of treatment setting
- Phase I*II-portion* only: Prior treatment with CDK4/6 inhibitor *for locally advanced unresectable or metastatic breast cancer*
- Concurrent hormone replacement therapy
- Prior treatment with a cytotoxic chemotherapy regimen for metastatic breast cancer

  Note: there is no restriction on the number of prior cytotoxic chemotherapy regimens in the neoadjuvant or adjuvant setting
- *Phase III portion only: No more than one prior line of endocrine-based therapy for locally advanced unresectable or metastatic breast cancer*
- Treatment with approved or investigational cancer therapy within 14 days prior to first dose of study treatment

  Local radiotherapy with palliative intent to non-target sites may be allowed within 14 days prior to first dose of study treatment if not feasible earlier and if discussed with the Medical Monitor (however, once irradiated, bone lesions are generally no longer evaluable).
- History of or known presence of brain or spinal cord metastases

  Patients with leptomeningeal carcinomatosis will be excluded.
- Uncontrolled pleural effusion, pericardial effusion, or ascites, as judged by the investigator
- Uncontrolled tumor-related pain, as judged by the investigator

  Patients requiring narcotic pain medication must be on a relatively stable regimen at study entry.

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to first dose of study treatment.

  Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to first dose of study treatment (however, once irradiated, lesions are generally no longer evaluable)
- Uncontrolled hypercalcemia or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy

  Patients who are receiving bisphosphonate therapy specifically to prevent/treat skeletal events (e.g., bone metastasis, osteoporosis) and who do not have a history of clinically significant hypercalcemia are eligible.
- Non–study-related minor surgical procedures $\leq$ 5 days or major (invasive) surgical procedure $\leq$ 14 days prior to first dose of study treatment.

  Patient must have sufficiently recovered from surgery and be stable, and wound healing must have occurred.
- History of Type I or Type II diabetes mellitus requiring insulin

  Patients who are on a stable dose of oral diabetes medication $\geq$ 2 weeks prior to initiation of study treatment are eligible for enrollment. Patients must meet the

laboratory eligibility criteria for fasting blood glucose and HbA1c as outlined in the inclusion criteria.

- History of or active inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis) or active bowel inflammation (e.g., diverticulitis)
- Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia)
- Grade $\geq$ 2 uncontrolled or untreated hypercholesterolemia or hypertriglyceridemia
- Patients with active (chronic or acute) hepatitis C virus (HCV) at screening

  Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

  Patients receiving anti-viral therapy for HCV are not eligible
- Hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test or a positive quantitative HBV DNA test at screening

  If a patient has a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test, a quantitative HBV DNA test must be *negative to be eligible*.

  Patients receiving anti-viral therapy for HBV are not eligible.
- Known HIV infection
- Illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment
- Active infection requiring systemic anti-microbial treatment (including antibiotics, anti-fungals, and anti-viral agents)
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that, in the investigator's opinion, gives reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
- History of malignancy other than breast cancer within 5 years prior to screening with the following exceptions:
  - Appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer,
  - Other malignancies where the patient has undergone potentially curative therapy with no evidence of disease and are deemed by the treating physician to have a recurrence rate of $<$5% at 5 years.
- History of clinically significant cardiovascular dysfunction, including the following:
  - History of stroke or transient ischemic attack within 6 months prior to first dose of study treatment
  - History of myocardial infarction within 6 months prior to first dose of study treatment
  - New York Heart Association Class III or IV cardiac disease
  - Unstable arrhythmias, active ventricular arrhythmia requiring medication, or unstable angina
  - Congenital long QT syndrome or screening QT interval corrected using Fridericia's formula (QTcF) $>$480 milliseconds based on the mean value of the triplicate ECGs
  - History or presence of an abnormal ECG that is clinically significant in the investigator's opinion (including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction)
- Presence of any other condition that may have increased the risk associated with study participation or may have interfered with the interpretation of study results, and, in the opinion of the investigator, would have made the patient inappropriate for entry into the study.

- Need for chronic corticosteroid therapy of ≥ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease
- Treatment with strong CYP3A inhibitors or strong CYP3A inducers within 14 days or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment
- Malabsorption syndrome or other condition that would interfere with enteral absorption
- Inability or unwillingness to swallow pills or receive intramuscular injections
- Known or possible hypersensitivity to *any of the study treatments, or to* goserelin or alternative LHRH agonist (if applicable), *including* any excipients

End of Study

The end of this study is defined as the date when the last patient last visit occurs (i.e., the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later). In addition, the Sponsor may decide to terminate the study or OS follow-up at any time.

Length of Study

Provided the Phase III portion is initiated, the total length of the global study, from screening of the first patient to the end of the study, is expected to be approximately 64 months.

Investigational Medicinal Products

Test Product (Investigational Drug)

The investigational medicinal products (IMPs) for this study are ipatasertib (RO5532961) or its placebo (in the randomized Phase III portion of the study), palbociclib, and fulvestrant.

Ipatasertib and Placebo

For patients enrolled in the Phase Ib portion only, 300 mg ipatasertib will be open label and will be administered PO QD in the clinic on Day -7 to Day -5, on Cycle 1 Day 1, on each subsequent cycle visit, and will be taken at home on non-clinic visit days *based on the 21/7 dose schedule*. Ipatasertib will be administered approximately 6 hours prior to palbociclib and fulvestrant to enable collection of post-dose samples, that is, palbociclib and fulvestrant will be administered after the PK sampling of ipatasertib for Cycle 1, Day 1 is completed. Starting from Cycle 1, Day 2, palbociclib will be given together with ipatasertib. For the first cycle, ipatasertib will be administered continuously for 26 to 28 days given the Day -7 to Day -5 window for the start of the single-agent ipatasertib run-in; however, starting with Cycle 2, Day 1 ipatasertib will be taken orally once daily on Days 1–21 of each 28-day cycle.

In the randomized Phase III portion of the study, ipatasertib/placebo is given orally QD on Days 1–21 of each 28-day cycle at the dose confirmed in the Phase Ib portion. Ipatasertib/placebo will be administered in the clinic on Cycle 1 Day 1 and on each subsequent cycle visit; it will be taken at home on non-clinic visit days *based on the 21/7 dose schedule*.

Palbociclib

In both open-label Phase Ib and the randomized Phase III portion of this study, palbociclib is given PO QD on Days 1–21 of each 28-day cycle. Palbociclib will be administered in the clinic on Cycle 1 Day 1 and each subsequent cycle visit and will be taken at home on non-clinic visit days *based on the 21/7 dose schedule*. Palbociclib should be taken at approximately the same time each day. Palbociclib capsules are taken with food to reduce the intersubject variability of palbociclib exposure (IBRANCE® U.S. Package Insert). *Palbociclib tablets, in contrast, may be taken with or without food (refer to the local prescribing information for additional details).*

Fulvestrant

Fulvestrant 500 mg will be administered in the clinic as two intramuscular injections of 250 mg each on Cycle 1 Days 1 and 15 and Day 1 of each subsequent 28-day cycle. Refer to the local prescribing information for more details.

For patients enrolled in the Phase Ib portion, it is recommended that fulvestrant be administered prior to the oral medications, ipatasertib and palbociclib, during all clinic visits following Cycle 1, Day 1. In contrast, on Cycle 1, Day 1, ipatasertib is administered first. For patients enrolled in

the Phase III portion, it is recommended that fulvestrant be administered prior to the oral medications, ipatasertib/placebo and palbociclib, during all clinic visits.

Non-Investigational Medicinal Products

Goserelin is a non-IMP in this study for pre- or peri-menopausal women who must have started treatment with goserelin or an alternative LHRH agonist at least *14* days prior to first dose of study treatment. *For men, treatment with goserelin or alternative LHRH agonist therapy is recommended beginning at least 14 days prior to first dose of study treatment and continuing for the duration of study treatment.* If patients have received an alternative LHRH agonist prior to study entry, it is recommended that they switch to goserelin for the duration of the trial, whenever possible. Every effort should be made to administer goserelin or alternative LHRH agonist as applicable on site at the time of fulvestrant administration *as applicable* in order to minimize the number of clinic visits. Patients may self-administer goserelin or alternative LHRH agonist as applicable at home per local standard of care if the administration does not coincide with a clinic visit. In that case, patients will complete a diary.

Loperamide is a non-IMP in this study. All patients should receive loperamide (2 mg PO twice a day [BID] or 4 mg QD) as prophylaxis for diarrhea upon start of study treatment through the first cycle if allowed by local guidance. Investigators are encouraged to continue this dosing for the remainder of the study; the prophylaxis dose may be adjusted as necessary, using their discretion based on clinical judgment and per local guidance.

Statistical Methods

Primary Analysis

The primary analysis of co-primary endpoint of PFS will take place when approximately 98 PFS events have occurred in patients with Tri-AKT+ tumors, as defined by baseline ctDNA and approximately 180 PFS events have occurred in ITT patients, whichever occurs later, on the basis of the following assumptions:

- 1:1 randomization ratio
- Two-sided significance level of 4% and at least 80% power for testing PFS in patients with Tri-AKT+ tumors, as defined by baseline ctDNA where median PFS is 10 months in the placebo + palbociclib + fulvestrant arm and 18 months in the ipatasertib + palbociclib + fulvestrant arm (hazard ratio = 0.56)
- Two-sided significance level of 1% and at least 80% power for testing PFS in ITT patients where median PFS is 12 months in the placebo + palbociclib + fulvestrant arm and 20 months in the ipatasertib + palbociclib + fulvestrant arm (hazard ratio = 0.60)
- An annual loss-to-follow-up rate of 5% for both arms
- No interim analysis of PFS

The enrollment duration is projected to be approximately 14 months from the first patient enrolled in the randomized Phase III portion of the study. With these assumptions, the analysis of the co-primary endpoint of PFS is projected to occur approximately 40 months after the first patient enrolled in the randomized Phase III portion of the study. In patients with Tri-AKT+ tumors, as defined by baseline ctDNA, it is projected that the largest HR deemed to be statistically significant at 4% level will be approximately 0.66 (with median PFS improvement from 10 months to 15.2 months). In ITT patients, it is predicted that there will be approximately 201 PFS events which allows for approximately 85% power for testing the assumed median PFS improvement from 12 to 20 months, and the projected largest HR deemed to be statistically significant at 1% level will be approximately 0.70 (with median PFS improvement from 12 months to 17.2 months).

Determination of Sample Size

This is a Phase III, randomized, multicenter, international, double blind, placebo controlled clinical study with an initial open-label Phase Ib portion. In the randomized portion of the study, approximately 340 patients will be enrolled and randomized in a 1:1 ratio to the experimental arm (ipatasertib + palbociclib + fulvestrant) and control arm (placebo + palbociclib + fulvestrant), including approximately 153 patients with Tri-AKT+ tumors, as defined by baseline ctDNA, assuming a prevalence rate of 45% for Tri-AKT+ status.

Interim Analyses

This study includes an initial open-label Phase Ib safety portion with internal Safety Review.

An external iDMC will be formed to evaluate safety data during the randomized Phase III portion of the study approximately every 6 months from the first patient randomized until the time of the primary analysis of PFS. The Sponsor will be blinded until the PFS primary analysis.

In the absence of extenuating circumstances, accrual will not be halted during the randomized Phase III portion of the study while the interim safety analysis is conducted. An iDCC will prepare all summaries and analyses for the iDMC's review. The safety summaries will include but not limit to demographic data, adverse events, serious adverse events, and relevant laboratory data. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. Any outcomes of the iDMC's reviews on the safety and benefit-risk balance that affect study conduct will be communicated in a timely manner to the investigators for notification of IRB/ECs and competent authorities as required. A detailed plan will be included in the iDMC Charter.

Following the data review, the iDMC will provide a recommendation to the Sponsor whether to continue the study, amend the protocol, or stop the study. The final decision will rest with the Sponsor. In addition, the Sponsor may request ad-hoc meetings of the iDMC at any time during the study to review ongoing safety summary data.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
1L	first line
2L	second line
AESI	adverse event of special interest
AI	aromatase inhibitor
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AUC	area under the concentration-time curve
AUC_{0-t}	AUC from hour 0 to the last measureable concentration
BID	twice daily
BPI-SF	*Brief Pain Inventory-Short Form*
CAP	*College of American Pathologists*
C_{max}	maximum concentration
CBR	clinical benefit rate
CR	complete response
CRF	Case Report Form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DOR	duration of objective response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC QLQ-BR23	*European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Breast Cancer Module 23*
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30
EQ-5D-5L	European Quality of Life 5Dimension, 5-Level questionnaire
ER	estrogen receptor
ER+	estrogen receptor positive
ESMO	European Society of Medical Oncology
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GHS	Global Health *Status*

Abbreviation	Definition
HbA1c	glycosylated hemoglobin
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2-	human epidermal growth factor receptor 2 negative
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
HR+	hormone receptor positive
ICH	International Council for Harmonisation
iDMC	Independent Data Monitoring Committee
iDCC	Independent Data Coordinating Center
IHC	immunohistochemistry
IM	intramuscular
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous
IxRS	interactive voice/web response system
LHRH	luteinizing hormone releasing hormone
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
mPFS	median progression-free survival
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NGS	next-generation sequencing
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PF	physical functioning
PFS	progression-free survival
PK	pharmacokinetic
PO	orally

Abbreviation	Definition
popPK	population PK
PR	partial response
PRO	patient-reported outcome
PTT	partial thromboplastin time
QD	once daily
RANKL	receptor activator of nuclear factor kappa-B ligand
RBR	Research Biosample Repository
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RF	role functioning
rPFS	radiographic progression-free survival
SAP	Statistical Analysis Plan
SERD	selective estrogen receptor down-regulator
SmPC	Summary of Product Characteristics
SOA	schedule of assessments
SOC	standard of care
SRE	skeletal-related event
t_{max}	time to C_{max}
TNBC	triple negative breast cancer
TTD	time to deterioration
ULN	upper limit of normal
VAS	visual analog scale
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON HR+ BREAST CANCER

Breast cancer is the most frequent cancer diagnosed in women, with an estimated global incidence of 2.09 million new cases reported in 2018 (Bray et al. 2018). Breast cancer accounts for approximately 7% (approximately 626,679 cases) of all cancer deaths. Breast cancer mortality rates differ by geographical region, with more favorable survival rates observed in more developed regions of the world (Bray et al. 2018).

Hormone receptor–positive (HR+) human epidermal growth factor receptor 2 negative (HER2-) breast cancer accounts for approximately 70% of all breast cancer subtypes (Fedele et al. 2018).

Endocrine therapy, alone or in combination with targeted therapy, is recommended for HR+ HER2- advanced or metastatic breast cancer according to the European Society of Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network guidelines, unless in visceral crisis when chemotherapy is indicated (Ngan 2018). Monotherapy of selective estrogen receptor modulator, selective estrogen receptor down-regulator (SERD), or aromatase inhibitor (AI), or more recently their combination with targeted therapy, have been the mainstay treatment options as first-line (1L) therapy for most patients. Mechanisms that can lead to primary and/or secondary endocrine resistance in HR+ breast cancer include a decrease or loss of hormone receptor expression, mutations in the gene that encodes estrogen receptor (ESR1), or an upregulation of growth factor signaling pathways, such as the epidermal growth factor receptor or HER2, the MAPK, or the PI3K/AKT/mTOR pathways (Johnston et al. 2009; Musgrove and Sutherland 2009; Robinson et al. 2013; Toy et al. 2013; Jeselsohn et al. 2014).

PIK3CA/AKT1/PTEN-altered tumors are frequently observed in breast cancer, and are reported in approximately 50% of HR+ HER2- breast cancers (Cancer Genome Atlas Network 2012). Hyperactivation of the PI3K/AKT/mTOR signaling pathway was shown to promote both *de novo* and acquired resistance to hormone therapy in estrogen receptor (ER) positive (ER+) breast cancer cell lines and xenograft models (Sabnis et al. 2007). Simultaneous blocking of the PI3K/AKT/mTOR pathway with everolimus and the ER pathway with letrozole enhances anti-tumor activity more than either agent alone (Boulay et al. 2005). A baseline protein signature of PI3K activation was found to be predictive of a poor prognosis after adjuvant endocrine therapy (Miller et al. 2010). These nonclinical data provided support to the hypothesis that blocking PI3K/AKT/mTOR pathway signaling may have a therapeutic benefit in patients with ER+ HER2- breast cancer.

In the clinical setting, results from the BOLERO-2 trial, which investigated the combination of exemestane and everolimus, an mTOR inhibitor, led to regulatory approval of everolimus (Baselga et al. 2012). This study compared everolimus and

exemestane with placebo and exemestane in postmenopausal patients with ER+ advanced breast cancer who had recurrence or progression of disease while receiving previous therapy with a nonsteroidal AI in the adjuvant setting and/or in advanced disease. Median progression-free survival (PFS) in the everolimus group was 6.9 months, compared with 2.8 months in the placebo group. The hazard ratio (HR) for PFS by investigator assessment was 0.43; $p < 0.001$.

Furthermore, in the randomized, double-blind, placebo-controlled, Phase II study PrE0102 (Kornblum et al. 2018) in postmenopausal women with ER+ HER2-, AI-resistant, metastatic breast cancer, the addition of everolimus to fulvestrant improved the median PFS (mPFS) from 5.1 to 10.3 months (HR = 0.61, stratified log-rank $p = 0.02$).

Several PI3K inhibitors have been combined with fulvestrant showing promising activity in Phase III studies in patients with ER+ HER2- advanced breast cancer who had progressed on or after an AI. In the Phase III BELLE-2 study, buparlisib (a pan-PI3K inhibitor) when combined with fulvestrant resulted in mPFS of 6.9 months versus 5.0 months in the placebo group (HR 0.78; one-sided $p = 0.00021$) in unselected patients (Baselga et al. 2017). In an exploratory analysis of patients with *PIK3CA*-mutant tumor by circulating tumor DNA (ctDNA), mPFS was 7.0 months in the buparlisib group versus 3.2 months in the placebo group (HR 0.58; one-sided $p = 0.001$).

In the Phase III study SANDPIPER, the addition of taselisib (a beta-sparing PI3K inhibitor) to fulvestrant showed a statistically significant improvement in investigator-assessed PFS in patients with *PIK3CA*-mutant tumors who comprised the primary endpoint population. Median PFS increased from 5.4 months in the placebo arm to 7.4 months in the taselisib arm (HR = 0.70, p-value = 0.0037) (Baselga et al. 2018). The study also enrolled a smaller cohort of patients without detectable *PIK3CA*-mutant tumors for exploratory analyses of PFS. Although the study was not powered to compare the two cohorts, the HR for PFS was similar in patients without detectable *PIK3CA*-mutant tumors and those with *PIK3CA*-mutant tumors based on an exploratory analysis. Thus, a treatment effect of taselisib and fulvestrant in patients without detectable PIK3CA mutations could not be completely ruled out.

Recently, in the Phase III study SOLAR-1, the addition of alpelisib (an alpha selective PI3K inhibitor) to fulvestrant showed a statistically significant improvement in investigator-assessed PFS in patients with *PIK3CA*-mutant tumors. Median PFS increased from 5.7 months in the placebo arm to 11 months in the alpelisib arm (HR = 0.65, p-value = 0.00065) (André et al. 2018). Based on the exploratory analysis, patients without detectable *PIK3CA*-mutant tumors did not seem to benefit from the addition of alpelisib to fulvestrant.

Recently, an investigator-led, double-blind, placebo-controlled, randomized Phase II trial (FAKTION) evaluated the addition of the AKT inhibitor capivasertib to fulvestrant in postmenopausal women with ER+ HER2– breast cancer after relapse or

disease progression on an AI (Jones et al. 2019). There were 140 patients-randomized to fulvestrant plus capivasertib (n=69) or fulvestrant plus placebo (n=71). In the biomarker unselected intent-to-treat (ITT) population, median PFS was 10.3 months for patients in the capivasertib arm compared to 4.8 months in the placebo arm (adjusted HR 0.57, two-sided p=0.0035). The HR for patients with or without PI3K/AKT pathway activation was similar. As seen with the mTOR inhibitor everolimus in the BOLERO-2 study, treatment benefit with an AKT inhibitor in combination with endocrine therapy seemed to also be independent of PI3K/AKT pathway activation.

Aside from everolimus and more recently alpelisib that have shown meaningful clinical activity when given in combination with endocrine therapy, CDK4/6 inhibitors have been approved as both 1L and second-line (2L) treatments in HR+ HER2- patients. Three CDK4/6 inhibitors are now in widespread clinical use: palbociclib, ribociclib, and abemaciclib. They have been shown to significantly improve PFS over endocrine therapy alone (Finn et al. 2015; Cristofanilli et al. 2016; Hortobagyi et al. 2016; Sledge et al. 2017; Goetz et al. 2017) and have very similar therapeutic efficacy with slight differences in dosing schedule and toxicity (Spring et al, 2017; Petrelli et al. 2019). Aside from abemaciclib, these agents are approved for use only in combination with endocrine agents – typically with an AI in the first-line setting and fulvestrant in AI-resistant patients. See Section 1.3 for additional details on palbociclib. Mechanisms of acquired resistance to CDK4/6 inhibitors are beginning to be elucidated (O'Leary et al. 2018). While the benefit of adding CDK4/6 inhibition to endocrine therapy is independent of *PIK3CA* mutation status, shorter survival has been observed in patients with PIK3CA mutations detectable in ctDNA (Turner et al. 2018). Additional ctDNA analysis of the PALOMA-3 study showed a median PFS of 5.8 months (95% CI 5.3-9.5) in patients with detectable *PIK3CA* mutations versus patients with no detectable mutations at 9.2 months (95% CI 7.5-10.8) (Cristofanilli et al. 2016).

Despite the multiple advances in improving the clinical benefit of endocrine therapy, many patients have poor response to these combinations due to highly endocrine resistant or refractory disease. These patients rapidly progress to require chemotherapy treatment and develop significant morbidity and mortality associated with treatment and progression of metastatic disease.

1.2 BACKGROUND ON IPATASERTIB

Ipatasertib is a potent, highly selective, small-molecule inhibitor of all three isoforms of the serine/threonine kinase *AKT*. Ipatasertib is being developed by Genentech/Roche as a single agent and in combination with other therapies for the treatment of cancers in which activation of the PI3K-AKT-mTOR pathway may be relevant for tumor growth or therapeutic resistance.

In nonclinical models with high levels of phosphorylated AKT or PI3K-AKT pathway activity (i.e., *PIK3CA* mutation, *PTEN* alterations), sensitivity to ipatasertib has been observed across different tumor models, including breast cancers (Lin et al. 2013).

In vivo efficacy studies support the use of ipatasertib as a single agent or in combination with chemotherapeutic, hormonal, or targeted agents for the treatment of patients with advanced or metastatic solid tumors (Lin et al. 2013).

Clinical studies in a variety of tumor types have been conducted with ipatasertib both as monotherapy and in combination. Combination partners have included hormonal therapies (i.e., abiraterone and enzalutamide), chemotherapy, and immunotherapy. Randomized studies with ipatasertib have been conducted in breast, prostate, and gastric cancer.

In the Phase Ib study PAM4983g, 2 of 5 patients with HR+ breast cancer, who were treated with the combination of ipatasertib and paclitaxel, had confirmed partial responses.

The randomized Phase Ib/II study GO27983 was conducted in patients with metastatic castration resistant prostate cancer (mCRPC) post-docetaxel. Ipatasertib (400-mg dose) when added to hormonal therapy abiraterone and prednisone/prednisolone showed improved radiographic PFS (rPFS) benefit compared with abiraterone and prednisone/prednisolone in the all-comer population and in patients with *PTEN*-loss tumors (HR = 0.75 for all-comer; HR = 0.39 for *PTEN*-loss by Immunologic Constant of Rejection immunohistochemistry [IHC] assay). There is an ongoing randomized Phase III study CO39303 evaluating 400 mg ipatasertib when added to abiraterone and prednisone/prednisolone compared to abiraterone and prednisone/prednisolone in front-line mCRPC.

The randomized Phase II study, GO29227, evaluated the addition of ipatasertib to paclitaxel in front-line metastatic triple-negative breast cancer (TNBC) patients and those with a *PTEN* loss (by IHC) and separately, patients with *PIK3CA/AKT1/PTEN*-altered tumors. Results from this study showed improvement in mPFS in the ITT population (HR = 0.60; 6.2 months in the ipatasertib arm compared with 4.9 months in the control arm); and more pronouncedly in the pre-specified patient population with *PIK3CA/AKT1/PTEN*-altered tumors (HR = 0.44; 9 months vs. 4.9 months). There is an ongoing randomized Phase III study CO40016 evaluating 400 mg ipatasertib when added to paclitaxel compared to paclitaxel in both first-line TNBC and HR+ HER2- breast cancer for patients with *PIK3CA/AKT1/PTEN*-altered tumors.

Refer to the Ipatasertib Investigator's Brochure for details on nonclinical and clinical studies.

1.3 BACKGROUND ON PALBOCICLIB

Palbociclib is a CDK4/6 inhibitor indicated for the treatment of HR+ HER2- advanced or metastatic breast cancer in combination with an AI as initial endocrine based therapy in postmenopausal women; or in combination with fulvestrant in women with disease progression following endocrine therapy. The approval in combination with fulvestrant

was based on the Phase III PALOMA-3 study which showed that in women with HR+ HER2- advanced or metastatic breast cancer who had disease progression following endocrine therapy, palbociclib-fulvestrant resulted in a mPFS of 9.2 months (95% CI, 7.5 to not estimable) versus 3.8 months (95% CI, 3.5 to 5.5) with placebo–fulvestrant (HR 0.42; 95% CI, 0.32 to 0.56; P<0.001) (Turner et al. 2015). Updated PFS analysis data from the PALOMA-3 study demonstrated a median PFS of 11.2 months in the palbociclib arm versus 4.6 months in the placebo arm (HR 0.497) (Cristofanilli et al. 2018).

Refer to the local prescribing information for details on nonclinical and clinical studies.

1.4 BACKGROUND ON FULVESTRANT

Fulvestrant is a SERD indicated for the treatment of postmenopausal women with ER+ advanced/metastatic breast cancer not previously treated with endocrine therapy, or with disease progression on antiestrogen therapy (Faslodex® package insert).

Fulvestrant binds to the ER, disrupting the signaling pathway, which leads to ER degradation. The recommended dose of fulvestrant is 500 mg given by intramuscular (IM) injection on Days 1, 15, and 29 of the first month, then monthly thereafter. This dose of fulvestrant was confirmed in a randomized clinical study of 250 mg versus 500 mg IM on a monthly basis (Di Leo et al. 2010). Fulvestrant 500 mg given on a monthly basis provided superior clinical benefit (PFS HR = 0.80; 95% CI: 0.68, 0.94; p = 0.006) compared with a 250-mg dose, but was accompanied by a higher rate of injection-site reactions (Di Leo et al. 2010).

The Phase III FALCON study investigated whether fulvestrant could improve PFS compared with anastrozole in postmenopausal patients with HR+ locally advanced or metastatic breast cancer who had not received previous endocrine therapy (Robertson et al., 2016). The median PFS was 16.6 months in the fulvestrant group versus 13.8 months in the anastrozole group (HR 0.797, p = 0.0486).

Fulvestrant has been successfully combined with CDK4/6 inhibitors, such as palbociclib (see Section 1.3).

Refer to the local prescribing information for details on nonclinical and clinical studies.

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Preclinical data suggests that an AKT inhibitor such as ipatasertib may be a good combination partner for a CDK4/6 inhibitor regimen. The combination of CDK4/6 inhibitors and PI3K inhibitors, which act upstream of AKT, synergistically reduced the viability of cancer cells with otherwise reduced sensitivity to PI3K inhibitors (Vora et al. 2014). Additional data indicated that ER+ breast cancer cells can adapt rapidly to CDK4/6 inhibition evading cytostasis and that a triplet combination of endocrine therapy, CDK4/6, and PI3K inhibition was more effective in patient-derived xenograft models than paired combinations (Herrera-Abreu et al. 2016). In another preclinical study, palbociclib

resistant ER+ breast cancer cells were shown to have a hyperactive PI3K/AKT/mTOR pathway and the mTOR inhibitor everolimus appeared to resensitize resistant cells to palbociclib (Chen et al. 2018). Importantly, fulvestrant/palbociclib double resistant cells maintained similar sensitivity to ipatasertib compared to parental cells (O'Brien et al. 2017).

Furthermore, exogenous expression of *AKT1* in HR+ breast cancer cell lines in vitro conferred resistance to palbociclib, abemaciclib, and anti-estrogen therapy and acquired *AKT1* alterations were identified in two patients with matched pre/post CDK4/6 inhibitor biopsy specimens (Wander et al. 2018).

This study will enroll patients with locally advanced unresectable or metastatic HR+ HER2- breast cancer expected to have a poor prognosis to currently available endocrine therapy in that they relapsed during adjuvant endocrine therapy or progressed during the initial 12 months of first-line endocrine therapy in HR+ HER2-, unresectable, locally advanced or metastatic breast cancer (see Section 4.1.1 for more details).

Although CDK4/6 inhibitor treatment regimens have resulted in considerable improvements in PFS in first- or second-line settings, limited data are available for patients with poorer prognosis who relapse or progress during endocrine therapy in the adjuvant or first-line metastatic setting. In addition, acquired resistance to CDK4/6 inhibitors has emerged, highlighting the need for identifying new therapeutic agents to help delay acquired resistance and thus increase clinical benefit of CDK4/6 inhibitor regimens especially in patients with poor prognosis (Garrido-Castro et al. 2017; O'Leary et al. 2018; Ballinger et al. 2018; Robert et al. 2018).

Despite the benefits from approved therapies, HR+ metastatic breast cancer remains an incurable disease and the majority of patients will eventually progress and subsequently die from the disease. Given the remaining unmet clinical need, this population is considered appropriate for trials of novel therapeutic candidates to identify therapies that could further enhance CDK4/6 inhibitor treatment regimens.

As a novel target along the validated PI3K/AKT/mTOR pathway, ipatasertib has shown promising clinical activity so far in randomized Phase II studies in TNBC (GO29227) and mCRPC (see Section 1.2 for details). In the Phase II study, GO27983, in mCRPC (de Bono et al. 2019), rPFS was prolonged in the ipatasertib cohort versus placebo with similar trends in overall survival and time-to-PSA progression. A larger rPFS prolongation for the combination was demonstrated in patients with tumor PTEN-loss versus those without (see Section 1.2 for details). In addition, the clinical safety profile of ipatasertib as a single agent in the Phase Ia study (PAM4743g) and in combination with paclitaxel in the Phase Ib (PAM4983g) and Phase II studies (GO29227 and GO29505) supports continued development of ipatasertib in breast cancer. Furthermore, in study GO27983 in prostate cancer the combination of ipatasertib with the endocrine agent abiraterone was well tolerated (de Bono et al. 2019). Consistent with

PI3K/mTOR/AKT pathway inhibition, ipatasertib has been associated with the risks presented in Section 5.1.1. Refer to Section 5 and the Ipatasertib Investigator's Brochure for further details.

There are limited overlapping toxicities and no expected drug-drug interactions between ipatasertib and fulvestrant (see Section 3.3.8). There are also limiting overlapping toxicities between ipatasertib and palbociclib with palbociclib being associated primarily with hematologic toxicities. However, potential exacerbation of toxicities, such as rash, mucositis/stomatitis, *pneumonitis,* and diarrhea may exist (Verma et al. 2016; IBRANCE® U.S. Package Insert). Therefore, patients will be monitored for these adverse events, and the potential for exacerbation of these toxicities is also being considered in the adverse event management guidelines (see Section 5.1). There are potential drug-drug interactions between ipatasertib and palbociclib (see Section 3.3.8). Therefore, the safety of combining ipatasertib with the labeled dose of palbociclib and fulvestrant will be assessed in the open-label Phase Ib portion to characterize the potential drug-drug interaction and identify the appropriate dose for the triplet combination (see Section 3.1.1).

As part of risk mitigation, there will be additional clinic visits during the first two cycles. In the randomized Phase III portion of the study, an independent Data Monitoring Committee (iDMC) will review cumulative safety data regularly throughout the study as outlined in a separate charter (see further details in Section 3.1.6 and Section 6.8.1). Detailed management guidelines for treatment-related symptoms or potential risks are provided as outlined in Section 5.4.2. To improve diarrhea management and patient experiences, anti-diarrhea prophylaxis (loperamide) will be mandated for the first cycle for all patients (where allowed by local guidance) and continued as clinically indicated (see Section 4.3.2.5).

In summary, the Sponsor has assessed that the potential benefit-risk profile of ipatasertib in combination with palbociclib and fulvestrant justifies the present clinical study. The anticipated or potential safety issues associated with the administration of ipatasertib in combination with palbociclib and fulvestrant and the measures to be taken that are intended to avoid or minimize such toxicities in this study are described in detail in Section 5.1.

2. OBJECTIVES AND ENDPOINTS

The open-label Phase Ib portion of this study will evaluate the safety and pharmacokinetics of ipatasertib in combination with palbociclib and fulvestrant to identify a dose of ipatasertib that can be combined with palbociclib and fulvestrant in the Phase III portion.

The randomized Phase III portion of this study will evaluate the efficacy, safety, and patient-reported outcome (PRO) objectives of ipatasertib + palbociclib + fulvestrant

compared with placebo + palbociclib + fulvestrant in patients with HR+ HER2-, locally advanced unresectable or metastatic breast cancer who had relapsed during adjuvant endocrine therapy or progressed during the initial 12 months of first-line endocrine therapy in locally advanced unresectable or metastatic breast cancer. Specific objectives and corresponding endpoints for the study are outlined in Section 2.

In this protocol, the term "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., ipatasertib/placebo, palbociclib, and fulvestrant). Treatment with placebo only applies to the Phase III portion of this study.

In this study, when describing the different analysis populations and endpoints, Tri-AKT positive (Tri-AKT+) corresponds to the presence of *PIK3CA/AKT1/PTEN* alterations.

2.1 EFFICACY OBJECTIVES

Efficacy objectives are applicable for only the randomized Phase III portion of this study as described below.

2.1.1 Primary Efficacy Objective

The primary efficacy objective for the randomized Phase III portion of this study is to evaluate the efficacy of ipatasertib + palbociclib + fulvestrant compared with placebo + palbociclib + fulvestrant on the basis of the following co-primary endpoints:

- Progression-free survival (PFS) in ITT patients, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), or death from any cause, whichever occurs first
- Progression-free survival (PFS) in patients with Tri-AKT+ tumors, as defined by baseline ctDNA, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for the randomized Phase III portion of this study is to evaluate the efficacy of ipatasertib + palbociclib + fulvestrant compared with placebo + palbociclib + fulvestrant on the basis of the following endpoints both in the ITT population and in patients with Tri-AKT+ tumors, as defined by baseline ctDNA:

- Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions $\geq$4 weeks apart, as determined by the investigator according to RECIST v1.1
- Duration of objective response (DOR), defined as the time from the first occurrence of a documented objective response to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first

- Clinical benefit rate (CBR), defined as the proportion of patients who have a CR or PR, or stable disease for at least 24 weeks, as determined by the investigator according to RECIST v1.1
- Overall survival (OS), defined as the time from randomization to death from any cause
- Time to deterioration (TTD) in *severity of* pain, defined as the time from randomization to the first documentation of a *2*-point or more increase from baseline *on the "worst pain" item from the Brief Pain Inventory-Short Form (BPI-SF)*
- *TTD in presence and interference of pain, defined as the time from randomization to the first documentation of a 10-point or more increase from baseline in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) pain scale (items 9 and 19)*
- TTD in physical functioning (PF), role functioning (RF), and Global Health *Status* (GHS)/Quality of Life (*QoL*)*,* defined as the time from randomization to the first documentation of a 10-point or more decrease from baseline in the following scales of the EORTC QLQ-C30: PF, RF, and GHS/*QoL*

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for the randomized Phase III portion of this study is to evaluate the efficacy of ipatasertib + palbociclib + fulvestrant compared with placebo + palbociclib + fulvestrant on the basis of the following endpoints both in the ITT patients and patients with Tri-AKT+ tumors, as defined by baseline ctDNA:

- Mean and mean changes from baseline scores in all functions (physical, role, cognitive, emotional, and social), GHS/*QoL*, and disease/ treatment-related symptoms, as measured by the scales of the EORTC QLQ-C30 *and the EORTC Breast Cancer Module 23 Questionnaire (QLQ-BR23)*
- Health utility and visual analog score (VAS) of the European Quality of Life 5-Dimension 5-Level (EQ-5D-5L) questionnaire for pharmacoeconomic modeling
- PFS2, defined as the time from randomization to second occurrence of objective disease progression through the use of RECIST v1.1, or death from any cause, whichever occurs first
- Time to first skeletal–related event (SRE), defined as the time from randomization to the first occurrence of an SRE (an SRE is a pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression)

In addition, this study will evaluate the efficacy of ipatasertib + palbociclib + fulvestrant compared with placebo + palbociclib + fulvestrant on the basis of the following endpoints in patients with Tri-AKT+ tumor tissue and PTEN loss in tumor tissue:

- PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first

2.2 SAFETY OBJECTIVES

Safety objectives are applicable for both the Phase Ib portion and the randomized Phase III portion of this study. The same endpoints as described below will be used for both portions.

2.2.1 Safety Objective

The safety objective for the Phase Ib portion of this study is to characterize the safety of combining ipatasertib with palbociclib + fulvestrant using endpoints listed below for the Phase III portion.

The safety objective for the randomized Phase III portion of this study is to evaluate the safety of ipatasertib + palbociclib + fulvestrant compared with placebo + palbociclib + fulvestrant in all randomized patients as well as patients with Tri-AKT+ tumors, as defined by baseline ctDNA, who received at least one dose of study treatment on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

2.2.2 Exploratory Safety Objective

The exploratory safety objective for the randomized Phase III portion of this study is to evaluate patient-reported symptomatic adverse events of ipatasertib + palbociclib + fulvestrant compared with placebo + palbociclib + fulvestrant in all randomized patients who received at least one dose of study treatment, on the basis of the following endpoints:

- Presence, frequency of occurrence, severity, and/or degree of interference with daily function of selected symptomatic treatment toxicities (i.e., diarrhea, nausea, vomiting, decreased appetite, fatigue, mouth sores, and rash symptoms and an additional item regarding the overall bother experienced due to side effects of treatment [see Appendix 13]), as measured by the NCI Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) instrument
- Change from baseline in symptomatic treatment toxicities, as measured by the PRO-CTCAE

2.3 PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objectives are applicable for both the open-label Phase Ib portion and the randomized Phase III portion of this study, unless otherwise specified below. The same endpoints, as described below, will be used for both portions, unless otherwise specified.

The PK objective for the open-label Phase Ib portion is to evaluate the effect of palbociclib, a weak time-dependent inhibitor of CYP3A, on the PK profile of ipatasertib.

The PK objective for the Phase III portion is to characterize the PK profiles of ipatasertib and its metabolite (G-037720) in combination with palbociclib and fulvestrant on the basis of the following endpoint:

- Plasma concentration of ipatasertib and its metabolite, G-037720, at specified timepoints for analysis using population PK methodology

The exploratory PK objectives for this study are as follows:

- To evaluate palbociclib trough concentrations and the effect of ipatasertib on palbociclib exposures in the open-label Phase Ib portion
- To evaluate potential relationships between drug exposure and the efficacy and safety of ipatasertib + palbociclib + fulvestrant in the randomized Phase III portion based on the following endpoints:
  - Relationship between plasma concentration or PK parameters for ipatasertib and efficacy endpoints
  - Relationship between plasma concentration or PK parameters for ipatasertib and safety endpoints

2.4 BIOMARKER OBJECTIVE

The exploratory biomarker objective for the open-label Phase Ib portion is to evaluate changes in plasma ctDNA levels.

The exploratory biomarker objectives for the randomized Phase III portion of this study are as follows:

- Evaluate the effect of Tri-AKT status in tissue or plasma on treatment benefit to ipatasertib + palbociclib + fulvestrant compared with placebo + palbociclib + fulvestrant
- Identify and evaluate predictive or prognostic biomarkers associated with disease activity status or response to treatment with ipatasertib + palbociclib + fulvestrant
- Identify possible mechanisms of resistance to ipatasertib + palbociclib + fulvestrant through the comparative analysis of potential biomarkers in pretreatment and post-progression biopsy tissue samples and in blood
- Evaluate safety and pharmacodynamics biomarkers that may lead to improved monitoring and to provide evidence of activity of ipatasertib + palbociclib + fulvestrant, respectively

- Evaluate the relationship between tissue-based and blood-based biomarkers and patient clinical features (e.g., baseline features) and outcome (e.g., duration of PFS)
- To increase the knowledge and understanding of disease biology and drug safety on the basis of the following endpoint:
- Relationship between biomarkers in blood and tumor tissue (listed in Section 4.5.8) and efficacy, safety, PK, or other biomarker endpoints including biomarker relevant therapies in development

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

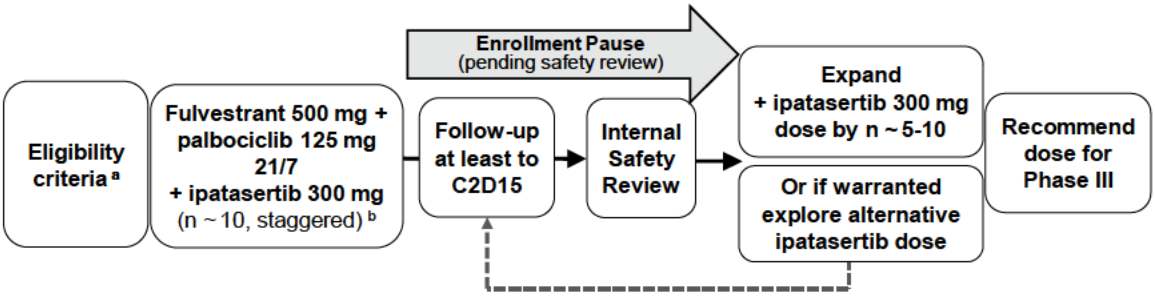
Study CO41012 is a Phase III, randomized, multicenter, international, double-blind, placebo-controlled clinical study with an initial open-label, Phase Ib, safety portion. The open-label Phase Ib portion is intended to evaluate the safety of the triplet combination and to further characterize the potential drug-drug interaction between ipatasertib and palbociclib and to determine the ipatasertib dose to be combined with palbociclib and fulvestrant. The randomized Phase III portion is designed to compare the efficacy, as measured by PFS, and safety of ipatasertib + palbociclib + fulvestrant with that of placebo + palbociclib + fulvestrant in patients with HR+ HER2- locally advanced unresectable or metastatic breast cancer who relapsed during adjuvant endocrine therapy or progressed during the initial 12 months of first-line endocrine therapy in locally advanced unresectable or metastatic breast cancer. Further details of the open-label Phase Ib and randomized Phase III portions are described below. An overview of the study flow of the open-label Phase Ib portion (Figure 1) as well as the dose schedule for each study drug (Figure 2) are shown below. The study schema for the Phase III portion (Figure 3) and the corresponding dose schedule for each study drug (Figure 4) are shown below.

3.1.1 Open-label Phase Ib Portion

Patients in the open-label Phase Ib portion are required to fulfill the same eligibility criteria as those in the randomized Phase III portion *unless otherwise indicated in Section 4.1.1 and Section 4.1.2*. Approximately 10 patients will initially be treated with a starting dose of 300 mg ipatasertib for 5-7 days as a single agent before palbociclib and fulvestrant will be started on Cycle 1, Day 1 (see additional details on the dose schedule below). All patients will be followed to at least Cycle 2, Day 15 before the initial safety review will be triggered. PK samples will be collected up to Cycle 3, Day 15 (see Appendix 4) and results will be included where available at the time of the safety review. If multiple patients come off prior to Cycle 2, Day 15 for reasons other than toxicity, the Sponsor may elect to replace the patients. The internal safety review will be conducted by the Sponsor and will include members of the study team including, but not limited to, the study Medical Monitor, Safety Scientist, and Clinical Pharmacologist. Further enrollment will be halted until after the internal safety review has been completed and a recommendation has been made to either expand the original cohort or explore an

alternative ipatasertib dose, if warranted (see Figure 1). In particular, if based on internal safety review, the 300 mg ipatasertib dose is comparable to the target 400-mg dose based on PK data and provides acceptable tolerability relative to historical data in ipatasertib clinical studies taking into consideration the palbociclib safety profile, the 300-mg dose cohort will be expanded further by approximately 5–10 patients. These additional patients may be able to start all three study drugs on Cycle 1, Day 1 if warranted by the initial PK data. On the other hand, if the 300-mg dose results in unacceptable toxicity, and if ipatasertib exposure is considerably above the target 400-mg dose equivalent, a lower dose will be explored as outlined in Figure 1. Depending on the safety and PK data, the Sponsor may also further explore the 400 mg starting dose used in other ipatasertib studies. For the second dose level, safety and PK data for up to 10 patients is expected to be sufficient to support the dose decision; however, the Sponsor may expand enrollment by approximately 5–10 patients if deemed necessary based on internal safety review.

Figure 1 Overview of Open-Label Phase Ib Portion



C = Cycle; D = Day; FFPE = formalin-fixed, paraffin-embedded.

[a] See key eligibility criteria in the randomized Phase III portion figure (Figure 3) and Section 4.1. Note: Criteria are the same for the open-label Phase Ib and randomized Phase III portions *unless otherwise indicated in Section 4.1.1 and Section 4.1.2.*

[b] See the open-label Phase Ib portion dosing schedule figure for more details (Figure 2).

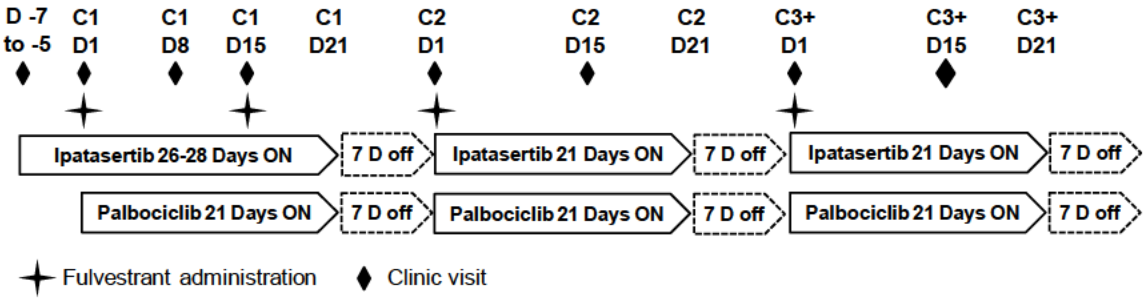
Study treatments in the open-label Phase Ib portion will be administered as shown in Figure 2 and as detailed below.

Patients will start with a 5–7 day run-in of single-agent ipatasertib (300-mg tablet dose once daily [QD]) prior to Cycle 1, Day 1. The single-agent run-in will allow ipatasertib to reach steady-state on Cycle 1, Day 1 and enable characterization of the potential drug-drug interaction between ipatasertib and palbociclib. For the first cycle, ipatasertib will be administered continuously for 26–28 days given the Day -7 to Day -5 window for the initial single-agent ipatasertib run-in; however, starting with Cycle 2, Day 1 ipatasertib will be taken orally (PO) QD on Days 1–21 of each 28-day cycle.

Starting on Cycle 1, Day 1, palbociclib 125 mg (capsule/*tablet*) will be taken PO QD on Days 1–21 of each 28-day cycle. Fulvestrant 500 mg will be administered by IM

injection on Cycle 1, Days 1 and 15 and then on Day 1 of each subsequent 28-day cycle. See details in Section 4.3.2.

Figure 2 Dose Schedule for Open-Label Phase Ib Portion



C=Cycle; D=Day.
Note: Mid-cycle phone visits will begin Cycle 4, Day 15; only Cycle 3, Day 15 is a clinic visit.
See Appendix 4 for the schedule of pharmacokinetic sample collection.

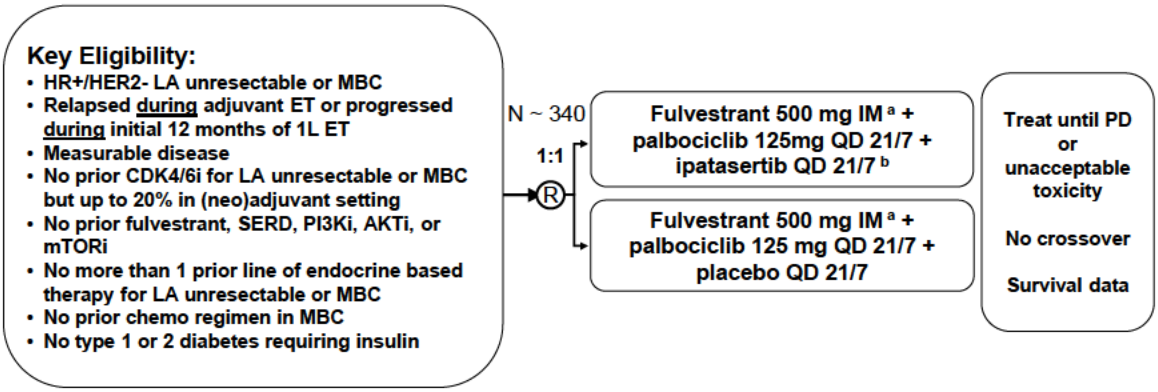
3.1.2 Randomized Phase III Portion

Enrollment to the randomized Phase III portion will be initiated only after the Sponsor has confirmed a dose of ipatasertib that can be combined with palbociclib and fulvestrant based on the internal safety review of the Phase Ib data. If no appropriate dose can be identified, for example if the combination is associated with high discontinuation rates due to unacceptable toxicity, the Phase III portion will not be initiated.

In the Phase III portion, approximately 340 patients will be randomized in a 1:1 ratio to either ipatasertib+palbociclib+fulvestrant or placebo+palbociclib+fulvestrant (see Figure 3). See Section 4.2 for additional details on randomization and stratification factors.

- **Ipatasertib Arm**: Ipatasertib tablet dose taken PO QD on Days 1–21 of each 28-day cycle beginning at Cycle 1, Day 1 and palbociclib 125-mg capsule/*tablet* dose taken PO QD on Days 1–21 of each 28-day cycle beginning at Cycle 1, Day 1 and fulvestrant 500 mg administered by IM injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28-day cycle. The ipatasertib dose will be established in the Phase Ib portion.
- **Control Arm**: Placebo taken PO QD on Days 1–21 of each 28-day cycle beginning at Cycle 1, Day 1 and palbociclib 125-mg capsule/*tablet* dose taken PO QD on Days 1–21 of each 28-day cycle beginning at Cycle 1, Day 1 and fulvestrant 500 mg administered by IM injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28-day cycle.

Figure 3 Study Schema for Randomized Phase III Portion

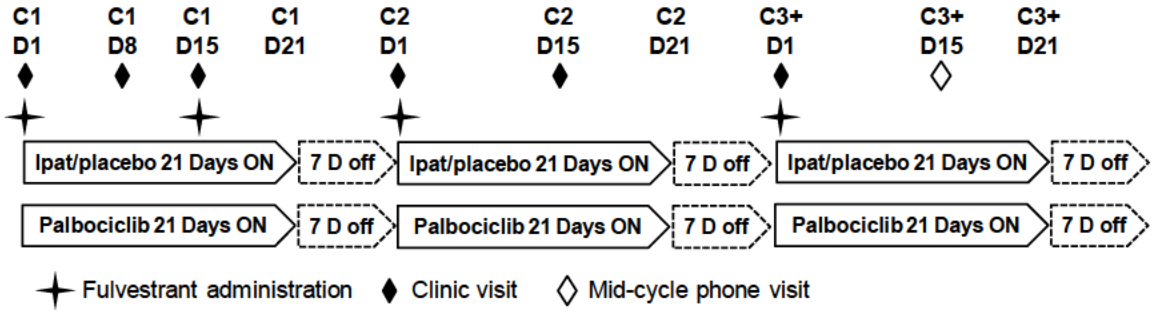


AKTi=protein kinase B inhibitor; 1L=first line; chemo=chemotherapy; ET= endocrine therapy; HR+=hormone receptor positive; HER2-=*human epidermal growth factor receptor 2* negative; IM=intramuscular; LA=locally advanced; MBC=metastatic breast cancer; *mTORi=mammalian target of rapamycin inhibitor;* PD=progressive disease; *PIK3i=phosphoinositide 3-kinase inhibitor;* QD=once daily; R=randomization; SERD=selective estrogen receptor down-regulator.
Note: See Section 4.1 for more details on eligibility criteria.

[a] Fulvestrant Cycle 1, Day 1; Cycle 1, Day 15; Cycle 2, Day 1; and Cycles 3+ Day 1.

[b] Ipatasertib dose confirmed in Phase Ib.

Figure 4 Dose Schedule for Randomized Phase III Portion



C=Cycle; D=Day.
For information concerning timing of tumor assessments, see Section 4.5.6 and Appendix 1.
See Appendix 2 for the schedule of pharmacokinetic sample collection.

3.1.3 Goserelin Treatment in Pre- and Peri-menopausal Women *and Men*

In both portions of the trial, pre- or peri-menopausal women must have started treatment with goserelin or an alternative luteinizing hormone releasing hormone (LHRH) agonist at least *14* days prior to first dose of study treatment. If patients have received an alternative LHRH agonist prior to study entry, it is recommended that they switch to goserelin for the duration of the trial, whenever possible (see Section 4.3.2.4 for more details). *For men, treatment with goserelin or alternative LHRH agonist therapy is recommended beginning at least 14 days prior to first dose of study treatment and continuing for the duration of study treatment.*

3.1.4 Key Study Parameters

Prior to enrollment but after signing the informed consent form, patients enrolled in the Phase III portion will have the Tri-AKT ctDNA test done by the central laboratory next-generation sequencing (NGS) assay within 6 weeks of first dose of study treatment. For patients enrolled in the Phase Ib portion, the test may be performed after enrollment. A valid result (Phase III only) will be required for patient stratification and therefore patients whose ctDNA samples have invalid test results will not be permitted to enroll in the Phase III portion of the study.

Patients must have measurable disease per RECIST v1.1 (see Section 4.1 and Appendix 9).

Primary endpoint is investigator-assessed PFS $(Phase\ III)$. Tumor assessments will be conducted as outlined in the schedule of assessments (Appendix 1 [Phase III schedule of assessments {SOA}] and Appendix 3 [Phase Ib SOA]) and Section 4.5.6.

3.1.5 Length of Treatment and Discontinuation

Study treatment will continue until disease progression, unacceptable toxicity, withdrawal from study, or study completion or termination. Upon treatment discontinuation, patients in the randomized Phase III portion will be followed for survival, PROs, and subsequent anti-cancer therapy (including outcome) as outlined in Section 4.6.1. Patients enrolled in the randomized Phase III portion who discontinue treatment without evidence of disease progression per RECIST v1.1, will be followed every 8 weeks $\pm 7\ days$ for tumor assessments until documented progression per RECIST v1.1.

Patients who need to discontinue any of the study drugs due to toxicity may continue on the other study drugs provided the toxicity is deemed unrelated to those:

- Patients who need to permanently discontinue ipatasertib/placebo may stay on palbociclib and/or fulvestrant at the discretion of the investigator without medical monitor approval.
- If patients need to permanently discontinue palbociclib and/or fulvestrant but not ipatasertib/placebo, medical monitor approval will be required to continue on ipatasertib/placebo alone or in combination with either palbociclib or fulvestrant.

Crossover is not allowed. See Section 4.6.2 for more details concerning patient discontinuations.

3.1.6 Independent Data Monitoring Committee

An iDMC will be used to evaluate safety during the randomized Phase III portion of the study as outlined in a separate charter and in Section 6.8. However, no interim analysis of the primary efficacy endpoint PFS is planned.

A schedule of study assessments is provided in Appendix 1 (Phase III SOA) and Appendix 3 (Phase Ib SOA).

3.1.7 Potential China Extension Cohort

This study plans to enroll approximately 340 patients across all sites in the global enrollment phase of the randomized Phase III portion. After completion of the global enrollment phase, additional patients may be enrolled in a China extension cohort at sites in mainland China, Hong Kong, and Taiwan (see Section 6.9 for details on the China subpopulation).

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient last visit occurs (i.e., the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later). In addition, the Sponsor may decide to terminate the study or OS follow-up at any time (see Section 4.6.3).

Provided the Phase III portion is initiated, the total length of the global study, from screening of the first patient to the end of the study, is expected to be approximately 64 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Ipatasertib Dose and Schedule

For ipatasertib, the target starting dose of 400 mg QD on Days 1–21 of each 28-day cycle is consistent with the dose used in Phase II (GO29227) and Phase III (CO40016) breast cancer trials. This dose is based on the safety and PK data from the combination treatment Arm C of Study PAM4983g and the combination treatment Arm 1 of Study GO29227 (Phase Ib and Phase II trials of ipatasertib combined with paclitaxel; refer to the Ipatasertib Investigator's Brochure for details). The 400 mg ipatasertib was previously better tolerated than 600 mg ipatasertib (refer to Study PAM4743g in Ipatasertib Investigator's Brochure for details). Even though there is no safety data, yet, in combination with fulvestrant, there are no expected drug-drug interactions between ipatasertib and fulvestrant (see Section 3.3.8). However, given potential drug-drug interactions of ipatasertib with palbociclib that may result in an increase in ipatasertib exposure (see Section 3.3.8), the starting dose of ipatasertib of 300 mg was selected for the initial Phase Ib portion. Based on study GP30057 (Phase I study evaluating the effect of itraconazole on ipatasertib) and drug interactions of palbociclib (refer to palbociclib label), the sponsor believes that the 300-mg dose in the presence of palbociclib *may* result in ipatasertib exposure that is similar to the target 400-mg dose in the absence of palbociclib (see further details on the rationale for the target 400-mg dose below). The Phase Ib portion of this study is intended to further characterize the drug-drug interaction and confirm the appropriate dose for the combination with palbociclib (see Section 3.1.1 for additional details on the open-label Phase Ib portion).

Ipatasertib in combination with chemotherapy at the 400-mg dose has resulted in acceptable tolerability based on data from the randomized, placebo-controlled, Phase II

study (GO29227) in patients with locally advanced or metastatic TNBC. In that study, the combination of ipatasertib 400 mg administered QD on Days 1–21 of each 28-day cycle and paclitaxel 80 mg/m^2 administered weekly on Days 1, 8, and 15 of each 28-day cycle was generally well tolerated and showed an improvement in PFS (refer to Ipatasertib Investigator's Brochure and Section 1.2). The sparse sampling exposure results in this study were also consistent with the known PK profiles of ipatasertib (and its metabolite G-037720).

In addition, results of pretreatment and on-treatment biopsies indicated that ipatasertib, beginning at 100 mg, downregulated multiple AKT effectors, including pPRAS40, pGSK3β, pS6, and p4EBP (Saura et al. 2016) suggesting robust target inhibition at 400 mg.

Overall, the PK data from the Phase I (PAM4743g, PK/pharmacodynamic analysis) as well as safety and efficacy data (including exploratory exposure-response analyses, data on file) from the randomized Phase II studies of ipatasertib (Study GO29227 in patients with locally advanced or metastatic TNBC and Study GO27983 in patients with mCRPC) support the starting dose of 400 mg ipatasertib for sufficient pathway inhibition and efficacy with a generally acceptable safety profile in combination regimens such as with chemotherapy (refer to the Ipatasertib Investigator's Brochure for details). In the ipatasertib + paclitaxel combination arm of the GO29227 study, despite dose reduction of ipatasertib that occurred in 21% of patients due to adverse events, discontinuation of ipatasertib due to any adverse event was 7% (Kim et al. 2017).

A relative bioavailability and food-effect study (GO29868) was conducted in healthy volunteers. The study confirmed that the Phase III tablet formulation of ipatasertib to be used in this study is anticipated to provide exposures similar to the exposures of ipatasertib Powder-In-Capsule and Phase II tablet formulations used in the Phase I (PAM4743g, PAM4983g) and Phase II (GO29227) studies, respectively.

3.3.2 Rationale for Fulvestrant Dose and Schedule

The dose of fulvestrant of 500 mg administered by IM injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28-day cycle was established in a randomized clinical study to be superior to the 250-mg dose (see Section 1.4) and was used in combination with palbociclib in the randomized clinical study PALOMA-3 that led to approval of palbociclib in combination with fulvestrant (see Section 1.3).

3.3.3 Rationale for Palbociclib Dose and Schedule

The 125-mg palbociclib dose taken PO QD on Days 1–21 of each 28-day cycle beginning at Cycle 1, Day 1 in combination with fulvestrant was established in the Phase III PALOMA-3 study (see Section 1.3) and is the approved starting dose of palbociclib.

3.3.4 Rationale for Patient Population and Control Group

The population based on the proposed eligibility criteria (see Section 4.1) reflects patients for whom palbociclib and fulvestrant represents an appropriate treatment option. Palbociclib in combination with an AI or fulvestrant has been approved by health authorities in many regions, including the U.S. Food and Drug Administration (FDA) and the EMA for women with locally advanced unresectable or metastatic breast cancer (see Section 1.4). Fulvestrant is not indicated for use in the adjuvant setting, whereas AIs are currently approved, thus switching patients who relapsed during adjuvant endocrine therapy (primarily AI based) or who progressed rapidly during front-line endocrine therapy to palbociclib and fulvestrant seems an appropriate treatment option. Despite recent PFS improvements with CDK4/6 inhibitors, the emergence of acquired resistance to CDK4/6 inhibitors highlights the continued unmet need to identify new treatment regimens including combination therapies for patients with HR+ breast cancer (O'Leary et al. 2016; O'Leary et al. 2018). Patients in this study are expected to have a poor prognosis and thus may benefit from the addition of new therapeutic agents such as an AKT inhibitor (see Section 1.5 for additional details).

Assumptions for the median PFS of the palbociclib and fulvestrant control arm in this trial are based on data from the two Phase III trials, PALOMA-3 (palbociclib and fulvestrant) and MONARCH-2 (abemaciclib and fulvestrant) and their subgroup analyses (Turner et al. 2015; Sledge et al 2017; Cristofanilli et al. 2018; Di Leo et al. 2018). Neither of these clinical studies were restricted to only patients who relapsed during adjuvant endocrine therapy or who progressed during the initial 12 months of 1L endocrine therapy in locally advanced unresectable or metastatic breast cancer to be enrolled in this study. In addition, these trials included patients who could have progressed within 12 months of end of adjuvant endocrine therapy or who could have progressed anytime during 1L endocrine therapy for metastatic disease. While different CDK4/6 inhibitors have demonstrated comparable efficacy reflected in comparable HR of 0.497 in PALOMA-3 (Cristofanilli et al. 2018) and HR of 0.553 in MONARCH-2 (Sledge et al. 2017), the trials enrolled slightly different patient populations, resulting in lower overall mPFS in the PALOMA-3 study in both treatment arms. In PALOMA-3 patients were allowed one prior chemotherapy in the metastatic setting and fewer patients presented with 1L metastatic disease compared to MONARCH-2. Based on PALOMA-3 subgroup analysis, mPFS of palbociclib and fulvestrant in patients with only one prior therapy was 13.3 months compared to 11.2 in the overall population (Cristofanilli et al. 2018). In contrast to PALOMA-3, this study will not allow prior chemotherapy in the metastatic setting, will only enroll patients with measurable disease and will exclude patients with bone-only disease. In both PALOMA-3 and MONARCH-2, patients with bone-only disease experienced considerably longer mPFS (Cristofanilli et al. 2018; Di Leo et al. 2018).

Thus, overall, the assumptions for the palbociclib and fulvestrant arm in this study for the ITT population are expected to fall between the overall data from PALOMA-3 (11.2 months) and MONARCH-2 (16.4 months), respectively (Cristofanilli et al. 2018; Sledge et al. 2017). The mPFS in patients with Tri-AKT+ tumors, as defined by baseline ctDNA, is expected to be lower given poorer prognosis observed in such patients (see Section 1.1).

3.3.5 Rationale for Analysis Groups

This trial includes a co-primary endpoint of PFS in two analyses groups, the all-comer ITT population and patients with Tri-AKT+ tumors, as defined by baseline ctDNA (see Section 2). The main rationale for the co-primary endpoint is that sponsor cannot rule out an all-comer benefit with ipatasertib especially in combination with palbociclib and fulvestrant. Although in nonclinical models sensitivity to ipatasertib seems enhanced with high levels of phosphorylated AKT or PI3K-AKT pathway activity (i.e., PIK3CA and PTEN alterations) (Lin et al. 2013), the all-comer benefit with the mTOR inhibitor everolimus e.g. in BOLERO-2 (Baselga et al. 2012; Moynahan et al, 2017), in contrast to the PI3K inhibitor alpelisib in SOLAR-1 (André et al. 2018) (see Section 1.1), suggests that targeting downstream of PI3K with an AKT inhibitor such as ipatasertib may provide benefit in unselected patients. *Recent data from the randomized Phase II FAKTION study that demonstrated efficacy of the AKT inhibitor capivasertib in combination with endocrine therapy fulvestrant in unselected patients supports this assumption (see Section 1.1)*. In addition, in the Phase II GO29227 study in TNBC, the addition of ipatasertib to paclitaxel prolonged PFS in a biomarker unselected population with enhanced efficacy in patients with Tri-AKT+ tumors (see Section 1.2 for details).

Therefore, the primary efficacy objective for this study is to evaluate the efficacy of ipatasertib + palbociclib + fulvestrant compared with placebo + palbociclib + fulvestrant in both ITT and patients with Tri-AKT+ tumors, as defined by baseline ctDNA.

3.3.6 Rationale for Skeletal-Related Events Assessments

Metastatic breast cancer is often associated with bone involvement, which may potentially lead to skeletal-related complications, possibly impacting a patient's quality of life. To describe the impact of bone involvement in breast cancer, SREs have previously been described as one or more of the following events (Coleman et al. 1985):

- Radiation to bone (for pain or impending fracture)
- Pathological fracture
- Spinal cord compression
- Surgery to the bone

SREs will be measured as an exploratory endpoint in the Phase III randomized portion of the study to describe the incidence of these events and to determine the potential

impact of treatment with ipatasertib in the locally advanced or metastatic breast cancer setting (Hortobagyi et al. 1996).

3.3.7 Rationale for Biomarker Assessments

HR+ HER2- breast cancer is a heterogeneous disease, and *PIK3CA/AKT1/PTEN* alteration (Tri-AKT+) status has been shown to vary among patients (Cancer Genome Atlas Network 2012; Curtis et al. 2012). In addition to the Tri-AKT status, samples will be assessed for additional biomarkers in an effort to identify factors that may correlate with the safety and efficacy of treatment with ipatasertib and/or palbociclib and fulvestrant.

3.3.7.1 Rationale for Using Circulating Tumor DNA (ctDNA) for Examining Tri-AKT Status

Activation of PI3K/AKT signaling frequently occurs in breast cancer through activating mutations in *PIK3CA* or *AKT1* as well as through alterations in *PTEN.* These alterations occur in approximately 45% of HR+ HER2- breast cancers (Pereira et al. 2016).

There is increasing evidence that circulating DNA obtained from blood specimens of cancer patients is representative of the DNA and mutational status of tumor cells (Diehl et al. 2008; Maheswaran et al. 2008). Assays are available that can detect the major *PIK3CA* mutations (and other cancer-related genes) in plasma, and results from this analysis may be correlated with the mutation result in tumor specimens. Comparisons between plasma and tissue-based NGS showed that *PIK3CA/AKT1* alterations detected in patients from the Phase II study GO29227 are largely concordant (Kim et al. 2017). The use of ctDNA to identify the Tri-AKT status through NGS is a non-invasive and quantifiable method for patient stratification.

3.3.7.2 Rationale for the Collection of Tissue Samples

To better understand the role of alterations detected in tissues, the use of archival tissue (i.e., sample from primary breast tumor) or a newly obtained biopsy at screening can be used to determine Tri-AKT status using NGS techniques, such as targeted sequencing.

This approach offers a unique opportunity to further our understanding of breast cancer biology by molecular subtyping, as well as analyzing responses to agents targeting the PI3K/AKT/mTOR pathway, especially in the metastatic setting. For example, mutations in the *ESR1* gene are more prevalent in metastatic ER+ tumors and have been correlated with resistance to anti-estrogen therapies (Robinson et al. 2013; Toy et al. 2013; Jeselsohn et al. 2014). Sequencing of cancer-related genes may result in the identification of *de novo* mechanisms of resistance to ipatasertib.

Tumor tissue may be collected at the time of disease progression for DNA and/or RNA extraction for exploratory NGS or other research on non-inherited biomarkers (including, but not limited to, cancer-related genes and biomarkers associated with common molecular and biological pathways). Understanding the mechanisms of resistance to the

combination of ipatasertib plus palbociclib and fulvestrant is critical for the further development of agents in the PI3K/AKT pathway and may provide an opportunity to develop next-generation inhibitors to prevent resistance.

Progression biopsy tissue samples will aid in determining a resistance mechanism for the combination of ipatasertib plus palbociclib and fulvestrant, which may potentially influence future therapies for patients who progress on a PI3K/Akt inhibitor. NGS will be performed by a clinical cancer genomic profiling laboratory (e.g., *Foundation Medicine, Inc.*).

See Section 4.5.8 for details on availability of results from the NGS testing.

3.3.7.3 Rationale for Collection of DNA (Blood) for Exploratory Whole Genome Sequencing

Genomics is increasingly informing researcher's understanding of disease pathobiology. Whole genome sequencing (WGS) provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data may be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For example, genetic variants of drug-metabolizing enzymes and transporters can alter the pharmacokinetics of drugs, affecting their safety and efficacy. For example, patients who carry defective alleles of the gene encoding uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), which facilitates the metabolism and excretion of SN-38 (the active metabolite of irinotecan), are at higher risk for adverse events associated with the use of standard doses of irinotecan (O'Dwyer and Catalano 2006). Preliminary results from in vitro metabolism studies suggest that ipatasertib is primarily metabolized by the cytochrome P (CYP) 450 enzyme CYP3A, with a minor contribution by CYP2D6. Although in vitro studies can help elucidate the roles of enzymes in the metabolism of the drug, these results are not always predictive of in vivo metabolism for a number of reasons, including differences in drug concentrations that the enzymes encounter in vitro and in vivo. For this reason, a blood sample for DNA isolation will be collected from patients in this study (where approved locally) for potential pharmacogenetic analysis of genes or biomarkers that may affect the pharmacokinetics of ipatasertib in combination with palbociclib and fulvestrant. The decision to analyze the samples will be based on a review of the PK data. For example, if a patient in a given cohort has substantially higher ipatasertib plasma levels than other patients in that cohort, the patient may carry a defective allele of a gene important in the metabolism or transport of ipatasertib. The genotyping efforts would be guided by results from in vitro metabolism studies and by results from ongoing clinical studies with ipatasertib.

The pharmacogenetic analysis, if needed, will be performed on identifiable (referring to the blinded clinical trial number assigned to the patient at the time of randomization and not to the actual name or other protected health information of the patient) DNA samples, because it is necessary to link a patient's PK data with genotype. This analysis will be restricted to the evaluation of genes that may be involved in the pharmacokinetics of ipatasertib (e.g., drug metabolism, disposition, or elimination genes, or genes influencing these processes).

In addition, tumor DNA can contain both reported and unreported chromosomal alterations resulting from the tumorigenesis process. To help control for sequencing calls in previously unreported genomic alterations, the WGS blood sample will help determine whether an observed alteration identified in the tumor tissue is somatic throughout the evaluation of the DNA isolated in peripheral blood. This sample for WGS will be collected if approved locally.

3.3.7.4 Rationale for Safety Biomarker Analysis

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

3.3.8 Rationale for the Pharmacokinetic Evaluation Schedule

In the Phase Ib portion, detailed sampling for PK characterization of ipatasertib and its metabolite G-037720, as well as palbociclib, is outlined in Appendix 4. The sampling schedule is designed to enable the comparison of single-agent ipatasertib PK with ipatasertib PK in the presence of palbociclib to evaluate the effect of palbociclib on ipatasertib exposures.

For the Phase III portion, a sparse sampling strategy will be applied to enable characterization of ipatasertib using population PK (popPK) methodology. Samples for PK characterization of ipatasertib and its metabolite G-037720 as well as palbociclib will be collected as outlined in Appendix 2.

Palbociclib is metabolized, in part, by CYP3A and co-administration of itraconazole (a strong CYP3A inhibitor) increased the plasma exposure of palbociclib in healthy subjects by 87% (IBRANCE® U.S. Package Insert). Additionally, the clinical drug-drug interaction study with midazolam (a sensitive CYP3A substrate) showed a 2.2-fold increase in midazolam exposures in the presence of 600 mg ipatasertib (Study PAM4743g; see the Ipatasertib Investigator's Brochure for details). Therefore, as a mild-to-moderate inhibitor of CYP3A4, ipatasertib at 400 mg is not expected to change palbociclib exposures in a clinically meaningful way. However, palbociclib levels will

also be measured in both Phase Ib and Phase III as outlined in Appendix 4 and Appendix 2, respectively, to confirm.

Ipatasertib is primarily metabolized by CYP3A (refer to Ipatasertib Investigator's Brochure), and itraconazole, a strong CYP3A4 inhibitor, increased ipatasertib area under the concentration-time curve (AUC) and maximum concentration (C_{max}) by approximately 5-fold and 2-fold, respectively as observed in Study GP30057. As a weak time-dependent inhibitor of CYP3A, palbociclib can potentially increase the plasma exposure of ipatasertib (refer to the local prescribing information for additional details for palbociclib) which has been taken into consideration in selecting the starting dose of ipatasertib in the Phase Ib portion (see Section 3.1.1).

Although fulvestrant is a CYP3A4 substrate, strong CYP3A inhibitors and inducers did not have clinically relevant effect on fulvestrant disposition (Faslodex® package insert). Based on this, although ipatasertib is a mild-to-moderate inhibitor of CYP3A4 (Study PAM4743g; see the Ipatasertib Investigator's Brochure for details), ipatasertib is not expected to alter the exposure of fulvestrant in a clinical meaningful way. Fulvestrant is not an inhibitor or inducer of CYP3A (Faslodex® package insert), and therefore, it is not expected to alter plasma exposure of ipatasertib. Based upon the labeling, an analysis of fulvestrant pharmacokinetics does not seem warranted for this study, however PK of fulvestrant may be analyzed using remaining samples, if needed.

Any PK samples that remain after the above evaluations have been completed may be used for exploratory evaluation of other analytes related to the administered drugs or biomarkers affecting their disposition and safety.

3.3.9 Rationale for Patient-Reported Outcome Assessments

As metastatic breast cancer is not curable with currently approved and available therapies, the primary focus for patients is on living as long as possible and delaying the progression of cancer while maintaining their quality of life and the ability to carry out daily activities (Cardoso et al. 2012). Research indicates that a higher proportion of HR+ patients have bone metastases compared to other subtypes which is often associated with pain (Irvin et al. 2011; Wood et al. 2016); thus, disease and treatment-related pain may be important components of the patient's treatment experience. Limited data are available characterizing the clinical presentation of disease in this population; however, it is hypothesized that progression of disease would be associated with an increase in pain symptoms. Examining and measuring patients' disease-related pain, treatment-related symptoms, and their interference with daily life is important to capture and will be assessed using validated PRO assessments in patients enrolled in the Phase III portion.

The "worst pain" item from the BPI-SF (Section 4.5.10.1 and Appendix 10*) will be used to gain further insight into increase in pain severity.* The EORTC QLQ-C30 will be administered to patients to assess disease *symptoms including pain presence and interference*, treatment-related symptoms, functioning, and health-related quality of life

*(*see Section 4.5.10.2 and Appendix 11). *The EORTC QLQ-BR23 will provide an additional assessment of treatment-related symptoms and symptoms that may occur with advanced disease (*Section 4.5.10.3 and Appendix 12*). As the EORTC QLQ-BR23 was not developed or tested and validated with men, male patients in this study will not complete the QLQ-BR23 measure.* In addition, selected symptomatic adverse event items from the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) and an additional item regarding bother due to side effects of treatment will be assessed (see Section 4.5.10.4 and Appendix 13*)*. The EQ-5D-5L (see Section 4.5.10.5 and Appendix 14*)* will also be collected and utilized to derive health states for use in economic models, and therefore the results will not be reported in the CSR *(see* Appendix 1 *Phase III SOA for further administration details)*.

The BPI-SF worst pain item, EORTC QLQ-C30, EORTC QLQ-BR23, selected items from the PRO-CTCAE, and EQ-5D-5L will be completed in this order as applicable: BPI-SF first, followed by the EORTC-QLQ-C30 second, followed by the EORTC QLQ-BR23 third, followed by the PRO-CTCAE fourth, and the EQ-5D-5L last. After treatment discontinuation, to minimize burden to patients and support market access requirements, the EORTC QLQ-C30 and EORTC QLQ-BR23 will be administered over the phone or in-clinic only once during the follow-up period at 3 months, while the BPI-SF and EQ-5D-5L will be administered over the phone or in-clinic at separate time points during the follow-up period of every 6 months for a duration of one year (see Appendix 1 *[Phase III SOA])*.

3.3.10 Rationale for Potential China Extension Cohort

To characterize the efficacy and safety profile of ipatasertib in combination with palbociclib and fulvestrant in a Chinese population to support a regulatory submission in China, a China extension phase may be included in the study. See Section 6.9 for additional details.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 370 patients with HR+ HER2- locally advanced unresectable or metastatic breast cancer will be enrolled overall in this study in both the Phase Ib and the global enrollment portion of the Phase III. After completion of the global enrollment phase, additional patients may be enrolled in an extended China enrollment phase.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment

- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (see Appendix 5)
- Histologically documented HR+ HER2- adenocarcinoma of the breast that is locally advanced or metastatic and is not amenable to surgical or local therapy with curative intent
- Documented ER and/or progesterone receptor positivity defined as ≥1% of tumor cell nuclei immunoreactive to the respective hormonal receptor based on most recent evaluable tumor biopsy as assessed locally (see Appendix 6 for additional information)
- Documented HER2- as assessed locally based on most recent evaluable tumor biopsy defined as immunohistochemistry *(IHC)* score 0/1+, or *an IHC score of 2+ accompanied* by *a* negative *fluorescence, chromogenic, or silver* ***in situ*** hybridization *test* (FISH/CISH/SISH) *indicating the absence of HER2 gene amplification, or a HER2/CEP17 ratio of <2.0* (see Appendix 7 for additional information)
- Either male

  OR
- Postmenopausal, defined as:
  - Age ≥60 years -OR-
  - Age <60 years AND have undergone bilateral oophorectomy, medically confirmed ovarian failure -OR-
  - Age <60 years AND have had cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have serum levels of estradiol and follicle-stimulating hormone within the laboratory's reference range for postmenopausal females

  OR
- Pre- or peri-menopausal and amenable to being treated with the LHRH agonist goserelin

  Patients must have started treatment with goserelin or an alternative LHRH agonist at least *14* days prior to first dose of study treatment. If patients have received an alternative LHRH agonist prior to study entry, it is recommended that they switch to goserelin for the duration of the trial, whenever possible. *See Section 3.1.3 for recommendations for male patients.*
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs as defined below:

  Women must remain abstinent or use non-hormonal contraceptive methods with a failure rate of <1% per year during the treatment period and for 90 days after the final dose of study treatment (or longer if required per the local prescribing information).

  Women must refrain from donating eggs during this same period.

A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

Examples of non-hormonal contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, and copper intrauterine devices.

Hormonal contraceptive methods may be used in accordance with specific country and local requirements for patients with breast cancer.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use *contraceptive methods*, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential *who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for 6 months after the final dose of study treatment (or longer if required per the local prescribing information). Men must refrain from donating sperm during this same period.*

  With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for *90 days* after the final dose of study treatment *(or longer if required per the local prescribing information)* to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure. If required per local guidelines or regulations, *locally recognized adequate methods of contraception and* information about the reliability of abstinence will be described in the local Informed Consent Form.

- Patients must have experienced radiologic/objective relapse during adjuvant endocrine therapy or radiologic/objective disease progression during the initial 12 months of 1L endocrine therapy in locally advanced unresectable or metastatic breast cancer

Up to 20% of patients enrolled in the Phase III portion may have received a CDK4/6 inhibitor as part of their *neoadjuvant/*adjuvant endocrine therapy.

If a CDK4/6 inhibitor *was included* as part of *a neoadjuvant/adjuvant* therapy*, relapse must be ≥ 12 months since completion of the CDK4/6 inhibitor portion of the neoadjuvant/adjuvant therapy.*

Phase III portion only: Prior CDK4/6 inhibitor is not permitted for locally advanced unresectable or metastatic breast cancer *(see Section 4.1.2).*

Phase Ib portion only: Prior CDK4/6 inhibitor is permitted and if previously treated with palbociclib, patient should have been on the 125-mg dose at the end of their palbociclib treatment period.

- Radiologic/objective evidence of recurrence or progression to the most recent systemic therapy for breast cancer
- Patients for whom endocrine-based therapy (e.g., palbociclib and fulvestrant) is recommended and treatment with cytotoxic chemotherapy is not indicated at time of entry into the study, as per national or local treatment guidelines.
- At least one measurable lesion via RECIST v1.1 (see Appendix 9 for details)

  Patients with bone only disease are not eligible even if a bone lesion qualifies as a measurable lesion.

  Bone lesions are generally followed as non-target lesions. However, lytic bone lesions or mixed lytic–blastic lesions (unless previously irradiated), with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) may be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions, however, are non-measurable.

  Previously irradiated lesions (other than bone) may be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.
- Have adequate organ and marrow function as defined below:
  - ANC ≥ 1500 cells/μL
  - Hemoglobin ≥ 9 g/dL
  - Platelet count ≥ 100,000/μL
  - AST and ALT ≤ 2.5 × upper limit of normal (ULN); with the following exception:

    Patients with liver or bone metastases may have AST and ALT ≤ 5 × ULN.
  - Alkaline phosphatase ≤ 2 × ULN (≤ 5 × ULN if liver metastases present; ≤ 7 × ULN if bone metastases present)
  - Total bilirubin ≤ 1.5 × ULN (≤ 3 x ULN if hyperbilirubinemia is due to Gilbert's syndrome)
  - Serum albumin ≥ 3.0 g/dL

- Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min as calculated using the method standard for the institution
- Fasting glucose ≤ 150 mg/dL and hemoglobin A1c (HbA1c) $\leq 7.5\%$
- PTT (or activated PTT [aPTT]) and INR $\leq 1.5 \times$ ULN (except for patients receiving anticoagulation therapy)

  Patients receiving heparin treatment should have a PTT (or aPTT) between 1.5 and $2.5 \times$ ULN (or patient value before starting heparin treatment). Patients receiving coumarin derivatives should have an INR between 2.0 and 3.0 assessed in two consecutive measurements 1 to 4 days apart.

- Life expectancy > 6 months
- Resolved or stabilized toxicities resulting from previous therapy to Grade 1

  An ongoing Grade 2 non-hematologic toxicity related to the most recent treatment regimen may be permitted with approval from the Sponsor based on consultation with the Medical Monitor (ongoing toxicities alopecia, neuropathy, and hot flashes do not require Sponsor approval)

- Phase III portion only: Consent to provide tumor specimen from the most recently collected, available tumor tissue (formalin-fixed, paraffin-embedded [FFPE] block [preferred] or a minimum of 12 slides containing unstained, freshly cut, serial sections)

  Cytologic or fine- needle aspiration samples and tumor tissue from bone metastases are not acceptable. Alternatively, a newly collected tumor tissue sample may be provided.

- Phase III portion only: Valid Tri-AKT ctDNA test result by *the central laboratory* NGS assay within 6 weeks prior to enrollment
- For patients enrolled in the China extension portion (if opened) of the Phase III: current resident of mainland China, Hong Kong, or Taiwan, and of Chinese ancestry

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 90 days after the final dose of study treatment (or longer if required per the local prescribing information).

  Women of childbearing potential must have a negative serum pregnancy test result within 96 hours of first dose of study treatment. Alternatively, if a negative serum pregnancy test was obtained within 7 days of first dose of study treatment, it needs to be confirmed by a negative urine pregnancy test on the day of the first administration of study treatment prior to dosing.

- Prior treatment with fulvestrant or other SERDs, regardless of treatment setting

- Prior treatment with PI3K inhibitor (such as alpelisib, taselisib, or buparlisib), mTOR inhibitor (such as everolimus) or AKT inhibitor (such as ipatasertib or capivasertib), regardless of treatment setting
- *Phase I/II portion* only: Prior treatment with CDK4/6 inhibitor *for locally advanced unresectable or metastatic breast cancer (see Section 4.1.1 for details on prior treatment of CDK4/6 inhibitor in the neoadjuvant/adjuvant setting)*
- Concurrent hormone replacement therapy
- Prior treatment with a cytotoxic chemotherapy regimen for metastatic breast cancer

  Note: there is no restriction on the number of prior cytotoxic chemotherapy regimens in the neoadjuvant or adjuvant setting
- *Phase III portion only: No more than one prior line of endocrine-based therapy for locally advanced unresectable or metastatic breast cancer*
- Treatment with approved or investigational cancer therapy within 14 days prior to first dose of study treatment

  Local radiotherapy with palliative intent to non-target sites may be allowed within 14 days prior to first dose of study treatment if not feasible earlier and if discussed with the Medical Monitor (however, once irradiated, bone lesions are generally no longer evaluable).
- History of or known presence of brain or spinal cord metastases

  Patients with leptomeningeal carcinomatosis will be excluded.
- Uncontrolled pleural effusion, pericardial effusion, or ascites, as judged by the investigator
- Uncontrolled tumor-related pain, as judged by the investigator

  Patients requiring narcotic pain medication must be on a relatively stable regimen at study entry.

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to first dose of study treatment.

  Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to first dose of study treatment (however, once irradiated, lesions are generally no longer evaluable)
- Uncontrolled hypercalcemia or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy

  Patients who are receiving bisphosphonate therapy specifically to prevent/treat skeletal events (e.g., bone metastasis, osteoporosis) and who do not have a history of clinically significant hypercalcemia are eligible.
- Non–study-related minor surgical procedures $\leq$ 5 days or major (invasive) surgical procedure $\leq$ 14 days prior to first dose of study treatment.

Patient must have sufficiently recovered from surgery and be stable, and wound healing must have occurred.

- History of Type I or Type II diabetes mellitus requiring insulin

  Patients who are on a stable dose of oral diabetes medication ≥2 weeks prior to initiation of study treatment are eligible for enrollment. Patients must meet the laboratory eligibility criteria for fasting blood glucose and HbA1c as outlined in the inclusion criteria.

- History of or active inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis) or active bowel inflammation (e.g., diverticulitis)
- Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia)
- Grade ≥2 uncontrolled or untreated hypercholesterolemia or hypertriglyceridemia
- Patients with active (chronic or acute) hepatitis C virus (HCV) at screening

  Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

  Patients receiving anti-viral therapy for HCV are not eligible

- Hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test or a positive quantitative HBV DNA test at screening

  If a patient has a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test, a quantitative HBV DNA test must be *negative to be eligible.*

  Patients receiving anti-viral therapy for HBV are not eligible.

- Known HIV infection
- Illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment
- Active infection requiring systemic anti-microbial treatment (including antibiotics, anti-fungals, and anti-viral agents)
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that, in the investigator's opinion, gives reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
- History of malignancy other than breast cancer within 5 years prior to screening with the following exceptions:
  - Appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer

  - Other malignancies where the patient has undergone potentially curative therapy with no evidence of disease and are deemed by the treating physician to have a recurrence rate of $<5\%$ at 5 years.
- History of clinically significant cardiovascular dysfunction, including the following:
  - History of stroke or transient ischemic attack within 6 months prior to first dose of study treatment
  - History of myocardial infarction within 6 months prior to first dose of study treatment
  - New York Heart Association Class III or IV cardiac disease
  - Unstable arrhythmias, active ventricular arrhythmia requiring medication, or unstable angina
  - Congenital long QT syndrome or screening QT interval corrected using Fridericia's formula (QTcF) >480 milliseconds based on the mean value of the triplicate ECGs
  - History or presence of an abnormal ECG that is clinically significant in the investigator's opinion (including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction)
- Presence of any other condition that may have increased the risk associated with study participation or may have interfered with the interpretation of study results, and, in the opinion of the investigator, would have made the patient inappropriate for entry into the study.
- Need for chronic corticosteroid therapy of ≥ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease
- Treatment with strong CYP3A inhibitors or strong CYP3A inducers within 14 days or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study treatment (see Appendix 8 for examples of strong CYP3A inducers and inhibitors)
- Malabsorption syndrome or other condition that would interfere with enteral absorption
- Inability or unwillingness to swallow pills or receive intramuscular injections
- Known or possible hypersensitivity to *any of the study treatments, or to* goserelin or alternative LHRH agonist (if applicable), *including* excipients

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This study includes an initial open-label Phase Ib safety portion and a randomized, double-blind, placebo-controlled Phase III portion.

After written informed consent has been obtained, eligibility has been established and patient has been approved (Phase Ib only), the study site will obtain the patient's identification number and treatment assignment (randomized Phase III portion, only) from the interactive voice/Web response system (IxRS).

For patients in the randomized Phase III portion of the study, randomization will occur in a 1:1 ratio using a permuted-block randomization method. Patients will be randomized to one of two treatment arms. The randomization scheme is designed to ensure that an approximately equal number of patients will be enrolled in each treatment arm within the stratum determined by the following stratification factors at baseline:

- Relapse <2 vs ≥ 2 years during adjuvant endocrine therapy (Y/N/NA)
- Tri-AKT status by ctDNA (positive/negative)
- *Baseline liver metastasis* (Y/N)
- Geographic region
  - Western Europe, United States, Canada, Australia
  - Asia
  - Rest of World (remaining countries)

Study site personnel and patients will be blinded to treatment assignment during the randomized Phase III portion of the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, the Independent Data Coordinating Center (iDCC) facilitating the iDMC meetings, and iDMC members.

While PK samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK assay results for these patients are generally not needed for the safe conduct or proper interpretation of the Phase III portion of this study. Laboratories responsible for performing study drug PK assays for the Phase III portion will be unblinded to patients' treatment assignments to identify appropriate samples to be analyzed. PK samples from patients assigned to the comparator arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing).

If unblinding is necessary for a patient enrolled in the Phase III portion for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to

break the treatment code by contacting IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. Provided the patient progressed on this study or had to permanently discontinue study treatment due to unacceptable toxicity, unblinding may be permitted if an investigator is deciding whether a patient should initiate treatment with a proven therapy or alternatively may participate in a clinical trial where blinded treatment would be exclusionary but patient fulfills all remaining eligibility criteria after having been enrolled in this study. The investigator should document and provide an explanation for any non-emergency unblinding. The investigator will be able to break the treatment code by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are ipatasertib (RO5532961) or its placebo (in the randomized Phase III portion of the study), palbociclib, and fulvestrant. *A pharmacy manual with additional details on IMP storage, handling, and administration will be provided by the Sponsor.*

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Ipatasertib and Placebo

Ipatasertib will be supplied by the Sponsor as 100-mg and 200-mg tablets in packaged bottles. The ipatasertib placebo tablets (Phase III only) have been manufactured to match the size, shape, and color of the ipatasertib active tablets (100 and 200 mg) and are indistinguishable in appearance from the active ipatasertib tablets. For information on the formulation and handling of ipatasertib/placebo, see the Ipatasertib Investigator's Brochure *and/or pharmacy manual as appropriate*.

4.3.1.2 Palbociclib

Palbociclib will be supplied by the Sponsor as 125-mg, 100-mg, and 75-mg capsules *and as 125-mg, 100-mg, and 75-mg tablets once tablet supply can be provided by the Sponsor; therefore, palbociclib is being referred to as capsule/tablet*. For information on

the formulation, packaging, and handling of palbociclib as well as the safety profile, refer to the local prescribing information *and/or pharmacy manual as appropriate.*

4.3.1.3 Fulvestrant

Fulvestrant will be supplied by the Sponsor in all participating countries, except the countries where procurement will be reimbursed. For countries in which the Sponsor is supplying fulvestrant, it will be supplied in sterile, single-patient, prefilled syringes containing 50 mg/mL fulvestrant as a 5-mL injection. For information on the formulation, packaging, and handling of fulvestrant as well as the safety profile, refer to the local prescribing information *and/or pharmacy manual as appropriate*.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.1 and Section 3.1.2.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.4.

4.3.2.1 Ipatasertib and Placebo

For patients enrolled in the Phase Ib portion only, ipatasertib will be open label and will be administered orally in the clinic on Day -7 to Day -5, on Cycle 1 Day 1 and on each subsequent cycle visit and will be taken at home on non-clinic visit days *based on the 21/7 dose schedule* (see Figure 2). Ipatasertib is initially given orally for 5-7 days as a single agent prior to Cycle 1, Day 1. On Cycle 1, Day 1, ipatasertib will be administered approximately 6 hours prior to palbociclib and fulvestrant to enable collection of post-dose samples (see Appendix 4), that is, palbociclib and fulvestrant will be administered after the PK sampling of ipatasertib for Cycle 1, Day 1 is completed. Starting from Cycle 1, Day 2, palbociclib will be given together with ipatasertib. For the first cycle, ipatasertib will be administered continuously for 26 to 28 days given the Day -7 to Day -5 window for the start of the single-agent ipatasertib run-in; however, starting with Cycle 2, Day 1 ipatasertib will be taken orally once daily on Days 1–21 of each 28-day cycle (see Figure 2).

In the randomized Phase III portion of the study, ipatasertib/placebo is given orally once daily on Days 1–21 of each 28-day cycle. Ipatasertib/placebo will be administered in the clinic on Cycle 1 Day 1 and on each subsequent cycle visit; it will be taken at home on non-clinic visit days *based on the 21/7 dose schedule*.

Ipatasertib/placebo may be taken with or without food. If a dose is missed (i.e., not taken within approximately 8 hours after the scheduled dosing time), the patient should

resume dosing with the next scheduled dose. Missed or vomited doses will not be made up. If ipatasertib/placebo cannot be safely administered during any of the Days 1–21 of any 28-day cycle, it is permitted to make up for the missed doses on any of the Days 22–28, if safe to do so.

On study days requiring a predose blood draw for PK sampling, patients will be instructed to take their daily oral dose of ipatasertib/placebo in the clinic after completion of the pretreatment assessments (see Appendix 1 [Phase III SOA] and Appendix 3 [Phase Ib SOA]). Ipatasertib/placebo should be taken at approximately the same time each day, and ideally, the time of dosing outside the clinic should be the same as the time of dosing during the clinic visit. Time of dose administration will be collected on the PK sampling day and for prior doses administered, for up to 2 days before a PK sampling visit. Importantly, the dosing time should be the same or similar on the 3 days prior to and on the day of the PK visit. Any incidence of vomiting within 3 hours post drug administration should also be recorded for the day of PK sampling.

A sufficient amount of ipatasertib/placebo should be provided to the patient to last one treatment cycle. Notably, there is one extra dose of ipatasertib/placebo in each bottle. This may be explained to the patient to minimize the risk that the patient mistakenly takes the extra dose. Patients will be instructed to bring their bottles of ipatasertib/placebo and their medication diaries to each study visit. Patients should use their medication diary to record daily ipatasertib/placebo dosing taken as applicable.

4.3.2.2 Palbociclib

In both open-label Phase Ib and the randomized Phase III portion of this study, palbociclib is given PO QD on Days 1–21 of each 28-day cycle. Palbociclib will be administered in the clinic on Cycle 1 Day 1 and each subsequent cycle visit and will be taken at home on non-clinic visit days *based on the 21/7 dose schedule*. Palbociclib should be taken at approximately the same time each day. Palbociclib capsules are taken with food to reduce the intersubject variability of palbociclib exposure (IBRANCE® U.S. Package Insert). *Palbociclib tablets, in contrast, may be taken with or without food (refer to the local prescribing information for additional details).* If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. Palbociclib capsules*/tablets* should be swallowed whole (they should not be chewed, crushed, or opened*/split* prior to swallowing). Capsules*/tablets* should not be ingested if they are broken, cracked, or otherwise not intact. Patients will be instructed to bring their bottles*/blister cards (as applicable)* of palbociclib and their medication diaries to each study visit. Patients should use their medication diary to record daily palbociclib dosing taken as applicable.

Refer to the local prescribing information for more details.

4.3.2.3 Fulvestrant

Fulvestrant 500 mg will be administered in the clinic as two intramuscular injections of 250 mg each on Cycle 1 Days 1 and 15 and Day 1 of each subsequent 28-day cycle. Refer to the local prescribing information for more details.

For patients enrolled in the Phase Ib portion, it is recommended that fulvestrant be administered prior to the oral medications, ipatasertib and palbociclib, during all clinic visits following Cycle 1, Day 1. In contrast, on Cycle 1, Day 1, ipatasertib is administered first (see Section 4.3.2.1). For patients enrolled in the Phase III portion, it is recommended that fulvestrant be administered prior to the oral medications, ipatasertib/placebo and palbociclib, during all clinic visits.

4.3.2.4 Goserelin

Goserelin is a non-IMP in this study for pre- or peri-menopausal women who must have started treatment with goserelin or an alternative LHRH agonist at least *14* days prior to first dose of study treatment. *For men, treatment with goserelin or alternative LHRH agonist therapy is recommended beginning at least 14 days prior to first dose of study treatment and continuing for the duration of study treatment.* If patients have received an alternative LHRH agonist prior to study entry, it is recommended that they switch to goserelin for the duration of the trial, whenever possible. Every effort should be made to administer goserelin or alternative LHRH agonist as applicable on site at the time of fulvestrant administration *as applicable* in order to minimize the number of clinic visits. Patients may self-administer goserelin or alternative LHRH agonist as applicable at home per local standard of care if the administration does not coincide with a clinic visit. In that case, patients will complete a diary.

Refer to the local prescribing information for more details.

4.3.2.5 Loperamide

Loperamide is a non-IMP in this study. All patients should receive loperamide (2 mg PO twice a day [BID] or 4 mg QD) as prophylaxis for diarrhea upon start of study treatment through the first cycle if allowed by local guidance. Investigators are encouraged to continue this dosing for the remainder of the study; the prophylaxis dose may be adjusted as necessary, using their discretion based on clinical judgment and per local guidance. *Patients should use their medication diary to record loperamide dosing taken as applicable.*

See Section 5.1.4.5.1 for additional details on loperamide use for treatment emergent diarrhea.

Refer to the local prescribing information for more details.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (i.e., ipatasertib or its placebo, palbociclib and fulvestrant) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS. Any damaged shipments will be replaced, if needed.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Continued Access to Ipatasertib

Currently, the Sponsor does not have any plans to provide the Roche IMP (ipatasertib) or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing ipatasertib in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

However, patients may be eligible to receive ipatasertib as part of an extension study if the Sponsor elects to initiate an extension study while this study is ongoing.

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/discontinuation visit or up to 30 days after last dose if medication was given for an Adverse Event, whichever is longer. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF (see Section 4.5.2 for additional information for specific concomitant medications).

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Loperamide as prophylaxis for diarrhea (racecadotril as used in Europe)

See Section 4.3.2.5 for further details. Patients who experience diarrhea should be on treatment doses of loperamide per the management guidelines (see Section 5.1.4.5.1).

- Goserelin or alternative LHRH agonist (as applicable for pre- or peri-menopausal women *and men*, see Section 4.3.2.4 and Section 4.1.1)
- Bisphosphonate therapy or receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor therapy

  Bisphosphonate therapy (e.g., zoledronic acid) or RANKL inhibitor therapy (e.g., denosumab) used specifically to prevent skeletal events (e.g., bone metastasis, osteoporosis) are allowed.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered at the discretion of the investigator. Antihistamine prophylaxis for potential adverse event of rash may be considered for the first cycle and as clinically indicated for subsequent cycles. *Note that primary prophylactic use of hematopoietic growth factors (e.g., erythropoietins, granulocyte colony-stimulating factor [G-CSF], and GM-CSF) is not permitted. However, they may be used to treat treatment-emergent neutropenia or anemia or as secondary prophylaxis if dose reduction or delay is not considered a reasonable alternative. The Medical Monitor may be consulted for further clarification.*

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice.

4.4.2 Cautionary Therapy

Palliative radiotherapy is permitted for the treatment of known bony metastases or symptomatic relief of pain provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be a site of measurable disease).

For patients who require radiation or surgery as part of medical treatment in the absence of radiographic disease progression, investigators must exercise caution. Ipatasertib/placebo should be temporarily held for at least 7 days before, if feasible, and 7 days after the procedure. For minor surgery or single-day radiotherapy, the ipatasertib/placebo hold may be shorter, if approved by the Medical Monitor. After the temporary treatment hold is complete, ipatasertib/placebo may be re-initiated when the patient has sufficiently recovered. Fulvestrant should not be administered on the day of surgery or radiation therapy, but otherwise, dosing does not generally need to be interrupted. Surgery should be performed after neutropenia and/or thrombocytopenia has been resolved whenever possible. Palbociclib may be held temporarily per investigator judgment.

Live vaccines should be used with caution and preferably only administered in patients not experiencing neutropenia or once neutropenia has resolved to Grade 1 or below.

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events (see Section 5 for details). Ipatasertib/placebo should be temporarily held during systemic corticosteroid treatment.

4.4.2.1 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

In vitro data suggest that ipatasertib is metabolized by CYP3A and may be a time-dependent inhibitor of CYP3A. A clinical drug–drug interaction study with midazolam (a sensitive CYP3A substrate) showed a 2.2-fold increase in midazolam exposures in presence of steady-state ipatasertib dosed at 600 mg QD.

Given that ipatasertib is primarily metabolized by CYP3A, there is a high potential for drug–drug interactions of ipatasertib with any medication that strongly inhibits or induces CYP3A. Data from clinical studies showed that ipatasertib exposures were reduced by ~50% when co-administered with enzalutamide, a strong CYP3A inducer and a strong CYP3A inhibitor itraconazole increased ipatasertib exposures by 5-fold.

In vitro data indicate that CYP3A and SULT2A1 are mainly involved in the metabolism of palbociclib and palbociclib is a weak time-dependent inhibitor of CYP3A. Co-administration of midazolam with multiple doses of palbociclib increased the midazolam exposure by 61%. Palbociclib exposures decreased by 85% with co-administration of rifampin, a strong CYP3A inducer. Co-administration of itraconazole with palbociclib increased palbociclib exposures by approximately 87%.

Therefore, the following drugs, and those listed in Appendix 8, should be used with caution when palbociclib and ipatasertib/placebo are given:

- Drugs that are strong CYP3A inhibitors, strong CYP3A inducers, and sensitive CYP3A substrates with narrow therapeutic window should be used with caution when these drugs need to be given intermittently for medical treatment. Ipatasertib/placebo should be temporarily held until at least 7 days after the last dose of strong CYP3A inhibitors and sensitive CYP3A substrates with a narrow therapeutic window. Avoid concurrent use of palbociclib with strong CYP3A inducers and with strong CYP3A inhibitors. If patients must be co-administered a strong CYP3A inhibitor, refer to the local prescribing information for guidance on the palbociclib dose. See Section 4.4.3 for further details on chronic use of strong CYP3A inhibitors, strong CYP3A inducers, and sensitive CYP3A substrates.
- Drugs that are moderate CYP3A inhibitors should be used with caution
- Since palbociclib and ipatasertib have overlapping CYP3A interactions, please refer to the ipatasertib Investigator's Brochure and to the local prescribing information for palbociclib for concomitant medication use for CYP3A inhibitors, CYP3A inducers, and sensitive CYP3A substrates with narrow therapeutic window.

Patients should be closely monitored. Refer to the following information for further guidance on CYP450 -drug interactions and a list of common substrates, inhibitors, and inducers:

Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers (U.S. FDA):

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

The lists of medications (see Appendix 8 and link above) are not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator. Herbal therapies that require caution or are prohibited due to CYP interactions, such as St. John's wort, are described in Section 4.4.2.1 and Section 4.4.3, respectively.

4.4.3 Prohibited Therapy, Foods, and Supplements

Use of the following concomitant therapies is prohibited as described below:

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 14 days prior to initiation of study treatment and during study treatment.
- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy [other than study treatment fulvestrant as well as goserelin for pre- and peri-menopausal women], immunotherapy, radiotherapy, and herbal therapy) is prohibited for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment, until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances (see Section 4.1.2 for details).
- Chronic use of strong CYP3A inhibitors, strong CYP3A inducers (see Appendix 8 for examples), or sensitive CYP3A substrates with narrow therapeutic window (refer to drug label) is prohibited within 14 days (or 5 drug-elimination half-lives, whichever is longer) prior to and during the study treatment period and for 7 days after the last dose of study treatment. Grapefruit juice, a potent CYP3A inhibitor, and St. John's wort, a potent CYP3A inducer, are also prohibited for similar duration.
- *Primary prophylactic use of hematopoietic growth factors (e.g., erythropoietins, granulocyte colony-stimulating factor [G-CSF], and GM-CSF) is not permitted (see* Section 4.4.1 *for use for treatment-emergent events or secondary prophylaxis).*

4.4.4 Additional Restrictions

No food or fluids other than water will be allowed for 8 hours prior to each study visit until after study laboratory samples for fasting glucose and fasting lipid profile, as applicable, are obtained.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1 (Phase III SOA) and Appendix 3 (Phase Ib SOA). All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations) and may be obtained more than 6 weeks before initiation of study treatment. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable. Patient re-screening may be considered under certain circumstances, after approval by the sponsor based on consultation with the Medical Monitor, as needed.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), and reproductive status, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

In addition, to assess the actual use of analgesic (Phase III only), and anti-diarrheal medications outside of the clinic/hospital setting, patients will complete a medication diary. Patients will receive the diary *at the start of the ipatasertib run-in period (Phase Ib only) and* on the first day of each cycle, with site staff completing relevant information on any prescribed analgesic or anti-diarrheal medications, including the recommended dosage and route of administration. The intake of analgesic medication (Phase III only),

and loperamide (or other anti-diarrheal) medication will be reported in the corresponding eCRFs.

Demographic data will include age, sex, and self-reported race/ethnicity. Race/ethnicity will be captured to assess if any differences in safety exist based on this entry.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, as specified in Appendix 1 (Phase III SOA) and Appendix 3 (Phase Ib SOA), should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified post-baseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature as specified in Appendix 1 (Phase III SOA) and Appendix 3 (Phase Ib SOA).

4.5.5 ECOG Performance Status

Performance status will be completed at screening and as specified in the SOA (see Appendix 1 [Phase III SOA] and Appendix 3 [Phase Ib SOA]) using the ECOG performance status scale (see Appendix 5) and recorded on the eCRF.

4.5.6 Tumor and Response Evaluations

All known sites of disease must be documented at screening (baseline) and re-assessed at each subsequent tumor evaluation, post-baseline. Post-baseline tumor assessments should be performed every 8 weeks ± 7 days from Cycle 1 Day 1 regardless of dose delay, treatment interruption, or early treatment discontinuation until disease progression.

Screening (baseline) tumor assessments should include CT scans of the chest, abdomen, and pelvis and be performed ≤28 days before Cycle 1, Day 1 (or first dose of study treatment for Phase Ib patients). CT scans of the neck and brain imaging should be included if clinically indicated. Screening (or documented standard of care [SOC]) bone scans (technetium) should be performed within 6 weeks before Cycle 1, Day 1 (or first dose of study treatment for Phase Ib patients). A documented standard-of-care tumor assessment performed within 28 days before Cycle 1, Day 1 (*or* first dose of study treatment for Phase Ib) may be used for the screening assessment, provided it meets the following requirements that apply to all study specific tumor assessments:

- CT scans are the preferred imaging modality for tumor assessments. Tumor assessments should include a diagnostic quality, contrast-enhanced CT scan of the chest, abdomen, and pelvis. To be suitable for RECIST assessments, CT scans should have a maximum slice thickness/interval of 5 mm and no gaps.
- In patients for whom a CT scan is contraindicated because of an allergy to intravenous (IV) radiographic contrast both a CT scan of the chest without contrast and an MRI scan of the abdomen and pelvis with contrast are recommended.
- MRI scans may be performed in lieu of CT scans. However, an MRI scan of the chest may be performed only with the approval from the Sponsor based on consultation with the Medical Monitor.

For patients with bone metastases, subsequent post-baseline bone scans should be performed with every other tumor assessment starting from Week 16 (±7 days), unless the bone lesions are followed via CT scan or other imaging modality (MRI or X-ray) during the regular tumor assessments every 8 weeks (±7 days), in which case additional post-baseline bone scans are only needed as clinically indicated. Bone disease and any changes in bone imaging should be evaluated radiographically by CT scan, MRI, or X-ray to verify the presence of bone destruction versus a healing reaction. If the patient presents with both irradiated and non-irradiated bone lesions, only the non-irradiated lesions should be followed for tumor assessments unless progression is documented after the radiation. If a bone scan cannot be performed during the course of the study due to for example a Technetium-99m shortage, alternative imaging options should be discussed with the Sponsor (e.g., sodium fluoride [NaF]).

Response assessments will be made by the investigator on the basis of physical examinations and imaging (CT, MRI, and bone scans) through use of RECIST v1.1 criteria (see Appendix 9).

To ensure a valid comparison of tumor data and uniformity in the assessment of tumor response during the study, the following procedures should be implemented at the study site:

- All lesions identified at baseline (target and non-target) will be reassessed using the same imaging method throughout the course of the study. The same radiographic procedure used to assess disease sites at screening should be used throughout the

study (e.g., the same contrast protocol for CT scans). Assessments should be performed by the same evaluator to ensure internal consistency across visits.

- All CT scans and other relevant imaging, such as MRIs, obtained for all patients enrolled at the center should be reviewed by the local radiologist who, together with the investigator, will determine the local assessment of response and progression. All bone scans obtained from patients with bone metastases should also be reviewed similarly.
- For patients in the Phase III portion only: All radiological data (e.g., CT scan, MRI, bone scan) and photos for skin lesions obtained at baseline, during the treatment period, and the follow-up period should be sent to a central imaging vendor contracted by the Sponsor within 2 weeks of imaging to enable retrospective blinded independent central review when needed. Additional details will be outlined in the statistical analysis plan and a separate charter.
- Tumor response and progression will be assessed and will be the basis for the efficacy analyses (along with survival information). The main analysis of the trial will be based on the local radiology review results.
- Confirmation of an objective response is only valid when the repeat assessments are performed $\geq$4 weeks after initial documentation.

At the investigator's discretion, and if clinically indicated, tumor assessments may be repeated at any time if progressive disease is suspected. For symptomatic deterioration attributed to disease progression (clinical progression), every effort should be made to document progression through use of objective criteria per RECIST v1.1.

Note: Pathologic fracture, new compression fracture, or bone metastases complications will not be considered generally as evidence of disease progression unless there is radiographic progression per RECIST v1.1. See Section 4.5.7 for the assessment of SREs. Patients with symptoms of rapidly progressing disease without radiographic (or photographic) evidence will not be considered to have progressed for efficacy analyses. The evaluation of overall lesion response will be performed according to RECIST v1.1 as described in Appendix 9.

Patients in the randomized Phase III portion who discontinue study treatment for any reason other than radiographic disease progression per RECIST v1.1, will be followed every 8 weeks $\pm 7\ days$ for tumor assessments until documented progression per RECIST v1.1 or death, whichever occurs first.

After the primary PFS analysis has been completed, tumor assessments may be done per local SOC.

Patients who are enrolled in the Phase Ib portion of the study may have post-baseline tumor assessments done per local SOC as the efficacy data will not be part of the primary PFS analysis.

4.5.7 Skeletal-Related Events Assessment

For this study, an SRE is defined as a pathologic fracture, radiation therapy to the bone, surgery to the bone, or a spinal cord compression. The investigator assessment for each adverse event, radiation or surgery relating to the bone or spinal cord, should be reported in the patient chart and in the corresponding eCRF. Patients in the Phase III portion should be monitored for any SREs during the study treatment and adverse event follow-up period of the study (see Appendix 1 [Phase III SOA], and Section 5.5).

4.5.8 Laboratory, Biomarker, and Other Biological Samples

Laboratory samples should be drawn according to the schedule of activities (see Appendix 1 [Phase III SOA] and Appendix 3 [Phase Ib SOA]). Results of the following assessments should be available for review at each clinic visit (as required per SOA) prior to dosing to inform dosing decisions: complete blood count, fasting glucose, bilirubin, total ALP, AST, and ALT.

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: RBC count, hemoglobin, hematocrit, WBC count with differential (i.e., must be sufficient for the determination of ANCs, lymphocytes), and platelet count
- Fasting serum chemistry: glucose (following ≥8-hour fast, plasma glucose is also acceptable per local practice), BUN (or urea), bicarbonate (or total carbon dioxide), creatinine, sodium, potassium, magnesium, calcium, phosphorus, albumin, total bilirubin, ALP (total ALP), AST, and ALT

  For investigational sites in countries where bicarbonate (or total carbon dioxide) may not be collected as part of the standard chemistry panel, bicarbonate (or total carbon dioxide) will not be measured.
- Home glucose monitoring: for any patients who initiate home glucose monitoring as a result of treatment emergent hyperglycemia (see Section 5.1.4.5.2 for management guidelines of fasting hyperglycemia), a glucose log will be made available for capturing these results.
- Glycosylated hemoglobin (HbA1c)
- Amylase and lipase
- Fasting lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides) performed following a ≥8 hour fast
- Urinalysis (dipstick allowed): pH, specific gravity, glucose, protein, ketones, and blood; microscopic examination if clinically indicated
- Screening viral serology: HBsAg, total HBcAb, HCV antibody

  Additional tests for HBV DNA or HCV RNA may be required to confirm eligibility (see Section 4.1.2).
- HIV serology: as per local standard, after any applicable local consenting requirements
- Coagulation: PTT (or aPTT) and INR

- Pregnancy test (see Section 4.1.2 regarding eligibility requirements)

The following samples will be sent to the Sponsor or a designee for analysis:

- Plasma samples for PK analysis of ipatasertib, G-037720, palbociclib and possibly fulvestrant (see Appendix 2 and Appendix 4 for details)
- Optional tumor biopsy (see Appendix 1 [Phase III SOA] and Appendix 3 [Phase Ib SOA])
- Blood samples for WGS (if approved locally)

  If approved by the local regulatory authority, gene mutations will be assayed by WGS or other acceptable methodology such as multiplex PCR or allele-specific PCR. Results may be correlated to ipatasertib exposure or other clinical measures to better understand the impact of genetic variants on drug metabolism, exposure, adverse events, and/or response (see Section 4.5.11 for more details).

- Biomarker assays in blood, tissue, and plasma
  - Blood samples acquired from all patients at screening will be processed to obtain plasma for the determination of Tri-AKT tumor status, as defined by baseline ctDNA. For patients in the Phase III portion a valid test result will be required for patient stratification.
  - Plasma samples will be collected at predefined timepoints during treatment (see Appendix 1 [Phase III SOA] and Appendix 3 [Phase Ib SOA]), and at the time of disease progression for the determination of changes in blood-based biomarkers (e.g. ctDNA).
  - Tissue biopsies (tissue blocks or unstained slides) may be processed for protein marker analysis (IHC) or for their derivatives (e.g. RNA, DNA, protein).
- For patients in the Phase III portion only: Archival or newly collected tumor tissue sample obtained at baseline for determination of *PIK3CA/AKT1/PTEN* status and for exploratory research on biomarkers

  A representative FFPE tumor specimen in a paraffin block (preferred) or at minimum of 12 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment. If only 10 slides are available, the patient may still be eligible for the study, after Sponsor approval has been obtained. Sponsor may consider approving up to 15 patients with fewer than 10 slides, thus sites may contact Sponsor if fewer than 10 but at least 8 slides are available.

  Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing,

cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases that have been decalcified is not acceptable.

If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required.

Exploratory biomarker research methods on the above biomarker samples may include, but will not be limited to, NGS, PCR, RNASeq, IHC, and proteomics-based approaches. These methods will be used to identify somatic mutations or signatures of mutations that are predictive of response to study drug, are associated with disease progression, are associated with acquired resistance to the study medications, or that can increase the knowledge and understanding of disease biology. NGS methods will not include WGS.

NGS may be performed by *Foundation Medicine, Inc. or other central laboratory selected by the Sponsor. Depending on the central laboratory performing the test,* the investigator may obtain results from these analyses by requesting an NGS report *upon patient's* screen failure or progression of disease. If allowed by local laws, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions. Results may not be available for samples that do not meet criteria for testing.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.13), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Plasma samples collected for PK analysis may be needed for additional PK characterization and assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood, plasma and tissue samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood samples collected for WGS will be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the Institutional Review Board/Ethics Committee (IRB/EC) approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or no later than the time of final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on mutations, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law (with the exception of the report from *the central laboratory* which may be requested at screen failure or progression of disease). The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.9 Electrocardiograms

Triplicate ECG recordings will be obtained at baseline to determine eligibility (see Section 4.1.2). Additional single ECG recordings will be obtained as outlined in the schedule of activities (see Appendix 1 [Phase III SOA] and Appendix 3 [Phase Ib SOA]).

Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

4.5.10 Patient-Reported Outcomes

PROs will be collected to more fully characterize ipatasertib in combination with palbociclib and fulvestrant compared with placebo+palbociclib+fulvestrant in patients enrolled in the randomized Phase III portion of the study. PRO data will be collected via paper questionnaires at the clinic sites using the following instruments: *BPI-SF "worst pain" item,* EORTC QLQ-C30*, EORTC QLQ-BR23*, select items of the PRO-CTCAE, and the EQ-5D-5L. The questionnaires, translated into the local language as appropriate, will be distributed by the site staff and completed in their entirety by the patient at baseline (Cycle 1, Day 1*)* and *at subsequent timepoints as* noted in the *schedule of assessments* (see Appendix 1 [Phase III SOA]). To minimize burden to patients *and support market access requirements*, after treatment discontinuation, *the*

EORTC QLQ-C30 and EORTC QLQ-BR23 will be administered over the phone or in-clinic only *once during the follow-up period at 3 months, and* the *BPI-SF and EQ-5D-5L will be administered over the phone or in-clinic* every *6* months for a duration of 1 year. To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self-administered or interviewer-administered (as appropriate*; see below*) before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

It is common for patients to complete laboratory assessments before a scheduled clinic visit. Completion of PROs after laboratory tests is permitted so long as there is no prior discussion of the patients' laboratory results or health record with clinic staff and that the PROs are completed before drug administration.

For patients who are unable to complete the measures on their own, interviewer assessment is allowed but can only be conducted by a member of the clinic staff who reads the questionnaire items to the patient verbatim; no interpretation, rephrasing, or rewording of the questions is allowed during interview-assisted completion.

Study personnel should review all questionnaires for completeness before the patient leaves the investigational site and should ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank. Hard copy originals of the questionnaires must be maintained as part of the patient's medical record at the site for source data verification. These originals should have the respondent's initials, study patient number and date, and time of completion recorded in compliance with good clinical practice. Sites will enter patient responses to the PRO questionnaires into the electronic data capture (EDC) system.

4.5.10.1 *BPI-SF "Worst Pain" Item*

The BPI-SF (see Appendix 10) is a widely used patient-reported outcome measure for assessing pain, and the "worst pain" item is frequently recommended for evaluating increases in the severity of pain (Cleeland, 2009; Shi et al., 2009). The item asks patients to rate their pain at its worst in the last week on a scale from 0 to 10. The BPI-SF worst pain item takes approximately 1 minute to complete.

4.5.10.2 EORTC QLQ-C30

The EORTC QLQ-C30 (see Appendix 11) is a validated and reliable self-reported measure (Aaronson et al. 1993; Sprangers et al. 1996; Fitzsimmons et al. 1999). It consists of 30 questions that assess 5 aspects of patient functioning (physical, emotional, role, cognitive, and social), eight symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea), financial difficulties, and GHS/*QoL* with a recall period of the previous week.

The EORTC QLQ-C30 data will be scored according to the EORTC scoring manual (Fayers et al. 2001). Scale scores will be obtained for each of the multi-item and single-items scales by using a linear transformation for standardization of the calculated raw score. The EORTC QLQ-C30 takes approximately 10 minutes to complete.

4.5.10.3 *EORTC QLQ-BR23*

The EORTC QLQ-BR23 (see Appendix 12) breast cancer module is meant for use among women diagnosed with breast cancer (Sprangers et al. 1996). The breast cancer module incorporates five, multiple-item scales to assess systemic therapy side effects, arm symptoms, breast symptoms, body image, and sexual functioning. In addition, single items assess sexual enjoyment, hair loss, and future perspective. The EORTC QLQ-BR23 takes approximately 10 minutes to complete. Because the QLQ-BR23 was not developed or tested and validated with men, male patients in this study will not complete the QLQ-BR23 measure.

4.5.10.4 PRO-CTCAE

The PRO-CTCAE (see Appendix 13) is an item bank reflecting 78 symptomatic adverse events rated according to their severity, interference with daily function, frequency, and/or occurrence. The item bank was designed and validated as a repository of standalone items (Basch et al. 2014). PRO-CTCAE will be completed per the Schedule of Activities (see Appendix 1 [Phase III SOA]), if available in the patient's preferred language.

Only adverse events that are patient self-reportable (Basch et al. 2014) were selected for assessment in this study. Adverse events of which assessments rely on laboratory testing (e.g., neutropenia) that are presented as being primarily asymptomatic or with nonspecific signs and symptoms were disregarded. Adverse events that did not have an identifiable symptom equivalent in the PRO-CTCAE were also excluded. Based on the above criteria, 7 symptomatic adverse events that have been associated with ipatasertib or palbociclib and fulvestrant treatment were selected from the PRO-CTCAE item bank: diarrhea, nausea, vomiting, decreased appetite, fatigue, mouth sores, and rash symptoms. An additional question from the PRO-CTCAE providing an overall assessment of the burden of side effects will also be collected. *The PRO-CTCAE takes approximately 5 minutes to complete.*

4.5.10.5 EQ-5D-5L

The EQ-5D-5L *(see* Appendix 14*)* is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a VAS that measures health state. Published weighting systems allow for creation of a single composite score of the patient's health status. The EQ-5D-5L takes

approximately 3 minutes to complete. The EQ-5D-5L will be collected to inform pharmacoeconomic modeling and will not be included in the Clinical Study Report.

4.5.11 Samples for Whole Genome Sequencing

At participating sites (where approved locally), blood samples will be collected for DNA extraction to enable WGS or alternative technology to identify mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research may aim to distinguish germline mutations from somatic mutations. The samples may be sent to one or more laboratories for analysis.

Collection and submission of WGS samples is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS sampling, this section of the protocol (see Section 4.5.11) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Patient medical information associated with WGS samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate

authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the WGS analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.12 Optional Tumor Biopsies

Consenting patients will undergo optional tumor biopsies at baseline and/or at disease progression (if deemed clinically feasible by the investigator). Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

The Informed Consent Form will contain a separate section that addresses optional biopsies. A separate, specific signature will be required to document a patient's agreement to undergo optional biopsies. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Biopsy Sample Informed Consent eCRF.

Samples may be used for exploratory biomarker research as described in Section 4.5.8. Refer to Section 4.5.13.3 for details on sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.13 Optional Samples for Research Biosample Repository

4.5.13.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety

- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.13.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (see Section 4.5.13) will not be applicable at that site.

4.5.13.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to ipatasertib or the PI3K/Akt/mTOR pathway, diseases, or drug safety:

- If patient provides consent, any leftover samples, such as blood, serum, plasma, and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites), and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), including leftover tissue samples from medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the course of the study

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via WGS, whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.13.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.13.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients 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. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.13.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical

Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.13.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Use of an anticancer therapy not required per protocol
- Disease progression per investigator assessment according to RECISTv1.1 (see Appendix 9).
    - Symptomatic deterioration (clinical progression) in the absence of radiographic disease progression does not require treatment discontinuation

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Patients will return to the clinic for a treatment discontinuation visit within approximately 30 days after the final dose of study drug (ipatasertib/placebo or palbociclib or fulvestrant, whichever is discontinued last). See Appendix 1 (Phase III SOA) and Appendix 3 (Phase Ib SOA) for additional details.

Patients in the randomized Phase III portion who discontinue study treatment for any reason other than radiographic disease progression per RECIST v1.1 will be followed every 8 weeks $\pm 7\ days$ for tumor assessments until documented progression per RECIST v1.1 or death, whichever occurs first.

For patients in the randomized Phase III portion of the study, after treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including outcome) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study or the survival follow-up). See Appendix 1 (Phase III SOA) for additional details.

Additional PRO assessments for patients in the randomized Phase III portion of the study will also be completed $at\ 3,\ 6,\ and\ 12\ months\ after\ treatment\ discontinuation$ unless the patient withdraws consent or the Sponsor terminates the study or the PRO follow-up. See Appendix 1 (Phase III SOA) for additional details.

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain information on patients who withdraw from the study but have not withdrawn consent. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Ipatasertib is not currently approved for any indication, and clinical development is ongoing. Palbociclib and fulvestrant have been approved for the treatment of HR+ HER2-advanced or metastatic breast cancer in women with disease progression following endocrine therapy (see Section 1.3).

The safety plan for patients in this study is based on clinical experience with ipatasertib in completed and ongoing studies as well as clinical experience with combined palbociclib and fulvestrant and fulvestrant alone or fulvestrant in combination with PI3K pathway inhibitors.

The anticipated important safety risks and management plan for ipatasertib plus palbociclib and fulvestrant are outlined below. Refer to the Ipatasertib Investigator's Brochure for a complete summary of safety information. Refer to the local prescribing information for a complete summary of safety information for fulvestrant and palbociclib (including in combination with fulvestrant), respectively.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. An initial open-label Phase Ib portion will investigate the tolerability and potential drug-drug interaction of combining ipatasertib

in combination with palbociclib and fulvestrant (see Section 3.1.1 for further details). In the randomized Phase III portion, an iDMC will review unblinded safety data regularly throughout the study (see Section 6.8 for further details). Furthermore, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below. These guidelines apply to both the open-label Phase Ib portion as well as the blinded Phase III portion. In addition to these guidelines, more conservative dose modifications of any study treatment for the management of adverse events are permitted at the discretion of the investigator when deemed to be in the best interest of the patient.

5.1.1 Risks Associated with Ipatasertib

Ipatasertib has been associated with identified risks including the following: nausea, vomiting, diarrhea, stomatitis/mucosal inflammation, asthenia/fatigue, hyperglycemia, erythema multiforme, and rash. Ipatasertib's potential risks include hematologic or immunosuppressant effects, hyperlipidemia, hepatotoxicity, pneumonitis, colitis, and developmental toxicity.

Refer to Section 6 of the ipatasertib Investigator's Brochure for a detailed description of anticipated safety risks for ipatasertib.

5.1.2 Risks Associated with Palbociclib

Palbociclib has been associated with adverse events such as the following: neutropenia, febrile neutropenia, infections, leukopenia, fatigue, nausea, stomatitis, ILD (interstitial lung disease)/pneumonitis, anemia, alopecia, diarrhea, thrombocytopenia, rash, vomiting, decreased appetite, asthenia, and pyrexia as well as dysgeusia, vision blurred, lacrimation increased, dry eye, epistaxis, dry skin, and ALT and AST increases. Palbociclib has been associated with embryo-fetal toxicity and can cause fetal harm.

For additional information on the safety profile of palbociclib, refer to the local prescribing information.

5.1.3 Risks Associated with Fulvestrant

Fulvestrant has been associated with risks such as the following: hypersensitivity reactions, hot flushes, nausea, elevated hepatic enzymes (ALT, AST, ALP), rash, joint and musculoskeletal pain, asthenia, injection site reactions, urinary tract infection, reduced platelet count, anorexia, headache, venous thromboembolism, vomiting, diarrhea, elevated bilirubin, back pain, vaginal hemorrhage, neuropathy peripheral, and sciatica. Uncommon risks include anaphylactic reactions, hepatic failure, hepatitis, elevated gamma-glutamyl transferase, vaginal moniliasis, leucorrhea, injection site hemorrhage, injection site hematoma, and neuralgia (Summary of Product Characteristics [SmPC]).

For additional information on the safety profile of fulvestrant, refer to the local prescribing information.

5.1.4 Management of Patients Who Experience Adverse Events

5.1.4.1 Dose Modification for Ipatasertib

Management of some adverse reactions may require temporary dose interruptions/delays, and/or dose reductions, or permanent discontinuation of ipatasertib as per dose reduction schedules provided in Table 1 and Section 5.1.4.5.

If the patient does not tolerate the QD dosing of the ipatasertib/placebo, dosing with food may be used to alleviate gastrointestinal symptoms, including nausea, vomiting, and/or diarrhea. No more than two dose reductions of ipatasertib/placebo per patient will be allowed (see Table 1 exemplified by the starting dose of 300 mg). If the starting dose for the Phase III portion is determined to be 400 mg, two dose reductions are allowed, the first to 300 mg and the second down to the 200 mg. If the starting dose is determined to be 200 mg, only one dose reduction to 100 mg will be allowed. Dose re-escalation is not permitted for ipatasertib/placebo, regardless of the dose level.

Table 1 Dose Reductions for Ipatasertib/Placebo (Exemplified by the Starting Dose of 300 mg)

Dose Level [a]	Ipatasertib/Placebo
Starting dose	300 mg
First dose reduction	200 mg
Second dose reduction	100 mg
Third dose reduction	Not permitted

[a] If the patient continues to experience specified drug-related adverse events after the second reduction, ipatasertib/placebo should be discontinued.

5.1.4.2 Dose Modification for Palbociclib

Management of some adverse reactions may require temporary dose interruptions/delays, and/or dose reductions, or permanent discontinuation of palbociclib as per dose reduction schedules provided in Table 2 and Section 5.1.4.5. In general, the investigator may consider continuing palbociclib if the observed adverse event is not thought to be palbociclib related. See Section 3.1.5 for additional details on conditions for permanent discontinuation of palbociclib. *Dose re-escalation of palbociclib is not permitted, regardless of the dose level.*

Table 2 Dose Reductions for Palbociclib

Dose Level	Palbociclib
Starting dose	125 mg
First dose reduction	100 mg
Second dose reduction	75 mg
Third dose reduction	Not permitted

5.1.4.3 Dose Modification for Fulvestrant

The fulvestrant dose level should generally not be modified unless required in accordance with the label as determined by the investigator. In general, the investigator may consider continuing fulvestrant if the observed adverse event is not thought to be fulvestrant related. See Section 3.1.5 for additional details on conditions for permanent discontinuation of fulvestrant.

5.1.4.4 Treatment Interruption

Ipatasertib/placebo and/or palbociclib and/or fulvestrant treatment may be temporarily interrupted in patients who experience toxicity considered to be related to study drug. If corticosteroids are initiated for treatment of the toxicity, they must be tapered to $\leq$10 mg/day oral prednisone or equivalent before ipatasertib/placebo can be resumed, if clinically appropriate. If ipatasertib/placebo has been withheld for $>$60 consecutive days because of treatment-related toxicity, the patient should be permanently discontinued from ipatasertib/placebo. See Section 3.1.5 for further details on considerations for palbociclib and fulvestrant once ipatasertib/placebo is permanently discontinued. If, in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming ipatasertib/placebo after a hold of $>$60 consecutive days, study drug may be restarted with the approval from the Sponsor based on consultation with the Medical Monitor. Ipatasertib/placebo and/or palbociclib and/or fulvestrant treatment may be temporarily interrupted for reasons other than toxicity (e.g., surgical procedures) with approval from the sponsor based on consultation with the Medical Monitor.

If a scheduled fulvestrant dose coincides with a holiday or inclement weather or other conditions that preclude dosing, dosing should commence on the nearest following date, and subsequent dosing can continue on a new 28-day schedule on the basis of the new IM injection date.

5.1.4.5 Adverse Event Management Guidelines

Guidelines for management of specific adverse events are provided in the subsections below. Educational materials related to diarrhea management will be provided to investigators and patients. Additional guidelines may be provided as needed.

5.1.4.5.1 Diarrhea Management Guidelines

Specific guidelines for managing diarrhea including treatment modifications to improve safety and tolerability are provided in Table 3 and should be instituted as early as possible once diarrhea of any grade occurs. Patients should be monitored closely and all events of diarrhea should be evaluated thoroughly for more common etiologies other than drug-induced effects, such as infectious etiology.

For diarrhea that persists for more than 5 days, despite treatment with anti-diarrheal agent(s) and/or withholding dosing of ipatasertib/placebo, gastroenterologists should be consulted to rule out the risk of colitis and infection (e.g., obtaining CT images or a stool culture for infectious workup [*Clostridium difficile*, enteric bacteria, cytomegalovirus]). Patients should be educated on the symptoms and importance of early reporting of

diarrhea to receive instructions of treatment and prevention of dehydration so that patients can be promptly and appropriately managed.

The palbociclib dose may be adjusted at the discretion of the investigator as clinically indicated unless otherwise specified below *or unless required by the local prescribing information*. See Table 2 for dose reductions with palbociclib. For additional information, refer to the local prescribing information for dose modifications of palbociclib.

Table 3 Diarrhea Management Guidelines

Severity of Diarrhea [a]	Management Guideline
Prevention	• All patients should receive loperamide (2 mg BID or 4 mg QD) as prophylaxis for diarrhea upon start of study treatment through the first cycle (if allowed by local guidance), except when the Medical Monitor approves omission, for example if there are clinical concerns that preclude the use of loperamide prophylaxis in the first cycle. Loperamide dose adjustments may be made per investigator discretion after discussion with the Medical Monitor. • After the first cycle, investigators are encouraged to continue this dosing for the remainder of the study using their discretion as clinically indicated.
Grade 1 Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	• Continue study drugs at the current dose level. • Manage with loperamide 4 mg initially and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea-free interval. • Dietary modifications, such as avoiding any lactose-containing foods and eating small meals. • Hydration with 8–10 glasses per day (~12 oz/glass) of clear liquid, such as broth or low-calorie drinks with electrolytes. • Upon resolution, loperamide prophylaxis can be considered and continues as clinically indicated, if allowed by local guidance. Please note, loperamide prophylaxis is to be taken throughout at least the first cycle.
Grade 2 Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	• Rule out infectious etiology. • Manage with loperamide as early as possible 4 mg initially and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea free interval. • Dietary modifications, such as avoiding any lactose-containing foods and eating small meals. • Hydration with 8–10 glasses per day (~12 oz/glass) of clear liquid, such as broth or low-calorie drinks with electrolytes. • For non-infectious diarrhea lasting more than 48 hours despite optimal loperamide treatment, manage with second-line anti-diarrheal agents, including, but not limited to Lomotil®, codeine, or octreotide, or as per institutional guidelines. • Interrupt ipatasertib/placebo until diarrhea improves to Grade 1 or better. Ipatasertib/placebo can be resumed at the same dose or one dose lower per investigator's evaluation upon improvement to Grade 1 or better. • Reduce ipatasertib/placebo by one (or one additional) dose level (see Section 5.1.4.1 for further details) for recurrent Grade 2 diarrhea. • When ipatasertib, or its placebo, is resumed, loperamide prophylaxis should also be resumed and continued as clinically indicated, if allowed by local guidance. Please note, loperamide prophylaxis is to be taken throughout at least the first cycle.

Table 3 Diarrhea Management Guidelines (cont.)

Severity of Diarrhea [a]	Management Guideline
Grade 3 Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	• Rule out infectious etiology. • Treat per Grade 2 management guidelines and supportive care. • Interrupt ipatasertib/placebo until diarrhea improves to Grade 1 or better. Consider interrupting palbociclib. Ipatasertib/placebo should be reduced by one dose level (see Section 5.1.4.1 for further details) when treatment is restarted. • For recurrent Grade 3 diarrhea, interrupt as above and reduce ipatasertib/placebo dose by one additional dose level when treatment is restarted (see Section 5.1.4.1 for further details). Consider interrupting palbociclib and resuming at the reduced dose when palbociclib is restarted (see Section 5.1.4.2). • When ipatasertib, or its placebo, is resumed, loperamide prophylaxis should also be resumed and continues as clinically indicated, if allowed by local guidance. Please note, loperamide prophylaxis is to be taken throughout at least the first cycle.
Grade 4 Life-threatening consequences; urgent intervention indicated	• Rule out infectious etiology. • Treat per Grade 2 management guidelines and supportive care. • Permanently discontinue ipatasertib/placebo. • If after permanent discontinuation of ipatasertib/placebo diarrhea persists, permanently discontinue palbociclib and fulvestrant.

ADL = activities of daily living; BID = twice a day; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; QD = once a day.

[a] Diarrhea, as defined by NCI CTCAE v5.0, a disorder characterized by an increase in frequency and/or loose or watery bowel movements.

5.1.4.5.2 Fasting Hyperglycemia

Fasting is defined as abstaining from food and drink (with the exception of water) for at least 8 hours.

Guidelines for fasting hyperglycemia attributable to ipatasertib/placebo are outlined below (see Table 4) based on fasting glucose measurements assessed in the clinic, *unless otherwise specified below.* This table is not meant to inform grading of adverse events, which should be conducted per NCI CTCAE v5.0.

All events of hyperglycemia should be thoroughly evaluated for more common etiologies other than drug-induced effects. As clinically indicated, the work-up should include confirmation of fasting blood glucose, urinary glucose and ketones, arterial blood gas, serum bicarbonate, and hemoglobin A_{1C}.

Hyperglycemia should be treated per institutional guidelines.

Home glucose measurements, where indicated based on the below management guidelines, may be used to trigger contact between patient and investigative site team and may lead to an unscheduled clinic visit to assess fasting glucose. Guidance for

when to call the investigator/site staff (or designated endocrinologist, if applicable) should be provided to patients for hypoglycemia (e.g., glucose value under 70 mg/dL) and hyperglycemia (e.g., glucose value over 300 mg/dL). Alternative thresholds may be selected as clinically indicated per investigator discretion or institutional guidance and noted in the source documents. For any patients performing home glucose monitoring, the blood glucose log should be reviewed at each clinic visit (and source data retained), entry of results into the patient's eCRF will be limited to values which result in intervention.

In the event of ipatasertib/placebo interruption, anti-diabetic medications may need to be held or reduced (per investigator judgment) and glucose should be monitored closely to minimize the risk of hypoglycemia.

Table 4 Fasting Hyperglycemia Management Guidelines

Severity of Fasting Hyperglycemia	Management Guideline
Fasting glucose value >ULN to 160 mg/dL (8.9 mmol/L)	• Continue ipatasertib/placebo. • Provide patient with education on a diabetic diet and consider home glucose monitoring. • Consider oral anti-diabetic medications (e.g., metformin).
Fasting glucose value >160 to 250 mg/dL (>8.9–13.9 mmol/L)	• Interruption of ipatasertib/placebo until fasting glucose values return to ≤160 mg/dL (8.9 mmol/L) • Encourage a diabetic diet and initiate home glucose monitoring. • Start oral anti-diabetic medications (e.g., metformin). • If patient is already on an oral anti-diabetic medication, the dose of ipatasertib/placebo should be reduced by one dose level (see Section 5.1.4.1 for further details). • If the patient previously has not been receiving any oral antidiabetic medication, ipatasertib/placebo may be resumed at the previous dose level with initiation of oral anti-diabetic medication.
Fasting *(or non-fasting)* glucose value >250 to 500 mg/dL (>13.9–27.8 mmol/L)	• Interrupt ipatasertib/placebo until fasting glucose values return to ≤160 mg/dL (8.9 mmol/L) • Encourage a diabetic diet and initiate home glucose monitoring. • Treat hyperglycemia as per standard of care, noting risk of hypoglycemia if insulin is used. • Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • If the patient is already on an oral anti-diabetic medication, ipatasertib/placebo should be reduced by one dose level when treatment is restarted. • If previously, the patient has not been receiving any oral anti-diabetic medication, ipatasertib/placebo may be resumed at the previous dose level with initiation of oral anti-diabetic medication.

Table 4 Fasting Hyperglycemia Management Guidelines (cont.)

	If fasting glucose value exceeds 250 mg/dL (13.9 mmol/L) again, the dose of ipatasertib/placebo should be reduced by one dose level when treatment is restarted (see Section 5.1.4.1 for further details).
Fasting *(or non-fasting)* glucose value >500 mg/dL (>27.8 mmol/L)*; Life-threatening consequences; urgent intervention indicated*	Interrupt ipatasertib/placebo until fasting glucose values return to ≤160 mg/dL (8.9 mmol/L). Encourage a diabetic diet and initiate home glucose monitoring. Treat hyperglycemia per standard of care, noting risk of hypoglycemia if insulin is used. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). Assess for volume depletion and appropriate intravenous or oral hydration. Reduce ipatasertib/placebo by one dose level when treatment is restarted (see Section 5.1.4.1 for further details). If fasting *(or non-fasting)* glucose value exceeds 500 mg/dL (27.8 mmol/L) again, permanently discontinue ipatasertib/placebo.

ULN = upper limit of normal.

Note: For all grades, the patient should receive education on a diabetic diet.

5.1.4.5.3 Nausea and/or Vomiting

Dose reductions for nausea and/or vomiting should occur only if the symptoms persist despite a minimum of two treatments with adequate (combination) anti-emetic treatment(s), including ondansetron and other anti-emetics (i.e., prochlorperazine or metoclopramide per institutional guidelines; see Table 5). For persistent nausea and/or vomiting attributable to ipatasertib/placebo, dosage modification guidelines are outlined in Section 5.1.4.1 and Table 5).

The palbociclib dose may be adjusted at the discretion of the investigator as clinically indicated *unless required by the local prescribing information.* For additional information, refer to the local prescribing information for dose modifications of palbociclib for non-hematologic toxicities.

Table 5 Nausea and Vomiting Management Guidelines

Severity of Nausea and /or Vomiting	Management Guideline
Grade 1	• Provide supportive care as needed.
Grade 2	• Provide maximum supportive care as needed per local guidelines, with a minimum of two anti-emetics, including ondansetron.
Grade ≥3	• Interrupt ipatasertib/placebo until nausea or vomiting resolves to Grade 2 or better. • Provide maximum supportive care per local guidelines, with a minimum of two anti-emetics, including ondansetron. • If Grade ≥3 nausea or vomiting recurs, ipatasertib/placebo should be reduced by one dose level (see Section 5.1.4.1 for further details) when treatment is restarted.

5.1.4.5.4 Rash

Ipatasertib/placebo and palbociclib should be permanently discontinued for rash associated with Stevens-Johnson syndrome, toxic epidermal necrolysis, or other suspected severe hypersensitivity or allergic reaction. Dosage modification and symptom management guidelines for skin toxicity attributable to study treatment are shown in Table 6.

The palbociclib dose may be adjusted at the discretion of the investigator as clinically indicated unless otherwise specified below *or unless required by the local prescribing information*. For additional information, refer to the local prescribing information for dose modifications of palbociclib for non-hematologic toxicities.

Table 6 Rash Management Guidelines

Severity of Rash	Management Guideline
Grade 1	• Continue study drugs. • Consider topical corticosteroids. • Consider antihistamine prophylaxis for the first cycle and as clinically indicated for subsequent cycles [a]
Grade 2	• Interrupt ipatasertib/placebo treatment until resolution to Grade 1 or better or the toxicity is no longer clinically significant. Consider interrupting palbociclib. • Treat rash with topical corticosteroids. • Consider treatment of rash with oral corticosteroids.
Grade 3	• Interrupt ipatasertib/placebo and palbociclib treatment until resolution to Grade 1 or better or the toxicity is no longer clinically significant. • Treat rash with topical and systemic corticosteroids. • Consider dermatological consultation. • If the skin toxicity resolves to Grade 1 or better or is no longer clinically significant following completion of the steroid taper, ipatasertib/placebo may be resumed at one dose level below the previous dose (see Section 5.1.4.1 for further details). Palbociclib may be resumed once skin toxicity resolves to Grade 1 even if corticosteroid taper has not been completed. • If skin toxicity remains clinically significant continuously for 4 weeks, or Grade 3 rash recurs, permanently discontinue ipatasertib/placebo and palbociclib and fulvestrant.
Grade 4	• Administration of systemic steroids (oral or intravenous) is recommended. Consider dermatological consultation and skin biopsy. • Ipatasertib/placebo plus palbociclib and fulvestrant should be permanently discontinued.

[a] *Sponsor will closely monitor the incidence of rash in this study and may advise investigators to consider antihistamine prophylaxis if warranted by the data.*

5.1.4.5.5 Pneumonitis

Pneumonitis has been observed with palbociclib and also with drugs that target pathways similar to ipatasertib. Every effort should be made to determine the etiology of dyspnea and changes in pulmonary function (see Table 7).

Severe, life-threatening, or fatal ILD and/or pneumonitis can occur in patients treated with palbociclib when it is taken in combination with endocrine therapy. In clinical trials (PALOMA-1, PALOMA-2, PALOMA-3), any grade and Grade ≥ 3 ILD/pneumonitis was reported in 1.0% and 0.1% of patients treated with palbociclib, respectively. Although no fatal cases were reported in these studies, additional cases of ILD/pneumonitis with fatalities have been observed in the post-marketing setting.

Patients should be closely monitored for pulmonary symptoms indicative of ILD/pneumonitis. Signs and symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams in patients in whom infectious, neoplastic, and other causes have been excluded. In patients who have new or worsening respiratory symptoms who are suspected to have developed ILD/pneumonitis, interrupt palbociclib immediately and evaluate the patient. Permanently discontinue palbociclib in patients with severe ILD or pneumonitis. See Table 7 for detailed guidance, including ipatasertib/*placebo* dose modifications and discontinuation.

Table 7 Interstitial Lung Disease/Pneumonitis Management Guidelines

Severity of ILD/ Pneumonitis	Management Guideline
Grade 1	• Interrupt palbociclib *until the event resolves to baseline* and continue the other study drugs. • Consider pulmonary consult. • Consider infectious work-up. [a] • Perform CT scan and PFTs. Repeat CT scan every 8 weeks until a return to baseline.
Grade 2	• Perform infectious work-up. [a] • If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Interrupt palbociclib and ipatasertib/placebo. • Consult with a pulmonologist and with the Medical Monitor. • Start treatment for ILD/pneumonitis as per pulmonologist guidance. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. • Interrupt ipatasertib/placebo treatment until improvement to Grade 1 or better. Consider resuming ipatasertib/placebo at same dose level or one dose level below (see Section 5.1.4.1 for further details) per investigator's assessment, but interrupt palbociclib until the event resolves to baseline. • For recurrent Grade 2 ILD/pneumonitis, palbociclib should be discontinued and ipatasertib/placebo must be resumed at one dose level below the previous dose (see Section 5.1.4.1 for further details).
Grade 3	• Perform infectious work-up. [a] • If infectious etiology is ruled out or if improvement is not evident with broad-spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Discontinue palbociclib and interrupt ipatasertib/placebo. • Consult with a pulmonologist and the Medical Monitor. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended. • Start treatment for ILD/pneumonitis as per pulmonologist guidance. • If permitted by the Medical Monitor, resume ipatasertib/placebo treatment once improved to Grade 1 or better at one dose level below (see Section 5.1.4.1 for further details) per investigator's assessment. • For recurrent non-infectious Grade 3 ILD/pneumonitis events, ipatasertib/placebo should be permanently discontinued.
Grade 4	• Perform infectious work-up. [a] • If infectious etiology is ruled out or if improvement is not evident with broad-spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Permanently discontinue ipatasertib/placebo and palbociclib. • Consult with a pulmonologist and the Medical Monitor. • Start treatment for ILD/pneumonitis as per pulmonologist guidance. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended.

CT = computed tomography; PFT = pulmonary function test.

[a] Such as for bacterial, viral, or fungal pneumonia (e.g., *Pneumocystis jiroveci* pneumonia or pneumonia aspergillus).

5.1.4.5.6 Mucositis

Mouthwash such as magic mouthwash (if inaccessible, warm salt or bicarbonate water) should be used as supportive care per institution guidelines. Brushing teeth after meals, keeping lips moisturized with non-Vaseline® products, and avoiding alcohol, spicy food, and smoking have all been shown to reduce pain and infection related to mucositis. Ranitidine or omeprazole may be helpful if patients have epigastric pain. Dosage modification guidelines for mucositis attributable to study treatment are outlined in Table 8.

The palbociclib dose may be adjusted at the discretion of the investigator as clinically indicated unless otherwise specified below *or unless required by the local prescribing information*. For additional information, refer to the local prescribing information for dose modifications of palbociclib for non-hematologic toxicities.

Table 8 Mucositis Management Guidelines

Severity of Mucositis	Management Guidelines
Grade 1 or 2	• Manage with maximum supportive care. • If Grade ≥ 2 mucositis recurs in subsequent 4 week cycles, despite maximal supportive care, the dose of ipatasertib/placebo should be reduced by one dose level (see Section 5.1.4.1 for further details).
Grade ≥ 3	• *Interrupt* ipatasertib/placebo until recovery to Grade 2 or better. If the mucositis resolves to Grade 2 or better, the dose of ipatasertib/placebo should be reduced by one dose level (see Section 5.1.4.1). Consider *interrupting* palbociclib. However, if mucositis persists despite optimal medical management, *interrupt* palbociclib until recovery to Grade 2 or better and resume at the reduced dose level.

5.1.4.5.7 Hematologic Toxicities

Palbociclib is associated with hematologic toxicities, in particular neutropenia. Monitor complete blood count per schedule in Appendix 1 (Phase III SOA) and Appendix 3 (Phase Ib SOA) and as clinically indicated. Refer to the local prescribing information for further details. Potential risks associated with ipatasertib include hematologic effects (see Section 5.1.1).

Dosage modification (for palbociclib as well as ipatasertib/placebo) and symptom management guidelines are shown in Table 9.

Table 9 Management of Hematologic Toxicities

Severity of Hematologic Toxicity	Management Guidelines [a]
Grade 1 or 2	• Continue study drugs.
Grade 3	Day 1 of cycle: • *Interrupt* palbociclib and ipatasertib/placebo, repeat complete blood count monitoring within 1 week. When recovered to Grade ≤2, start the next cycle at the same dose. Day 15 of first 2 cycles: • If Grade 3 on Day 15, continue palbociclib *and ipatasertib/placebo* at current dose to complete cycle and repeat complete blood count on Day 22. • If Grade 4 on Day 22, see Grade 4 dose modification guidelines below. • Consider *palbociclib* dose reduction in cases of prolonged (*> 1* week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia on Day 1 of subsequent cycles.
Grade 3 neutropenia[b] with fever ≥38.5 ºC and/or infection	At any time: • *Interrupt* palbociclib and ipatasertib/placebo until recovery to Grade ≤2, *then r*esume palbociclib at the next lower dose *and ipatasertib/placebo at the same dose level.* • *For recurrent Grade 3 event, resume both palbociclib and ipatasertib/placebo at the next lower dose level once recovery to Grade ≤2.*
Grade 4	At any time: • *Interrupt* palbociclib and ipatasertib/placebo until recovery to Grade ≤2*, then r*esume palbociclib at the next lower dose *and ipatasertib/placebo at the next lower dose level if patient was previously at the full dose level. If ipatasertib/placebo was previously reduced, resume at the same ipatasertib/placebo dose level.* • *If recurrent Grade 4 event, permanently discontinue palbociclib and ipatasertib/placebo.*

LLN=lower limit of normal.

See Sections 5.1.4.1 and 5.1.4.2 for further details on allowed dose modifications with ipatasertib/placebo and palbociclib, respectively.

[a] Table applies to all hematologic adverse reactions except lymphopenia, unless associated with clinical events (e.g., opportunistic infections).

[b] ANC: Grade 1: ANC <LLN – 1500/mm^3; Grade 2: ANC 1000 – <1500/mm^3; Grade 3: ANC 500 – <1000/mm^3; Grade 4: ANC <500/mm^3.

5.1.4.5.8 Hepatotoxicity

Elevations in liver enzyme concentrations have been associated with ipatasertib, palbociclib, and fulvestrant administration and specific management guidelines are outlined in Table 10.

Permanently discontinue ipatasertib/placebo, palbociclib, and fulvestrant for any patients who develop a concurrent elevation of ALT and/or AST greater than 3 × baseline and total bilirubin greater than 2 × ULN and/or clinical jaundice in the absence of biliary obstruction or other causes responsible for the concurrent elevation, including patients having abnormal liver function tests that meet Hy's law criteria (see Section 5.3.5.7).

The palbociclib dose may be adjusted at the discretion of the investigator as clinically indicated unless otherwise specified below *or unless required by the local prescribing information*. For additional information, refer to the local prescribing information for dose modifications of palbociclib for non-hematologic toxicities.

Table 10 Hepatotoxicity Management Guidelines

Severity of LFT Elevation	Management Guideline
Grade 1 AST or ALT > ULN–3.0 × ULN if baseline was normal; 1.5–3.0 × baseline if baseline was abnormal or Total bilirubin > ULN–1.5 × ULN if baseline was normal; > 1.0–1.5 × baseline if baseline was abnormal	• Continue study drugs. • Monitor LFTs until values resolve to baseline values.
Grade 2 AST or ALT > 3.0–5.0 × ULN if baseline was normal; > 3.0–5.0 × baseline if baseline was abnormal or Total bilirubin > 1.5–3.0 × ULN if baseline was normal; > 1.5–3.0 × baseline if baseline was abnormal	• Continue study drugs. • The frequency of liver function test monitoring should be increased as clinically indicated if the investigator judges that the laboratory abnormalities are potentially related to study medication.
Grade 3 AST or ALT > 5.0–20.0 × ULN if baseline was normal; > 5.0–20.0 × baseline if baseline was abnormal or Total bilirubin > 3.0 - 10.0 × ULN if baseline was normal; > 3.0–10.0 × baseline if baseline was abnormal	• Interrupt ipatasertib/placebo, palbociclib and fulvestrant until improvement of AST/ALT to Grade ≤ 2 at which point treatment may be resumed at the previous dose level. • Consider hepatology consult • Following treatment resumption, monitor serum transaminases and bilirubin at a minimum every 2 weeks for 3 months and monthly thereafter. • If another Grade 3 event occurs, interrupt ipatasertib/placebo, palbociclib and fulvestrant. On return of LFTs to Grade ≤ 2 resume ipatasertib/placebo reducing the dose by one level. Palbociclib and fulvestrant may be resumed at the original dose. • Permanently discontinue treatment with ipatasertib/placebo, palbociclib, and fulvestrant for further Grade 3 occurrences.
Grade 4 AST or ALT > 20.0 × ULN if baseline was normal; > 20.0 × baseline if baseline was abnormal or Total bilirubin > 10.0 × ULN if baseline was normal; > 10.0 × baseline if baseline was abnormal	• Permanently discontinue treatment with ipatasertib/placebo, palbociclib, and fulvestrant.

LFT = liver function test; QD = once daily; ULN = upper limit of normal.

See Section 5.1.4.1 for further details on dose modifications of ipatasertib/placebo.

5.1.4.5.9 Hypersensitivity

If a hypersensitivity reaction due to injection of fulvestrant develops in patients, treatment for the hypersensitivity reaction, including the possibility of rechallenging with the attributable agent, should be administered as per institutional guidelines or at the discretion of the investigator. The patient may continue the other study treatment components not associated with the toxicity (i.e., palbociclib or ipatasertib/placebo).

5.1.4.5.10 Management of Other Clinically Significant Adverse Events

If other Grade ≥3 toxicities not described above develop in patients, any study treatment may be held, depending on the attribution of the toxicity, at the discretion of the investigator. During this time, treatment may continue with the other non-attributable treatment agent (i.e., either ipatasertib/placebo or palbociclib or fulvestrant). Grade ≥3 clinically significant toxicity should be monitored at least weekly.

If the toxicity resolves to Grade 1 or better treatment may resume with the attributable agent.

If the toxicity is deemed related to ipatasertib/placebo and resolves to Grade 1 or better in 2–4 weeks, the dose of ipatasertib/placebo should be reduced by one level per the suggested guidelines in Table 1.

For Grade ≥3 toxicities associated primarily with laboratory abnormalities only (e.g., *increases in* lipase, or amylase, or decreases in phosphorus without clinical or other evidence of pancreatitis), study treatment may continue without interruption and/or dose reduction (in case of ipatasertib/placebo) at the discretion of the investigator per institutional practice.

See Section 5.1.4.4 for further details on the allowed duration of treatment interruptions.

Refer to the local prescribing information for additional details on dose modifications with palbociclib and/or fulvestrant.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.9 and Section 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Grade ≥3 fasting hyperglycemia
- Grade ≥3 hepatotoxicity
- Grade ≥3 ALT/AST elevations
- Grade ≥2 colitis/enterocolitis
- Grade ≥3 diarrhea
- Grade ≥3 rash
- Grade ≥2 pneumonitis
- Grade ≥4 neutropenia (including febrile neutropenia)
- Erythema multiforme

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4, Section 5.5, Section 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 30 days after the final dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 11 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 11 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 12):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 12 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection Reactions

Adverse events that occur during or within 24 hours after fulvestrant injection should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of injection-related reaction).

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than injection reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF (for patients enrolled in the Phase Ib portion only, additional details regarding any increases in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF). If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms

- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of the underlying breast cancer should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An iDMC will monitor the frequency of deaths from all causes *during the Phase III portion*.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Breast Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, qualifies as an adverse event of special interest (AESI) or is a pregnancy, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4). For ipatasertib/placebo, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with ipatasertib/placebo, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for adverse events.

5.3.5.14 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor:	[redacted] M.D. (Primary)
Mobile Telephone No.:	[redacted]
Backup Medical Monitor: (Secondary)	[redacted] M.D., Ph.D.
Mobile Telephone No.:	[redacted]
Backup Medical Monitor: (Tertiary)	[redacted] M.D.
Mobile Telephone No.:	[redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 30 days after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more

than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur > 30 days after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 90 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the final dose of any study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 30 days after the final dose of study drug), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF *for patients in the Phase III portion (see Section 4.6.1). Patients in the Phase Ib portion will not be followed for long-term survival.*

For all patients, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study drug, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Ipatasertib Investigator's Brochure
- Palbociclib EU SmPC
- Fulvestrant EU SmPC

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Unless otherwise specified, statistical considerations and analysis plan in this section will only focus on the randomized Phase III portion of the study for the global population, and further analysis details will be documented in the Statistical Analysis Plan.

Separate analyses will be performed for the global population and the potential China subpopulation (see Section 6.9).

6.1 DETERMINATION OF SAMPLE SIZE

This is a Phase III, randomized, multicenter, international, double blind, placebo controlled clinical study with an initial open-label Phase Ib portion. In the randomized portion of the study, approximately 340 patients will be enrolled and randomized in a 1:1 ratio to the experimental arm (ipatasertib + palbociclib + fulvestrant) and control arm (placebo + palbociclib + fulvestrant), including approximately 153 patients with Tri-AKT+ tumors, as defined by baseline ctDNA, assuming a prevalence rate of 45% for Tri-AKT+ status.

6.1.1 Type I Error Control

The Type I error (α) for this study is 0.05 (two-sided). The overall type I error (α) for this study is 0.05 (two sided) and is split between the following two co-primary efficacy endpoints of PFS in ITT patients (α of 0.01) and PFS in patients with Tri-AKT+ tumors, as defined by baseline ctDNA (α of 0.04). PFS testing for both ITT and patients with Tri-AKT+ tumors, as defined by baseline ctDNA will be performed independently at the same time.

6.1.2 Co-Primary Endpoint: Progression-Free Survival

The primary analysis of co-primary endpoint of PFS will take place when approximately 98 PFS events have occurred in patients with Tri-AKT+ tumors, as defined by baseline ctDNA and approximately 180 PFS events have occurred in ITT patients, whichever occurs later, on the basis of the following assumptions:

- 1:1 randomization ratio
- Two-sided significance level of 4% and at least 80% power for testing PFS in patients with Tri-AKT+ tumors, as defined by baseline ctDNA where median PFS is 10 months in the placebo + palbociclib + fulvestrant arm and 18 months in the ipatasertib + palbociclib + fulvestrant arm (hazard ratio = 0.56)
- Two-sided significance level of 1% and at least 80% power for testing PFS in ITT patients where median PFS is 12 months in the placebo + palbociclib + fulvestrant arm and 20 months in the ipatasertib + palbociclib + fulvestrant arm (hazard ratio = 0.60)
- An annual loss-to-follow-up rate of 5% for both arms
- No interim analysis of PFS

The enrollment duration is projected to be approximately 14 months from the first patient enrolled in the randomized Phase III portion of the study. With these assumptions, the analysis of the co-primary endpoint of PFS is projected to occur approximately 40 months after the first patient enrolled in the randomized Phase III portion of the study. In patients with Tri-AKT+ tumors, as defined by baseline ctDNA, it is projected that the largest HR deemed to be statistically significant at 4% level will be approximately 0.66

(with median PFS improvement from 10 months to 15.2 months). In ITT patients, it is predicted that there will be approximately 201 PFS events which allows for approximately 85% power for testing the assumed median PFS improvement from 12 to 20 months, and the projected largest HR deemed to be statistically significant at 1% level will be approximately 0.70 (with median PFS improvement from 12 months to 17.2 months).

6.2 SUMMARIES OF CONDUCT OF STUDY

Study enrollment and duration, study drug discontinuation, study discontinuation, reasons for study drug discontinuation and study discontinuation will be summarized by treatment arm. Major protocol deviations, including major deviations of inclusion/exclusion criteria, will be reported and summarized by treatment arm.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

The evaluation of treatment group comparability between the two treatment arms will include demographics summaries, stratification factors, patient treatment history, and other baseline disease characteristics.

Continuous data will be summarized with means, standard deviations, and medians and ranges. Categorical data will be summarized by counts and proportions.

6.4 EFFICACY ANALYSES

For all efficacy analyses, patients will be grouped according to the treatment assigned at randomization.

6.4.1 Co-Primary Efficacy Endpoint

The co-primary efficacy endpoints are as follows:

- PFS in ITT patients, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first.
- PFS in patients with Tri-AKT+ tumors, as defined by baseline ctDNA, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first.

Data for patients without the recurrence of disease progression or death as of the clinical data cutoff date will be censored at the time of the last tumor assessment (or at the time of randomization plus 1 day if no tumor assessment was performed after the baseline visit).

PFS will be compared between treatment arms using the stratified log-rank test. The HR will be estimated using a stratified Cox proportional hazards model. The 95% CI for the HR will be provided. The stratification factors to be used will be the same as the randomization stratification factors, except for geographic region. Results from an unstratified analysis will also be provided. Kaplan-Meier methodology will be used to

estimate the mPFS for each treatment arm, and Kaplan-Meier curves will be produced. The Brookmeyer-Crowley method will be used to construct the 95% CI for the mPFS for each treatment arm (Brookmeyer and Crowley 1982).

6.4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints will also be evaluated separately in both ITT patients and patients with Tri-AKT+ tumors, as defined by baseline ctDNA, unless specified otherwise.

6.4.2.1 Objective Response Rate

An objective response is defined as response (CR or PR) on two consecutive occasions $\geq$4 weeks apart, as determined by the investigator using RECIST v1.1. Patients not meeting these criteria, including patients without any post-baseline tumor assessment, will be considered non-responders. ORR is defined as the proportion of patients who had an objective response. The analysis population for ORR will be ITT patients with measurable disease at baseline.

An estimate of ORR and its 95% CI will be calculated using the Clopper Pearson method for each treatment arm. Response rates in the treatment arms will be compared using the stratified Mantel-Haenszel test. The stratification factors to be used will be the same as those used for the investigator-assessed PFS analysis. The difference in ORR between treatment arms will be calculated, and its 95% CI will be calculated using the normal approximation to the binomial distribution.

6.4.2.2 Duration of Response

DOR will be assessed in patients who had an objective response as determined by the investigator using RECIST v1.1. DOR is defined as the time from the first occurrence of a documented objective response (CR or PR, whichever status is recorded first) until the first occurrence of progressive disease, as determined by the investigator according to RECIST v1.1, or death, whichever occurs first. Patients who have not progressed and who have not died at the time of analysis will be censored at the time of last tumor assessment date. DOR is based on a non-randomized subset of patients (specifically, patients who achieved an objective response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes. The methodologies detailed for the investigator-assessed PFS analysis will be used for the DOR analysis.

6.4.2.3 Clinical Benefit Rate

CBR is defined as the proportion of patients who have a CR, PR or stable disease for at least 24 weeks, as determined by the investigator using RECIST v1.1. CBR will be analyzed using methods similar to those used for ORR.

6.4.2.4 Overall Survival

OS is defined as the time from randomization to death from any cause. Data for patients who have not died as of the clinical data cutoff date will be censored at the date when

they are known to be alive. Data for patients who do not have post-baseline information will be censored at the time of randomization plus 1 day. The methodologies detailed for the investigator-assessed PFS analysis will be used for the OS analysis.

6.4.2.5 Patient- Reported Outcomes (TTD of Pain; TTD of PF, RF, and GHS/QoL)

To evaluate TTD in severity of pain, the "worst pain" item from the BPI-SF will be assessed. TTD is defined as the time from randomization to the first documentation of a 2-point increase from baseline in "worst pain". A 2-point change is defined as clinically meaningful (Mathias et al. 2010).

To evaluate TTD in presence and interference of pain, changes in the pain scale (items 9 and 19) of the EORTC QLQ-C30 will be assessed. TTD is defined as the time from randomization to the first documentation of a 10-point increase from baseline on the pain scale. A ≥ 10-point change is defined as clinically meaningful (Osoba et al. 1998).

To evaluate TTD of PF, RF, and GHS/QoL, changes in the PF, RF, GHS/QoL scales of the EORTC QLQ-C30 will be assessed. TTD of PF, RF, and GHS/QoL is defined as the time from randomization to the first documentation of a 10-point or more decrease from baseline on the functioning and GHS/QoL scales. A ≥ 10 point change is defined as a clinically meaningful difference (Osoba et al. 1998) on all scales of the EORTC QLQ C30; additional sensitivity analyses using different thresholds will be conducted.

Patients who do not have an observed deterioration at the time of clinical data cut-off will be censored at the last non-missing assessment date. Patients without a post-baseline assessment will be censored at the time of randomization plus 1 day.

6.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy will be evaluated separately in both ITT patients and patients with Tri-AKT+ tumors, as defined by baseline ctDNA, unless otherwise specified. p-values will be reported for descriptive purposes only.

6.4.3.1 Progression-Free Survival 2

PFS2 is defined as the time from randomization to second occurrence of objective disease progression through the use of RECIST v1.1, or death from any cause, whichever occurs first. Patients alive and for whom a second objective disease progression has not been observed will be censored at the last time known to be alive and without second objective disease progression. This analysis will be performed as data allows.

6.4.3.2 Time to First Skeletal-Related Event

Time to first SRE is defined as the time from randomization to the first occurrence of an SRE. An SRE is a pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. Patients for whom an SRE has not been observed will be

censored at the last time known to be alive and without an SRE. This analysis will be performed as data allow.

6.4.3.3 Exploratory Patient-Reported Outcome Analyses

Summary statistics (mean, SD, median, 25th and 75th percentiles, and range) *for each assessment timepoint will be reported for the "worst pain" item of the BPI-SF as well as for* linear*ly* transformed scores *of* all scales (symptoms, functional domains, and GHS/*QoL*) of the EORTC QLQ-C30 *and EORTC QLQ-BR23 questionnaires* according to the EORTC scoring manual guidelines (Fayers et al. 2001). The mean change of the linear*ly* transformed scores from baseline (and 95% CI using the normal approximation) will also be reported independently for each treatment arm. Line charts depicting the mean and mean changes from the baseline assessment (and 95% confidence intervals) of items and scales over time will be provided for each treatment arm. In the event of incomplete data, for all questionnaire scales, if more than 50% of the constituent items are completed, a prorated score will be computed consistent with the scoring manuals and validation papers. For scales with less than 50% of the items completed, the scale will be considered as missing.

PRO completion, compliance rates, and reasons for missing data will be summarized at each timepoint by treatment arm for each measure in ITT patients. The compliance rate will be based on the total number of patients expected to complete the questionnaire at a particular timepoint.

The EQ-5D-5L *(*Appendix 14*)* will be scored according to its manual, and results will be reported separately from the clinical study report.

6.4.3.4 Investigator-Assessed PFS in Patients with Tri-AKT+ Tumor Tissue and PTEN Loss in Tumor Tissue

The methodologies detailed for the investigator-assessed PFS analysis will be used to analyze PFS in patients with Tri-AKT+ tumor tissue and PTEN loss in tumor tissue.

6.5 SAFETY ANALYSES

6.5.1 Analyses of Exposure, Adverse Event, Laboratory, and Vital Sign Data

Safety analyses for the Phase Ib portion will be conducted and reported separately from the Phase III analyses but will include similar analyses as those listed below for Phase III.

Safety analyses for the Phase III portion will be performed on the safety-evaluable population, including all randomized patients who received any amount of study treatment (i.e., ipatasertib, placebo, palbociclib, or fulvestrant). In addition, key safety analyses will also be performed for patients with Tri-AKT+ tumors, as defined by baseline ctDNA, in both treatment arms. For all safety analyses, patients will be grouped according to whether any amount of ipatasertib was received, including the case when ipatasertib was received in error.

Frequency, nature, and severity of treatment-emergent adverse events, adverse events leading to death, adverse events leading to study drug discontinuation and dose modification, serious adverse events, and adverse events of special interest will be summarized. All deaths will be summarized. Laboratory measurements outside of the normal range will be identified. Selected laboratory data will be summarized by treatment received and grade compared with baseline. Relevant vital signs will be presented using summary statistics by treatment received and visit. Drug exposure will be summarized as well, including duration of treatment, cumulative dose, and dose intensity.

Treatment-emergent adverse events are defined as adverse events that occur after the first dose of study treatment. Adverse events will be summarized by mapped Medical Dictionary for Regulatory Activities (MedDRA) preferred terms and appropriate MedDRA hierarchy. Adverse event severity will be graded according to NCI CTCAE v5.0. Multiple occurrences of the same event will be counted once at the maximum severity.

6.5.2 Exploratory Safety Analysis of Patient-Reported Symptomatic Adverse Events: PRO CTCAE Data

PRO-CTCAE analyses will be primarily descriptive, with a focus on characterizing the pattern of patient-reported symptomatic adverse event occurrence over the course of the trial. Results from these analyses will be presented separately from the safety analyses. PRO-CTCAE data will be analyzed at the item level in line with current NCI recommendations for data handling (Basch et al. 2014).

PRO-CTCAE data will be summarized over time. The proportion of missing data at each assessment timepoint will also be summarized to facilitate interpretation of data. The number and percentage of patients reporting each symptom, including overall side effect bother, and the change from baseline by category (frequency of occurrence, severity, interference) will be summarized at each assessment timepoint by treatment arm. For items that are rated on a 5-point Likert scale, the maximum post-baseline score and

change from baseline will be summarized by treatment arm. Graphical representation of PRO-CTCAE data over time will also be provided.

6.6 PHARMACOKINETIC ANALYSES

Ipatasertib concentrations will be measured as outlined in Appendix 4 (Phase Ib) and Appendix 2 (Phase III), respectively. For Phase Ib, the following PK parameters will be derived from the plasma concentrations of ipatasertib and its metabolite G-037720 using the noncompartmental methods, when appropriate as data allow:

- Maximum observed concentration (C_{max})
- Time to maximum observed concentration (t_{max})
- AUC from hour 0 to the last measurable concentration (AUC_{0-t})

Additional PK analyses will be conducted as appropriate.

Appropriate PK parameters from Day 1 and Day 15 will be compared to assess the effect of palbociclib on the PK profile of ipatasertib.

For the randomized Phase III portion, ipatasertib plasma concentration versus time data, together with information on dosing and patient characteristics, will be pooled and analyzed using a popPK analysis approach and reported separately. Nonlinear mixed-effect modeling will be used for the estimation of popPK parameters for ipatasertib. Covariates such as patient demographics (e.g., age and body size), serum albumin, liver function tests (e.g., AST, ALT, alkaline phosphatase), and serum creatinine will be tested for significance on PK parameters of interest.

Palbociclib levels will be measured as outlined in Appendix 4 (Phase Ib) and Appendix 2 (Phase III), respectively. Plasma concentrations of palbociclib will be compared to available historical and/or literature values.

The PK data will be combined with the safety and efficacy (e.g., PFS) data for exposure–response modeling as data permit. PK and PK/pharmacodynamic analyses may be reported in separate stand-alone reports. Additional analyses may be explored as warranted by the data.

6.7 EXPLORATORY BIOMARKER ANALYSES

Exploratory biomarker analyses may be performed in an effort to understand the association of these markers with study treatment response. Results will be presented in a separate report.

6.8 INTERIM ANALYSES

6.8.1 Planned Interim Safety Analyses

This study includes an initial open-label Phase Ib safety portion with internal Safety Review (see further details in Section 3.1.1).

An external iDMC will be formed to evaluate safety data during the randomized Phase III portion of the study approximately every 6 months from the first patient randomized until the time of the primary analysis of PFS (see Section 6.4.1). The Sponsor will be blinded until the PFS primary analysis.

In the absence of extenuating circumstances, accrual will not be halted during the randomized Phase III portion of the study while the interim safety analysis is conducted. An iDCC will prepare all summaries and analyses for the iDMC's review. The safety summaries will include but not limit to demographic data, adverse events, serious adverse events, and relevant laboratory data. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. Any outcomes of the iDMC's reviews on the safety and benefit-risk balance that affect study conduct will be communicated in a timely manner to the investigators for notification of IRB/ECs and competent authorities as required. A detailed plan will be included in the iDMC Charter.

Following the data review, the iDMC will provide a recommendation to the Sponsor whether to continue the study, amend the protocol, or stop the study. The final decision will rest with the Sponsor. In addition, the Sponsor may request ad-hoc meetings of the iDMC at any time during the study to review ongoing safety summary data.

6.8.2 Planned Interim Efficacy Analyses

No interim efficacy analyses are planned for the co-primary endpoint of PFS.

6.8.3 Optional Interim Analysis

To adapt to information that may emerge during the study, the Sponsor may choose to conduct an optional interim efficacy analysis, prior to the time of the primary analysis for PFS. For example, availability of clinical trial results for a specific external competitor molecule during this study might (depending on the data) trigger an interim analysis, or the existence of an internal competitor molecule might necessitate an interim analysis to enable decision-making regarding continued development of the study drug ipatasertib. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

The interim analysis will be conducted by an iDCC and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the Statistical Analysis Plan (SAP), and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis. The iDMC charter will be updated to document potential recommendations the iDMC can make to the Sponsor as a result of

the analysis (e.g., stop the study for positive efficacy, stop the study for futility), and the iDMC charter will also be made available to relevant health authorities.

If there is a potential for the study to be stopped for positive efficacy as a result of the interim analysis, the type I error rate will be controlled to ensure statistical validity is maintained. Specifically, the Lan-DeMets α-spending function that approximates the O'Brien-Fleming boundary will be applied on the primary endpoint of PFS to determine the critical value for stopping for positive efficacy at the interim analysis (DeMets and Lan 1994). Additional criteria for recommending that the study be stopped for positive efficacy may be added to the iDMC charter. If the study continues beyond the interim analysis, the critical value at the final analysis would be adjusted accordingly to maintain the protocol-specified overall type I error rate, per standard Lan-DeMets methodology.

6.9 CHINA SUBPOPULATION ANALYSES (AS APPLICABLE)

After the enrollment of patients in the global phase of this study is complete, additional Chinese patients may be recruited into the China extension cohort. The analysis population for China subpopulation analyses includes Chinese patients recruited in the global study population and China extension cohort combined. The total number of patients in the China subpopulation is aimed to show treatment benefit consistency between the global population and the China subpopulation. A pre-specified clinical data cutoff for the China subgroup analysis will be planned before the PFS primary analysis.

China subpopulation analyses will be performed and summarized in a separate study report. Further details will be provided in the SAP.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable)

will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on germline mutations for patients in the randomized portion of the study, may be submitted to government or other health

research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health 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 (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 *MANAGEMENT OF STUDY QUALITY*

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. The Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these

parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 145 sites globally will participate to enroll approximately 370 patients in both Phase Ib and Phase III portions of the protocol. Enrollment will occur through an IxRS.

Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5.

An iDMC will be employed to monitor and evaluate patient safety throughout the Phase III portion of the study.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of

the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center 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. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities (Phase III Portion)

	Screening [a]		Cycle 1			Cycle 2		Cycles ≥ 3		Tx DC [b]	Long-Term FU [c]
Day (Window)	-42 to -29	-28 to -1	1	8 (±1)	15 (+2)	1 (+2)	15 (±2)	1 (±3)	15 (±3) [d]		
Informed consent	x [e]										
Whole Blood Sample: somatic tumor mutations	x [f]										
Archival tumor tissue for biomarker analysis	x										
Demographics, medical history/baseline conditions, prior cancer treatment		x									
Vital signs [g]		x	x	x	x	x	x	x		x	
Weight		x	x			x		x		x	
Height		x									
Complete physical examination [h]		x								x	
Limited physical examination [i]			x [j]		x	x	x	x			
ECOG Performance Status		x	x [k]			x		x		x	
12-Lead electrocardiogram (ECG) [l]		x	As clinically indicated							x	
Pregnancy test [m]		x	x			x		x		x	
Viral serology (hepatitis) [n]		x									
Hematology [o]		x	x	x	x	x	x	x		x	
INR and PTT (or aPTT)		x								x	
Fasting serum chemistry [p]		x	x	x	x	x	x	x		x	
Fasting lipid profile, amylase, lipase [q]		x						x [q]		x	
HbA_{1c}		x						x [q]		x	

Appendix 1: Schedule of Activities (Phase III Portion)

	Screening [a]		Cycle 1			Cycle 2		Cycles ≥ 3		Tx DC [b]	Long-Term FU [c]
Day (Window)	-42 to -29	-28 to -1	1	8 (±1)	15 (+2)	1 (+2)	15 (±2)	1 (±3)	15 (±3) [d]		
Urinalysis [r]		x	As clinically indicated							x	
Anti-diarrheal prophylaxis [s]			See Section 4.3.2.5 (prophylaxis)/ Table 3 (management)								
In clinic palbociclib administration (otherwise taken at home based on QD dosing Days 1–21 of each cycle)			x [t]	x	x	x	x	x			
In clinic ipatasertib/placebo administration (otherwise taken at home based on QD dosing Days 1–21 of each cycle)			x [t]	x	x	x	x	x			
Ipatasertib/placebo dispensing and drug accountability *as applicable*			x			x		x		x	
Palbociclib dispensing and drug accountability *as applicable*			x			x		x		x	
Medication Diary (palbociclib, ipatasertib or placebo, loperamide or other anti-diarrheal; as well as analgesic medication and goserelin or alternative LHRH agonist as applicable)			Complete at home *and as applicable during* clinic *visits* when medication is taken *as instructed in the diary*								
Fulvestrant administration [u]			x [t]		x	x		x			
For pre-/peri-menopausal women *and recommended for men*: Goserelin administration [v]	Switch to goserelin (if needed)		Administer at time of fulvestrant administration whenever possible *(as applicable);* may be self-administered at home per local standard of care if the administration does not coincide with a clinic visit.								

Appendix 1: Schedule of Activities (Phase III Portion)

	Screening [a]		Cycle 1			Cycle 2		Cycles ≥ 3		Tx DC [b]	Long-Term FU [c]
Day (Window)	-42 to -29	-28 to -1	1	8 (±1)	15 (+2)	1 (+2)	15 (±2)	1 (±3)	15 (±3) [d]		
BPI-SF "worst pain" item, EORTC QLQ-C30, and EQ-5D-5L [w]			x			x		x		x	x [x]
EORTC QLQ-BR23 [w]			*x*					*x* [w]		*x*	*x* [x]
NCI PRO-CTCAE [w]			*x*			*x*		*x*		*x*	
Tumor assessments [y]		x	Every 8 weeks (±7 days) from Cycle 1 Day 1 regardless of dose modifications (see Section 4.5.6 for more details)								
Bone scan [z]	x		Every 16 weeks (±7 days) from Cycle 1 Day 1 regardless of dose modifications (see Section 4.5.6 for more details)								
Concomitant medications [aa]		x	x	x	x	x	x	x	x [d]	x	
Adverse events [bb, cc]		x	x	x	x	x	x	x	x [d]	x	
Mid-cycle phone visit [d]									x [d]		
Record cancer-related radiotherapy/surgical procedures [cc]		x	As clinically indicated (see Section *4.5.7*)								
Survival/anti-cancer therapy follow-up											x
Plasma sample: somatic tumor mutations			x		x					x	
Optional tumor biopsy [dd]	x									x	
Blood sample for WGS if approved locally [ee]			x								
Plasma PK sample			See Appendix 2								

Appendix 1: Schedule of Activities (Phase III Portion)

aPTT = activated PTT; BID = twice a day; *BPI-SF=Brief Pain Inventory- Short Form;* CT = computed tomography; ctDNA = circulating tumor DNA; eCRF = electronic Case Report Form; ECOG = Eastern Cooperative Oncology Group; EORTC *BR23=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer Module 23; EORTC* QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30; EQ-5D-5L = European Quality of Life 5-*Dimension, 5*-Level questionnaire; FU = Follow Up; HbA1c = glycosylated hemoglobin; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; LHRH = luteinizing hormone releasing hormone; INR = international normalized ratio; MRI = magnetic resonance imaging; NGS = next generation sequencing; PK = pharmacokinetic; PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; PO = by mouth; QD = once daily; RBR = Research Biosample Repository; SOC = standard of care; SRE = skeletal-related event; PTT = partial thromboplastin time; Tx DC = Treatment Discontinuation; WGS = whole genome sequencing.

Notes: All assessments should be performed within 2 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. Additional assessments may also be done at unplanned visits if clinically indicated.

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days before Cycle 1 Day 1 may be used (for bone scans, standard-of-care scans within 6 weeks before Cycle 1 Day 1 may be used, see Section 4.5.6 for details); such tests do not need to be repeated for screening. Unless otherwise stated, screening assessments that are done within 2 days prior to Cycle 1 Day 1 do not need to be repeated on Cycle 1 Day 1.

[b] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit within approximately 30 days after their final dose of study drug (ipatasertib/placebo, palbociclib or fulvestrant, whichever is discontinued last). The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

[c] Required follow-up information will be collected via telephone calls and/or clinic visits approximately every 3 months until death, loss to follow-up, or study termination or termination of follow-up by the Sponsor.

[d] Mid-cycle phone call starting at Cycle 3 Day 15 from the site to the patient to assess adverse events as well as concomitant medications. This will allow site staff to implement adequate adverse event management in a timely manner once clinic visits occur every 28 days.

[e] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 6 weeks before initiation of study treatment.

[f] Valid Tri-AKT ctDNA test result by *the central laboratory* NGS assay within 6 weeks prior to enrollment required for stratification.

[g] Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressure, while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] Complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] Perform a limited, symptom-directed physical examination at specified timepoints and as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[j] If the complete physical examination required at screening was done within 4 days of Cycle 1 Day 1, a limited physical examination is no longer required

[k] If ECOG Performance status completed at screening was done within 4 days of Cycle 1 Day 1, a Cycle 1 Day 1 assessment is no longer required

[l] Triplicate ECG recordings will be obtained at baseline to determine eligibility (see Section 4.1.2), otherwise single ECG recordings are sufficient. See Section 4.5.9 for more details.

[m] Women of childbearing potential must have a negative serum pregnancy test result within 96 hours of first dose of study treatment. Alternatively, if a negative serum pregnancy test was obtained within 7 days of first dose of study treatment, it needs to be confirmed by a negative urine pregnancy test on the day of the first administration of study treatment prior to dosing. Urine/serum pregnancy tests will be performed at the specified subsequent visits (or within 96 hours of the visit). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. For all other women, documentation must be present in medical history confirming that patient is not of childbearing potential.

[n] HBsAg, total HBcAb, and HCV antibody; additional tests for HBV DNA or HCV RNA may be required to confirm eligibility (see Section 4.1.2).

[o] Hematology includes RBC count, hemoglobin, hematocrit, WBC count with differential (i.e., must be sufficient for the determination of absolute neutrophil counts, lymphocytes) and platelet count. *Laboratory samples should be drawn within 48 hours prior to study drug administration at the clinic; results should be available to assess prior to dosing for complete blood count as indicated in Section 4.5.8.*

[p] Fasting serum chemistry panel includes glucose (following ≥8-hour fast, plasma glucose is also acceptable per local practice), BUN (or urea), bicarbonate (or total carbon dioxide if considered standard of care for the region), creatinine, sodium, potassium, magnesium, calcium, phosphorus, albumin, total bilirubin, ALP (total ALP), AST, and ALT. Laboratory samples should be drawn within 48 hours prior to study drug administration at the clinic; results should be available to assess prior to dosing for fasting glucose, bilirubin, total ALP, AST, and ALT, as indicated in Section 4.5.8.

[q] Fasting lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides following a ≥8 hour fast), amylase, lipase, and HbA1c will be assessed at screening, every 3 cycles starting on Day 1 of Cycle 3, and at SDDV visit. *Laboratory samples should be drawn within 48 hours prior to study drug administration at the clinic.*

[r] Urinalysis (dipstick allowed): pH, specific gravity, glucose, protein, ketones, and blood; microscopic examination if clinically indicated (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria). *Laboratory samples should be taken within 48 hours prior to study drug administration at the clinic.*

[s] Anti-diarrheal prophylaxis: All patients should receive loperamide (2 mg PO twice a day [BID] or 4 mg QD) as prophylaxis for diarrhea in the first cycle if allowed by local guidance. Investigators are encouraged to continue this dosing for the remainder of the study; the prophylaxis dose may be adjusted as necessary, using their discretion based on clinical judgment and per local guidance. If diarrhea occurs, it should be managed per guidelines in Table 3.

[t] Patients should receive their first dose of study drug on the day of randomization, if possible. If this is not possible, the first dose should occur no later than 4 days after randomization.

[u] It is recommended to administer fulvestrant prior to the oral medications (i.e., ipatasertib/placebo and palbociclib) during all clinic visits (see Section 4.3.2.1).

[v] Pre- or peri-menopausal women must have started treatment with goserelin or an alternative LHRH agonist at least *14* days prior to first dose of study treatment *(for men this is recommended)*. If patients have received an alternative LHRH agonist prior to study entry, it is recommended that they switch to goserelin for the duration of the trial, whenever possible. Every effort should be made to administer goserelin or alternative LHRH agonist as applicable on site at the time of fulvestrant administration *as applicable* in order to minimize the number of clinic visits. Patients may self-administer goserelin or alternative LHRH agonist as applicable at home per local standard of care if the administration does not coincide with a clinic visit. In that case, patients will complete a diary.

[w] Patient-reported outcomes: The *BPI-SF worst pain item (Appendix 10),* EORTC QLQ-C30~~,~~ *(Appendix 11),* PRO-CTCAE~~,~~ *(Appendix 13),* and EQ-5D-5L *(Appendix 14)* questionnaires will be completed on paper starting on Cycle 1 Day 1*,* and Day 1 of every cycle~~,~~ thereafter, *as well as* at the Tx DC visit. *The EORTC QLQ-BR23 (Appendix 12) will be completed on paper starting on Cycle 1 Day 1, Cycle 3 Day 1, and Day 1 of every third cycle, thereafter (i.e., Cycles 6, 9, 12, 15, etc.), as well as at the Tx DC visit. The BPI-SF worst pain item, EORTC QLQ-C30, EORTC QLQ-BR23, PRO-CTCAE, and EQ-5D-5L should be completed in this order, as applicable. Male patients will not complete the QLQ-BR23, as this measure has not been validated in men.* All PRO questionnaires scheduled for administration during a clinic visit are required to be completed by the patient at the investigational site at the start of the clinic visit before discussion of the patient's health state, laboratory results or health record, before administration of study treatment, and/or prior to any other study assessment(s) that could bias patients' responses to ensure that the validity of the instrument is not compromised and that data quality meets regulatory requirements. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site.

[x] During long-term follow-up, the EORTC QLQ-C30 *and EORTC QLQ-BR23 will be completed either in-clinic or over the phone* only once at 3 months *after the Tx DC visit. The BPI-SF worst pain item* and the EQ-5D-5L questionnaire will be completed every *6* months for a duration of 1 year, unless the patient withdraws consent or the Sponsor terminates the study or the PRO follow-up. PRO questionnaires during the long-term follow-up period may be completed at the investigational site should the patient come in for a clinic visit or be administered via telephone calls.

[y] Tumor assessments performed according to RECIST v1.1. Post-baseline tumor assessments should be performed every 8 weeks ±7 days from Cycle 1 Day 1 regardless of dose delay, treatment interruption or early treatment discontinuation until disease progression. The method used for a patient (CT or MRI scan or photographic measurements) must be the same throughout the study. A missed tumor assessment should be rescheduled as soon as possible. See Section 4.5.6 for more details.

[z] A screening (or documented SOC) technetium bone scan should be performed within 6 weeks before Cycle 1, Day 1. For patients with known or suspected bone metastasis, subsequent post-baseline bone scans should be performed with every other tumor assessment starting from Week 16 (±7 days), unless the bone lesions are followed via CT scan or other imaging modality (MRI or X-ray) during the regular tumor assessments every 8 weeks (±7 days), in which case additional post-baseline bone scans are only needed as clinically indicated. Bone disease and any changes in bone imaging should be evaluated radiographically by CT scan, MRI, or X-ray to ascertain the presence of bone destruction versus a healing reaction. See Section 4.5.6 for more details.

[aa] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 30 days after the final dose of study drug.

[bb] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 30 days after the final dose of study drug. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[cc] An SRE is defined as either a pathologic fracture, radiation therapy to the bone, surgery to the bone, or spinal cord compression. Any cancer-related radiation or surgery to the bone (on–study treatment and during the adverse event follow-up), or adverse events with diagnosis of pathologic fracture or spinal cord compression, should be assessed according to the SRE criteria and reported with this assessment on the relevant eCRF page.

[dd] Optional fresh biopsy at screening and at disease progression prior to start of next cancer therapy (can be collected anytime at or after progression), see Section 4.5.8. *For patients without adequate tumor specimen per Section 4.1.1, alternatively, a newly collected tumor tissue sample may be provided at screening.*

[ee] Blood sample collection on Cycle 1 Day 1 for WGS unless prohibited by local regulations (see details in Section 4.5.11).

Appendix 2
Schedule of Pharmacokinetic Samples (Phase III portion)

Visit	Timepoint	Sample Type
Cycle 1, Day 1	2–4 hours after ipatasertib or its placebo	Plasma sample for ipatasertib or its placebo and G-037720
Cycle 1, Day 15 [a]	Predose [b]	Plasma sample for ipatasertib or its placebo and G-037720 and palbociclib
Cycle 1, Day 15 [a]	2–4 hours after ipatasertib or its placebo	Plasma sample for ipatasertib or its placebo and G-037720
Cycle 2, Day 15 [a]	Predose [b]	Plasma sample for ipatasertib or its placebo and G-037720 and palbociclib
Cycle 2, Day 15 [a]	2–4 hours after ipatasertib or its placebo	Plasma sample for ipatasertib or its placebo and G-037720

PK = pharmacokinetic.

Notes: Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays.

- Dose time on the day before and day of PK sampling should be accurately reported.
- Any incidence of vomiting within 3 hours post drug administration should also be recorded for the day of PK sampling.

PK sampling timepoint should be accurately reported.

[a] Other than the Cycle 1, Day 1 visit, if 3 or more consecutive doses of ipatasertib/placebo were withheld immediately prior to the PK sample collection (including the day of PK collection visit), the sample collection may be delayed to another day after at least 3 consecutive days of ipatasertib/placebo dosing have been administered (including the day of PK collection visit). The sampling can be done any day after Day 12 of the relevant cycle corresponding with a planned ipatasertib/placebo dosing day.

[b] Predose = 0 to 3 hours prior to dosing with ipatasertib/placebo on the day of the visit.

Appendix 3
Schedule of Activities (Phase Ib Portion)

	Screening [a]		Start of Ipatasertib Only Run In	Cycle 1			Cycle 2		Cycle 3		Cycles ≥ 4		Tx DC [b]
Day (Window)	-49 to -*36*	-*35* to -8	-7 to -5	1	8 (±1)	15 (+2)	1 (+2)	15 (±2)	1 (±3)	15 (±3)	1 (±3)	15 (±3) [v]	
Informed consent	x [c]												
Whole Blood Sample: somatic tumor mutations	x [d]												
Demographics, medical history/baseline conditions, prior cancer treatment		x											
Vital signs [e]		x	x	x	x	x	x	x	x		x		x
Weight		x	x	x			x		x		x		x
Height		x											
Complete physical examination [f]		x											x
Limited physical examination [g]			x [h]	x		x	x		x		x		
ECOG Performance Status		x	x [i]			x			x		x		x
12-Lead electrocardiogram (ECG) [j]		x		As clinically indicated									x
Pregnancy test [k]		x	x				x		x		x		x
Viral serology (hepatitis) [l]		x											
Hematology [m]		x	x	x	x	x	x	x	x	x	x		x
INR and PTT (or aPTT)		x											x
Fasting serum chemistry [n]		x	x	x	x	x	x	x	x	x	x		x
Fasting lipid profile, amylase, lipase [o]		x							x [o]		x [o]		x
HbA_{1c}		x							x [o]		x [o]		x
Urinalysis [p]		x		As clinically indicated									x

Appendix 3: Schedule of Activities (Phase Ib Portion)

	Screening [a]		Start of Ipatasertib Only Run In	Cycle 1			Cycle 2		Cycle 3		Cycles ≥4		Tx DC [b]
Day (Window)	-49 to -36	-35 to -8	-7 to -5	1	8 (±1)	15 (+2)	1 (+2)	15 (±2)	1 (±3)	15 (±3)	1 (±3)	15 (±3) [v]	
Anti-diarrheal prophylaxis [q]			See Section 4.3.2.5 (prophylaxis)/Table 3 (management)										
In clinic palbociclib administration (otherwise taken at home based on QD dosing Days 1–21 of each cycle)				x	x	x	x	x	x	x	x		
In clinic ipatasertib administration (otherwise taken at home based on QD dosing during the initial 5-7 day single-agent run-in and on Days 1–21 of each cycle)			x [r, s]	x	x	x	x	x	x	x	x		
Ipatasertib dispensing and drug accountability *as applicable*			x [r]	x			x		x		x		x
Palbociclib dispensing and drug accountability *as applicable*				x			x		x		x		x
Medication Diary (palbociclib, ipatasertib, loperamide or other anti-diarrheal, as well as goserelin or alternative LHRH agonist if applicable as applicable)			Complete at home *and as applicable during* clinic *visits* when medication is taken *as instructed in the diary*										
Fulvestrant administration [z]				x		x	x		x		x		
For pre-/peri-menopausal women *and recommended for men*: Goserelin administration [t]	Switch to goserelin (if needed)		Administer at time of fulvestrant administration whenever possible *(as applicable);* may be self-administered at home per local standard of care if the administration does not coincide with a clinic visit.										
Tumor Assessments		x		Post-baseline tumor assessments may be performed per local SOC									
Bone scan	x			Post-baseline tumor assessments may be									

Appendix 3: Schedule of Activities (Phase Ib Portion)

	Screening [a]		Start of Ipatasertib Only Run In	Cycle 1			Cycle 2		Cycle 3		Cycles ≥ 4		Tx DC [b]
Day (Window)	-49 to -36	-35 to -8	-7 to -5	1	8 (±1)	15 (+2)	1 (+2)	15 (±2)	1 (±3)	15 (±3)	1 (±3)	15 (±3) [v]	
				performed per local SOC									
Concomitant medications [u]		x	x	x	x	x	x	x	x	x	x	x [v]	x
Adverse events [w]		x	x	x	x	x	x	x	x	x	x	x [v]	x
Mid-cycle phone visit [v]												x [v]	
Optional tumor biopsy [x]	x												x
Blood sample for WGS if approved locally [y]			x										
Plasma sample: somatic tumor mutations			x			x							
Plasma PK sample				See Appendix 4									

aPTT = activated PTT; BID = twice a day; ctDNA = circulating tumor DNA; eCRF = electronic Case Report Form; ECOG = Eastern Cooperative Oncology Group; HbA1c = glycosylated hemoglobin; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; LHRH = luteinizing hormone releasing hormone; INR = international normalized ratio; NGS = next generation sequencing; PK = pharmacokinetic; PO = by mouth; QD = once daily; SOC = standard of care; PTT = partial thromboplastin time; Tx DC = Treatment Discontinuation; WGS = whole genome sequencing.

Notes: All assessments should be performed within 2 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. Additional assessments may also be done at unplanned visits if clinically indicated.

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days before first dose of study treatment may be used (for bone scans, standard-of-care scans within 6 weeks before first dose of study treatment may be used, see Section 4.5.6 for details); such tests do not need to be repeated for screening. Unless otherwise stated, screening assessments that are done within 2 days prior to first dose of study treatment do not need to be repeated on the Day -7 to Day -5 clinic visit.

[b] Patients who discontinue study drug will return to the clinic for a treatment discontinuation visit within approximately 30 days after their final dose of study drug (ipatasertib/placebo, palbociclib or fulvestrant, whichever is discontinued last). The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

[c] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 6 weeks before initiation of study treatment.

[d] Sample should be collected during screening and immediately submitted for testing but a valid ctDNA test result for Tri-AKT status by *the central laboratory* NGS assay is not required prior to enrollment.

[e] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure, while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[f] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[g] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] If the complete physical examination required at screening was done within 4 days of first dose of study treatment, a limited physical examination is no longer required at the Day -7 to Day -5 clinic visit.

[i] If the ECOG performance status completed at screening was done within 4 days of first dose of study treatment, the assessment is no longer required at the Day -7 to Day -5 clinic visit.

[j] Triplicate ECG recordings will be obtained at baseline to determine eligibility (see Section 4.1.2), otherwise single ECG recordings are sufficient. See Section 4.5.9 for more details.

[k] All women of childbearing potential will have a serum pregnancy test within 96 hours of first dose of study treatment. Alternatively, if a negative serum pregnancy test was obtained within 7 days of first dose of study treatment, it needs to be confirmed by a negative urine pregnancy test on the day of the first administration of study treatment prior to dosing. Urine/serum pregnancy tests will be performed at the specified subsequent visits (or within 96 hours of the visit). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. For all other women, documentation must be present in medical history confirming that patient is not of childbearing potential.

[l] HBsAg, total HBcAb, and HCV antibody; additional tests for HBV DNA or HCV RNA may be required to confirm eligibility (see Section 4.1.2).

[m] Hematology includes RBC count, hemoglobin, hematocrit, WBC count with differential (i.e., must be sufficient for the determination of absolute neutrophil counts, lymphocytes) and platelet count. *Laboratory samples should be drawn within 48 hours prior to study drug administration at the clinic; results should be available to assess prior to dosing for complete blood count as indicated in Section 4.5.8.*

[n] Fasting serum chemistry panel includes glucose (following ≥8-hour fast, plasma glucose is also acceptable per local practice), BUN or urea, bicarbonate or total carbon dioxide (if considered standard of care for the region), creatinine, sodium, potassium, magnesium, calcium, phosphorus, albumin, total bilirubin, ALP (total ALP), ALT, and AST. Laboratory samples should be drawn within 48 hours prior to study drug administration at the clinic; results should be available to assess prior to dosing for fasting glucose, bilirubin, total ALP, AST, and ALT, as indicated in Section 4.5.8.

[o] Fasting lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides following a ≥8 hour fast), amylase, lipase, and HbA1c will be assessed at screening, every 3 cycles starting on Day 1 of Cycle 3, and at SDDV visit. *Laboratory samples should be drawn within 48 hours prior to study drug administration at the clinic.*

[p] Urinalysis (dipstick allowed): pH, specific gravity, glucose, protein, ketones, and blood; microscopic examination if clinically indicated (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria). *Laboratory samples should be taken within 48 hours prior to study drug administration at the clinic.*

[q] Anti-diarrheal prophylaxis: All patients should receive loperamide (2 mg PO BID or 4 mg QD) as prophylaxis for diarrhea once ipatasertib study treatment is started and in the first cycle if allowed by local guidance. Investigators are encouraged to continue this dosing for the remainder of the study; the prophylaxis dose may be adjusted as necessary, using their discretion based on clinical judgment and per local guidance. If diarrhea occurs, it should be managed per guidelines in Table 3; anti-diarrheal prophylaxis with loperamide should also be resumed as needed.

[r] Start of ipatasertib only Run In: On clinic visit Day -7 to -5, patients are to start ipatasertib as a single agent for 5-7 days prior to Cycle 1, Day 1.

[s] Patients should receive their first dose of ipatasertib (given first as a single agent for 5-7 days) on the day of enrollment, if possible. If this is not possible, the first dose should occur no later than 4 days after. Note that patients should be on a minimum of 5 days of single-agent ipatasertib before the Cycle 1, Day 1 visit. On Cycle 1, Day 1, palbociclib and fulvestrant should be administered after PK sampling is completed (see Section 4.3.2.1); thereafter, ipatasertib and palbociclib are to be administered at the same time.

[t] Pre- or peri-menopausal women must have started treatment with goserelin or an alternative LHRH agonist at least *14* days prior to first dose of study treatment *(for men this is recommended)*. If patients have received an alternative LHRH agonist prior to study entry, it is recommended that they switch to goserelin for the duration of the trial, whenever possible. Every effort should be made to administer goserelin or alternative LHRH agonist as applicable on site at the time of fulvestrant administration *as applicable* in order to minimize the number of clinic visits. Patients may self-administer goserelin or alternative LHRH agonist as applicable at home per local standard of care if the administration does not coincide with a clinic visit. In that case, patients will complete a diary.

[u] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug until 30 days after the final dose of study drug.

[v] Mid-cycle phone calls from the site to the patient to assess adverse events as well as concomitant medications will start at Cycle 4, Day 15. This will allow site staff to implement adequate adverse event management in a timely manner once clinic visits occur every 28 days.

[w] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 30 days after the final dose of study drug. After that point patients in the Phase Ib will permanently discontinue from the study as they do not undergo any long-term follow-up. The Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[x] Optional fresh biopsy at screening and at disease progression prior to start of next cancer therapy (can be collected anytime at or after progression), see Section 4.5.8.

[y] Blood sample collection on first dose of study treatment for WGS unless prohibited by local regulations (see details in Section 4.5.11).

[z] It is recommended that fulvestrant be administered prior to the oral medications, ipatasertib and palbociclib, during all clinic visits following Cycle 1, Day 1. In contrast, on Cycle 1, Day 1, ipatasertib is administered first (see Section 4.3.2.1).

Appendix 4
Schedule of Pharmacokinetic Samples (Phase Ib portion)

Visit [a]	Timepoint	Sample Type
Cycle 1, Day 1	15 min pre-dose *(±10 min)*	Plasma sample for ipatasertib and G-037720
	0.5 hr post-dose (±5 min)	Plasma sample for ipatasertib and G-037720
	1 hr post-dose (± 5 min)	Plasma sample for ipatasertib and G-037720
	2 hr post-dose (±10 min)	Plasma sample for ipatasertib and G-037720
	3 hr post-dose (±10 min)	Plasma sample for ipatasertib and G-037720
	4 hr post-dose (±15 min)	Plasma sample for ipatasertib and G-037720
	6 hr post-dose (±15 min)	Plasma sample for ipatasertib and G-037720
Cycle 1, Day 15 [b]	15 min pre-dose *(±10 min)*	Plasma sample for ipatasertib and G-037720 and palbociclib
	0.5 hr post-dose (± 5 min)	Plasma sample for ipatasertib and G-037720
	1 hr post-dose (± 5 min)	Plasma sample for ipatasertib and G-037720
	2 hr post-dose (±10 min)	Plasma sample for ipatasertib and G-037720
	3 hr post-dose (±10 min)	Plasma sample for ipatasertib and G-037720
	4 hr post-dose (±15 min)	Plasma sample for ipatasertib and G-037720
	6 hr post-dose (±15 min)	Plasma sample for ipatasertib and G-037720
Cycle 2, Day 15 [c]	15 min pre-dose *(±10 min)*	Plasma sample for ipatasertib and G-037720 and palbociclib
Cycle 3, Day 15 [c]	15 min pre-dose *(±10 min)*	Plasma sample for ipatasertib and G-037720 and palbociclib
	2 hr post-dose (±10 min)	Plasma sample for ipatasertib and G-037720

hr=hour; min=minute; PK=pharmacokinetic.

Notes: Timepoints listed are for the pre-dose and post-dose of ipatasertib. The actual PK sampling times need to be recorded, including samples collected outside of the sampling window.

[a] *With exception to Cycle 1 Day 1, sampling can be done any day after Day 12 of the relevant cycle corresponding with a planned ipatasertib dosing day (i.e., Days 12–21).*

[b] *If 3 or more consecutive doses of ipatasertib were withheld immediately prior to the PK sample collection (including the day of PK collection visit), the sample collection may be delayed to another day* ***after at least 12 consecutive days*** *of ipatasertib and palbociclib dosing have been administered (including the day of PK collection visit).*

[c] *If 3 or more consecutive doses of ipatasertib were withheld immediately prior to the PK sample collection (including the day of PK collection visit), the sample collection may be delayed to another day* ***after at least 3 consecutive days*** *of ipatasertib and palbociclib dosing have been administered (including the day of PK collection visit).*

Appendix 5
Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about $>$ 50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair $>$ 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Appendix 6
ASCO/CAP Estrogen Receptor and Progesterone Receptor Guideline Recommendations

Additional details *and the most current version of* the guideline recommendations can be found at the URL below:

https://www.cap.org/protocols-and-guidelines/cap-guidelines/current-cap-guidelines/guideline-recommendations-for-immunohistochemical-testing-of-estrogen-and-progesterone-receptors-in-breast-cancer

COLLEGE of AMERICAN PATHOLOGISTS

ASCO GUIDELINES

Summary of ASCO/CAP ER and PgR Guideline Recommendations

Optimal algorithm for ER/PgR testing

Recommendation:

Positive for ER or PgR if finding of ≥ 1% of tumor cell nuclei are immunoreactive.

Negative for ER or PgR if finding of < 1% of tumor cell nuclei are immunoreactive in the presence of evidence that the sample can express ER or PgR (positive intrinsic controls are seen).

Uninterpretable for ER or PgR if finding that no tumor nuclei are immunoreactive and that internal epithelial elements present in the sample or separately submitted from the same sample lack any nuclear staining.

Comments:

These definitions depend on laboratory documentation of the following:

1. Proof of initial validation in which positive ER or PgR categories are 90% concordant and negative ER or PgR categories are 95% concordant with a clinically validated ER or PgR assay.
2. Ongoing internal QA procedures, including use of external controls of variable ER and PgR activity with each run of assay, regular assay reassessment, and competency assessment of technicians and pathologists.
3. Participation in external proficiency testing according to the proficiency testing program guidelines.
4. Biennial accreditation by valid accrediting agency.

Optimal testing conditions

Recommendation:

Large, preferably multiple core biopsies of tumor are preferred for testing if they are representative of the tumor (grade and type) at resection.

Comments:

Specimen should be rejected and testing repeated on a separate sample if any of the following conditions exist:

1. External controls are not as expected (scores recorded daily show variation).
2. Artifacts involve most of sample.

Specimen may also be rejected and testing repeated on another sample if:

1. Slide has no staining of included normal epithelial elements and/or normal positive control on same slide.
2. Specimen has been decalcified using strong acids.
3. Specimen shows an ER-negative/PgR-positive phenotype (to rule out a false-negative ER assay or a false-positive PgR assay).
4. Sample has prolonged cold ischemia time or fixation duration, < 6 hours or > 72 hours and is negative on testing in the absence of internal control elements.

Recommendation:

Interpretation follows guideline recommendation.

Comments:

Positive ER or PgR requires that ≥ 1% of tumor cells are immunoreactive. Both average intensity and extent of staining are reported. Image analysis is a desirable method of quantifying percentage of tumor cells that are immunoreactive.

H score, Allred score, or Quick score may be provided.

Negative ER or PgR requires < 1% of tumor cells with ER or PgR staining. Interpreters have method to maintain consistency and competency documented regularly.

Accession slip and report must include guideline-detailed elements.

Recommendation:

Accession slip and report must include guideline-detailed elements.

Hammond MEH, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *Arch Pathol Lab Med*. 2010;134:907–922.

Appendix 6: ASCO/CAP Estrogen Receptor and Progesterone Receptor Guideline Recommendations

Summary of ASCO/CAP ER and PgR Guideline Recommendations

Optimal tissue handling requirements*
***Revised per the 2011 ASCO/CAP Clinical Notice on HER2 and ER/PgR**

Recommendation:

Time from tissue acquisition to fixation should be ≤ one hour. Samples for ER and PgR testing are fixed in 10% NBF for 6–72 hours. Samples should be sliced at 5-mm intervals after appropriate gross inspection and margins designation and placed in sufficient volume of NBF to allow adequate tissue penetration. If tumor comes from remote location, it should be bisected through the tumor on removal and sent to the laboratory immersed in a sufficient volume of NBF. Cold ischemia time, fixative type, and time the sample was placed in NBF must be recorded.

As in the ASCO/CAP HER2 guideline, storage of slides for more than 6 weeks before analysis is not recommended.

Time tissue is removed from patient, time tissue is placed in fixative, duration of fixation, and fixative type must be recorded and noted on accession slip or in report.

Optimal internal validation procedure

Recommendation:

Validation of any test must be done before test is offered. See separate article on testing validation (Fitzgibbons et al[1]).

Validation must be done using a clinically validated ER or PgR test method.

Revalidation should be done whenever there is a significant change to the test system, such as a change in the primary antibody clone or introduction of new antigen retrieval or detection systems.

Optimal internal QA procedures

Recommendation:

Initial test validation. See separate article on testing validation (Fitzgibbons et al[1]).

Ongoing quality control and equipment maintenance.

Initial and ongoing laboratory personnel training and competency assessment.

Use of standardized operating procedures including routine use of external control materials with each batch of testing and routine evaluation of internal normal epithelial elements or the inclusion of normal breast sections on each tested slide, wherever possible.

Regular, ongoing assay reassessment should be done at least semiannually (as described in Fitzgibbons et al[1]). Revalidation is needed whenever there is a significant change to the test system.

Ongoing competency assessment and education of pathologists.

Optimal external proficiency assessment

Recommendation:

Mandatory participation in external proficiency testing program with at least two testing events (mailings) per year.

Satisfactory performance requires at least 90% correct responses on graded challenges for either test.

Comments:

Unsatisfactory performance will require laboratory to respond according to accreditation agency program requirements.

Optimal laboratory accreditation

Recommendation:

On-site inspection every other year with annual requirement for self-inspection.

Comments:

Reviews laboratory validation, procedures, QA results and processes, and reports.

Unsuccessful performance results in suspension of laboratory testing for ER or PgR.

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor; IHC, immunohistochemistry; QA, quality assurance; NBF, neutral buffered formalin; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; HER2, human epidermal growth factor receptor 2.

1. Fitzgibbons PL, Murphy DA, Hammond ME, et al. Recommendations for validating estrogen and progesterone receptor immunohistochemistry assays. *Arch Pathol Lab Med.* 2010;134:930–935.

Appendix 7
ASCO/CAP HER2 Test Guideline Recommendations

Updates to the ASCO/CAP HER2 Test Guideline Recommendations are summarized below as found in the following article:

Wolff AC, Hammond ME, Hicks DG, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol 2018;36(20):2105-2122.

The complete guidelines can also be accessed at the following website URL:

https://www.cap.org/protocols-and-guidelines/cap-guidelines/current-cap-guidelines/recommendations-for-human-epidermal-growth-factor-2-testing-in-breast-cancer

Appendix 7: ASCO/CAP HER2 Test Guideline Recommendations

Table 1. Summary of All Recommendations (original recommendations and focused update recommendations)

Topic	2013 Recommendations	2018 Focused Update Recommendations
Specimens to be tested	All newly diagnosed patients with breast cancer must have a HER2 test performed. Patients who then develop metastatic disease must have a HER2 test performed in a metastatic site, if tissue sample is available.	No change.
Optimal algorithm for HER2 testing	Must report HER2 test result as positive for HER2 if: IHC 3+ based on circumferential membrane staining that is complete, intense ISH positive based on: Single-probe average *HER2* copy number ≥ 6.0 signals/cell Dual-probe *HER2*/CEP17 ratio of ≥ 2.0; with an average *HER2* copy number ≥ 4.0 signals/cell Dual-probe *HER2*/CEP17 ratio of ≥ 2.0; with an average *HER2* copy number < 4.0; Dual-probe *HER2*/CEP17 ratio of < 2.0 with an average *HER2* copy number ≥ 6.0 signals/cell Must report HER2 test result as equivocal and order reflex test (same specimen using the alternative test) or new test (new specimen, if available, using same or alternative test) if: IHC 2+ based on circumferential membrane staining that is incomplete and/or weak to moderate and within > 10% of the invasive tumor cells or complete and circumferential membrane staining that is intense and within ≤ 10% of the invasive tumor cells ISH equivocal based on: Single-probe ISH average *HER2* copy number ≥ 4.0 and ≤ 6.0 signals/cell Dual-probe *HER2*/CEP17 ratio of < 2.0 with an average *HER2* copy number ≥ 4.0 and ≤ 6.0 signals/cell Must report HER2 test result as negative if a single test (or both tests) performed show: IHC 1+ as defined by incomplete membrane staining that is faint or barely perceptible and within > 10% of the invasive tumor cells IHC 0 as defined by no staining observed or membrane staining that is incomplete and is faint or barely perceptible and within ≤ 10% of the invasive tumor cells ISH negative based on: Single-probe average *HER2* copy number < 4.0 signals/cell Dual-probe *HER2*/CEP17 ratio of < 2.0 with an average *HER2* copy number of 4.0 signals/cell Must report HER2 test result as indeterminate if technical issues prevent one or both tests (IHC and ISH) from being reported as positive, negative, or equivocal. Conditions may include: Inadequate specimen handling Artifacts (crush or edge artifacts) that make interpretation difficult Analytic testing failure Another specimen should be requested for testing to determine HER2 status. Reason for indeterminate testing should be noted in a comment in the report.	1. In the revised Figure 1, the revised definition of IHC 2+ (equivocal) is invasive breast cancer with "weak to moderate complete membrane staining observed in > 10% of tumor cells." 2. In the revised Table 2, it is now stated that, on the basis of some criteria (including a tumor grade 3), "If the initial HER2 test result in a core needle biopsy specimen of a primary breast cancer is negative, a new HER2 test may be ordered on the excision specimen . . ." 3. If a case has a *HER2*/CEP17 ratio of ≥ 2.0 but the average *HER2* signals/cell is < 4.0, a definitive diagnosis will be rendered based on additional work-up. If not already assessed by the institution or laboratory performing the ISH test, IHC testing for HER2 should be performed using sections from the same tissue sample used for ISH, and the slides from both ISH and IHC should be reviewed together to guide the selection of areas to score by ISH (local practice considerations will dictate the best procedure to accomplish this concomitant assessment): a. If the IHC result is 3+, diagnosis is HER2 positive b. If the IHC result is 2+, recount ISH by having an additional observer, blinded to previous ISH results, count at least 20 cells that include the area of invasive cancer with IHC 2+ staining: If reviewing the count by the additional observer changes the result into another ISH category, the result should be adjudicated per internal procedures to define the final category. If the count remains an average of < 4.0 *HER2* signals/cell and the *HER2*/CEP17 ratio is ≥ 2.0, diagnosis is HER2 negative with a comment* c. If the IHC result is 0 or 1+, diagnosis is HER2 negative with a comment.* 4. If a case has an average of ≥ 6.0 *HER2* signals/cell with a *HER2*/CEP17 ratio of < 2.0, formerly diagnosed as ISH positive for HER2, a definitive diagnosis will be rendered based on additional work-up. If not already assessed by the institution or laboratory performing the ISH test, IHC testing for HER2 should be performed using sections from the same tissue sample used for ISH, and the slides from both ISH and IHC should be reviewed together to guide the selection of areas to score by ISH (local practice considerations will dictate the best procedure to accomplish this concomitant review): a. If the IHC result is 3+, diagnosis is HER2 positive b. If the IHC result is 2+, recount ISH by having an additional observer, blinded to previous ISH results, count at least 20 cells that include the area of invasion with IHC 2+ staining: If reviewing the count by the additional observer changes the result into another ISH category, the result should be adjudicated per internal procedures to define the final category If the *HER2*/CEP17 ratio remains < 2.0 with ≥ 6.0 *HER2* signals/cell, diagnosis is HER2 positive c. If the IHC result is 0 or 1+, diagnosis is HER2 negative with a comment* 5. If the case has an average *HER2* signals/tumor cell of ≥ 4.0 and < 6.0 and the *HER2*/CEP17 ratio is < 2.0, formerly diagnosed as ISH equivocal for HER2, a definitive diagnosis will be rendered based on additional work-up. 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(continued on following page)

Appendix 7: ASCO/CAP HER2 Test Guideline Recommendations

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Specimens to be tested	All newly diagnosed patients with breast cancer must have a HER2 test performed. Patients who then develop metastatic disease must have a HER2 test performed in a metastatic site, if tissue sample is available.	No change.
Optimal algorithm for HER2 testing	Must report HER2 test result as positive for HER2 if: IHC 3+ based on circumferential membrane staining that is complete, intense ISH positive based on: Single-probe average *HER2* copy number ≥ 6.0 signals/cell Dual-probe *HER2*/CEP17 ratio of ≥ 2.0; with an average *HER2* copy number ≥ 4.0 signals/cell Dual-probe *HER2*/CEP17 ratio of ≥ 2.0; with an average *HER2* copy number < 4.0; Dual-probe *HER2*/CEP17 ratio of < 2.0 with an average *HER2* copy number ≥ 6.0 signals/cell Must report HER2 test result as equivocal and order reflex test (same specimen using the alternative test) or new test (new specimen, if available, using same or alternative test) if: IHC 2+ based on circumferential membrane staining that is incomplete and/or weak to moderate and within > 10% of the invasive tumor cells or complete and circumferential membrane staining that is intense and within ≤ 10% of the invasive tumor cells ISH equivocal based on: Single-probe ISH average *HER2* copy number ≥ 4.0 and ≤ 6.0 signals/cell Dual-probe *HER2*/CEP17 ratio of < 2.0 with an average *HER2* copy number ≥ 4.0 and ≤ 6.0 signals/cell Must report HER2 test result as negative if a single test (or both tests) performed show: IHC 1+ as defined by incomplete membrane staining that is faint or barely perceptible and within > 10% of the invasive tumor cells IHC 0 as defined by no staining observed or membrane staining that is incomplete and is faint or barely perceptible and within ≤ 10% of the invasive tumor cells ISH negative based on: Single-probe average *HER2* copy number < 4.0 signals/cell Dual-probe *HER2*/CEP17 ratio of < 2.0 with an average *HER2* copy number of 4.0 signals/cell Must report HER2 test result as indeterminate if technical issues prevent one or both tests (IHC and ISH) from being reported as positive, negative, or equivocal. Conditions may include: Inadequate specimen handling Artifacts (crush or edge artifacts) that make interpretation difficult Analytic testing failure Another specimen should be requested for testing to determine HER2 status. Reason for indeterminate testing should be noted in a comment in the report.	1. In the revised Figure 1, the revised definition of IHC 2+ (equivocal) is invasive breast cancer with "weak to moderate complete membrane staining observed in > 10% of tumor cells." 2. In the revised Table 2, it is now stated that, on the basis of some criteria (including a tumor grade 3), "If the initial HER2 test result in a core needle biopsy specimen of a primary breast cancer is negative, a new HER2 test may be ordered on the excision specimen . . ." 3. If a case has a *HER2*/CEP17 ratio of ≥ 2.0 but the average *HER2* signals/cell is < 4.0, a definitive diagnosis will be rendered based on additional work-up. If not already assessed by the institution or laboratory performing the ISH test, IHC testing for HER2 should be performed using sections from the same tissue sample used for ISH, and the slides from both ISH and IHC should be reviewed together to guide the selection of areas to score by ISH (local practice considerations will dictate the best procedure to accomplish this concomitant assessment): a. If the IHC result is 3+, diagnosis is HER2 positive b. If the IHC result is 2+, recount ISH by having an additional observer, blinded to previous ISH results, count at least 20 cells that include the area of invasive cancer with IHC 2+ staining: If reviewing the count by the additional observer changes the result into another ISH category, the result should be adjudicated per internal procedures to define the final category. If the count remains an average of < 4.0 *HER2* signals/cell and the *HER2*/CEP17 ratio is ≥ 2.0, diagnosis is HER2 negative with a comment* c. If the IHC result is 0 or 1+, diagnosis is HER2 negative with a comment.* 4. If a case has an average of ≥ 6.0 *HER2* signals/cell with a *HER2*/CEP17 ratio of < 2.0, formerly diagnosed as ISH positive for HER2, a definitive diagnosis will be rendered based on additional work-up. If not already assessed by the institution or laboratory performing the ISH test, IHC testing for HER2 should be performed using sections from the same tissue sample used for ISH, and the slides from both ISH and IHC should be reviewed together to guide the selection of areas to score by ISH (local practice considerations will dictate the best procedure to accomplish this concomitant review): a. If the IHC result is 3+, diagnosis is HER2 positive b. If the IHC result is 2+, recount ISH by having an additional observer, blinded to previous ISH results, count at least 20 cells that include the area of invasion with IHC 2+ staining: If reviewing the count by the additional observer changes the result into another ISH category, the result should be adjudicated per internal procedures to define the final category If the *HER2*/CEP17 ratio remains < 2.0 with ≥ 6.0 *HER2* signals/cell, diagnosis is HER2 positive c. If the IHC result is 0 or 1+, diagnosis is HER2 negative with a comment* 5. If the case has an average *HER2* signals/tumor cell of ≥ 4.0 and < 6.0 and the *HER2*/CEP17 ratio is < 2.0, formerly diagnosed as ISH equivocal for HER2, a definitive diagnosis will be rendered based on additional work-up. If not already assessed by the institution or laboratory performing the ISH test, IHC testing for HER2 should be performed using sections from the same tissue sample used for ISH, and the slides from both ISH and IHC should be reviewed together to guide the selection of areas to score by ISH (local practice considerations will dictate the best procedure to accomplish this concomitant review): a. If the IHC result is 3+, diagnosis is HER2 positive b. If the IHC result is 2+, recount ISH by having an additional observer, blinded to previous ISH results, count at least 20 cells that include the area of invasion with IHC 2+ staining:

(continued on following page)

Appendix 8
Examples of Strong and Moderate CYP3A Inhibitors and Strong CYP3A Inducers

This table is to provide examples and is not intended to be a complete list; names may vary in different locations.

Strong CYP3A inhibitors	Moderate CYP3A inhibitors	Strong CYP3A inducers
VIEKIRA PAK[1]*	erythromycin*	rifampin*
indinavir*	fluconazole*	mitotane*
tipranavir*	darunavir	avasimibe
ritonavir*	dronedarone*	rifapentine
cobicistat*	crizotinib*	apalutamide
ketoconazole*	atazanavir	phenytoin*
idelalisib*	letermovir	carbamazepine*
troleandomycin*	GSK2647544	enzalutamide*
telaprevir*	aprepitant*	St John's Wort[3]*
danoprevir*	casopitant	lumacaftor
elvitegravir*	amprenavir	rifabutin
lopinavir*	faldaprevir	phenobarbital
itraconazole*	imatinib*	
voriconazole*	verapamil*	
mibefradil	netupitant	
LCL161	nilotinib	
clarithromycin*	grapefruit juice[2]	
posaconazole*	tofisopam*	
telithromycin	cyclosporine*	
grapefruit juice[2]*	ACT-178882	
conivaptan*	ciprofloxacin*	
nefazodone*	magnolia vine (*Schisandra sphenanthera*)	
nelfinavir*	isavuconazole	
saquinavir*	cimetidine*	
ribociclib	FK1706	
diltiazem*	clotrimazole*	
boceprevir*	fluvoxamine*	

Source: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

This table is prepared to provide examples of clinical inhibitors and inducers of CYP3A. Data were collected based on a search of the University of Washington Drug Interaction Database

[1] VIEKIRA PAK = paritaprevir/ritonavir + ombitasvir + dasabuvir

[2] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength)

[3] The effect of St. John's wort varies widely and is preparation-dependent.

* Drugs listed in FDA website

Appendix 9
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

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 as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval ≤ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that 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 the short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤5 mm). At baseline and at follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

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[1] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

DEFINITION OF NON-MEASURABLE TUMOR LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 but < 15 mm) as well as truly nonmeasurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring 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 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 loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion

METHODS FOR ASSESSING 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.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

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 AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not-evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of

non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. 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 of <10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target

lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non-lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- 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 and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be

assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is <5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non-lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. 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 maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in short axis. Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size ($<$10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

Patients with Non-Measurable Disease Only

For patients with non-measurable disease only, the same general concepts apply as noted above. However, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-measurable 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, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread. If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to

have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, 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 patient'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 during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

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

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Timepoint Response: Patients with Target Lesions (with or without Non-Target Lesions)

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

Table 2 Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

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

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some studies; thus, assigning "stable disease" when no lesions can be measured is not advised.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as having "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 lesions as shown in Table 1 and Table 2.

For equivocal findings of progression (e.g., 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.

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.

Appendix 10

Brief Pain Inventory-Short Form "Worst Pain" Item (BPI-SF)

Please rate your pain by circling the one number that best describes your pain at its worst in the last week.										
0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Appendix 11
European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 12

European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Breast Cancer Module 23 (EORTC QLQ-BR23)

EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have a dry mouth?	1	2	3	4
32. Did food and drink taste different than usual?	1	2	3	4
33. Were your eyes painful, irritated or watery?	1	2	3	4
34. Have you lost any hair?	1	2	3	4
35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36. Did you feel ill or unwell?	1	2	3	4
37. Did you have hot flushes?	1	2	3	4
38. Did you have headaches?	1	2	3	4
39. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41. Did you find it difficult to look at yourself naked?	1	2	3	4
42. Have you been dissatisfied with your body?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
44. To what extent were you interested in sex?	1	2	3	4
45. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Did you have any pain in your arm or shoulder?	1	2	3	4
48. Did you have a swollen arm or hand?	1	2	3	4
49. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50. Have you had any pain in the area of your affected breast?	1	2	3	4
51. Was the area of your affected breast swollen?	1	2	3	4
52. Was the area of your affected breast oversensitive?	1	2	3	4
53. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4

Appendix 13
National Cancer Institute Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (NCI PRO-CTCAE) Items

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much
2.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much
3.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

NCI PRO-CTCAE™ ITEMS

Item Library Version 1.0

6.	In the last 7 days, did you have any RASH?				
	○ Yes	○ No			

7.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

8.	In the last 7 days, how BOTHERED were you by the side effect(s) of your treatment?				
	O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

Appendix 14
European Quality of Life 5Dimension, 5-Level questionnaire (EQ-5D-5L) Health Questionnaire

Health Questionnaire

English version for the USA

Appendix 14: European Quality of Life 5Dimension, 5 Level questionnaire (EQ 5D 5L) Health Questionnaire

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐