Official Title: **A Phase III, Double-Blind, Placebo-Controlled, Randomized Study of Taselisib Plus Fulvestrant Versus Placebo Plus Fulvestrant in Postmenopausal Women With Estrogen Receptor-Positive and HER2-Negative Locally Advanced or Metastatic Breast Cancer Who Have Disease Recurrence or Progression During or After Aromatase Inhibitor Therapy**

NCT Number: NCT02340221

Document Dates: Protocol Version 4: 24 June 2018

Statistical Analysis Plan (SAP) Version 2: 3 March 2017

PROTOCOL

TITLE:	**A PHASE III, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED STUDY OF TASELISIB PLUS FULVESTRANT VERSUS PLACEBO PLUS FULVESTRANT IN POSTMENOPAUSAL WOMEN WITH ESTROGEN RECEPTOR-POSITIVE AND HER2-NEGATIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER WHO HAVE DISEASE RECURRENCE OR PROGRESSION DURING OR AFTER AROMATASE INHIBITOR THERAPY**
PROTOCOL NUMBER:	GO29058/ NCT02340221
VERSION NUMBER:	4
EUDRACT NUMBER:	2014-003185-25
IND NUMBER:	121658
TEST PRODUCT:	Taselisib (RO5537381, GDC-0032)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	13 October 2014
DATES AMENDED:	Version 2: 10 December 2015 Version 3: 15 January 2017 Version 4: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	24-Jun-2018 10:41:30

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

The primary progression-free survival (PFS) analysis was conducted in January 2018. At that time, the addition of taselisib to fulvestrant showed a statistically significant improvement in investigator-assessed PFS in patients with *PIK3CA*-mutant tumors. Median PFS increased from 5.4 months in the placebo arm to 7.4 months in the taselisib arm (stratified hazard ratio=0.70, p-value=0.0037). Patients treated with taselisib (versus placebo) experienced more serious adverse events (32.0% vs 8.9%), had higher rates of Grade ≥3 adverse events (49.5% vs 16.4%), had more frequent adverse events leading to discontinuation of taselisib/placebo (16.8% vs 2.3%), and had a slightly increased incidence of Grade 5 adverse events (1.9% vs 0.5%). The clinical benefit of the combination of taselisib and fulvestrant was considered modest, and the overall tolerability was limited.

On the basis of the results, the Sponsor decided to simplify or limit certain protocol assessments because sufficient data have been gathered for these assessments. Therefore, the primary goals of this amendment are to simplify regular tumor assessments, reduce the timeframe of the overall survival (OS) follow-up, and limit assessments in support of exploratory analyses. Safety assessments and regular clinic visits (days that fulvestrant is administered) will remain unchanged.

Changes to the protocol, along with a rationale for each change, are summarized below:

- Sections 1.3.2, 5.1.1.1.1, and 5.1.1.1.8 were updated with new taselisib adverse drug reactions detected in the primary PFS analysis and with management guidelines for infection.
- Sections 3.1, 4.5.3, 4.5.5, and Appendix 1 were updated to indicate that, after approximately the end of August 2018, tumor assessments may be conducted per local standard of care because sufficient data have been gathered for these assessments.
- Sections 3.1, 4.5.3, 4.5.5, 4.5.6, 4.5.11, 4.6.1, Appendix 1, and Appendix 2 were updated to indicate that, after approximately the end of August 2018, the following assessment are no longer required as sufficient data have been gathered for these assessments:

    Tumor assessments for patients who are discontinued from study treatment for reasons other than disease progression and tumor assessments 4–6 weeks after disease progression

    All patient-reported outcome (PRO) assessments

    Survival and subsequent anti-cancer therapies after study treatment discontinuation

    Eastern Cooperative Oncology Group (ECOG) Performance Status

    Optional post-progression core tumor biopsy and Roche Clinical Repository (RCR) blood samples (for DNA extraction)

Plasma samples for pharmacokinetic (PK) and exploratory research and blood samples for next-generation sequencing (NGS) and pharmacogenetic assessment

- Sections 3.1, 5.3.5.7, 5.7, 6.9.1, and 9.4 were updated to clarify the independent Data Monitoring Committee (iDMC) will only oversee safety monitoring until the primary PFS analysis has been completed and the Sponsor is unblinded.
- Section 3.2 was updated to change the definition for the end of the global study to when the last patient, last visit (LPLV) has occurred or safety follow-up is received from the last patient (28 days after the last dose of study drug), whichever occurs later, or when the Sponsor decides to stop the study.
- Sections 4.2 and 6.4.2.2 were updated to clarify that, after approximately the end of August 2018, unblinding is permitted at the discretion of the investigator or Sponsor because the primary PFS analysis will have been competed, and blinding is no longer required.
- Section 4.4.2 was updated to reduce, after approximately the end of August 2018, the list of prohibited therapies requiring Medical Monitor approval to initiate because the primary PFS analysis has been completed and these restrictions are no longer required.
- Section 4.6.2 was updated to indicate that patients must discontinue study drugs if they experience disease progression (as assessed by the investigator) in order to align with Section 3.1.
- Sections 5.5.1 and Appendix 1 were updated to clarify that adverse event follow-up will not be done after a patient is no longer being followed for survival because patients will have been withdrawn from the study at that point.
- Sections 6.4.2.2 and 6.9.1 were updated to indicate that the OS follow-up has been limited to one additional analysis because sufficient data have been gathered for this assessment. This additional OS analysis coincides with the originally planned second OS interim analysis.

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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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED STUDY OF TASELISIB PLUS FULVESTRANT VERSUS PLACEBO PLUS FULVESTRANT IN POSTMENOPAUSAL WOMEN WITH ESTROGEN RECEPTOR-POSITIVE AND HER2-NEGATIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER WHO HAVE DISEASE RECURRENCE OR PROGRESSION DURING OR AFTER AROMATASE INHIBITOR THERAPY**
PROTOCOL NUMBER:	GO29058
VERSION NUMBER:	4
EUDRACT NUMBER:	2014-003185-25
IND NUMBER:	121658
TEST PRODUCT:	Taselisib (RO5537381, GDC-0032)
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 return the signed original of this form to your local study monitor. Please retain a copy for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED STUDY OF TASELISIB PLUS FULVESTRANT VERSUS PLACEBO PLUS FULVESTRANT IN POSTMENOPAUSAL WOMEN WITH ESTROGEN RECEPTOR-POSITIVE AND HER2-NEGATIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER WHO HAVE DISEASE RECURRENCE OR PROGRESSION DURING OR AFTER AROMATASE INHIBITOR THERAPY**
PROTOCOL NUMBER:	GO29058
VERSION NUMBER:	4
EUDRACT NUMBER:	2014-003185-25
IND NUMBER:	121658
TEST PRODUCT:	Taselisib (RO5537381, GDC-0032)
PHASE:	III
INDICATION:	ER-positive/HER2-negative locally advanced or metastatic breast cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Efficacy Objectives

The primary efficacy objective for this study is as follows:

- To compare the efficacy between taselisib + fulvestrant versus placebo + fulvestrant as measured by investigator-assessed progression-free survival (PFS) in patients with *PIK3CA*-mutant tumors

The secondary efficacy objectives for this study are as follows:

- To compare the efficacy between taselisib + fulvestrant versus placebo + fulvestrant as measured by overall survival (OS) in patients with PIK3CA-mutant tumors
- To compare the overall objective response rate (ORR) between taselisib + fulvestrant versus placebo + fulvestrant in patients with PIK3CA-mutant tumors, on the basis of tumor assessments made by the investigator
- To estimate the duration of objective response (DOR) within taselisib + fulvestrant versus placebo + fulvestrant in patients with PIK3CA-mutant tumors, on the basis of tumor assessments made by the investigator
- To compare the clinical benefit rate (CBR) between taselisib + fulvestrant versus placebo + fulvestrant in patients with PIK3CA-mutant tumors, on the basis of tumor assessments made by the investigator
- To compare the efficacy between taselisib + fulvestrant versus placebo + fulvestrant as measured by PFS determined by blinded independent central review (BICR) in patients with PIK3CA-mutant tumors

Safety Objective

The safety objective for this study is to evaluate the safety of taselisib + fulvestrant versus placebo + fulvestrant in patients with locally advanced or metastatic breast cancer (MBC) in all randomized patients who receive at least one dose of taselisib/placebo or fulvestrant, regardless of the *PIK3CA*-mutation status of their tumors, and separately in the subgroups of patients with and without detectable *PIK3CA*-mutant tumors.

Pharmacokinetic Objective

The pharmacokinetic objective for this study is to evaluate the pharmacokinetics of taselisib when taken with fulvestrant

Patient-Reported Outcome Objective

The patient-reported outcome (PRO) objective for this study is as follows:

- To evaluate and compare PROs of treatment-related symptoms, patient functioning, and health-related quality-of-life (HRQoL) as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the modified Breast Cancer Module (QLQ-BR23) between the taselisib + fulvestrant versus placebo + fulvestrant treatment arms

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate the PFS, ORR, CBR, and DOR of taselisib + fulvestrant versus placebo + fulvestrant in patients with locally advanced or MBC where a *PIK3CA* mutation was not detected
- To evaluate PFS, ORR, CBR, and DOR of taselisib + fulvestrant versus placebo + fulvestrant in patients with locally advanced or MBC whose tumor *PIK3CA*-mutation status is determined by plasma DNA analysis
- To explore the potential relationship between pharmacogenetic differences in drug-metabolizing enzymes, transporters, and other patient-specific covariates with pharmacokinetics and safety of taselisib when administered in combination with fulvestrant in patients with locally advanced or MBC
- To explore the potential taselisib exposure-response (efficacy and safety) relationship in patients with locally advanced or MBC receiving taselisib in combination with fulvestrant
- To explore fulvestrant concentrations in patients with locally advanced or MBC who receive fulvestrant alone or in combination with taselisib
- To evaluate predictive and prognostic plasma or tissue biomarkers associated with disease activity status or response to treatment
- To identify possible mechanisms of resistance to fulvestrant + taselisib through the comparative analysis of potential biomarkers in the pretreatment and post-progression biopsy tissue samples and in blood
- To assess health status as measured using the EuroQol 5-Dimension Questionnaire (EQ-5D) for health economic modeling

Study Design

Description of Study

Study GO29058 (SANDPIPER) is a Phase III, randomized, multicenter, international, double-blind, placebo-controlled clinical study designed to compare the efficacy, as measured by PFS, and safety of fulvestrant + taselisib with that of fulvestrant + placebo after recurrence or progression following treatment with an AI for patients with ER+, HER2-negative, *PIK3CA*-mutant, unresectable, locally advanced or MBC. *PIK3CA*-mutation status in all patients will be assessed by a central laboratory using the cobas® *PIK3CA* mutation test. In order to explore efficacy and differential benefit-risk in patients without a detectable *PIK3CA* mutation, 120 patients belonging to this category are planned for enrollment.

Study GO29058 will consist of a global study that will provide the evidence to determine the benefit-risk of taselisib plus fulvestrant in the target population; a possible extension cohort may continue to enroll only in China to meet local regulatory requirements.

In the global study, approximately 600 patients will be randomized in a 2:1 ratio to either fulvestrant + taselisib or fulvestrant + placebo unless the independent Data Monitoring Committee (iDMC) recommends stopping the study early and the Sponsor accepts the iDMC's recommendation. Patients whose tumors contain a PIK3CA-mutation (n = 480) and patients whose tumors do not contain a detectable PIK3CA-mutation (n = 120) will be randomized separately. After the global enrollment closes, additional Chinese patients may continue to be recruited into the China extension cohort. A total of up to 150 Chinese patients with detectable PIK3CA-mutant tumors may be enrolled as part of the global study population and extension cohort combined. Patients enrolled as part of the China extension cohort will also be randomized in a 2:1 ratio to either fulvestrant + taselisib or fulvestrant + placebo.

Number of Patients

Approximately 600 patients are planned for enrollment. After the global enrollment closes, additional Chinese patients may continue to be recruited into the China extension cohort. A total of up to 150 Chinese patients with detectable PIK3CA-mutant tumors may be enrolled as part of the global study population and extension cohort combined.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

Disease-Specific Inclusion Criteria

- Women with histologically or cytologically confirmed invasive, ER+ breast cancer: metastatic or inoperable (not amenable to resection or other local therapy with curative intent) locally advanced breast cancer
- Patients for whom endocrine therapy (e.g., 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.
- Radiologic/objective evidence of recurrence or progression to the most recent systemic therapy for breast cancer
- Radiologic/objective evidence of breast cancer recurrence or progression while on or within 12 months of the end of adjuvant treatment with an AI, or progression while on or within 1 month of the end of prior AI treatment for locally advanced or MBC. The AI (letrozole, anastrozole, or exemestane) does not have to be the most recent treatment before randomization.
- Measurable disease via RECIST v1.1 or non-measurable, evaluable disease with at least one evaluable bone lesion via RECIST v1.1. Bone lesions that have been irradiated are not evaluable.

General Inclusion Criteria

- Able and willing to provide written informed consent and to comply with the study protocol
- Age ≥ 18 years
- ECOG Performance Status of 0 or 1
- Postmenopausal status defined as one of the following:

  Age ≥ 60 years

  Age < 60 years and postmenopausal as defined by documented follicle-stimulating hormone and estradiol in the postmenopausal ranges in addition to being amenorrheic for 12 months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression

  Prior bilateral oophorectomy (≥ 28 days prior to first fulvestrant treatment on Cycle 1 Day 1)

- Consent to provide a formalin-fixed paraffin-embedded (FFPE) tissue block (preferred) or a minimum of 20 (25 preferred) freshly cut unstained tumor slides from the most recently collected, available tumor tissue for *PIK3CA*-mutation testing and for other protocol-mandated exploratory assessments
- A valid cobas *PIK3CA* mutation result (per central testing) is required for all patients (e.g., patients with an "invalid" or "failed" *PIK3CA* mutation result are not permitted to enroll)

  After 120 patients whose breast cancers have a "wild-type" (mutation not detected result) *PIK3CA* status have been enrolled, all remaining enrolled patients must have a breast cancer sample that tests positive for *PIK3CA* mutation to be eligible.
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 28 days prior to Cycle 1 Day 1:

  ANC $\geq 1500/\mu L$ ($1.5 \times 10^9/L$)

  Platelet count $\geq 100{,}000/\mu L$ ($100 \times 10^9/L$)

  Hemoglobin ≥ 9.0 g/dL (90 g/L)

  Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN) except in patients with previously documented Gilbert's syndrome, in which case total bilirubin ≤ 3 mg/dL

  AST and ALT $\leq 1.5 \times$ ULN, with the following exceptions:

  Patients with documented liver metastases: AST and/or ALT $\leq 5.0 \times$ ULN

  Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min based on Cockcroft–Gault glomerular filtration rate estimation

  $$\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine})}$$

  INR < 1.5 and aPTT (or PTT) $< 1.5 \times$ ULN; for patients requiring therapeutic anticoagulation therapy, a stable INR ≤ 2.5
- Fasting glucose ≤ 125 mg/dL (6.94 mmol/L)
- For enrollment into the China extension cohort, residence in the People's Republic of China

Exclusion Criteria

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

Disease-Specific Exclusion Criteria

- HER2-positive disease by local laboratory testing (IHC 3+ staining or in situ hybridization positive)
- Prior treatment with fulvestrant
- Prior treatment with a PI3K inhibitor, mTOR inhibitor (such as everolimus), or AKT inhibitor.
- Prior anti-cancer therapy within 2 weeks prior to Cycle 1 Day 1
- Prior radiation therapy within 2 weeks prior to Cycle 1 Day 1
- All acute treatment-related toxicity must have resolved to Grade ≤ 1 or be deemed stable by the investigator
- Prior treatment with > 1 cytotoxic chemotherapy regimen for MBC
- Symptomatic hypercalcemia requiring continued use of bisphosphonate or denosumab therapy

  Use of bisphosphonate therapy or denosumab for other reasons (e.g., bone metastasis, osteoporosis, etc.) is allowed
- Concurrent hormone replacement therapy
- Known untreated or active CNS metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control); a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain will be performed at screening if required by the local health authority

Patients with a history of treated CNS metastases are eligible, provided they meet all of the following criteria:

Evaluable or measurable disease per inclusion criteria outside the CNS is present.

Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

No history of intracranial hemorrhage or spinal cord hemorrhage

Minimum of 2 weeks between completion of radiotherapy and Cycle 1 Day 1 and recovery from significant (Grade ≥ 3) acute toxicity with no ongoing requirement for ≥ 10 mg of prednisone per day or an equivalent dose of other corticosteroid

- History of other malignancy within the previous 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or patients who have undergone potentially curative therapy with no evidence of disease and are deemed by the treating physician to be at low risk for recurrence

General Exclusion Criteria

- Type 1 or Type 2 diabetes mellitus requiring anti-hyperglycemic medications
- Clinically significant cardiac or pulmonary dysfunction, including the following:

  Current uncontrolled Grade ≥ 2 hypertension or unstable angina

  Symptomatic congestive heart failure or serious cardiac arrhythmia requiring treatment, with the exceptions of atrial fibrillation and paroxysmal supraventricular tachycardia or a conduction abnormality that has been treated and for which the patient is no longer at risk for serious arrhythmia (e.g., Wolff-Parkinson-White syndrome treated with surgical ablation)
- Current dyspnea at rest or any requirement for supplemental oxygen therapy to perform activities of daily living
- History of malabsorption syndrome or other condition that would interfere with enteral absorption
- Inability or unwillingness to swallow pills or receive intramuscular injections
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, or current known active infection with HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV)

  Active infection is defined as requiring treatment with antiviral therapy or presence of positive test results for hepatitis B (hepatitis B surface antigen and/or total hepatitis B core antibody) or HCV antibody. Unless required by local regulations, patients are not required to have HIV, HBV, or HCV assessments at screening if these assessments have not been previously performed.

  Patients who test positive for hepatitis B core antibody are eligible only if test results are also positive for hepatitis B surface antibody and polymerase chain reaction (PCR) is negative for HBV DNA.

  Patients who are positive for HCV serology are only eligible if testing for HCV RNA is negative.
- History of inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis)
- Active bowel inflammation (e.g., diverticulitis)
- Immunocompromised status due to current known active infection with HIV or because of the use of immunosuppressive therapies for other conditions
- Need for current chronic corticosteroid therapy (≥ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids)

  Stable use (i.e., no change in dose within 3 months prior to Cycle 1 Day 1) of inhaled corticosteroids is allowed.
- Pregnancy, lactation, or breastfeeding

- Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic or infectious disease)
- Major surgical procedure or significant traumatic injury within 28 days prior to Cycle 1 Day 1 or anticipation of the need for major surgery during the course of study treatment
- Inability to comply with study and follow-up procedures
- Inability to understand the local language(s) for which the EORTC QLQ-C30, the modified Breast Cancer module QLQ-BR23, and the EQ-5D questionnaires are available

Length of Study

The enrollment duration will be driven by enrollment of patients with *PIK3CA*-mutant tumors and is projected to be approximately 28 months (after first patient enrolled). The last PFS event (the 287th PFS event) for the final PFS analysis in patients with *PIK3CA*-mutant tumors is projected to occur approximately 29 months after the first patient is enrolled.

End of Study

The global study will be considered completed when the last patient, last visit or safety follow-up with the last patient has occurred (28 days after the last dose of study drug), whichever occurs later, or when the Sponsor decides to stop the study.

Outcome Measures

Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

- Investigator-assessed PFS, defined as the time from randomization to the first occurrence of disease progression, as determined with the use of Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or death from any cause (whichever occurs earlier)
- Objective response (PR + CR) as determined by using RECIST v1.1
- OS, defined as the time from randomization to death from any cause
- Clinical benefit, defined as objective response or no disease progression lasting for $\geq$ 24 weeks since randomization
- DOR, defined as the time from the first occurrence of a documented objective response to the time of the first documented disease progression, as determined by the investigator using RECIST v1.1, or death from any cause (whichever occurs earlier)
- BICR-assessed PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the BICR with the use of RECIST v1.1, or death from any cause (whichever occurs earlier)

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, type, and severity of adverse events (based on the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 [NCI CTCAE v4.0])
- Incidence, type, and severity of serious adverse events
- Incidence of adverse events leading to study treatment discontinuation, modification, or interruption
- Abnormal laboratory values
- Death and cause of death

Pharmacokinetic Outcome Measure

The pharmacokinetic (PK) outcome measure for this study is:

- Taselisib PK parameters including but not limited to plasma C_{max} and minimum plasma concentration under steady-state conditions within a dosing interval

Patient-Reported Outcome Measure

The PRO measure for this study is as follows:

- HRQoL, including treatment-related symptoms (e.g., oral mucositis, diarrhea, skin problems) and patient functioning, as measured by the EORTC QLQ–C30 and the modified QLQ-BR23 breast cancer module

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Correlation of efficacy with molecular markers related to the mechanism of action of taselisib and endocrine therapy that include the following:
  - Alterations in DNA and RNA, including DNA mutational status, RNA expression levels, DNA copy number and protein expression
  - Alteration in tumor tissue biomarkers including but not limited to PTEN
  - Assessment of PI3K pathway status (e.g., *PIK3CA* mutation status) in ctDNA from peripheral blood, as well as additional cancer related mutations (e.g., *ESR1*)
  - Cancer-related plasma biomarkers including assessment of cytokines and chemokines
- Association between genetic polymorphisms of drug metabolic enzymes or transporters and taselisib pharmacokinetics
- Fulvestrant concentration in the presence and absence of taselisib
- Genetic variants and association with drug-related safety assessments, including but not limited to HLA

Investigational Medicinal Products

Test Product

The test product for this study is taselisib. The taselisib tablet is a white to off-white, film coated, immediate release formulation of 2-mg strength. The taselisib 4-mg dose will be taken orally (PO) once a day (QD). Taselisib is formulated as 2-mg tablets, so patients will take two 2-mg tablets daily to receive a 4-mg dose. Taselisib will be administered in the clinic on Cycle 1 Day 1 and Cycle 1 Day 15 and on each subsequent day that a cycle visit is scheduled, after the predose assessments and procedures, and after the fulvestrant administration (except for Cycle 2 Day 15). Taselisib will be administered at home on all non-clinic visit days. Patients should take the taselisib dose at the same approximate time each day without regard to the timing of administration of food. If a dose is missed (not taken within 6 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.

Placebo

The taselisib placebo (corresponding to a 4-mg dose) will be two tablets taken PO QD. Taselisib placebo will be administered in the clinic on Cycle 1 Day 1 and Cycle 1 Day 15 and on each subsequent day that a cycle visit is scheduled, after the predose assessments and procedures, and after the fulvestrant administration (except for Cycle 2 Day 15). Taselisib placebo will be administered at home on all non-clinic visit days. Taselisib placebo should be taken at the same approximate time each day without regard to the timing of administration of food. If a dose is missed (not taken within 6 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.

Background Therapy

Fulvestrant will be supplied by the Sponsor per country-specific requirements. 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. Fulvestrant 500 mg will be administered in the clinic (before administration of taselisib or placebo) as two intramuscular injections of 250 mg each on Cycle 1 Days 1 and 15 and Day 1 of each subsequent 28-day cycle.

Non-Investigational Medicinal Products

None.

Statistical Methods

Primary Analysis

The primary efficacy endpoint is investigator-assessed PFS (PFS in this document refers to investigator-assessed PFS, unless stated otherwise). The primary efficacy analysis population will include all randomized patients with *PIK3CA*-mutant tumors. The primary efficacy endpoint, PFS, and the secondary efficacy endpoints will be analyzed in this population as the primary and the secondary objectives.

In addition, these efficacy endpoints, unless otherwise specified, will be analyzed in all randomized patients without detectable *PIK3CA*-mutant tumors at the same time as the analyses are conducted for the patients with *PIK3CA*-mutant tumors.

PIK3CA-mutant tumor status will be determined by the cobas *PIK3CA* mutation test of the patient's tissue sample.

The primary PFS analysis will be conducted in all randomized patients with *PIK3CA*-mutant tumors, with patients grouped according to the treatment arm assigned at randomization.

An interim efficacy analysis will be conducted for investigator-assessed PFS at the time of 172 investigator-assessed PFS events (expected 21 months after the first patient is enrolled), and the final efficacy analysis will be conducted at the time 287 investigator-assessed PFS events (expected 29 months after the first patient is enrolled) are observed in patients with *PIK3CA*-mutant tumors. The α-spending function is specified as Gamma (-16), which allocates two-sided $\alpha = 1.7 \times 10^{-5}$ at the interim efficacy analysis of investigator-assessed PFS, when 172 PFS events have occurred and preserves the two-sided 1% α-level at the final PFS analysis. The exact boundary will be calculated on the basis of the exact number of PFS events observed at the interim analysis. The associated minimal detectable difference for the investigator-assessed PFS hazard ratio at the interim efficacy analysis is 0.5 (i.e., 100% improvement in median investigator-assessed PFS from 4.5 months in the control arm to 9 months in the treatment arm).

An exploratory analysis for investigator-assessed PFS will also be conducted in all randomized patients without detectable *PIK3CA*-mutant tumors at the time of the primary PFS analysis in all randomized patients with PIK3CA-mutant tumors.

Data for patients without the occurrence 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 if no tumor assessment was performed after the baseline visit).

Determination of Sample Size

The global study plans to enroll approximately 600 patients, including 480 patients with detectable *PIK3CA*-mutant tumors, and 120 patients without detectable *PIK3CA*-mutant tumors (tumor status determined by the cobas *PIK3CA* mutation test).

After the global enrollment closes, additional Chinese patients may continue to be recruited into the China extension cohort. A total of up to 150 patients with detectable PIK3CA-mutant tumors may be enrolled as part of the global study population and the China extension cohort combined.

The sample size of 480 patients with *PIK3CA*-mutant tumors is determined on the basis of the power calculation for the PFS and the OS endpoints, whichever requires a larger sample size. In this case, the sample size is driven by OS.

In 480 patients with PIK3CA-mutant tumors, approximately 287 investigator-assessed PFS events will be required to detect a hazard ratio of 0.59 in PFS (3.1 months of improvement in median PFS) with 95% power at the a two-sided significance level of 1%, assuming a median PFS of 4.5 months in the control arm (Mauriac et al. 2009; Johnston et al. 2013). One interim efficacy analysis of investigator-assessed PFS will be conducted at 60% of PFS. The α-spending function specified as Gamma (-16), which allocates two-sided $\alpha = 1.7 \times 10$-5 at the interim efficacy analysis of investigator-assessed PFS, when 172 investigator-assessed PFS events have occurred. The minimal detectable difference for investigator-assessed PFS hazard ratio at final PFS analysis is 0.72 (i.e., 39% improvement in median investigator-assessed PFS from 4.5 months in the control arm compared with 6.2 months in the treatment arm), when 287 investigator-assessed PFS events have occurred.

With the aforementioned sample size of 480 patients with *PIK3CA*-mutant tumors, the OS analyses in this population will require 330 deaths to detect an hazard ratio of 0.7 in OS (11.1 months of improvement in median OS) with 80% power at a two-sided significance level of 5%, assuming a median OS of 26 months in the control arm based on the OS of 26.4 months in patients treated with 500 mg fulvestrant in the CONFIRM study, which investigated 500 mg fulvestrant versus 250 mg fulvestrant in a similar patient population (Di Leo et al. 2014).

The study plans to enroll 120 patients who do not have a detectable *PIK3CA*-mutant tumor, on the basis of the result of the cobas *PIK3CA* mutation test, to evaluate the clinical benefit in this population. If the observed hazard ratio in investigator-assessed PFS is 1 (no benefit), approximately 111 investigator-assessed PFS events will be observed at the analysis, and the 90% confidence interval will exclude a true hazard ratio < 0.72 (i.e., $>$ 1.8-month improvement in median PFS).

In total, approximately 400 patients will be treated with the combination of taselisib + fulvestrant in this study (320 patients with *PIK3CA*-mutant tumors and 80 patients without detectable *PIK3CA*-mutant tumors), which will enable the Sponsor to better characterize any rare but clinically significant safety events (e.g., for an adverse event with 4% frequency, there is 96% probability to observe ≥ 10 patients with such adverse event on the basis of 400 taselisib + fulvestrant-treated patients) to help enable the development of effective toxicity prevention and management guidelines for patients treated with the combination of taselisib and fulvestrant.

Interim Analyses

The iDMC will convene to review cumulative safety data approximately every 6 months. Data on serious adverse events, death, and adverse events of special interest will be monitored by the iDMC approximately every 3 months.

One efficacy and one futility analysis for investigator-assessed PFS will be conducted in the patients with *PIK3CA*-mutant tumors when approximately 172 (60% of the information, expected at 21 months after the first patient is enrolled) investigator-assessed PFS events have occurred in patients with *PIK3CA*-mutant tumors. Approximately 320 patients with *PIK3CA*-mutant tumors and approximately 120 patients without detectable *PIK3CA*-mutant tumors will have been randomized into the study by the time of the interim analysis. The actual timing of the interim analysis and the number of patients randomized will depend on the accrual rate and actual accumulation of PFS events observed in the study.

The iDMC will review the efficacy data , while the Sponsor and investigators remain blinded to the treatment assignment until the iDMC recommends stopping the study for efficacy or futility at the specified interim analysis and the Sponsor decides to stop the study.

The iDMC may recommend stopping the study for efficacy at the interim efficacy analysis of investigator-assessed PFS, when the two-sided p-value $\leq 1.7 \times 10^{-5}$, with approximately 172 investigator-assessed PFS events at the interim efficacy analysis. The α-spending function specified as Gamma (-16), which allocates two-sided $\alpha = 1.7 \times 10^{-5}$ at the interim efficacy analysis, when approximately 172 PFS events are reached and preserves the two-sided 1% α-level at the final PFS analysis. The actual boundary will be adjusted based on the actual number of investigator-assessed PFS events at IA. Should the iDMC recommend stopping the study for efficacy at interim analysis and the Sponsor decides to stop the study, the study team will be unblinded, and the investigators and patients will remain blinded to individual patient-level treatment assignment until the final OS analysis.

The iDMC may recommend stopping the study for futility at the interim efficacy analysis of investigator-assessed PFS, when the observed PFS hazard ratio is above 0.85, which provides a probability of approximately 85% to stop the study if the true PFS hazard ratio is 1.0 (i.e., no treatment benefit). The purpose of the futility analysis is not to stop the study for a positive (significant) efficacy PFS outcome. Therefore, statistical significance level for the interim or final efficacy analysis of PFS does not need to be adjusted for this futility analysis. The overall type I error is under strong control.

Three interim analyses for OS *were originally* planned in patients with *PIK3CA*-mutant tumors on the basis of the cobas *PIK3CA* mutation test. *As a result of the completion of the primary PFS analysis, the Sponsor has decided to limit the additional OS follow-up to one additional*

analysis. This additional OS analysis coincides with the originally planned second OS interim analysis.

The type I error is under strong control by using the Generalized Haybittle-Peto method.

No formal interim analysis is planned for the patients without detectable *PIK3CA* mutations.

The responsibility, membership, and communication flow of the iDMC are specified in the iDMC Charter.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AI	aromatase inhibitor
AKT	protein kinase B
BICR	blinded independent central review
BRAF	murine sarcoma viral oncogene homolog B
AUC	area under the concentration–time curve
AUC_{0-24}	area under the concentration–time curve from 0 to 24 hours
$AUC_{0-\infty}$	area under the concentration–time curve from Time 0 to infinity
CFDA	China Food and Drug Administration
CBR	clinical benefit rate
C_{max}	maximum observed plasma concentration
CR	complete response
CT	computed tomography
ctDNA	circulating-tumor DNA
CV	coefficient of variation
CYP3A4	cytochrome P450 3A4
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQol 5-Dimension Questionnaire
ER	estrogen receptor
FA	final analysis
FDA	(U.S.) Food and Drug Administration
FDG-PET	fluorodeoxyglucose positron emission tomography
FFPE	formalin-fixed paraffin-embedded
HbA1c	glycosylated hemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal receptor 2
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation	Definition
HLA	human leukocyte antigen
HR	hazard ratio
HR+	hormone receptor positive
HRQoL	health-related quality of life
IA	interim analysis
ICH	International Conference on Harmonisation
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
IM	intramuscular
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
ISH	in situ hybridization
IxRS	interactive voice/Web response system
MAPK	mitogen-activated protein kinase
MBC	metastatic breast cancer
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSAID	nonsteroidal anti-inflammatory drug
NGS	next-generation sequencing
ORR	objective response rate
OS	overall survival
pAKT	phosphorylated form of protein kinase B
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PI3K	phosphatidylinositol 3-kinase
PIK3CA	oncogene that encodes for phosphatidylinositol-4,5-bisphosphate 3-kinase
PIP2	4,5-phosphatidylinositol bisphosphate
PIP3	3,4,5-phosphatidylinositol triphosphate
PK	pharmacokinetic
PgR	progesterone receptor
PO	by mouth; orally

Abbreviation	Definition
PR	partial response
PRO	patient-reported outcome
PTEN	phosphatase and tensin homolog
QD	once daily
QLQ-BR23	Quality of Life Questionnaire Breast Cancer Module
QLQ-C30	Quality of Life Questionnaire Core 30
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RCR	Roche Clinical Repository
RT-PCR	reverse transcriptase polymerase chain reaction
SD	stable disease
SmPC	summary of product characteristics
TGI	tumor growth inhibition
TSC	tuberous sclerosis
TTD	time to deterioration
ULN	upper limit of normal
WT	wild type

1. BACKGROUND

1.1 BACKGROUND ON ESTROGEN RECEPTOR–POSITIVE, HER2-NEGATIVE ADVANCED OR METASTATIC BREAST CANCER

Breast cancer is the most frequent cancer diagnosed in women, with an estimated global incidence of 1.67 million new cases reported in 2012 (Ferlay et al. 2013). Breast cancer accounts for approximately 15% (approximately 522,000 cases) of all cancer deaths. Breast cancer mortality rates differ by geographical region, with more favorable survival rates in more developed regions of the world (Ferlay et al. 2013).

Estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2 (HER2)-negative breast cancer accounts for 60%–70% of all breast cancers. The standard-of-care treatment for patients with ER+ breast cancer takes several factors into consideration including the stage of disease and recurrence score (Senkus et al. 2013; NCCN Clinical Practice Guideline in Oncology 2014). In the adjuvant treatment setting, endocrine therapy alone may be considered for patients with low volume disease (tumor size $\leq$0.5 cm, node-negative disease) and in patients with a low ($<$18) recurrence score using a 21-gene reverse transcriptase polymerase chain reaction (RT-PCR) assay. Sequential treatment with chemotherapy followed by endocrine treatment should be considered for those patients with node-positive cancers or tumors $>$0.5 cm in size, and intermediate (18–30) to high ($\geq$31) recurrence scores. Administration of tamoxifen with consideration for ovarian ablation or suppression is recommended in premenopausal women (Senkus et al. 2013). The administration of aromatase inhibitors as initial treatment or as a sequential treatment following tamoxifen has been recommended for postmenopausal women (Burstein et al. 2010; Senkus et al. 2013).

Treatment for patients whose disease recurs following adjuvant treatment may include continued endocrine therapy (including combination endocrine therapy) or chemotherapy. Chemotherapy is indicated in patients with symptomatic visceral disease or in patients with disease progression after multiple consecutive endocrine therapy regimens (Senkus et al. 2013). The appropriate endocrine agent used in the metastatic setting is dependent on the menopausal status of the patient. In premenopausal women, ovarian ablation or suppression is generally recommended.

Endocrine treatment options in the treatment of postmenopausal women whose cancer has recurred after adjuvant therapy include nonsteroidal aromatase inhibitors (anastrozole, letrozole), steroidal aromatase inhibitors (exemestane), estrogen receptor down-regulators (fulvestrant), and estrogen receptor modulators (tamoxifen, toremifene). Meta-analyses suggest that aromatase inhibitors may be superior to tamoxifen in prolonging the time to disease progression in this treatment setting (Bonneterre et al. 2000; Nabholtz et al. 2000; Paridaens et al. 2008; Gibson et al. 2009). Treatment with fulvestrant may offer a survival advantage over anastrozole

(Gibson et al. 2009). Very little evidence is available to support an optimal endocrine therapy sequence in the metastatic setting (NCCN Clinical Practice Guideline in Oncology 2014). The choice of agent, sequence of agents, and duration of treatment should be guided by practical considerations, such as prior endocrine treatment response and each agent's safety profile.

Not all ER+ breast cancers respond optimally to endocrine therapy and recently, CDK4/6 inhibitors such as palbociclib and ribociclib have been shown to significantly improve progression-free survival (PFS) over endocrine therapy alone (Finn et al. 2015; Cristofanilli et al. 2016; Hortobagyi et al. 2016). Mechanisms that can lead to primary and/or secondary hormonal resistance in ER+ breast cancer include a decrease or loss of ER expression or an up-regulation of growth factor signaling pathways, such as the epidermal growth factor receptor (EGFR) or HER2, the mitogen-activated protein kinase (MAPK), or the PI3K/AKT/mTOR pathways (Johnston 2009; Musgrove and Sutherland 2009). Recently, mutations in the gene that encodes ER (ESR1) have been identified in metastatic ER+ tumors and are associated with resistance to anti-estrogen therapies (Robinson et al. 2013; Toy et al. 2013; Jeselsohn et al. 2014).

1.2 BACKGROUND ON THE PI3K/AKT/MTOR PATHWAY AND BREAST CANCER

The phosphatidylinositol 3-kinase (PI3K), protein kinase B (AKT), and mammalian target of rapamycin (mTOR) are major nodes in the PI3K/AKT/mTOR intracellular signaling pathway and are critical for cell-cycle modulation, cell growth, metabolism, motility, and survival (Cantrell 2001; Hanahan and Weinberg 2011; Vanhaesebroeck et al. 2012). The PI3K/AKT/mTOR pathway is generally activated following ligand-receptor tyrosine kinase interactions. Under physiologic conditions, the main role of PI3K is to facilitate the metabolism of inositol phospolipids for intracellular signal transduction.

There are three classes of PI3K, with Class I being the most responsive to external stimuli. Class I PI3Ks comprise two subunits: a p110 catalytic subunit and a regulatory adapter subunit p85. There are four isoforms of the p110 catalytic subunit of PI3K: α, β, δ, and γ. These four isoforms are the product of three genes: *PIK3CA*, *PIK3CB*, and *PIK3CD*.

Dysregulation of the PI3K/AKT/mTOR signaling pathway has been described in multiple solid tumor malignancies: glioblastoma, colorectal, gastric, lung, endometrial, ovarian, prostate, and breast cancer (Gustin et al. 2008). Pathway activation may occur through multiple mechanisms: the loss of the tumor suppressor phosphatase and tensin homolog (PTEN), amplification or somatic mutations in *PIK3CA*, mutations in AKT, mutations in the regulatory subunit p85, mutations and/or amplification of upstream-receptor tyrosine kinases, mutations in RAS, loss of liver kinase B1 (LKB1), type II inositol polyphosphate-4-phosphatase (INPP4B), or tuberous sclerosis (TSC) (Staal 1987; Cheng et al. 1992; Bellacosa et al. 1995; Li et al. 1997; Steck et al. 1997;

Aoki et al. 1998). Activating mutations in the *PIK3CA* gene are the most common genomic alterations and occur primarily in exons 9 and 20 ("hotspot" regions), which encode the helical and kinase domains of PI3Kα protein (Bachman et al. 2004; Samuels et al. 2004).

Up to 70% of breast cancers can have some form of molecular aberration of the PI3K/AKT/mTOR pathway (Cancer Genome Atlas Network 2012). Hyperactivation of the PI3K/AKT/mTOR signaling pathway was proven to promote both *de novo* and acquired resistance to hormone therapy in ER+ breast cancer cell lines and xenograft models (Sabnis et al. 2007), and 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 provide support to the hypothesis that blocking PI3K/AKT/mTOR pathway signaling may have a therapeutic benefit in patients with ER+, HER2-negative breast cancer. The combination of everolimus and exemestane has received regulatory approval, and many agents that target PI3K and AKT are in various stages of development.

In the clinical setting, results of the combination of exemestane and everolimus, an mTOR inhibitor, were reported in the BOLERO-2 trial (Baselga et al. 2012). This study compared everolimus and exemestane with placebo and exemestane in 724 postmenopausal patients with ER+ advanced breast cancer who had experienced recurrence or progression of disease while receiving previous therapy with a nonsteroidal aromatase inhibitor in the adjuvant setting and/or in advanced disease. Median 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 (95% CI: 0.35, 0.54; $p < 0.001$). The magnitude of the effect was even greater with central independent review: $HR = 0.36$ (95% CI: 0.27, 0.47; $p < 0.001$). In the open-label Phase II TAMRAD study, patients with aromatase inhibitor (AI)-resistant metastatic breast cancer (MBC) received tamoxifen plus everolimus or tamoxifen alone (Bachelot et al. 2012). The 6-month clinical benefit rate was 61% (95% CI: 47%, 74%) with tamoxifen plus everolimus and 42% (95% CI: 29%, 56%) with tamoxifen alone. Time to progression increased from 4.5 months with tamoxifen alone to 8.6 months with tamoxifen plus everolimus, corresponding to a 46% reduction in risk of progression with the combination ($HR = 0.54$; 95% CI: 0.36, 0.81). The risk of death was reduced by 55% with tamoxifen plus everolimus versus tamoxifen alone ($HR = 0.45$; 95% CI: 0.24, 0.81).

An important finding in studies with mTOR-targeting drugs such as everolimus is that these drugs produce a pharmacodynamic paradox: while inhibiting mTOR, the administration of these drugs leads to an up-regulation of the phosphorylated form of AKT (pAKT), resulting in feedback PI3K/AKT/mTOR pathway activation

(Tabernero et al. 2008). This finding suggests that alternative pharmacologic strategies to effectively shut down the pathway upstream of AKT should be pursued. One of these strategies is inhibiting the PI3K/AKT/mTOR pathway with agents that specifically target PI3K.

1.3 BACKGROUND ON TASELISIB

1.3.1 Taselisib Nonclinical Data

Taselisib (RO5537381, GDC-0032) is a potent selective inhibitor of Class I PI3K α, δ, and γ isoforms, with 30-fold less potent biochemical inhibition of the β isoform and increased potency in tumor cells bearing mutant PI3K over wild-type (WT) PI3K cells. Taselisib exerts its activity by binding to the ATP binding site of PI3K, thereby inhibiting the phosphorylation of membrane-bound 4,5-phosphatidylinositol bisphosphate (PIP2) to 3,4,5-phosphatidylinositol triphosphate (PIP3). Inhibiting the phosphorylation of PIP2 to PIP3 decreases downstream activation of AKT and mTOR, resulting in decreased cellular proliferation, metabolism, and angiogenesis (Ndubaku et al. 2013). Nonclinical studies demonstrate that taselisib inhibits proliferation and induces apoptosis of PI3Kα-mutant breast cell lines, inhibits tumor growth in human breast xenograft models harboring PI3K mutations, and reduces downstream PI3K-pathway markers, including pAKT, pPRAS40, and pS6.

Results of in vitro combination studies indicated positive combination effects between taselisib and endocrine therapies. In the *PIK3CA*-mutant aromatase-expressing breast cancer cell line (MCF7X2.3.ARO), taselisib alone caused growth inhibition (50% effective concentration [i.e., concentration resulting in one-half the maximum effect] = 95 nM). Effects on growth were also observed with letrozole and fulvestrant. Combined treatment of cells with taselisib and letrozole caused dose-dependent inhibition of cell viability at lower concentrations of either taselisib or letrozole resulting in enhanced activity for the combination. In addition, combination activity was demonstrated in the *PIK3CA* WT cell line ZR75-1 when taselisib was added to either fulvestrant or tamoxifen endocrine therapies (combination with letrozole is not available in this cell line). However, in vivo data in a *PIK3CA* WT model are not available because these cell lines do not grow as xenografts.

Enhanced efficacy was demonstrated in combination with tamoxifen, another endocrine therapy used in the treatment of hormone receptor−positive (HR+) advanced breast cancer. In the human MCF7-neo/HER2 (*PIK3CA* mutant [MT]) breast cancer xenograft model in immune-compromised nude mice, administration of taselisib at all doses tested (5, 10, or 20 mg/kg) in combination with tamoxifen (5-mg/pellet) resulted in greater efficacy (shown as a percentage of tumor growth inhibition [TGI]: 82% TGI, 80% TGI, and 102% TGI, respectively) compared with tamoxifen alone (73% TGI) or taselisib as a single agent (71% TGI at 20 mg/kg). All combinations were well-tolerated with no increase in mortality and no greater body weight loss than with single agents alone.

In vivo anti-tumor activity by taselisib, as characterized by TGI and PI3K pathway inhibition, was demonstrated in pharmacology studies with human tumor xenograft models with use of differing mechanisms of PI3K pathway activation in immunocompromised mice (see the Taselisib Investigator's Brochure). All dosing regimens in the summarized efficacy studies were tolerated with generally $<20\%$ body weight loss. A summary of findings included the following:

- Administration of single-agent taselisib resulted in 128% TGI at a maximum efficacious dose of 25 mg/kg once daily (QD) (7 partial responses [PRs] and 1 complete response [CR] out of 8 animals) in the KPL 4 human breast cancer xenograft model, which contains a *PIK3CA* mutation in the catalytic domain of p110α (H1047R).
- Efficacy was improved when taselisib was used in combination with fulvestrant, leading to 83% TGI (10 mg/kg taselisib QD $+5$ mg fulvestrant subcutaneously) compared with 63% TGI for taselisib and 34% for fulvestrant for either agent alone.
- PI3K pathway markers pAKT, pPRAS40, and pS6 were reduced from 1–24 hours in response to a single dose of taselisib, and a substantial reduction of pathway markers was associated with plasma concentrations >2.7 μM in the KPL4 breast cancer xenograft model (see the Taselisib Investigator's Brochure).

No safety pharmacology findings were noted, including cardiovascular effects of taselisib in telemetry-instrumented dogs, neurobehavioral and/or motor activity effects in rats, or respiratory effects in dogs.

1.3.2 Taselisib Clinical Data

As of 30 April 2014, 191 patients have been treated with taselisib capsules in the Phase I/II study PMT4979g, either as single agent ($n=108$) or in combination with fulvestrant ($n=83$).

As of 30 April 2014, enrollment into the single-agent dose-escalation stage of Study PMT4979g was completed with 34 patients enrolled at taselisib doses ranging from 3 to 16-mg capsules daily. Taselisib was well-tolerated in the first three cohorts (3, 5, and 8 mg), with no patients experiencing a dose-limiting toxicity (DLT). At the 16-mg dose level, 2 of the 11 safety-evaluable patients experienced a DLT (Grade 4 hyperglycemia and Grade 3 fatigue). At the 12-mg dose level, 1 of the 10 safety-evaluable patients experienced a DLT of Grade 3 acute renal failure. Although the single-agent taselisib maximum tolerated dose was not exceeded at the 16-mg dose level, the recommended taselisib dose and schedule for the single-agent expansion cohorts is 9 mg daily on the basis of long-term safety data through multiple treatment cycles. As of the cutoff date, a total of 74 patients had been enrolled in the 9-mg daily dosing expansion cohorts.

As of 30 April 2014, adverse events of any grade that occurred in $\geq 10\%$ of the 108 patients treated with daily single-agent taselisib capsules and were assessed by the

investigator as taselisib-related were as follows: diarrhea (54%), nausea (36%), hyperglycemia (35%), fatigue (32%), decreased appetite (26%), rash (19%), stomatitis (15%), vomiting (13%), and mucosal inflammation (12%). Grade 3 and 4 adverse events assessed by the investigator as taselisib-related included hyperglycemia (14%), colitis (7%), rash (5%), pneumonitis (4%), diarrhea (4%), fatigue (4%), pruritus (2%), stomatitis (2%), vomiting (1%), increased alanine aminotransferase levels (1%), anemia (1%), increased blood creatinine (1%), exfoliative rash (1%), hypokalemia (1%), hypophosphatemia (1%), lung infection (1%), pneumonia (1%), erythematous rash (1%), generalized rash (1%), maculopapular rash (1%), skin exfoliation (1%), diabetic ketoacidosis (1%), enterocolitis (1%), impaired glucose intolerance (1%), mucosal inflammation (1%), neutropenia (1%), and acute renal failure (1%).

As of 30 April 2014, a total of 83 patients have been treated with a combination of taselisib + fulvestrant as part of the PMT4979g study. Of the 83 patients, 27 have been enrolled in the expansion cohort of taselisib at dose levels of 6 mg (21 patients) and 9 mg (6 patients) daily in combination with fulvestrant (Cohort F). No DLTs were observed at either dose level. An additional 56 patients have been enrolled in the Phase II part of Study PMT4979g with 6 mg taselisib administered in combination with fulvestrant. Adverse events assessed by the investigator as taselisib-related and of any grade that occurred in ≥ 10% of the 83 patients treated with a combination of taselisib + fulvestrant were diarrhea (59%), nausea (31%), fatigue (28%), decreased appetite (23%), rash (21%), mucosal inflammation (19%), hyperglycemia (18%), stomatitis (17%), asthenia (16%), and dry skin (13%). Grade 3 and 4 adverse events assessed by the investigator as taselisib-related included colitis (8%), diarrhea (8%), hyperglycemia (7%), rash (4%), hyponatremia (2%), mucosal inflammation (2%), maculopapular rash (1%), anemia (1%), asthenia (1%), cytomegalovirus colitis (1%), dyspnea (1%), enterocolitis (1%), flank pain (1%), neutropenia (1%), pruritis (1%), transaminases increased (1%), and vomiting (1%).

Refer to the current Taselisib Investigator's Brochure for further details and the most recent data.

*In addition, after unblinding and completion of the primary PFS analysis of this Study GO29058, the following new taseli*si*b adverse drug reactions were detected: infection (including serious infection), alopecia, fever, dyspepsia, and weight loss.*

1.3.3 Clinical Pharmacokinetics of Taselisib

The pharmacokinetics of taselisib have been characterized in patients with cancer, following oral administration after single and multiple dosing in the Phase Ia dose-escalation portion of Study PMT4979g. After a single dose of a 3–16-mg taselisib capsule, the mean half-life ($t_{1/2}$: time for drug in the body to be reduced by one-half) is approximately 40 hours. The apparent taselisib clearance at steady state (CLss/F) had a range of 4320–9170 mL/hr. Taselisib demonstrated a moderate rate of absorption with

a median time to maximum concentration of 3 hours. Following a dosage of 6-mg taselisib capsule QD, the mean (CV%) maximum observed plasma concentration (C_{max}) and area under the concentration–time curve from 0 to 24 hours (AUC_{0-24}) at steady state were 0.172 μM (51%) and 3.024 μM • hr (56%), respectively. The taselisib exposures, as measured by C_{max} and AUC_{0-24}, were approximately dose-proportional with 2- to 4-fold accumulation and moderate variability in C_{max} and AUC_{0-24}. No apparent time-dependent changes in pharmacokinetic (PK) exposure were observed.

Taselisib has also been administered to healthy subjects in the clinical pharmacology studies summarized in Table 1.

Table 1 Clinical Pharmacology Studies in Healthy Subjects

Study Number	Study Objective	Taselisib Formulation	No. of PK-Evaluable Subjects
GP28617	To determine the effect of steady-state rifampicin or itraconazole on the PK of taselisib capsule	Capsule	29
GP28755	To characterize the mass balance and metabolite profile of taselisib capsule by comparing oral and IV administration of taselisib	Capsule, IV solution	14
GP28619	Part 1: To determine relative bioavailability of taselisib tablet vs. capsule; to determine the effect of a high fat meal on the PK of taselisib tablet	Part 1: Prototype tablet, capsule	22
	Part 2: To determine the effect of particle size on the oral bioavailability of taselisib tablet	Part 2: Prototype tablet with 2 different API particle sizes	12
	Part 3: To determine the relative bioavailability of 2 different lots of taselisib API in capsule formulation under fasting conditions	Part 3: Capsule with 2 different API particle sizes	20
	Part 4 : To investigate the effect of formulation on taselisib administered as a 2 mg tablet relative to the 3 mg original powder-in capsule	Part 4: Phase III tablet, capsule	20

API = active pharmaceutical ingredient; IV = intravenous; PK = pharmacokinetic.

Results from the food-effect study in healthy volunteers (Study GP28619) indicate that the pharmacokinetics of the prototype taselisib tablet is minimally altered by food. The food-effect results in healthy volunteers are consistent with those observed in the pilot food-effect study, Study PMT4979 (n = 10 patients), conducted in patients with cancer that utilized a capsule formulation of taselisib.

The relative bioavailability of a 3-mg taselisib tablet versus 3-mg capsule formulation was 152% (142%–163%) for taselisib AUC and 196% (177%–217%) for taselisib C_{max} in healthy volunteers (Study GP28619). In Part 4 of the same study, the 2-mg taselisib tablet demonstrated pharmacokinetics comparable to the 3-mg capsule dose. Relative

bioavailability of a 2-mg tablet versus a 3-mg capsule was 101% (90% CI: 94.8%–107%) for AUC and 117% (90% CI: 106%–128%) for C_{max}. A 4-mg taselisib tablet dose is estimated to provide an AUC equivalent to a 6-mg capsule dose due to the ability of taselisib to demonstrate linear, dose-proportional pharmacokinetics over a broad dose-range (3–16 mg).

Results from the mass-balance study suggest that hepatic elimination of unchanged taselisib represents the predominant pathway of elimination, and renal clearance represents a very small contribution of total taselisib clearance. The mean (range) absolute bioavailability of the taselisib capsule was approximately 64% (40.8%–91.5%). No [^{14}C] taselisib-related metabolites were present in systemic circulation.

In vitro metabolism studies with taselisib indicate that it is a substrate of CYP3A4. In clinical studies in healthy subjects, the pharmacokinetics of taselisib were minimally affected by rifampicin, a potent CYP3A4 inducer, and moderately altered by itraconazole, a potent CYP3A4 inhibitor. Rifampicin was found to produce an approximate 16% decrease in taselisib C_{max} (90% CI: 73.5%, 96.9%) and an approximate 23% decrease in taselisib area under the concentration–time curve from Time 0 to infinity ($AUC_{0-\infty}$) (90% CI: 70.2%, 82.4%). After co-administration with itraconazole, there was an approximate 9% increase in C_{max} (90% CI: 89.8%, 131%) and an approximate 49% increase in taselisib $AUC_{0-\infty}$ (90% CI: 128%, 173%).

In vitro, taselisib was not a potent inhibitor of CYP isoforms 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4 ($IC_{50} > 30$ μM) but displayed weak time-dependent inhibition of CYP3A4. In patients with cancer (Study PMT4979g), the pharmacokinetics of midazolam, an in vivo marker of CYP3A4 enzymatic activity, were unaffected by taselisib (geometric mean ratio [90% CI] of 0.98 [0.70–1.37] for C_{max} and 1.04 [0.68–1.60] for AUC_{0-24}). Consistent with these findings, codaminstration of taselisib with letrozole or fulvestrant in cancer patients (Study PMT4979g) did not result in any apparent change in the pharmacokinetics of these CYP3A4 substrates. For more information, refer to the Taselisib Investigator's Brochure.

1.4 BACKGROUND ON FULVESTRANT

Fulvestrant is an ER antagonist approved for the treatment of postmenopausal patients with HR+ breast cancer who have disease progression following other anti-estrogen therapy (MedImmune 2013). 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 (progression-free survival 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). This dose of fulvestrant has also shown a trend toward improvement in overall survival compared

with the 250-mg fulvestrant dose (median duration of overall survival [OS] is 26.4 months vs. 22.3 months). The lower dose of fulvestrant (250 mg) is recommended in patients who have liver dysfunction (Child-Pugh Class B disease).

Clinical studies comparing fulvestrant 250 mg given once a month with anastrozole 1 mg daily have demonstrated similar efficacy between the two agents (Osborne et al 2002; Robertson et al. 2009). Similar rates of objective responses (15%–20%), median time to progression (3.4–5.5 months), and duration of OS (25–30 months) were reported and were not statistically different. Similar efficacy (measured by median time to progression) between fulvestrant and exemestane has also been demonstrated in postmenopausal women who had received prior aromatase-inhibitor therapy for advanced breast cancer (Chia et al. 2008).

The common adverse events associated with the use of fulvestrant include injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, extremity pain, hot flashes, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea, and constipation. Increases in liver enzymes (AST, ALT, alkaline phosphatase [ALP]) have also been reported in approximately 15% of patients. In randomized studies that compared fulvestrant with anastrozole, similar rates of common adverse events were reported, with the exception of injection-site pain.

1.4.1 Clinical Pharmacokinetics of Fulvestrant

At the 500-mg monthly dosing regimen, the geometric mean (CV%) C_{max} and AUC of fulvestrant at steady state were 28.0 ng/mL (27.9%) and 13,100 ng • hr/mL (23.4%), respectively. Following a single IM injection of fulvestrant 250 mg, the apparent clearance (mean ± SD) of fulvestrant was 690 ± 226 mL/min with an apparent half-life of approximately 40 days. The ^{14}C-labeled studies with fulvestrant indicate that fulvestrant is rapidly cleared by the hepatobiliary route with excretion primarily via the feces (approximately 90%). Less than 1% of fulvestrant was excreted unchanged in the urine.

Fulvestrant has no known drug interactions. It does not significantly inhibit or induce any of the major CYP isoenzymes in vitro. Although it is partially metabolized by CYP3A4, coadministration of fulvestrant with either rifampicin (a potent CYP3A4 inducer) or ketoconazole (a potent CYP3A4 inhibitor) had no effect on its pharmacokinetics. Preliminary PK data of fulvestrant from 14 postmenopausal patients with HR+ breast cancer were evaluated in Study PMT4979g. Results of the study suggest that the pharmacokinetics of fulvestrant is comparable with historical data, which suggest that taselisib does not alter the pharmacokinetics of fulvestrant.

For more information, refer to the local prescribing information for fulvestrant (i.e., package insert or Summary of Product Characteristics [SmPC]).

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The activity of endocrine therapy, including tamoxifen and AIs, is the primary reason for the sustained improvement in survival for patients with HR+ breast cancer. However,

nearly half of the patients that present with HR+ MBC do not respond to front-line endocrine treatment, and nearly all patients who do respond eventually develop resistance to endocrine therapy.

The mechanisms of resistance to hormonal therapies in HR+ MBC patients are likely multifactorial: estrogen-independent tumor growth; loss of ER expression; or activation of intracellular signaling pathways, including MAPK and PI3K (Acconcia et al. 2005; Björnström and Sjöberg 2005; Gutierrez et al. 2005; Johnston et al. 2009; Osborne and Schiff 2011).

The scientific rationale for combining a PI3K pathway inhibitor with endocrine therapy is supported by nonclinical and clinical data. Activation of the PI3K pathway (via *PIK3CA* mutations, PTEN expression loss, or HER2 overexpression) has been demonstrated to promote resistance to anti-estrogen therapy and hormonal independence in ER+ breast cancer models (Shou et al. 2004; Miller et al. 2009, 2010). Proteomic and transcriptional profiling of human HR+ tumors suggest that increased PI3K signaling is associated with lower ER levels, which has been correlated with resistance to endocrine therapy (Creighton et al. 2010; Miller et al. 2010). Inhibition of the PI3K/mTOR pathway in nonclinical models has been shown to upregulate ER/progesterone receptor (PgR) expression (Creighton et al. 2010) and enhance the anti-tumor effect of letrozole (Boulay et al. 2005). Retrospective analyses of tumor samples from patients who are HR+ treated with tamoxifen lend support to the nonclinical observations linking the PI3K pathway to resistance to anti-estrogen therapy; patients with an activated PI3K pathway have been found to have decreased OS (Kirkegaard et al. 2005) and shorter relapse-free survival (Shoman et al. 2005).

In the clinical setting, data from two Phase II studies and one Phase III study suggest that the combined inhibition of the PI3K/mTOR and estrogen-signaling pathways may provide superior benefit when compared with single-agent endocrine therapies. Administration of an mTOR inhibitor, everolimus, increased the efficacy of letrozole in the neoadjuvant setting in patients with ER+ cancer evidenced by increased clinical response rate (68% vs. 59%) and by a reduction in Ki67 expression in patients who received everolimus and letrozole compared with those who received letrozole (Baselga et al. 2009). The addition of everolimus to tamoxifen in a Phase II study with ER+ patients who received prior treatment with an AI significantly improved the clinical benefit rate (CBR), time to progression, and overall survival compared with single-agent tamoxifen (Bachelot et al. 2012). Finally, data from the Phase III BOLERO-2 study demonstrated that the addition of everolimus to exemestane more than doubled PFS compared with single-agent exemestane in ER+, HER2-negative MBC patients whose disease was refractory to prior treatment with letrozole or anastrozole (Baselga et al. 2012). Therefore, the combined inhibition of the ER and PI3K-pathways may prove to be an effective therapeutic approach in patients with MBC who experience recurrent or progressive disease (PD) while receiving treatment with an AI.

Activating mutations of *PIK3CA* (the PI3K α isoform), which belongs to the class IA PI3K family, have been observed in a number of different tumor types, including breast cancer (Bachman et al. 2004; Samuels et al. 2004). These activating mutations have been shown to promote growth and invasion in cancer cells, effects that are abrogated by PI3K inhibitors.

As described in Section 1.3.1, taselisib is a very potent PI3K inhibitor. Sixty percent TGI was observed when taselisib was administered to a *PIK3CA*-mutant breast cancer xenograft model (KPL4) at a nonclinical dose of 0.5 mg/kg, which is equivalent to the AUC exposure corresponding to the 3 mg capsule QD dose in humans. Further, taselisib in combination with fulvestrant showed greater efficacy than either agent administered alone in another breast cancer xenograft model (MCF7). On the basis of data in these two breast cancer models, the Sponsor estimated that robust pathway inhibition and anti-tumor activity could occur with a 3-mg capsule clinical dose as a single agent and when administered in combination with fulvestrant. In addition, clinical data from Study PMT4979g further support the finding that taselisib inhibits the PI3K pathway in patient samples and, importantly, has demonstrable anti-tumor activity when given as a single agent or when combined with endocrine therapy, as summarized below.

- Inhibition of the PI3K pathway was observed in paired tumor biopsy tissue samples (pretreatment and during taselisib treatment) at the lowest dose tested of single-agent 3-mg capsule QD.
- Decreases in the mean standardized uptake value via fluorodeoxyglucose positron emission tomography (FDG-PET) analysis that correlate with inhibited glucose uptake are another pharmacodynamic marker of PI3K pathway inhibition. Such decreases have also been observed beginning at the lowest dosage of single-agent taselisib tested, 3-mg capsule QD.

In addition, clinical efficacy data from patients with breast cancer treated with single-agent taselisib support the proposed Phase III dose and schedule. Confirmed partial responses in patients with breast cancer treated with single-agent taselisib have only been observed in those with *PIK3CA*-mutant tumors, including 1 patient with a *PIK3CA*-mutant tumor at the 5-mg capsule QD single-agent dose. Although the 3-mg capsule dose has demonstrated evidence of pharmacodynamic modulation and anti-tumor activity, it is thought that increasing the drug exposure will lead to increased inhibition of the PI3K pathway and enhance tumor shrinkage. While the number of patients in the 12-mg cohort was small, there did appear to be a higher confirmed response rate (3 out of 4 patients with breast cancer with *PIK3CA*-mutant tumors). However, given the overall tolerability with the 12-mg dose and evidence of strong activity with the 6-mg capsule dose, particularly in combination with fulvestrant, a 6-mg capsule dose is thought to maximize dose intensity and drug exposure while maintaining a suitable safety profile in this patient population.

The clinical efficacy data observed at the 6-mg capsule taselisib dose in combination with fulvestrant in the Phase I/II study also support further testing of this regimen in the Phase III Study in the proposed biomarker-positive subgroup of patients with *PIK3CA*-mutant breast cancer. Of the Phase Ib and Phase II patients in Study PMT4979g who were treated at the 6-mg capsule dose level, confirmed partial responses were observed in patients with *PIK3CA*-mutant breast cancer. These findings are consistent with the hypothesis that the combination of taselisib and fulvestrant will provide the most benefit to this patient population.

Although letrozole is a different endocrine therapy than fulvestrant, clinical efficacy data of letrozole in combination with taselisib is also supportive of the 4-mg tablet dose (equivalent to 6-mg capsule dose, see Section 1.3.3). In a heavily pretreated Phase Ib population, confirmed partial responses were also observed in multiple patients with *PIK3CA*-mutant breast cancer.

In summary, the available nonclinical and clinical data for taselisib support the proposed Phase III dosing regimen of taselisib in combination with fulvestrant. On the basis of taselisib bioavailability data, the Phase III dosing regimen with tablets will be 4-mg QD to deliver exposure equivalent to the 6-mg QD capsule exposure that was tested in Study PMT4979g. The proposed Phase III population usually receives single-agent endocrine therapy, which has a very favorable toxicity profile. However, it is clear that second- or third-line regimens that contain only endocrine therapies have not demonstrated impressive activity in randomized controlled studies when administered as single agents (Chia et al. 2008) or in combinations (Johnston et al. 2013). The anticipated or potential safety issues associated with the administration of taselisib in combination with 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.

There is a need to develop improved anti-cancer therapies in ER+ advanced breast cancer. Because of this need and on the basis of the clinical and nonclinical data available for taselisib, the Sponsor has assessed the benefit-risk profile of taselisib in combination with fulvestrant to be appropriate for initiating the proposed clinical study.

2. OBJECTIVES

The efficacy, safety, pharmacology, and patient-reported outcome (PRO) objectives of this study will be evaluated in postmenopausal women with ER+, HER2-negative, locally advanced or MBC and who have had recurrence or progression of disease on or after administration of an aromatase-inhibitor therapy.

2.1 EFFICACY OBJECTIVES

The primary efficacy objective for this study is as follows:

- To compare the efficacy between taselisib + fulvestrant versus placebo + fulvestrant as measured by investigator-assessed PFS in patients with *PIK3CA*-mutant tumors

The secondary efficacy objectives for this study are as follows:

- To compare the overall objective response rate (ORR) between taselisib + fulvestrant versus placebo + fulvestrant in patients with *PIK3CA*-mutant tumors, on the basis of tumor assessments made by the investigator
- To compare the efficacy between taselisib + fulvestrant versus placebo + fulvestrant as measured by OS in patients with *PIK3CA*-mutant tumors
- To estimate the duration of objective response (DOR) within taselisib + fulvestrant versus placebo + fulvestrant in patients with *PIK3CA*-mutant tumors, on the basis of tumor assessments made by the investigator
- To compare the clinical benefit rate (CBR) between taselisib + fulvestrant versus placebo + fulvestrant in patients with PIK3CA-mutant tumors, on the basis of tumor assessments made by the investigator
- To compare the efficacy between taselisib + fulvestrant versus placebo + fulvestrant as measured by PFS determined by blinded independent central review (BICR) in patients with PIK3CA-mutant tumors

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of taselisib + fulvestrant versus placebo + fulvestrant in patients with locally advanced or MBC in all randomized patients who receive at least one dose of taselisib/placebo or fulvestrant, regardless of the *PIK3CA* mutation status of their tumors, and separately in the subgroups of patients with and without detectable *PIK3CA*-mutant tumors.

2.3 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is to evaluate the pharmacokinetics of taselisib when taken with fulvestrant

2.4 PATIENT-REPORTED OUTCOME OBJECTIVE

The PRO objective for this study is as follows:

- To evaluate and compare PROs of treatment-related symptoms, patient functioning, and health-related quality of life (HRQoL) as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the modified Breast Cancer Module (QLQ-BR23) between the taselisib + fulvestrant versus placebo + fulvestrant treatment arms

2.5 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To evaluate the PFS, ORR, CBR, and DOR of taselisib + fulvestrant versus placebo + fulvestrant in patients with locally advanced or MBC where a *PIK3CA* mutation was not detected

- To evaluate PFS, ORR, CBR, and DOR of taselisib + fulvestrant versus placebo + fulvestrant in patients with locally advanced or MBC whose tumor *PIK3CA*-mutation status is determined by plasma DNA analysis
- To explore the potential relationship between pharmacogenetic differences in drug-metabolizing enzymes, transporters, and other patient-specific covariates with pharmacokinetics and safety of taselisib when administered in combination with fulvestrant in patients with locally advanced or MBC
- To explore the potential taselisib exposure-response (efficacy and safety) relationship in patients with locally advanced or MBC receiving taselisib in combination with fulvestrant
- To explore fulvestrant concentrations in patients with locally advanced or MBC who receive fulvestrant alone or in combination with taselisib
- To evaluate predictive and prognostic plasma or tissue biomarkers associated with disease activity status or response to treatment
- To identify possible mechanisms of resistance to fulvestrant + taselisib through the comparative analysis of potential biomarkers in the pretreatment and post-progression biopsy tissue samples and in blood
- To assess health status as measured using the EuroQol 5-Dimension Questionnaire (EQ-5D) for health economic modeling

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

Study GO29058 (SANDPIPER) is a Phase III, randomized, multicenter, international, double-blind, placebo-controlled clinical study designed to compare the efficacy, as measured by PFS, and safety of fulvestrant + taselisib with that of fulvestrant + placebo after recurrence or progression following treatment with an AI for patients with ER+, HER2-negative, *PIK3CA*-mutant, unresectable, locally advanced or MBC. *PIK3CA* mutation status in all patients will be assessed by a central laboratory using the cobas® PIK3CA mutation test. In order to explore efficacy and differential benefit-risk in patients without a detectable *PIK3CA* mutation, 120 patients belonging to this category are planned for enrollment.

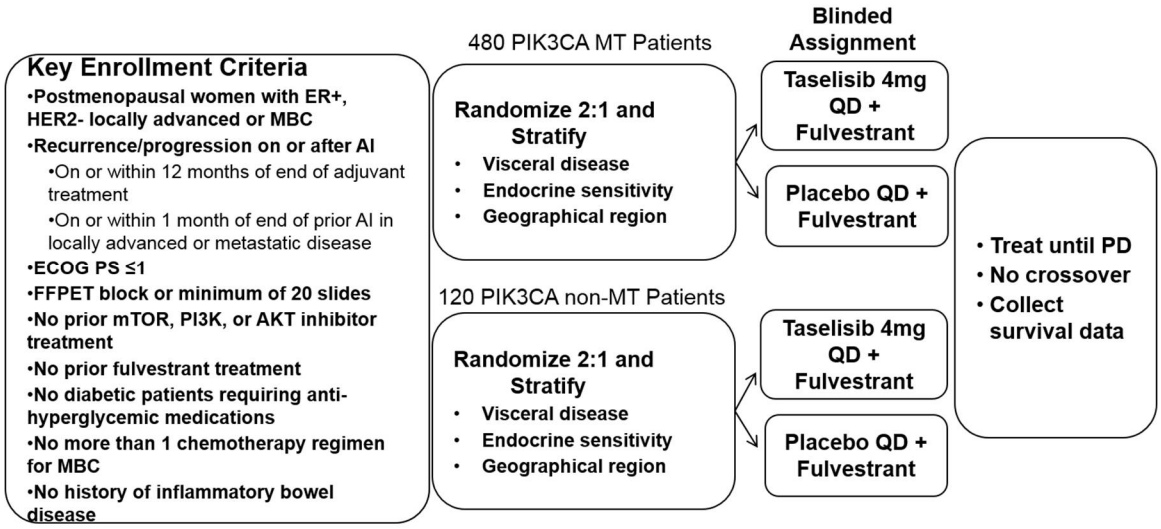
Study GO29058 will consist of a global study that will provide the evidence to determine the benefit-risk of taselisib plus fulvestrant in the target population; a possible extension cohort may continue to enroll only in China to meet local regulatory requirements.

In the global study, approximately 600 patients will be randomized in a 2:1 ratio to either fulvestrant + taselisib or fulvestrant + placebo (see Figure 1). unless the independent Data Monitoring Committee (iDMC) recommends stopping the study early and the Sponsor accepts the iDMC's recommendation. Patients whose tumors contain a *PIK3CA*-mutation (n = 480) and patients whose tumors do not contain a detectable *PIK3CA*-mutation (n = 120) will be randomized separately. After the global enrollment

closes, additional Chinese patients may continue to be recruited into the China extension cohort. A total of up to 150 Chinese patients with detectable PIK3CA-mutant tumors may be enrolled as part of the global study population and extension cohort combined (see Section 6.10). Patients enrolled as part of the China extension cohort will also be randomized in a 2:1 ratio to either fulvestrant + taselisib or fulvestrant + placebo.

- **Taselisib Arm**: Taselisib 4-mg tablet dose (2 × 2 mg tablet formulation) taken orally (PO) QD 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
- **Control Arm**: Placebo taken PO QD 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 1 Schematic of Randomized Controlled Study GO29058 (Global Study)



AKT = protein kinase B; AI = aromatase inhibitor; ECOG = Eastern Cooperative Oncology Group; ER+ = estrogen receptor-positive; FFPET = formalin-fixed paraffin-embedded tissue; HER2− = human epidermal growth factor receptor 2-negative; MBC = metastatic breast cancer; MT = mutation; mTOR = mammalian target of rapamycin; non-MT = no detectable mutation; PD = progressive disease; PI3K = phosphatidylinositol 3-kinase; PS = performance status; QD = once daily.

A permuted block randomization scheme will be used to ensure an approximate 2:1 allocation of patients who receive active taselisib + fulvestrant versus patients who receive placebo + fulvestrant with respect to the following stratification factors per local assessment:

- Visceral versus non-visceral disease

- Sensitivity versus non-sensitivity to their most recently administered endocrine therapy, with sensitivity defined as patients who meet either criterion listed below:

  For patients with no endocrine treatment in the advanced or metastatic setting, at least 24 months of adjuvant endocrine therapy prior to disease recurrence

  Documented clinical benefit (CR, PR, or stable disease [SD] ≥24 weeks) to most recent endocrine treatment in the advanced or metastatic treatment setting
- Geographical region

Prior to enrollment but after signing the informed consent document, patients will have the *PIK3CA*-mutant status of their tumor assessed by the central laboratory using the cobas PIK3CA mutation test. Patients may be prescreened for *PIK3CA*-mutation status using the cobas PIK3CA mutation test by participating in a separate prescreening consent or as part of the eligibility evaluation for this study. Patients whose tumor samples have invalid test results will not be permitted to enroll in the study.

Patients may have either measurable disease (per Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1]; see Appendix 6) and/or non-measurable, but evaluable, locally advanced or metastatic disease with at least one evaluable bone lesion. Detailed information is listed in the inclusion and exclusion criteria in Section 4.1. Locally advanced disease must not be amenable to resection or other local therapy with curative intent.

Until approximately the end of August 2018, tumor assessments will be conducted for all patients 8 weeks (±5 days) from the date of randomization and then every 8 weeks (±5 days) thereafter, regardless of dose delays or dose interruptions, until 4–6 weeks after investigator-assessed disease progression or until death, whichever occurs first. *After approximately the end of August 2018, tumor assessments may be conducted per local standard of care.*

Patients may *remain on* study treatment until disease progression (as assessed by the investigator), unmanageable toxicity, or study termination by the Sponsor. Patients who discontinue taselisib/placebo due to toxicity may continue on single-agent fulvestrant at the discretion of the investigator. Discontinuation of fulvestrant for adverse events is very rare. However, in the unlikely event that the patient discontinues fulvestrant and is able to continue on taselisib/placebo, the investigator should contact the Medical Monitor to discuss the benefit-risk assessment of continuing with single-agent taselisib/placebo. All patients who are discontinued from all study treatment will return for a study drug discontinuation visit within 28 days after the last dose of study treatment (see Section 4.5.10 for additional details).

Until approximately the end of August 2018, patients who are discontinued from study treatment for reasons other than disease progression will be asked to continue to have

tumor assessments performed and to complete the PRO assessments approximately every 8 weeks (±5 days) until disease progression.

Until approximately the end of August 2018, after study treatment discontinuation, patients will be followed for survival and subsequent anti-cancer therapies approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor.

Until approximately the end of August 2018, after experiencing disease progression, patients will also be asked to return to the clinic approximately 4–6 weeks (for tumor and PRO assessments) and 12 weeks ([±1 week] for PRO assessments), even if a patient initiates anti-cancer therapy subsequent to study drug discontinuation.

Until the primary PFS analysis has been completed, an iDMC will monitor accumulating patient safety data and will also review efficacy data at the time of the interim analysis of investigator-assessed PFS (see Section 6.9). The iDMC will convene to review cumulative safety data approximately every 6 months. The data regarding serious adverse events, death, and adverse events of special interest will be monitored by the iDMC approximately every 3 months. Further specific details are listed in Section 5.3.

3.2 END OF STUDY

The global study will be considered completed when the last patient, last visit (LPLV) *or safety follow-up with the last patient has occurred (28 days after the last dose of study drug), whichever occurs later,* or when the Sponsor decides to stop the study.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population

The population described by the proposed eligibility criteria reflects patients for whom fulvestrant represents an appropriate standard of care therapy. Postmenopausal women with advanced ER+, HER2-negative breast cancer could have clinical benefit from the addition of a PI3K inhibitor, especially if their breast tumors contain the *PIK3CA* mutation. The requirement for prior treatment with an aromatase inhibitor identifies patients who have become resistant to endocrine therapy and would be an appropriate population for a fulvestrant-based endocrine combination. The allowance of up to one prior cytotoxic chemotherapy regimen in the metastatic setting is consistent with prior studies with fulvestrant in a similar patient population, as well as a more recent study for patients who had become resistant to prior aromatase inhibitor treatment. Patients treated with one prior metastatic chemotherapy regimen are not expected to be predisposed to having more severe drug-related toxicities. The inclusion criterion of Eastern Cooperative Oncology Group (ECOG) Performance Status of 0–1 has been selected to test a more homogeneous patient population and to mitigate potential extra toxicities incurred by the addition of taselisib to fulvestrant treatment.

3.3.2 Rationale for China Extension Cohort

In order to characterize the efficacy and safety profile of taselisib in combination with fulvestrant in Chinese patients and to potentially support a regulatory submission in China, a China extension cohort is planned in the study. After the global enrollment closes, additional Chinese patients may continue to be recruited into the China extension cohort. A total of up to 150 Chinese patients with detectable PIK3CA-mutant tumors may be enrolled as part of the global study population and extension cohort combined.

3.3.3 Rationale for the Control Treatment

Treatment for HR+, HER2-negative breast cancer usually consists of multiple rounds of single-agent endocrine therapy followed by cytotoxic chemotherapy once all endocrine therapy options have been exhausted or symptomatic or rapid disease progression warrants the use of cytotoxic chemotherapy. Fulvestrant has been approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency for the treatment of HR+ or ER+, locally advanced or MBC in postmenopausal women with disease progression following prior anti-estrogen therapy (Howell et al. 2002; Osborne et al. 2002; Di Leo et al. 2010).

Fulvestrant is not indicated for use in the adjuvant setting, whereas AIs are currently approved for use and are considered the standard of care (in the United States and European Union) in this setting. Therefore, given the unique mechanism of action and the current treatment paradigm that indicates the sequential use of endocrine therapies for patients without visceral crisis (Senkus et al. 2013) for treatment of locally recurrent or MBC, fulvestrant represents an appropriate treatment option for patients whose disease failed to respond to prior AI therapy.

3.3.4 Rationale for Double-Blind Design

A double-blind, placebo-controlled design was chosen for this study to reduce the potential for bias by patients and investigators that would be related to knowledge of the treatment assignment. For patients, the design is anticipated to minimize dropout and increase compliance; for investigators, the design facilitates objectivity in outcome assessments. This design is especially important when investigator-assessed PFS is the primary endpoint.

3.3.5 Rationale for Taselisib Dose and Schedule

3.3.5.1 Safety Rationale

The clinical safety profile of taselisib at the 4-mg tablet dose level in combination with fulvestrant is expected to be acceptable for the intended Phase III population. Adverse events associated with the combination of the equivalent exposure of taselisib in capsule form are those that have been observed with other PI3K pathway inhibitors and include diarrhea, colitis, pneumonitis, rash, and hyperglycemia. These adverse events are monitorable, manageable, and reversible. Preliminary clinical safety data from the open-

label Phase Ib and II portions of Study PMT4979g with a taselisib 6-mg capsule dose QD in combination with fulvestrant also support testing the 4-mg tablet dose in the Phase III population. No DLTs were observed at either the 6-mg or 9-mg capsule dose levels in the Phase Ib Study PMT4979g; however, patients treated with the 9-mg capsule dose of taselisib experienced a Grade 3 adverse event more frequently than patients treated at the 6-mg capsule dose level of taselisib.

No QT prolongation risk was observed at tested doses. On the basis of the acceptable safety profile for the taselisib 6-mg capsule QD dose in combination with fulvestrant and the expected equivalent exposure of the 4-mg tablet dose and 6-mg capsule dose, a 4-mg dose of taselisib tablet is the Phase III dose used in this study.

3.3.5.2 Efficacy-Response Rationale

When administered to a PIK3CA-mutant breast cancer xenograft model (KPL4) at a preclinical dose that is equivalent to the 3-mg QD capsule dose in humans, 60% TGI was observed in the KPL4 mouse model. Furthermore, PK and pharmacodynamic modeling and human PK simulations based on these preclinical data suggest that 80% of the patient population receiving taselisib is likely to achieve the efficacious exposure target at a $\geq$3-mg QD capsule dose.

The taselisib dose and schedule was derived from data generated in the Phase I/II open-label Study PMT4979g where taselisib doses ranging between 3 and 16 mg were administered to patients with solid tumor malignancies. Enrollment in the Phase II part of the study was enriched for patients with breast cancer. In addition to the finding of a linear- and dose-proportional PK profile within this dose range, the mean elimination half-life of taselisib ranged between 37 and 44 hours, which support a QD dosing schedule. Additional information for the choice of dose and schedule is found in the Taselisib Investigator's Brochure.

3.3.6 Rationale for PK Sampling and Schedule

A sparse sampling strategy will be applied in the study on the basis of the PK data already obtained for taselisib, which supports an expected half-life of approximately 40 hours. PK data from the taselisib arm will allow comparison to single-agent taselisib data to evaluate whether taselisib exposures are altered when administered in combination with fulvestrant. The data collected from this study will enable a further understanding of taselisib pharmacokinetics and identification of potential sources of variability influencing taselisib pharmacokinetics.

3.3.7 Rationale for Patient-Reported Outcome Assessments

MBC is not currently considered curable; therefore, a patient's HRQoL is an important multi-dimensional construct to measure because impairment of function and experience of treatment-related symptoms affect patient outcomes (Beslija et al. 2009; Irwin et al. 2011). Elucidating treatment effect on HRQoL, specifically during PFS,

provides supportive evidence to the benefit-risk assessment of a medicine and informs the treatment decision-making between patient and clinician.

PRO measures will contextualize a patient's experiences in the study. Since treatment-related side effects (e.g., oral mucositis, diarrhea, and skin problems) have the potential to affect HRQoL, it is crucial to characterize not only the incidence of these side effects but also the impact from the patient's perspective. Assessment of global quality of life, impairment of function, and symptoms of special interest will provide a more comprehensive understanding of treatment impact and tolerability.

The EORTC QLQ-C30 and QLQ-BR23 demonstrate strong psychometric properties, of both reliability and validity, and capture important constructs of interest. The QLQ-BR23 will be modified to include validated items on oral mucositis (2 items) and skin problems (2 items) to characterize these symptoms of special interest.

3.3.8 Rationale for Biomarker Assessments

Breast cancer is a heterogeneous disease, and *PIK3CA*-mutation status has been shown to vary among patients (The Cancer Genome Atlas Network 2012). In addition to PIK3CA-mutation 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 taselisib and/or fulvestrant.

3.3.9 Tissue and Circulating Biomarker Assessments

3.3.9.1 PIK3CA Mutation Status

Mutations in *PIK3CA* occur at a frequency of approximately 40% in MBC and have been shown to correlate with response to PI3K inhibitors (O'Brien et al. 2010; Schleifman et al. 2014). Taselisib is a potent PI3K inhibitor, and a strong correlation has been observed between *PIK3CA*-mutant tumors and response to taselisib. *PIK3CA* mutation status will be determined using the Roche cobas *PIK3CA* mutation test that detects 17 of the most frequent *PIK3CA* mutations in human cancer. Based on data from the COSMIC database (v66), the assay covers approximately 92% of the reported *PIK3CA* mutations in breast cancer that have been identified; all detected mutations are known or suspected to be oncogenic (Kang et al. 2005; Bader et al. 2006). Previous studies suggest that the acquisition of *PIK3CA* mutations is an early event in breast cancer (Miron et al. 2010), and a 84%–90% concordance rate has been observed when comparing primary to matched MBC samples, suggesting that analysis of archival tissue is a sufficient surrogate for the identification of patients with *PIK3CA*-mutant tumors (Aurthur et al. 2014; Schleifman et al. 2014).

3.3.9.2 Phosphatase Tensin Homolog Expression Analysis

Published data suggests that loss of the tumor suppressor PTEN can activate the PI3K pathway through the β isoform of p110 (*PIK3CB*) (Jia et al. 2008). PTEN expression may be assessed using established immunohistological techniques, or mutations within PTEN may be assessed using next-generation sequencing techniques.

3.3.9.3 Estrogen Receptor and Progesterone Receptor Analysis

Expression of PgR is a favorable prognostic factor in ER+ positive breast cancer, and expression has been demonstrated to be discordant among pathology laboratories (Arpino et al. 2005). Expression of PgR has been linked to estrogen sensitivity and response to anti-hormone agents (Elledge et al. 2000; Arpino et al. 2005; Stuart-Harris et al. 2009), and receptor expression can change over the course of anti-estrogen therapy (Broom et al. 2009; DeDuenas et al. 2014). PgR and ER expression may be determined using established immunohistochemistry (IHC) techniques.

3.3.9.4 Sequencing of Genes Related to Resistance to PI3K Inhibitors

Next-generation sequencing (NGS) techniques, such as targeted exome sequencing, may offer a unique opportunity to identify biomarkers of response. For example, using whole genome sequencing, a two base-pair deletion in the *TSC1* gene was found in a patient with metastatic bladder cancer with a prolonged response (>2 years) to everolimus as single agent (Iyer et al. 2012). Similar approaches could be of great value when analyzing responses to agents targeting the PI3K/AKT/mTOR pathway, especially in the metastatic setting. In addition, 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 taselisib.

3.3.9.5 Blood Sample for Next-Generation Sequencing

NGS technologies generate a large quantity of sequencing data. Tumor DNA can contain both reported and unreported chromosomal alterations because of the tumorigenesis process. To help control for sequencing calls in previously unreported genomic alterations, a blood sample will be taken during predose to determine whether the alteration is somatic.

3.3.9.6 RNA and DNA Analysis

In addition to mutational activation of proteins, levels of RNA and DNA can also activate the PI3K pathway. For example, increases in DNA copy number in genes such as *CCND1*, *FGFR1/2* and *IGF-1R*, which occur at some frequency in breast cancer, can activate downstream–cell cycle and PI3K pathway. HR+ breast cancer can be divided into luminal A and luminal B subtypes, with the luminal B subtype displaying a higher proliferative index and a poorer prognosis. Therefore, the RNA profiling of tumors will allow intrinsic subtyping of patients enrolled onto study. In addition, PI3K transcription activation signatures may identify additional patients who could respond to PI3K inhibitors independent of *PIK3CA* mutation status.

3.3.9.7 Plasma Sample for Somatic Tumor Mutation Analysis

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. The use of circulating tumor DNA (ctDNA) to monitor response to treatment is an area of great interest. It could allow for an early, non-invasive, and quantifiable method for use in the clinical setting to identify candidates for specific therapies and monitoring of disease mutation status over time (Higgins et al. 2012).

3.3.9.8 Blood Sample for the Detection of Plasma Protein Biomarkers

Emerging evidence indicates that increases in levels of systemic cytokines and chemokines, such as receptor tyrosine kinase growth factors, can attenuate response to drugs, particularly, targeted agents such as taselisib (Wilson et al. 2012). Assays that assess the expression of soluble, systemic cytokines and chemokines from the plasma of patients may be performed using ELISA-based, mass spectrometry or appropriate methodologies.

3.3.9.9 Optional Tumor Biopsy Sample at the Time of Disease Progression

Tumor tissue may be collected at the time of 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 taselisib is critical for the development of agents in the PI3K pathway and may provide an opportunity to develop next-generation inhibitors to prevent resistance. Notable examples include the T790M gatekeeper acquired mutation in EGFR in patients who progress on EGFR inhibitors and reactivation of the MAPK pathway in murine sarcoma viral oncogene homolog B (BRAF)-mutant melanoma cancers that progress on BRAF inhibitors. Obtaining progression biopsy tissue samples will aid in determining a resistance mechanism to taselisib and potentially influence future therapies for patients who progress on a PI3K inhibitor and may be part of a potential substudy. NGS may be performed by a clinical cancer genomic profiling laboratory (e.g., Foundation Medicine). If performed, the investigator can obtain results from the samples collected at the time of disease progression in the form of an NGS report, which is available upon request directly from the clinical cancer genomic profiling laboratory (e.g., Foundation Medicine). The investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The Foundation Medicine NGS assay has not been cleared or approved by the U.S. FDA or is it CE marked in Europe; results from these investigational tests are intended for exploratory purposes only and should not be used to guide future treatment decisions.

3.3.9.10 Pharmacokinetic Sample Collection Schedule

A sparse sampling strategy will be applied in the study. A total of four plasma samples will be collected as outlined in Appendix 2. Samples will be collected at Cycle 1, Day 1, Cycle 2, Day 1, and Cycle 6, Day 1. The sampling schedule is designed to enable

characterization of taselisib pharmacokinetics using population PK methodology following first dose (Cycle 1, Day 1) and steady-state (Cycle 2, Day 1 and Cycle 6, Day 1) as well as exploration of fulvestrant concentrations at steady state (Cycle 6, Day 1).

3.3.9.11 DNA for Exploratory Pharmacogenetic Polymorphisms

Blood samples will be used for the evaluation of genetic polymorphisms of drug metabolic enzymes (including but not limited to CYP2C9, CYP3A4/5, and UGT1A1 and transporters [e.g., OATP1B1]) and genetic variants that could contribute to a potentially drug-related rash and/or colitis safety assessments (including but not limited to human leukocyte antigen [HLA]). For sample handling procedures, storage conditions, and shipment instructions, see the laboratory manual. Only in circumstances where there is concern for the collection of this genetic material for the above evaluations can this assessment be considered not mandatory as part of study assessments in this study. Results of any analyses from these samples will be reported outside the clinical study report.

It is established that genetic variants of drug-metabolizing enzymes and transporters can affect the pharmacokinetics of drugs, which affects their safety and efficacy. For example, patients who carry defective alleles of the gene encoding uridine diphosphate glucuronosyltransferase 1A1, which facilitates the metabolism and excretion of SN-38 (the active metabolite of irinotecan), are at a higher risk for adverse effects associated with the use of standard doses of irinotecan (O'Dwyer and Catalano 2006). Preliminary results from in vitro metabolism studies with taselisib suggest that taselisib is partially metabolized by multiple phase I cytochrome P450 enzymes, including CYP3A4. 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, such as differences in drug concentrations that the enzymes encounter in vitro and in vivo. For this reason, a blood sample for DNA isolation is to be collected from all patients in this study for potential pharmacogenetic analysis of genes or biomarkers that may affect the pharmacokinetics or response to taselisib. The decision to analyze the samples will be based on a review of the pharmacokinetics and response data. Most recently, HLA has been demonstrated to play an important role in the development of drug-induced rash for some drugs (carbamazepine, abacavir, and allopurinol). Therefore, evaluation of genetic variants of genes that may regulate the immune response (including but not limited to HLA) may also be investigated to characterize unusual safety responses that are not predicted by taselisib pharmacokinetics.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

- Investigator-assessed PFS, defined as the time from randomization to the first occurrence of disease progression, as determined with the use of Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or death from any cause (whichever occurs earlier)
- Objective response (PR + CR) as determined by using RECIST v1.1
- OS, defined as the time from randomization to death from any cause
- Clinical benefit, defined as objective response or no disease progression lasting for ≥ 24 weeks since randomization
- DOR, defined as the time from the first occurrence of a documented objective response to the time of the first documented disease progression, as determined by the investigator using RECIST v1.1, or death from any cause (whichever occurs earlier)
- BICR-assessed PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the BICR with the use of RECIST v1.1, or death from any cause (whichever occurs earlier)

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, type, and severity of adverse events (based on the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 [NCI CTCAE v4.0])
- Incidence, type, and severity of serious adverse events
- Incidence of adverse events leading to study treatment discontinuation, modification, or interruption
- Abnormal laboratory values
- Death and cause of death

3.4.3 Pharmacokinetic Outcome Measure

The PK outcome measure for this study is as follows:

- Taselisib PK parameters including but not limited to plasma C_{max} and minimum plasma concentration under steady-state conditions within a dosing interval

3.4.4 Patient-Reported Outcome Measure

The PRO measure for this study is as follows:

- HRQoL, including treatment-related symptoms (e.g., oral mucositis, diarrhea, skin problems) and patient functioning, as measured by the EORTC QLQ–C30 and the modified QLQ–BR23 breast cancer module

3.4.5 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Correlation of efficacy with molecular markers related to the mechanism of action of taselisib and endocrine therapy that include the following:

  Alterations in DNA and RNA, including DNA mutational status, RNA expression levels, DNA copy number and protein expression

  Alteration in tumor tissue biomarkers including but not limited to PTEN

  Assessment of PI3K pathway status (e.g., *PIK3CA* mutation status) in ctDNA from peripheral blood, as well as additional cancer related mutations (e.g., *ESR1*)

  Cancer-related plasma biomarkers including assessment of cytokines and chemokines

- Association between genetic polymorphisms of drug metabolic enzymes or transporters and taselisib pharmacokinetics
- Fulvestrant concentration in the presence and absence of taselisib
- Genetic variants and association with drug-related safety assessments, including but not limited to HLA

3.4.6 Exploratory Health Economic Outcome Measure

The EQ-5D will be used to obtain health status information for health economic modeling (see Appendix 9).

The EQ-5D is a generic, preference-based health utility measure with questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that are used to build a composite of the patient's health status. A single summary index from the EQ-5D health states will be utilized in this study for economic modeling.

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

Disease-Specific Inclusion Criteria

- Women with histologically or cytologically confirmed invasive, ER+ breast cancer: metastatic or inoperable (not amenable to resection or other local therapy with curative intent) locally advanced breast cancer
- Patients for whom endocrine therapy (e.g., 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.
- Radiologic/objective evidence of recurrence or progression to the most recent systemic therapy for breast cancer

- Radiologic/objective evidence of breast cancer recurrence or progression while on or within 12 months of the end of adjuvant treatment with an AI, or progression while on or within 1 month of the end of prior AI treatment for locally advanced or MBC. The AI (letrozole, anastrozole, or exemestane) does not have to be the most recent treatment before randomization.
- Measurable disease via RECIST v1.1 or non-measurable, evaluable disease with at least one evaluable bone lesion via RECIST v1.1. Bone lesions that have been irradiated are not evaluable.

General Inclusion Criteria

- Able and willing to provide written informed consent and to comply with the study protocol
- Age ≥ 18 years
- ECOG Performance Status of 0 or 1
- Postmenopausal status defined as one of the following:

  Age ≥ 60 years

  Age < 60 years and postmenopausal as defined by documented follicle-stimulating hormone and estradiol in the postmenopausal ranges in addition to being amenorrheic for 12 months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression

  Prior bilateral oophorectomy ($\geq$ 28 days prior to first fulvestrant treatment at Cycle 1, Day 1)
- Consent to provide a formalin-fixed, paraffin-embedded (FFPE) tissue block (preferred) or a minimum of 20 (25 preferred) freshly cut unstained tumor slides from the most recently collected, available tumor tissue for *PIK3CA*-mutation testing and for other protocol-mandated exploratory assessments
- A valid cobas *PIK3CA* mutation result (per central testing) is required for all patients (e.g., patients with an “invalid” or “failed” *PIK3CA* mutation result are not permitted to enroll)

  After 120 patients whose breast cancers have a “wild-type” (mutation not detected result) *PIK3CA* status have been enrolled, all remaining enrolled patients must have a breast cancer sample that tests positive for *PIK3CA* mutation to be eligible.
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 28 days prior to Cycle 1 Day 1:

  ANC $\geq 1500/\mu L$ ($1.5 \times 10^9/L$)

  Platelet count $\geq 100{,}000/\mu L$ ($100 \times 10^9/L$)

  Hemoglobin ≥ 9.0 g/dL (90 g/L)

  Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN) except in patients with previously documented Gilbert’s syndrome, in which case total bilirubin ≤ 3 mg/dL

AST and ALT $\leq 1.5 \times$ ULN, with the following exceptions:

Patients with documented liver metastases: AST and/or ALT $\leq 5.0 \times$ ULN

Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min based on Cockcroft–Gault glomerular filtration rate estimation

$$\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine})}$$

INR < 1.5 and aPTT (or PTT) $< 1.5 \times$ ULN; for patients requiring therapeutic anticoagulation therapy, a stable INR ≤ 2.5

- Fasting glucose ≤ 125 mg/dL (6.94 mmol/L)
- For enrollment into the China extension cohort, residence in the People's Republic of China

4.1.2 Exclusion Criteria

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

Disease-Specific Exclusion Criteria

- HER2-positive disease by local laboratory testing (IHC 3+ staining or in situ hybridization positive)
- Prior treatment with fulvestrant
- Prior treatment with a PI3K inhibitor, mTOR inhibitor (such as everolimus), or AKT inhibitor. See Appendix 5 for a comprehensive list of excluded treatments.
- Prior anti-cancer therapy within 2 weeks prior to Cycle 1 Day 1
- Prior radiation therapy within 2 weeks prior to Cycle 1 Day 1
- All acute treatment-related toxicity must have resolved to Grade ≤ 1 or be deemed stable by the investigator
- Prior treatment with > 1 cytotoxic chemotherapy regimen for MBC
- Symptomatic hypercalcemia requiring continued use of bisphosphonate or denosumab therapy

  Use of bisphosphonate therapy or denosumab for other reasons (e.g., bone metastasis, osteoporosis, etc.) is allowed
- Concurrent hormone replacement therapy
- Known untreated or active CNS metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control); a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain will be performed at screening if required by the local health authority

  Patients with a history of treated CNS metastases are eligible, provided they meet all of the following criteria:

  Evaluable or measurable disease per inclusion criteria outside the CNS is present.

Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

No history of intracranial hemorrhage or spinal cord hemorrhage

Minimum of 2 weeks between completion of radiotherapy and Cycle 1, Day 1 and recovery from significant (Grade $\geq$3) acute toxicity with no ongoing requirement for $\geq$10 mg of prednisone per day or an equivalent dose of other corticosteroid

- History of other malignancy within the previous 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or patients who have undergone potentially curative therapy with no evidence of disease and are deemed by the treating physician to be at low risk for recurrence

General Exclusion Criteria

- Type 1 or Type 2 diabetes mellitus requiring anti-hyperglycemic medications
- Clinically significant cardiac or pulmonary dysfunction, including the following:

  Current uncontrolled Grade $\geq$2 hypertension or unstable angina

  Symptomatic congestive heart failure or serious cardiac arrhythmia requiring treatment, with the exceptions of atrial fibrillation and paroxysmal supraventricular tachycardia or a conduction abnormality that has been treated and for which the patient is no longer at risk for serious arrhythmia (e.g., Wolff-Parkinson-White syndrome treated with surgical ablation)
- Current dyspnea at rest or any requirement for supplemental oxygen therapy to perform activities of daily living
- History of malabsorption syndrome or other condition that would interfere with enteral absorption
- Inability or unwillingness to swallow pills or receive intramuscular injections
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, or current known active infection with HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV)

  Active infection is defined as requiring treatment with antiviral therapy or presence of positive test results for hepatitis B (hepatitis B surface antigen and/or total hepatitis B core antibody) or HCV antibody. Unless required by local regulations, patients are not required to have HIV, HBV, or HCV assessments at screening if these assessments have not been previously performed.

  Patients who test positive for hepatitis B core antibody are eligible only if test results are also positive for hepatitis B surface antibody and polymerase chain reaction (PCR) is negative for HBV DNA.

Patients who are positive for HCV serology are only eligible if testing for HCV RNA is negative.

- History of inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis)
- Active bowel inflammation (e.g., diverticulitis)
- Immunocompromised status due to current known active infection with HIV or because of the use of immunosuppressive therapies for other conditions
- Need for current chronic corticosteroid therapy (≥10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids)

  Stable use (i.e., no change in dose within 3 months prior to Cycle 1 Day 1) of inhaled corticosteroids is allowed.
- Pregnancy, lactation, or breastfeeding
- Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic or infectious disease)
- Major surgical procedure or significant traumatic injury within 28 days prior to Cycle 1, Day 1 or anticipation of the need for major surgery during the course of study treatment
- Inability to comply with study and follow-up procedures
- Inability to understand the local language(s) for which the EORTC QLQ-C30, the modified Breast Cancer module QLQ-BR23, and the EQ-5D questionnaires are available (see Appendix 7, Appendix 8, and Appendix 9).

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

After written informed consent has been obtained and eligibility has been established and approved, the study site will obtain the patient's identification number and treatment assignment from the interactive voice/Web response system (IxRS). Patients will be randomized to receive either taselisib + fulvestrant or the placebo + fulvestrant on the basis of a 2:1 randomization ratio. Patients with *PIK3CA*-mutant tumors and patients without detectable *PIK3CA*-mutant tumors will be randomized separately using a permuted-block randomization method.

Randomization will be stratified by the following criteria:

- Visceral versus non-visceral disease

  Visceral disease: Metastatic disease in the lung, liver, adrenal glands, brain, heart, pericardium, pleura, peritoneum, or other end-organs of the chest, abdomen, and pelvis

  Non-visceral disease: Absence of metastatic disease in visceral organs. Pleural effusions, ascites, disease involving lymph nodes, and disease involving bone are not considered to be visceral disease.

- Sensitivity versus non-sensitivity to the patient's most recently administered endocrine therapy

    Sensitive to most recently administered endocrine therapy (fulfilling either of the criteria below:

        For patients with no endocrine treatment in the advanced or metastatic setting, at least 24 months of adjuvant endocrine therapy prior to disease recurrence

        Documented clinical benefit (CR, PR, or SD $\geq$24 weeks) to most recent endocrine treatment in the advanced or metastatic treatment setting

    Non-sensitive: not satisfying criteria listed as sensitive

- Geographical region:

    Western Europe, United States, Canada, Australia

    Asia

    Rest of World (remaining countries)

The iDMC, the independent statistical group (an independent vendor) facilitating the iDMC meetings, and the Sponsor-independent PK bioanalytical personnel will be unblinded to the treatment assignment. The study team will be unblinded at the time when the iDMC recommends to stop the trial and the Sponsor decides to stop the trial or at the time of the final PFS analysis if the study is not stopped early. Investigators and patients will remain blinded to individual patient-level treatment assignment until *approximately the end of August 2018, at which time unblinding is permitted at the discretion of the investigator or Sponsor*.

Although 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 this trial. Sponsor personnel responsible for performing PK assays will be unblinded to patients' treatment assignments to identify appropriate PK samples to be analyzed. Samples from patients assigned to the comparator arm will not be analyzed except by request (i.e., to evaluate a possible error in dosing).

Until approximately the end of August 2018, if unblinding is necessary for patient management (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 the IxRS. Treatment codes should not be broken except in emergency situations. If the investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding or unblinding due to a serious adverse event).

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or the Sponsor to be related to study drug.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Taselisib

The taselisib tablet is a white to off-white, film-coated, immediate-release formulation of 2 mg strength.

4.3.1.2 Fulvestrant

Fulvestrant will be supplied by the Sponsor per country-specific requirements. 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 details regarding storage of fulvestrant, refer to the fulvestrant package insert or SmPC.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Taselisib

The taselisib 4-mg dose will be taken orally once a day (4 mg PO QD). Taselisib is formulated as 2-mg tablets, so patients will take two 2-mg tablets daily to receive a 4-mg dose. Taselisib will be administered in the clinic at Cycle 1, Day 1 and Cycle 1 Day 15 and on each subsequent day that a cycle visit is scheduled, after the predose assessments and procedures, and after the fulvestrant administration (except for Cycle 2 Day 15). Taselisib will be administered at home on all non-clinic visit days. Patients should take the taselisib dose at the same approximate time each day without regard to the timing of administration of food. If a dose is missed (not taken within 6 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. For additional details, see Appendix 1.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.1.1.

4.3.2.2 Placebo

The taselisib placebo (corresponding to 4-mg dose) dosage will be supplied as 2 tablets PO QD. Taselisib placebo will be administered in the clinic at Cycle 1, Day 1 and Cycle 1, Day 15 and on each subsequent day that a cycle visit is scheduled, after the predose assessments and procedures, and after the fulvestrant administration (except for Cycle 2, Day 15). Taselisib placebo will be administered at home on all non-clinic visit days. Taselisib placebo should be taken at the same approximate time each day without regard to the timing of administration of food. If a dose is missed (not taken within 6 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. For additional details, see Appendix 1.

4.3.2.3 Fulvestrant

Fulvestrant 500 mg will be administered in the clinic (before administration of taselisib/placebo) as two IM injections of 250 mg each at Cycle 1, Days 1 and 15 and Day 1 of each subsequent 28-day cycle. For details regarding the dosing instructions and safety profile of fulvestrant, refer to the fulvestrant package insert or SmPC.

The fulvestrant dose level cannot be modified. In general, the investigator may consider continuing fulvestrant if the adverse event observed is not thought to be fulvestrant-related. See Section 5.1.2.1 for guidelines for treatment interruption or discontinuation of fulvestrant.

4.3.3 Investigational Medicinal Product Accountability

Taselisib and placebo will be supplied by the Sponsor in all participating countries. Fulvestrant will be supplied by the Sponsor in all participating countries except the countries where procurement will be reimbursed. The study site will acknowledge receipt of Sponsor-supplied study drugs using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

Sponsor-supplied study drugs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The Sponsor must agree with the method of destruction at each investigational site. The site must obtain written authorization from the Sponsor before any Sponsor-supplied medication is destroyed, and destruction must be documented on the appropriate form.

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

4.3.4 Post-Study Access to Taselisib

Currently, the Sponsor does not have any plans to provide taselisib or any other study treatments or interventions after the end of the study or for any patient who has discontinued or withdrawn from the study. Crossover from the control arm to the taselisib arm is not allowed. The Sponsor will evaluate whether to continue providing taselisib after the main study is over in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product.

In the event that the Sponsor deems post-trial access to taselisib to be appropriate, the Sponsor may offer post-trial access to the study drug (taselisib) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after the end of the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being.
- There are no appropriate alternative treatments available to the patient.
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A patient will not be eligible to receive study drug after the end of the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient).
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for ER+, HER2-negative MBC.
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for ER+, HER2-negative MBC.
- Provision of study drug is not permitted under the laws and regulations of the patient's country.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:
http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf.

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

Concomitant therapy includes any prescription medication, over-the-counter preparations, herbal or homeopathic remedies, and nutritional supplements used by a patient from 7 days prior to the screening visit through to Study Drug Discontinuation Visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

Patients who experience toxicities should be treated symptomatically as clinically indicated. Patients treated with anti-seizure medications should have levels monitored regularly.

Patients who require maintenance therapy as specified in the eligibility criteria (see Sections 4.1.1 and 4.1.2) should continue to receive maintenance therapy.

Anti-emetics and anti-diarrheal medications should not be administered prophylactically before initial treatment with study drug. At the discretion of the investigator, prophylactic anti-emetic and anti-diarrheal medication(s) may be used as per standard clinical practice before subsequent doses of study drug.

Pain medications administered per standard clinical practice are acceptable while the patient is enrolled in the study.

4.4.2 Prohibited Therapy

Use of the following concomitant therapies is prohibited for at least 7 days prior to Cycle 1, Day 1 dosing (unless a longer washout is required as outlined in the exclusion criteria in Section 4.1.2) and during the study treatment *unless otherwise specified below*:

- Therapy intended for the treatment of cancer (regulatory-approved or experimental), including chemotherapy, radiation therapy, immunotherapy, biologic therapy, herbal therapy, radiopharmaceutical therapy, or endocrine therapy.

  Until approximately the end of August 2018, local radiotherapy is not permitted. It is understood that there may be extreme circumstances requiring local radiotherapy in which the investigator does not believe that the symptoms are a result of disease progression (e.g., impending fracture) and the radiation field does not encompass a target/non-target lesion. In such cases, the investigator must obtain approval from the Medical Monitor, and such patients should have a tumor assessment of the lesion(s) before they actually receive the radiotherapy. If a patient received radiation therapy and a target or non-target lesion is included in the field of radiation, the lesion(s) will become unevaluable for tumor response.

  Further reasons for avoiding local radiotherapy include the difficulty in distinguishing new symptomatic pain or worsening of lytic bone lesions from disease progression. Radiation therapy to a specific site renders that lesion unevaluable for tumor response. Few clinical data are available about potential toxicities of radiation and treatment with taselisib. Previous clinical experience also suggests that new bone pain is frequently a symptom of disease progression. Bone pain secondary to fulvestrant treatment can be treated with pain medications, nonsteroidal anti-inflammatory drugs (NSAIDs), or corticosteroids.

  After approximately the end of August 2018, local radiotherapy is permitted at the discretion of the investigator. Disease progression should be ruled out as taselisib/placebo and fulvestrant must be permanently discontinued for disease progression. It is recommended to hold taselisib/placebo for the duration of the local radiotherapy.

- *Until approximately the end of August 2018, initiation* of bisphosphonate or denosumab therapy or modification of the pre-study bisphosphonate or denosumab treatment regimen (e.g., for bone metastasis) should be strongly avoided. Such actions would require the approval of the Medical Monitor. *After approximately the end of August 2018, initiation of bisphosphonate or denosumab therapy or modification of the pre-study bisphosphonate or denosumab treatment regimen (e.g., for bone metastasis) is permitted at the discretion of the investigator.*

- *Until approximately the end of August 2018, hematopoietic* growth factors (e.g., erythropoietins, G-CSF, and GM-CSF) are not to be administered prophylactically. Use of these agents should be reserved for cases of severe neutropenia and anemia per the labeling of these agents and require the approval of the Medical Monitor. *After approximately the end of August 2018, prophylactic administration of hematopoietic growth factors (e.g., erythropoietins, G-CSF, and GM-CSF) is permitted at the discretion of the investigator.*
- Hormone replacement therapy, topical estrogens (including any intra-vaginal preparations), megestrol acetate and selective ER modulators (e.g., raloxifene) are prohibited *unless required to treat adverse events*.

In vitro data with taselisib indicate that it is a substrate of CYP3A4, and results of a clinical study with a potent CYP3A4 inhibitor (itraconazole) suggest that there is a moderate potential for a drug-drug interaction between taselisib and any medication that strongly inhibits CYP3A4. Therefore, the concomitant use of strong CYP3A4 inhibitors including but not limited to ketoconazole, itraconazole, clarithromycin, atazanavir, telithromycin, ritonavir, indinavir, and voriconazole, should be avoided. Caution should be exercised when moderate CYP3A4 inhibitors, including but not limited to fluconazole, ciprofloxacin, cyclosporine, and verapamil are co-administered with taselisib.

On the basis of findings from a clinical study with a potent CYP3A4 inducer (rifampicin), there is a low potential for a drug-drug interaction when taselisib is co-administered with a strong CYP3A4 inducer. Therefore, caution should be exercised when strong CYP3A4 inducers, including but not limited to St John's wort, phenytoin, carbamazepine, rifampicin, rifabutin, and phenobarbital are co-administered with taselisib.

The above lists of medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication when determining whether a certain medication strongly induces or moderately inhibits CYP3A4.

In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

Food to Avoid

Grapefruit or grapefruit juice (strong CYP3A4 inhibitor) should be avoided during the study and for at least 7 days prior to Cycle 1 Day 1 of study treatment.

4.5 STUDY ASSESSMENTS

See Appendix 1 and Appendix 2 for the schedule of assessments performed during 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-specific screening tests or evaluations. Prior to signing the main

consent form for the study, patients may specifically allow for the collection and testing of archival tumor tissue or fresh tumor tissue (e.g., biopsy of a new metastatic lesion) by signing the prescreening consent form. 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 randomization. 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.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases that have occurred within the previous 5 years before Cycle 1, Day 1, breast cancer history (including tumor characteristics such as hormone receptor status, prior cancer therapies, surgeries, and procedures), smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the screening visit.

Demographic data will include age, sex, and self-reported race/ethnicity in accordance with the applicable laws (e.g., health authority requirements).

4.5.3 Physical Examinations

A complete physical examination should include measurement of height (at screening visit only) and weight; an evaluation of the head, eyes, ears, nose, and throat; and an evaluation of the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Until approximately the end of August 2018, an assessment of the patient's ECOG Performance Status (see Appendix 4) will be completed at screening and as specified in the schedule of assessments (see Appendix 1).

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Particular attention should be given to symptoms related to adverse events of special interest (e.g., diarrhea, colitis, pneumonitis). 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.

Until approximately the end of August 2018, as part of tumor assessments, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly. *After approximately the end of August 2018, as part of tumor assessments, evaluation of the presence and degree of*

enlarged lymph nodes, hepatomegaly, and splenomegaly by physical examination should be included per local standard of care.

4.5.4 Vital Signs

Vital signs, collected at screening and at each subsequent visit, will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressures (while the patient is in a seated position), temperature, and pulse oximetry for oxygen saturation measurement.

4.5.5 Tumor and Response Evaluations

All known sites of disease must be documented at screening (within 28 days prior to Cycle 1, Day 1) and*, until approximately the end of August 2018,* re-assessed at each subsequent tumor evaluation (every 8 weeks ±5 days from the date of randomization). *After approximately the end of August 2018, subsequent tumor evaluations may be conducted per local standard of care.*

Screening assessments must include CT scans of the chest, abdomen, and pelvis; CT scans of the neck and brain imaging should be included if clinically indicated. A documented standard-of-care tumor assessment performed within 28 days prior to Cycle 1, Day 1 may be used for the screening assessment provided it meets the above requirements. Tumor assessments should be performed on this schedule regardless of dose delay or early discontinuation until disease progression.

*Until approximately the end of August 2018, r*esponse assessment will be made by the investigator on the basis of physical examinations, CT scans, or MRI, and/or bone scans using criteria outlined in RECIST v1.1 (Appendix 6). 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. *After approximately the end of August 2018, subsequent tumor evaluations may be conducted per local standard of care.*

Until approximately the end of August 2018, CT scans throughout the study should include chest, abdomen, and pelvic scans. CT scans of the neck and brain imaging should be included if clinically indicated. At the investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected. *After approximately the end of August 2018, subsequent tumor evaluations may be conducted per local standard of care.*

Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. The special considerations regarding the measurability of bone lesions are outlined in RECIST v1.1 (see Appendix 6).

Bone scans and/or skeletal survey should be performed within 28 days prior to Cycle 1, Day 1. Positive areas on bone scans must be assessed by either CT scan with bone windows, MRI, or X-ray prior to randomization. Bone lesions identified at baseline by CT scan, MRI or X-ray should be assessed using the same modality (CT scan, MRI, or X-ray) and following the same schedule for measurable lesions until disease progression, as described above. Additional bone scans or skeletal surveys should be performed if clinically indicated. *Until approximately the end of August 2018, f*or patients with bone-only disease not visible on CT/MRI scan or X-ray at baseline, additional bone scans should be repeated every 8 weeks (±5 days) from the date of randomization and when clinically indicated until disease progression. 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]). *After approximately the end of August 2018, subsequent tumor evaluations may be conducted per local standard of care.*

*Until approximately the end of August 2018, a*bnormalities found on subsequent bone scans must also be confirmed by CT scan, MRI scan, or X-ray assessment. *After approximately the end of August 2018, subsequent tumor evaluations may be conducted per local standard of care.*

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.

In the absence of measurable disease at baseline, the following will be considered progression among patients with lytic or mixed (lytic+sclerotic) bone lesions:

- The appearance of one or more new lytic lesions in bone
- The appearance of one or more new lesions outside of bone
- Unequivocal progression of existing bone lesions

Note: Pathologic fracture, new compression fracture, or bone metastases complications will not be considered as evidence of disease progression unless one of the above-mentioned criteria is fulfilled. Patients with symptoms of rapidly progressing disease without radiological (or photographical) 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 6. For patients with only bone lesions, RECIST, v1.1 will be extended to include the evaluation of overall lesion response, which will be based solely on non-target lesion responses. Specifically, in the absence of new lesions, the overall lesion response at each assessment will be one of the following: CR, SD, unknown, or PD based on non-target lesion responses. Stable disease would include all assessments not qualifying for complete response, progressive disease, or unknown. In the presence of any new lesion, the overall lesion response will be progressive disease.

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

- *Until approximately the end of August 2018, all* lesions identified at baseline (target and non-target) will be reassessed using the same method throughout the course of the study. *After approximately the end of August 2018, tumor assessments may be conducted per local standard of care.*
- All CT scans and 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 the patient with bone metastases at baseline also should be reviewed similarly.
- *Until the clinical cutoff date for the primary PFS analysis, which was 15 October 2017, all* radiologic data (CT scan, MRI and bone scan, etc.) and photos for skin lesions obtained at baseline, during the treatment period, and the follow-up period must be sent to a central imaging vendor contracted by the Sponsor within 2 weeks of imaging for blinded independent central review (BICR). Additional details regarding the BICR will be outlined in 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.

Until approximately the end of August 2018, patients who discontinue study treatment for any reason other than disease progression will continue to undergo tumor-response evaluations until progressive disease. *Until approximately the end of August 2018, patients* who are discontinued from study treatment because of disease progression will be asked to return for a repeat tumor assessment 4-6 weeks after experiencing disease progression.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Samples for hematology, blood chemistries, and urinalysis will be analyzed at the study site's local laboratory. Samples for biologic markers and pharmacokinetics will be sent to one or more central laboratories or to the Sponsor or designee for analysis.

Instruction manuals and supply kits will be provided for all central laboratory assessments.

All screening laboratory assessments should be obtained within 28 days prior to Cycle 1, Day 1.

Laboratory assessments will include the following:

- Hematology: Hemoglobin, hematocrit, RBC count, platelet count, WBC count, and WBC differential count (neutrophils, bands [optional], lymphocytes, eosinophils, basophils, monocytes)

Reporting the differential as absolute counts is preferred, but percent is accepted.

- Fasting blood chemistry (≥ 8 hours): ALT, AST, ALP, total bilirubin, total protein, albumin, BUN [or urea], creatinine, glucose, calcium, phosphorus, sodium, potassium, chloride, magnesium, and bicarbonate

  Note: For investigational sites in countries where bicarbonate may not be collected as part of the standard chemistry panel, bicarbonate will not be measured.

- Fasting lipid profile (≥ 8 hours): total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, amylase, and lipase
- Glycosylated hemoglobin (HbA_{1c})
- Plasma samples for determination of taselisib concentrations
- Coagulation: INR and aPTT (or PTT) required for all patients within 28 days prior to Cycle 1 Day 1 and then as clinically indicated

  Patients taking warfarin or its equivalent: INR and aPTT (or PTT) twice in the first week of taselisib administration, then weekly for 3 weeks, and then as clinically necessary

- Urinalysis: Specific gravity, pH, glucose, protein, ketones, and blood. Required for all patients within 28 days prior to Cycle 1, Day 1 and then as clinically indicated

Until approximately the end of August 2018, the following assessments will be performed at an investigational testing site. Instruction manuals outlining sampling procedures, storage conditions, and shipment instructions and supply kits will be provided for all investigational assessments:

- Tumor tissue samples. All patients must consent to *PIK3CA*-mutation testing as well as to other protocol-mandated exploratory assessments at baseline.

  Tumor tissue should be of good quality on the basis of total and evaluable tumor content. Evaluation of the patient's tumor sample for adequate tumor tissue content and determination of *PIK3CA*-mutation status by a central laboratory must occur prior to initiation of study treatment. A tumor block or a minimum of 20 (25 preferred) unstained slides from a FFPE tissue sample will be required for enrollment eligibility purposes. An associated pathology report should also be sent with the sample. If slides are provided, the 20–25 slides should originate from the same tumor block. If fewer than 20 slides are available, the Medical Monitor should be consulted. Alternatively, the patient may agree to the collection of a fresh tumor sample if feasible. Tissue samples, including tumor blocks, from patients who are not eligible to enroll in the study will be returned as soon as possible but no later than 4 weeks after eligibility determination. If a patient is determined to be eligible for the study, the remaining tumor block will be returned once all sections required for the protocol assessments have been obtained or upon request. A detailed description of tissue quality requirements and procedures for collection, handling, and shipping of the samples will be provided in a separate Laboratory Manual.

The specimens will be used for central assessment of *PIK3CA* mutation status and PgR expression. In addition, other exploratory assessments, including but not limited to PI3K signaling pathway status may be evaluated, including protein expression (e.g., PTEN) and molecular profiling studies such as NGS and gene-expression.

- Enrolled patients who are willing to consent will also undergo an optional post-progression core biopsy of the tumor if it is anatomically feasible and if there are no medical contraindications, if the biopsy can be obtained prior to the initiation of new cancer treatment, or within approximately 14 days of the start of the new cancer treatment as long it is deemed safe by the investigator to obtain the biopsy, and the procedure does not impede or delay planned cancer treatment. If the patient consents and is medically fit (ECOG Performance Status of 0 or 1), no anti-coagulation therapy and no acetylsalicylic acid (aspirin) or NSAIDs should be taken prior to the procedure. The obtained tissue sample will be used 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 pathways). See Section 3.3.9.9 for additional details. Collection Instructions for post-progression biopsies will be provided in a separate Laboratory Manual. Priority should be given to the submission of a FFPE tissue block over a minimum of 20 (25 preferred) slides.
- Plasma samples for exploratory research on candidate biomarkers (e.g., *PIK3CA*) include but are not limited to the following: ctDNA and plasma protein biomarkers
- Baseline (pretreatment) plasma sample to be banked for future blood-based biomarker discovery and/or development
- Blood for NGS (if approved by local regulatory authorities)
- Blood for pharmacogenetic assessment (if approved by local regulatory authorities)

4.5.7 Assay Methods

4.5.7.1 Mutational Analysis for *PIK3CA*

The *PIK3CA*-mutation assay will be performed by a central investigational testing site.

Somatic mutations in the *PIK3CA* gene are found in approximately 40% of MBCs and occur most commonly in exons 9 and 20 in the codons encoding amino acids E542, E545, and H1047 (Saal et al. 2005). RT-PCR assays that amplify exons that are commonly mutated in *PIK3CA* offer a sensitive and quantitative method to detect mutations from a tumor specimen. DNA will be extracted from tumor samples and subjected to allele-specific PCR assays that detect the WT allele as well as to assays for nucleotide substitutions that include but are not limited to the following amino acid changes: R88Q, N345K, C420R, E542K, E545K/A/G/D, E546K/E/R/L, M1043I, H1047R/L/Y, and H1049R. Following histopathological review, samples with $<$10% tumor content may not be evaluable for the *PIK3CA* assay. Samples will be run on cobas 4800 platform, and *PIK3CA*-mutation status (mutation detected or mutation not detected) will be determined using appropriate cutoffs and automated software.

A designation of *PIK3CA*-status unknown will be assigned to a sample wherein any one of the predefined mutations was not conclusively assessed (e.g., patients with an “invalid” or “failed” *PIK3CA*-mutation result will not be eligible for enrollment).

If multiple tumor samples that were surgically obtained at different times are submitted to satisfy this enrollment criterion, the *PIK3CA*-mutation status will be on the basis of a valid result on the tumor sample that was most recently collected. If the most recently collected tumor tissue does not provide a valid result, mutation status will be determined using other available tissue.

If multiple tumor samples that were surgically obtained at the same time are submitted to satisfy this enrollment criterion, the patient will be categorized as containing a *PIK3CA*-mutant tumor based on a valid *PIK3CA*-detectable result from either tumor sample.

4.5.7.2 Analysis of Phosphatase Tensin Homolog Expression

PTEN status may be examined by IHC or NGS using appropriate platforms. For IHC, tumor specimens will be scored only if appropriate staining is observed in internal control stromal or normal (non-tumor) tissue elements.

4.5.7.3 Progesterone Receptor Analysis

PgR status will be determined at a central laboratory using standardized immunohistochemical procedures.

4.5.7.4 Circulating Tumor DNA Analysis

ctDNA will be extracted from plasma samples collected from patients and used for the detection of oncogenic mutations and DNA methylation using appropriate technologies. The prevalence of the mutations measured at baseline and post-treatment may provide information on response or resistance to therapy.

4.5.7.5 Messenger RNA Expression Profiling

In cases where there is sufficient archival tissue to isolate RNA, gene expression may be performed using gene expression assays conducted using appropriate technologies. Analysis may include but is not limited to a panel of genes that are important for intrinsic subtyping, breast cancer biology, and immune-related and PI3K signaling. The goal will be to generate a database of expression status to examine whether there are gene expression patterns associated with clinical response to taselisib.

4.5.7.6 Tumor Somatic Mutation Analysis

In cases where there is sufficient material to isolate DNA, NGS may be performed using an appropriate NGS platform, such as Illumina or an equivalent. The goal will be to determine whether the somatic mutations are associated with clinical response to taselisib.

4.5.7.7 Copy Number Analysis

The level of copy number alterations in cancer-related genes may be determined using DNA-based technologies, either cytogenetically, using chromosomal in situ hybridization (ISH), next-generation sequencing platforms, RT-PCR–based or using equivalent technologies. For cytogenetic assays, detection may be either fluorescence-based (fluorescence ISH assay) or chromogenic-based (chromogenic ISH). Data on increased copy number of PI3K pathways–activating genes may provide information on response or resistance to therapy.

4.5.7.8 Plasma Biomarker Analyses

Assays that assess the expression of soluble, systemic cytokines, and chemokines from the plasma of patients will be completed using appropriate methodologies, such as ELISA-based, mass spectrometry-based or equivalent technologies.

4.5.7.9 Plasma Pharmacokinetic Samples

Plasma samples will be evaluated for taselisib concentrations through the use of a validated liquid chromatography tandem mass spectrometry assay. Plasma samples may be used for the exploratory evaluation of safety and/or response biomarkers, the identification and profiling of potential taselisib-related metabolites, ex-vivo protein binding, PK or pharmacodynamic assay development purposes, and/or determination of fulvestrant levels.

4.5.7.10 Pharmacogenetic Polymorphism Assay

If approved by the local regulatory authority, gene mutations will be assayed using multiplex PCR, allele-specific PCR, direct sequencing, or other acceptable methods. Results may be correlated to taselisib exposure or other clinical measures to better understand the impact of genetic variants on drug metabolism, exposure, adverse events, and/or response.

A blood sample will also be utilized as a source of normal DNA to determine whether sequence variants in the *PIK3CA* gene and in other relevant oncogenes in the tumor DNA are somatic mutations or single nucleotide polymorphisms.

Data arising from clinical genotyping will be subject to the confidentiality standards described in Section 8.4.

4.5.8 Electrocardiograms

An ECG (12-lead) is required at screening and may be repeated during the study as clinically indicated.

All ECG recordings should be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. 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.

Clinically significant abnormalities observed during screening will be recorded on the General Medical History and Baseline Conditions eCRF. New or worsened clinically significant abnormalities will be recorded on the Adverse Event eCRF.

4.5.9 Patient-Reported Outcomes

PRO data will be elicited from the patients to more fully characterize the clinical profile of taselisib. The PRO instruments, translated as required into the local language, will be distributed by the investigator or research staff and must be completed in their entirety by the patient. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires should be self-administered at the investigational site prior to the completion of other study assessments and the administration of study treatment.

The EORTC QLQ-C30 (see Appendix 7) and the modified Breast Cancer module QLQ-BR23 (see Appendix 8) questionnaires will be used to assess HRQoL, including side effects of therapy (e.g., oral mucositis, diarrhea, and skin issues) and patient functioning (refer to Schedule of Assessments in Appendix 1 for detailed description of timepoints).

The EORTC QLQ-C30 is a validated and reliable self-reported measure (Aaronson et al. 1993; Sprangers et al. 1998; Fitzsimmons et al. 1999) that consists of 30 questions that comprise five aspects of patient functioning assessment (physical, emotional, role, cognitive, and social); three symptom scales (fatigue; nausea, vomiting, and pain; and the global health/quality of life [QoL]); and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), within a recall period of “the past week.” Scale scores can be obtained for each of the multi-item scales, the global health status/QoL scale, and the six single items by using a linear transformation for standardization of the calculated raw score.

The EORTC QLQ-BR23 breast cancer module, which was first validated for use in 1995, uses a recall period of “the past week,” and is intended for use across multiple treatment modalities (i.e., surgery, chemotherapy, radiotherapy, and hormonal treatment). As oral mucositis (2 items) and skin problems (2 items) are key symptoms of therapy that are not assessed by currently available tools, validated items from the EORTC item bank will

be added to assess these treatment-related symptoms. Data analysis will be performed on the final modified BR23 data set in parallel with the final data analysis to assess the psychometric properties of the modified instrument and will be reported along with the clinical trial results. Scale scores can be obtained for each of the multi-item and single-item scales by using a linear transformation for standardization of the calculated raw score.

The EQ-5D will be used to obtain health status information for health economic modeling. The EQ-5D is a generic, preference-based health utility measure with questions about mobility, self-care, usual activities, pain and discomfort, and anxiety and depression that are used to build a composite of the patient's health status (see Appendix 9). A single summary index from the EQ-5D health states will be utilized in this study for economic modeling. These data will not be reported in the clinical study report.

4.5.10 Assessments at Study Drug Discontinuation Visit

All patients who are discontinued from all study treatments will return for a study drug discontinuation visit within ≤28 days after the last dose of study treatment. If study treatment had been interrupted for >28 days before the decision to permanently discontinue all study treatment, the study drug discontinuation visit should be performed as soon as possible after permanent study drug discontinuation.

The visit at which disease progression is recorded may serve as the study drug discontinuation visit, provided that all tests required at the study drug discontinuation visit are performed. See Appendix 1 and Appendix 2 for the schedule of assessments performed at the study drug discontinuation visit.

4.5.11 Follow-Up Assessments

Until approximately the end of August 2018, patients who are discontinued from study treatment for reasons other than disease progression will be asked to continue to have tumor assessments performed and complete the PRO assessments approximately every 8 weeks (±5 days) until disease progression.

Until approximately the end of August 2018, after study treatment discontinuation, patients will be followed for survival and subsequent anti-cancer therapies approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor.

Until approximately the end of August 2018, after experiencing disease progression, patients will also be asked to return to the clinic 4–6 weeks (for tumor and PRO assessments) and 12 weeks ±7 days (for PRO assessments), even if a patient initiates anti-cancer therapy subsequent to study drug discontinuation.

4.5.12 Samples for Roche Clinical Repository

4.5.12.1 Overview of the Roche Clinical Repository

The Roche Clinical Repository (RCR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens 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.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- 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

4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (see Section 4.5.12) will not be applicable at that site.

4.5.12.3 Sample Collection

The following samples will be used for research purposes, including but not limited to research on dynamic (non-inherited) biomarkers related to taselisib, PI3K, or breast cancer:

- Remaining plasma samples
- Remaining whole blood for DNA/RNA extraction

The following sample *may* be collected for research purposes, including but not limited to research on genetic (inherited) biomarkers related to taselisib, PI3K or breast cancer: whole blood for DNA extraction.

The following sample may be collected for research purposes, including 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 pathways). See Section 3.3.9.9 for additional details:

- *An optional post-progression core biopsy of the tumor*

For all samples, dates of consent and specimen collection should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

The following sample may be collected for research purposes to enable a more detailed analysis of specific adverse events:

- *Tissue (e.g., biopsies from colitis or rash, if appropriate)*

For these samples, dates of consent and specimen collection should be recorded in the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

4.5.12.4 Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

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

Patient medical information associated with RCR specimens 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.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

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

4.5.12.5 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens 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 RCR specimens. 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 by completing the RCR Research Sample Informed Consent eCRF.

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

4.5.12.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study GO29058 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study GO29058.

4.5.12.7 Monitoring and Oversight

RCR specimens 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 specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB or EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from study drug or 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 withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if the patient continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance, defined as failure to comply with the protocol requirements for assessments of safety and efficacy of the study medications, as well as failure to comply with study drug administration.

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. *Until approximately the end of August 2018, patients* who withdraw from study drug may decide to continue on study to allow follow-up for survival. Patients who withdraw from the study will not be replaced.

4.6.2 Study Drug(s) Discontinuation

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

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if the patient continues to receive study drug(s)
- *D*isease progression *(as assessed by the investigator)*
- Unacceptable toxicity
- Non-compliance with protocol specified drug administration and follow-up tests

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment will not be replaced.

4.6.3 Study and Site 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.

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 Conference on Harmonisation (ICH) guidelines for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Taselisib is not approved and is currently in clinical development. Thus, the entire safety profile is not known at this time. The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and appropriate safety assessments.

5.1.1 Management of Selected Toxicities Observed with Taselisib in Clinical Studies

Experience with PI3K inhibitors to date has demonstrated that the agents are generally well-tolerated. Common adverse events seen in ongoing clinical trials that are testing PI3K inhibitors include fatigue, diarrhea, skin rash, altered taste, pneumonitis, and hyperglycemia. In general, these agents appear to be reasonably well-tolerated at doses examined to date without irreversible and/or intolerable toxicities.

The toxicities observed with taselisib are consistent with those observed with other PI3K inhibitors. Selected toxicities of interest for taselisib include gastrointestinal toxicities, pneumonitis, rash, stomatitis, and hyperglycemia. Certain adverse events (e.g., rash, colitis, and pneumonitis) may also occur within 4 weeks of holding or stopping taselisib.On the basis of prior clinical experience with the taselisib and fulvestrant combination, some patients have continued to derive clinical benefit with single-agent fulvestrant even after discontinuation of taselisib. Therefore, in some cases per

investigator assessment, fulvestrant dosing may be continued while taselisib or placebo is being held or discontinued (e.g., for adverse events). The fulvestrant dose level should not be modified.

5.1.1.1 Dose Modification of Taselisib/Placebo due to Toxicity

The taselisib or placebo dose reduction instructions provided in Table 2 are intended to serve as recommended guidelines to allow ongoing treatment for patients experiencing clinical benefit without signs or symptoms of progression while monitoring patient safety. In addition to these guidelines, more conservative drug interruptions or dose reductions 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.

Due to the approximately 40-hour half-life for taselisib, investigators should consider holding taselisib or placebo for certain Grade 2 toxicities until the adverse events resolve to Grade ≤ 1 as discussed below (e.g., stomatitis, oral mucositis, rash, diarrhea). Certain toxicities may occur or worsen within 4 weeks of holding or discontinuing taselisib (e.g., pneumonitis, colitis, rash). These adverse events may eventually resolve but also may require the use of corticosteroids. Investigators should follow management guidelines for toxicities as described below, including administration of topical or systemic corticosteroids as appropriate.

Table 2 Overall Dose Modification Guideline for Taselisib-Related Adverse Events

	Taselisib/Placebo
Starting dose	4 mg QD
First reduction	2 mg QD
Second reduction	2 mg QOD [a]

QD = once daily; QOD = every other day.

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

The investigator may temporarily suspend taselisib/placebo dosing in the patient due to a taselisib-related toxicity or an unanticipated medical event not associated with study treatment toxicity or with disease progression. Depending on the nature and the severity of the taselisib-related toxicity, the investigator may resume taselisib/placebo dosing in the patient at the same dose or at one dose level lower (as detailed in Tables 3–8).

5.1.1.1.1 Gastrointestinal Toxicity

Nausea, vomiting, *dyspepsia,* diarrhea, stomatitis, and oral mucositis have been observed in patients who receive taselisib. Colitis was diagnosed by several methods, including endoscopy and abdominal imaging (CT scans). Pathology from biopsies obtained from endoscopy confirmed colitis. Patients usually present with Grade 2 or Grade 3 diarrhea that has been refractory to antidiarrheal agents. The time (from the

first dose of study treatment) to onset (formal diagnosis of colitis) ranged from approximately 2–8 months. Patients had resolution or improvement of gastrointestinal toxicities upon holding study drug and/or initiating corticosteroid therapy. Perforated duodenal ulcer was observed in 2 patients (1 patient at 6-mg capsule dose in combination with letrozole; another patient at 6-mg capsule dose in combination with fulvestrant). Appropriate caution should be taken with the administration of medications such as aspirin, NSAIDs, and corticosteroids, which can increase the risk of gastritis, peptic ulcers, or gastrointestinal perforation.

Patients with inflammatory bowel disease, such as Crohn's disease or ulcerative colitis, are excluded from this study. Patients who resume taselisib/placebo treatment should be monitored closely for signs of renewed diarrhea.

Dose delay and modification guidelines for patients who experience gastrointestinal toxicities (diarrhea, colitis, stomatitis and oral mucositis) can be found in Table 3 and Table 4.

Table 3 Management Guidelines for Diarrhea and Colitis

Grade	Taselisib/Placebo Dose Modification and Management
1	Manage per standard-of-care with anti-diarrheal agents [a] (e.g., loperamide) For Grade 1 diarrhea occurring after Cycle 2 that persists > 5 days despite treatment with anti-diarrheal agents, obtain stool culture for infectious workup [b]. Infections (e.g., *Clostridium difficile*, enteric bacteria, CMV) should be treated with the appropriate antibiotic. For non-infectious diarrhea, consider holding taselisib/placebo and treating with a corticosteroid taper (20–40 mg prednisone PO QD starting dose) or budesonide 9 mg PO QD. Upon completion of corticosteroid treatment, resume taselisib/placebo dosing at same dose or one dose level lower per investigator evaluation. (Note: Table continued on next page)
2	Hold taselisib/placebo and initially manage with anti-diarrheal agents [a]. Obtain stool culture for infectious workup [b]. Infections (e.g., *Clostridium difficile*, enteric bacteria, CMV) should be treated with the appropriate antibiotic. For non-infectious Grade 2 diarrhea that has not improved to Grade ≤ 1 despite 48 hours of anti-diarrheal treatment or for Grade 2 colitis, treat with corticosteroid taper (20–40 mg prednisone PO QD starting dose) or budesonide 9 mg PO QD. Steroid dosage can be increased if diarrhea does not improve. If diarrhea or colitis does not improve after 48 hours of corticosteroid treatment, a colonoscopy should be considered to evaluate for other causes of diarrhea (e.g., CMV colitis). If Grade 2 diarrhea occurred after Cycle 2 or improved with corticosteroid treatment or for Grade 2 colitis, resume taselisib/placebo dosing at one dose level lower upon improvement to Grade ≤ 1 and after completion of any corticosteroid taper. If Grade 2 diarrhea occurred before Cycle 2 and did not require corticosteroid treatment, resume taselisib/placebo dosing at the same dose level or one dose level lower per investigator evaluation upon improvement to Grade ≤ 1. For recurrent Grade 2 diarrhea, resume taselisib/placebo dosing at one dose level lower upon improvement to Grade ≤ 1. For patients with a second Grade 2 diarrhea event that is confirmed to be infectious on the basis of results from the stool culture, taselisib/placebo may be resumed at the same dose level if approved by the Medical Monitor.

Table 3 Management Guidelines for Diarrhea and Colitis (cont.)

Grade	Taselisib/Placebo Dose Modification and Management
3	Hold taselisib/placebo dosing and initially manage with anti-diarrheal agents [a]. Obtain stool culture for infectious workup [b]. Infections (e.g., *Clostridium difficile*, enteric bacteria, CMV) should be treated with the appropriate antibiotic. For Grade 3 diarrhea or colitis, treat with systemic corticosteroids (IV solumedrol 16–20 mg every 8 hours or prednisone 60–80 mg PO QD equivalent to start). Can increase steroid dosage if diarrhea does not improve. Consider colonoscopy as part of further gastrointestinal workup. If diarrhea does not improve after 48 hours of corticosteroid treatment, a colonoscopy should be considered to evaluate for other causes of diarrhea (e.g., CMV colitis). If diarrhea or colitis improves to Grade $\leq$ 1 and upon completion of any steroid taper, resume taselisib/placebo dosing at one dose level lower. For patients with Grade 3 diarrhea that is confirmed to be infectious on the basis of results from the stool culture, taselisib/placebo may be resumed at the same dose level if approved by the Medical Monitor. Patients with recurrent Grade 3 diarrhea or colitis must be permanently discontinued from taselisib/placebo.
4	Permanently discontinue taselisib/placebo. Manage as per Grade 3 diarrhea guidelines.

IV = intravenous; PO = taken by mouth; QD = once daily.

[a] Suggested anti-diarrheal medications include the following:

- Loperamide (initial: 4 mg, followed by 2 mg after each loose stool, up to 16 mg/day)
- Diphenoxylate and atropine (diphenoxylate 5 mg, four times daily, until control achieved [maximum: 20 mg/day], then reduce dose as needed; some patients may achieve control with doses of 5 mg/day)
- Tincture of opium (6 mg of undiluted opium tincture [10 mg/mL] four times daily).

[b] Non-infectious diarrhea can be diagnosed by stool culture with work-up for *Clostridium difficile* and for various enteric bacteria. Fecal calprotectin is a possible marker for bowel inflammation. Blood-based cytomegalovirus polymerase chain reaction test can also be used to detect cytomegalovirus infection.

Table 4 Management Guidelines for Stomatitis and Oral Mucositis

Grade	Taselisib/Placebo Dose Modification and Management Guidelines
All grades	Aggressive mouth care that includes mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, anti-fungal and/or antibiotics) may be implemented to help manage symptoms Diet management (e.g., avoidance of spicy foods)
1	Monitor symptoms and initiate management (see above). Re-evaluate within 48–72 hours.
2	Hold taselisib/placebo, and manage until Grade ≤ 1. If stomatitis or mucositis improves to Grade ≤ 1, resume taselisib/placebo dosing at the same dose or one dose level lower per investigator evaluation. For recurrent Grade 2 stomatitis or mucositis, resume taselisib/placebo dosing at one dose level lower.
3	Hold taselisib/placebo and manage until Grade ≤ 1. If stomatitis or mucositis improves to Grade ≤ 1, resume taselisib/placebo dosing at one dose level lower.
4	Permanently discontinue taselisib/placebo.

5.1.1.1.2 Pneumonitis

Pneumonitis has been observed in patients treated with taselisib. Symptoms associated with pneumonitis were reversible upon treatment with corticosteroids. Dose delay and modification guidelines for patients who experience pneumonitis are presented in Table 5.

Table 5 Management Guidelines for Pneumonitis

Pneumonitis Grade	Intervention	Investigations	Taselisib/Placebo Dose Modification and Management
1	No specific therapy required	Consider infectious work-up [a]. CT scan and consider PFTs [b]. Repeat CT Q8W until return to baseline.	No change
2	Symptomatic only. Prescribe corticosteroids if cough is troublesome and infectious etiology is ruled out.	Infectious work-up [a]. CT scan. Repeat CT Q4W until return to baseline. Consider PFTs [b] and bronchoscopy.	Hold taselisib/placebo as long as corticosteroids are being given. If pneumonitis improves to Grade $\leq$ 1 and upon completion of any corticosteroid treatment, resume taselisib/placebo dosing at the same taselisib dose or one dose level lower per investigator evaluation. For recurrent Grade 2 event, resume taselisib/placebo dosing at one dose level lower.
3	Prescribe corticosteroids if infectious etiology is ruled out. Taper as clinically indicated.	Infectious work-up [a]. CT scan. Repeat CT Q4W until return to baseline. Consider PFTs [b] and bronchoscopy.	Hold taselisib/placebo as long as corticosteroids are being given. If pneumonitis improves to Grade $\leq$ 1 and upon completion of any corticosteroids, resume taselisib/placebo dosing at one dose level lower.
4	Prescribe corticosteroids if infectious etiology is ruled out. Taper as clinically indicated.	Infectious work-up [a]. CT scan. Repeat CT Q4W until return to baseline. Consider PFTs [b]. Bronchoscopy is recommended.	Permanently discontinue taselisib/placebo.

CT = computed tomography; PFT = pulmonary function test; Q4W = every 4 weeks; Q8W = every 8 weeks.

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

[b] PFTs may be useful to monitor the effect of interventions such as dose reduction/discontinuation and corticosteroids, in conjunction with imaging (White et al. 2010). It is strongly recommended to perform disease monitoring according to guidelines from White et al. if possible or according to clinical practice.

5.1.1.1.3 Rash

Treatment-related rash is commonly manifested as maculo-papular with or without pruritus. The rash has usually resolved upon holding taselisib and/or giving supportive therapy (e.g., topical or systemic steroids). Dose delay and modification guidelines for patients who experience rash are presented in Table 6.

Table 6 Management Guidelines for Rash

Grade of Rash	Taselisib/Placebo Dose Modification and Management Guidelines
1	Continue dosing at current taselisib/placebo dose, and monitor for change in severity. Consider prescribing topical corticosteroids [a].
2	Hold taselisib/placebo. Treat rash with topical corticosteroids. Consider treatment of rash with oral corticosteroids [b]. Hold taselisib/placebo treatment as long as oral corticosteroids are being administered. If rash improves to Grade ≤ 1 and upon completion of any systemic corticosteroids, resume taselisib/placebo at the same dose or one dose level lower per investigator evaluation. For recurrent Grade 2 rash, resume taselisib/placebo at one dose level lower.
3	Hold taselisib/placebo Treat rash with topical corticosteroids and/or systemic corticosteroids (oral or intravenous). Hold taselisib/placebo as long as systemic corticosteroids are being administered. Consider dermatological consultation and skin biopsy. If rash improves to Grade ≤ 1 and upon completion of any systemic corticosteroids, resume taselisib/placebo at one dose level lower.
4	Permanently discontinue taselisib/placebo. Treat with topical corticosteroids and/or systemic corticosteroids. Consider dermatological consultation and skin biopsy.

[a] Suggested topical steroids include hydrocortisone 2.5% to face twice daily, triamcinolone 0.1% or fluocinonide 0.1% cream to body twice daily.

[b] Suggested oral steroids include methylprednisolone dose pack or prednisone 60 mg daily followed by a taper (e.g., 60 mg $\times$ 2 days, 40 mg $\times$ 2 days, 20 mg $\times$ 2 days, etc.).

5.1.1.1.4 Hyperglycemia

Hyperglycemia has been observed in patients who received taselisib while participating in other studies. Hyperglycemia has been reversible upon holding taselisib and/or initiating anti-hyperglycemic medication (e.g., metformin).

Patients with diabetes requiring anti-hyperglycemic medication or who have a fasting blood glucose level $>$ 125 mg/dL will be excluded from the study. HbA_{1c} and fasting glucose levels will be monitored at baseline, and regular monitoring of fasting glucose

levels will occur during the study. Dose delay and modification guidelines for patients who experience hyperglycemia are presented in Table 7.

Table 7 Management Guidelines for Hyperglycemia

Grade of Hyperglycemia	Taselisib/Placebo Dose Modification and Management Guidelines
1 or 2	Initiation of or an increase [a] in the dose of an anti-hyperglycemic agent (e.g., metformin) and additional glucose monitoring will be implemented. Taselisib/placebo dosing may either be held or continued per investigator evaluation.
3 (asymptomatic)	Hold taselisib/placebo. Treat hyperglycemia per standard of care, including implementation of additional glucose monitoring and initiation of or an increase in the dose of an anti-hyperglycemic therapy (e.g., metformin). If improves to Grade ≤ 1, may resume taselisib/placebo dosing at one dose level lower.
3 (symptomatic), 3 (requiring hospitalization), or 4	Hold taselisib/placebo. Treat hyperglycemia per standard of care, including implementation of additional glucose monitoring and initiation of or an increase in the dose of anti-hyperglycemic therapy. If improves to Grade ≤ 1, may resume taselisib/placebo dosing at one dose level lower. For recurrent symptomatic Grade 3 or Grade 4 hyperglycemic event, taselisib/placebo must be permanently discontinued.

[a] If initiated after randomization, because patients with diabetes who require anti-hyperglycemic medications are not eligible.

5.1.1.1.5 Potential Abnormal Liver Function Tests

Some patients have experienced elevations of liver function test results (e.g., AST or ALT) while receiving taselisib in prior clinical studies. Patients will be monitored throughout the study treatment for changes in liver function tests. Given the potential for hepatic toxicity, all patients must have adequate liver function as manifested by measurements of serum bilirubin and hepatic transaminases for initial and continued dosing. Separate criteria for eligibility are given for patients with hepatic metastases.

For new abnormal liver function test results (e.g., elevated AST or ALT), a standard clinical work-up to understand the etiology of the abnormality should take place per local guidelines. In many cases, elevated liver function test results may be a result of liver metastases, concomitant medications, or biliary obstruction. Dose delay and modification for patients who experience abnormal liver function test results can also follow the guidelines in Table 8 if deemed clinically appropriate by the investigator.

5.1.1.1.6 Management of Asymptomatic Lipase and/or Amylase Elevations

Some patients who have been treated with taselisib have experienced asymptomatic lipase and/or amylase elevations in blood tests without any clinical or radiographic

symptoms of pancreatitis or another clear etiology for the abnormal laboratory test values. Elevated lipase may sometimes be associated with corticosteroid treatment. Upon discussion with the Medical Monitor and after a benefit-risk assessment, investigators may consider continuing taselisib therapy in such patients at the same dose or one dose level lower. Investigators should have a low threshold for interrupting taselisib/placebo for any clinical gastrointestinal toxicities of concern.

5.1.1.1.7 Potential Inflammatory or Immunosuppressant Effects

On the basis of taselisib data from nonclinical toxicity studies showing changes in WBC and absolute lymphocyte and/or neutrophil counts, patients will be required to have adequate hematologic function to participate in the study, and any bone marrow toxicities from prior therapies must be resolved before initiation of taselisib. Patients will be monitored throughout the study treatment for changes in blood counts and signs of infection. Dose delay and modification for patients who experience changes in blood counts or show signs of infections can also follow the guidelines in Table 8 if deemed clinically appropriate by the investigator.

5.1.1.1.8 *Infection*

At the time of the primary PFS analysis of Study GO29058, 41.8% of patients in the taselisib arm had developed infections compared with 23.9% of patients in the control (placebo) arm. Serious infections occurred in 7.5% of patients in the taselisib arm compared with 0.9% of patients in the control (placebo) arm. A total of 0.5% of patients died on account of infection in the taselisib arm compared with no patients in the control (placebo) arm.

Urinary tract infections were the most commonly reported infection; however, respiratory tract, gastrointestinal tract, and skin infections were also common in the taselisib arm.

Investigators and patients should be aware of the increased risk of infection with taselisib. If a diagnosis of infection is made, appropriate treatment should be initiated promptly and consideration given to holding or discontinuing taselisib/placebo as per the guidelines in Table 8.

5.1.1.1.9 Management of Other Clinically Significant Adverse Events

See Table 8 for the dose modifications for other clinically significant adverse events.

Table 8 Taselisib/Placebo Dose Delay and Modification Guidelines for Other Clinically Significant Adverse Events

Grade	Taselisib/Placebo
3, first event	Hold taselisib/placebo until Grade ≤ 1. Resume taselisib/placebo at the same dose or one dose level lower per investigator evaluation.
3, recurrent or 4, non–life threatening	Hold taselisib/placebo until Grade ≤ 1. Resume taselisib/placebo dosing at one dose level lower.
4, life-threatening	Permanently discontinue taselisib/placebo. Single-agent fulvestrant may be continued per investigator evaluation.

5.1.2 Safety Plan for Fulvestrant

Fulvestrant is an ER antagonist indicated for the treatment of HR+ MBC in postmenopausal women with disease progression following anti-estrogen therapy.

In a study with postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease, the most frequently reported adverse events were injection-site pain (11.6% of patients), nausea (9.7%), and bone pain (9.4%). Because fulvestrant is administered intramuscularly, it should be used with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use. For details regarding the safety profile of fulvestrant, refer to the fulvestrant package insert or SmPC.

Discontinuation of fulvestrant for adverse events is very rare. However, in the unlikely event that the patient discontinues fulvestrant and is able to continue on taselisib or placebo, the investigator should contact the Medical Monitor to discuss the benefit-risk assessment of continuing with single-agent taselisib or placebo.

There are no expected significant overlapping toxicities between taselisib and fulvestrant. Routine safety monitoring and periodic laboratory tests for the fulvestrant and taselisib combination will occur throughout the study.

5.1.2.1 General Guidance for Dose Modifications and Delays for Fulvestrant

The fulvestrant dose level cannot be modified. In general, the investigator may consider continuing fulvestrant if the observed adverse event is not thought to be fulvestrant-related.

If a scheduled 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.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

Certain types of adverse events require immediate reporting to the Sponsor, as outlined 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), except as described Section 5.3.5.9
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test results (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 5.3.5.10)

- 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 v4.0 criteria (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 include the following serious and non-serious events:

- 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 5.3.5.6)
- 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 $\geq$3 symptomatic hyperglycemia
- Grade $\geq$2 colitis or enterocolitis
- Grade $\geq$2 diarrhea
- Grade $\geq$3 rash
- Grade $\geq$2 pneumonitis

- Grade ≥3 stomatitis

5.2.4 Events to Monitor

Additional data collection will occur for all grades of specific adverse events (e.g., symptomatic hyperglycemia, colitis, enterocolitis, diarrhea, stomatitis, pneumonitis, and rash) to enable a more detailed analysis of these events. The Sponsor may ask sites to send confirmatory data for adverse events (e.g., CT scans and reports for pneumonitis or colitis; biopsy reports for colitis, rash). The Sponsor may also ask sites to send tissue (e.g., biopsies from colitis or rash, if appropriate).

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 Sections 5.4–5.7.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2), 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 28 days after the last dose of study drug. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see 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 (v4.0) will be used for assessing adverse event severity. Table 9 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 9 Adverse Event Severity Grading Scale for Events Not Specifically Listed in National Cancer Institute Common Terminology Criteria for Adverse Events

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 (v4.0), 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 or not 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 Table 10):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially 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 10 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 and 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 Diagnosis versus Signs and Symptoms

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.

5.3.5.2 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.

5.3.5.3 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 specific adverse events (hyperglycemia, colitis or enterocolitis, diarrhea, rash, pneumonitis, and stomatitis), all grade changes will be tracked on a supplemental 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.

5.3.5.4 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:

- 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
- Clinically significant in the investigator's judgment

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 if 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 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:

- 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
- 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology

changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 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. 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 5.3.5.4) 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 a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.7 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 underlying breast cancer should be recorded only on the Study Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.2.2). *Until the primary PFS analysis has been completed, an* independent monitoring committee will monitor the frequency of deaths from all causes.

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").

During survival follow-up, deaths attributed to progression of underlying breast cancer should be recorded only on the Study Discontinuation eCRF.

5.3.5.8 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").

5.3.5.9 Lack of Efficacy or Worsening of Metastatic 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.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient 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 due solely to progression of the underlying cancer
- Planned hospitalization required by the protocol
- 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

5.3.5.11 Adverse Events Associated with an Overdose

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events

associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No safety data related to taselisib overdose is available.

5.3.5.12 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. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

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
- Non-serious adverse events of special interest
- Pregnancies

The investigator must report new significant follow-up information for these events 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

Medical Monitor: [redacted], M.D.

Telephone No.: [redacted]

Alternate No.: +1 (888) 835-2555

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 Monitor, 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 and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information & List of 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. A paper Serious Adverse Event Reporting Form and fax cover sheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event), with use of the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and non-serious adverse events of special interest will be reported until 28 days after the last 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 electronic data capture (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, a paper 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 post-study adverse events 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 6 months after the last dose of fulvestrant. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. 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 the event that the EDC system is unavailable, a paper Clinical Trial Pregnancy Reporting Form and fax cover sheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3.2 Abortions

Any 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).

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug 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, the patient withdraws consent*, or the patient is no longer being followed for survival*. 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. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, 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 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occur after the end of the adverse event reporting period (defined as 28 days after the last dose of study drug [see Section 5.3.1]), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to Roche or its designee, either by faxing or by scanning and emailing the 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 non-serious 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 document:

- Taselisib Investigator's Brochure
- Fulvestrant 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.

Certain adverse events are anticipated to occur in the study population at some frequency independent of study drug exposure and will be excluded from expedited reporting. These anticipated events include, but are not limited to, the following:

- Nausea
- Vomiting
- Fatigue
- Injection-site pain
- Injection-site reaction
- Muscle pain
- Joint pain
- Tumor pain
- Hot flashes
- Weakness
- Loss of appetite
- Weight loss
- Worsening of general condition
- Failure to thrive

Until the primary PFS analysis has been completed, an iDMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

The global study plans to enroll approximately 600 patients, including 480 patients with detectable *PIK3CA*-mutant tumors, and 120 patients without detectable *PIK3CA*-mutant tumors (tumor status determined by the cobas PIK3CA mutation test).

After the global enrollment closes, additional Chinese patients may continue to be recruited into the China extension cohort. A total of up to 150 patients with detectable PIK3CA-mutant tumors may be enrolled as part of the global study population and the China extension cohort combined (see Section 6.10 for further details).

The sample size of 480 patients with *PIK3CA*-mutant tumors is determined on the basis of the power calculation for the PFS and the OS endpoints, whichever requires a larger sample size. In this case, the sample size is driven by OS.

In 480 patients with *PIK3CA*-mutant tumors, approximately 287 investigator-assessed PFS events will be required to detect a hazard ratio of 0.59 in PFS (3.1 months of

improvement in median PFS) with 95% power at the a two-sided significance level of 1%, assuming a median PFS of 4.5 months in the control arm (Mauriac et al. 2009; Johnston et al. 2013). One interim efficacy analysis of investigator-assessed PFS will be conducted at 60% of PFS information (see Section 6.9.1 for more details). The α-spending function specified as Gamma (-16), which allocates two-sided $\alpha = 1.7 \times 10^{-5}$ at the interim efficacy analysis of investigator-assessed PFS, when 172 investigator-assessed PFS events have occurred. The minimal detectable difference for investigator-assessed PFS hazard ratio at final PFS analysis is 0.72 (i.e., 39% improvement in median investigator-assessed PFS from 4.5 months in the control arm compared with 6.2 months in the treatment arm), when 287 investigator-assessed PFS events have occurred.

With the aforementioned sample size of 480 patients with *PIK3CA*-mutant tumors, the OS analyses in this population will require 330 deaths to detect an hazard ratio of 0.7 in OS (11.1 months of improvement in median OS) with 80% power at a two-sided significance level of 5%, assuming a median OS of 26 months in the control arm based on the OS of 26.4 months in patients treated with 500 mg fulvestrant in the CONFIRM study, which investigated 500 mg fulvestrant versus 250 mg fulvestrant in a similar patient population (Di Leo et al. 2014).

The study plans to enroll 120 patients who do not have a detectable *PIK3CA*-mutant tumor, on the basis of the result of the cobas *PIK3CA* mutation test, to evaluate the clinical benefit in this population. If the observed hazard ratio in investigator-assessed PFS is 1 (no benefit), approximately 111 investigator-assessed PFS events will be observed at the analysis, and the 90% confidence interval will exclude a true hazard ratio < 0.72 (i.e., > 1.8-month improvement in median PFS).

In total, approximately 400 patients will be treated with the combination of taselisib + fulvestrant in this study (320 patients with *PIK3CA*-mutant tumors and 80 patients without detectable *PIK3CA*-mutant tumors), which will enable the Sponsor to better characterize any rare but clinically significant safety events (e.g., for an adverse event with 4% frequency, there is 96% probability to observe ≥ 10 patients with such adverse event on the basis of 400 taselisib + fulvestrant-treated patients) to help enable the development of effective toxicity prevention and management guidelines for patients treated with the combination of taselisib and fulvestrant.

Assuming a 12-month site ramp-up period and a total of 200 sites, the enrollment duration will be driven by enrollment of patients with *PIK3CA*-mutant tumors and is projected to be approximately 28 months (from the first patient enrolled). The last PFS event (the 287th investigator-assessed PFS event) for the final PFS analysis in patients with *PIK3CA*-mutant tumors is projected to occur approximately 29 months after the first patient is enrolled.

6.2 SUMMARIES OF CONDUCT OF STUDY

Patient enrollment, follow-up duration, study discontinuation, and discontinuation reasons will be summarized by treatment arm for all randomized patients. In addition, major protocol violations, including violations of inclusion and/or exclusion criteria, will be summarized by treatment arm. All of the analyses will be performed separately for patients with *PIK3CA*-mutant tumors and for patients without detectable *PIK3CA*-mutant tumors.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

The evaluation of treatment group comparability between the two treatment arms will include demographics summaries, baseline disease characteristics (including *PIK3CA*-mutation status), and patient treatment history.

Descriptive summaries of continuous data will present the group mean, standard deviation, median, minimum, and maximum. Descriptive summaries of discrete data will present the category counts as frequencies and percentages.

All of the analyses will be performed separately for patients with *PIK3CA*-mutant tumors and for patients without detectable *PIK3CA*-mutant tumors.

6.4 EFFICACY ANALYSES

The primary efficacy analysis population will include all randomized patients with *PIK3CA*-mutant tumors. The primary efficacy endpoint, investigator-assessed PFS, and the secondary efficacy endpoints will be analyzed in this population as the primary and the secondary objectives.

In addition, these efficacy endpoints, unless otherwise specified, will be analyzed in all randomized patients without detectable *PIK3CA*-mutant tumors at the same time as the analyses are conducted for the patients with *PIK3CA*-mutant tumors.

PIK3CA-mutant tumor status will be determined by the cobas PIK3CA mutation test of the patient's tissue sample.

The treatment arm assigned at randomization will be used for all efficacy analyses.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is investigator-assessed PFS (PFS in this document refers to investigator-assessed PFS, unless stated otherwise). The primary PFS analysis will be conducted in all randomized patients with *PIK3CA*-mutant tumors, with patients grouped according to the treatment arm assigned at randomization.

An interim efficacy analysis will be conducted for investigator-assessed PFS at the time of 172 investigator-assessed PFS events (expected 21 months after the first patient is enrolled), and the final efficacy analysis will be conducted at the time

287 investigator-assessed PFS events (expected 29 months after the first patient is enrolled) are observed in patients with *PIK3CA*-mutant tumors. The α-spending function is specified as Gamma (-16), which allocates two-sided $\alpha = 1.7 \times 10^{-5}$ at the interim efficacy analysis of investigator-assessed PFS, when 172 PFS events have occurred and preserves the two-sided 1% α-level at the final PFS analysis. The exact boundary will be calculated on the basis of the exact number of PFS events observed at the interim analysis. The associated minimal detectable difference for the investigator-assessed PFS hazard ratio at the interim efficacy analysis is 0.5 (i.e., 100% improvement in median investigator-assessed PFS from 4.5 months in the control arm to 9 months in the treatment arm). Refer to Section 6.9.1 for additional details on the interim analysis.

Table 11 PFS Analyses

	Estimated Timing (Clinical Data Cutoff)	PFS Events	Two-Sided p-Value Boundary	Rejection HR Boundary [a]	Percentage Information
PFS IA	~21 months after FPI	~172	1.7×10^{-5}	0.5	60%
PFS FA	~29 months after FPI	~287	0.01	0.72	100%

IA = interim analysis; FA = final analysis; FPI = first patient in; HR = hazard ratio; PFS = progression-free survival.

[a] Assuming exponential distributions for the PFS event time of the two treatment arms.

An exploratory analysis for investigator-assessed PFS will also be conducted in all randomized patients without detectable *PIK3CA*-mutant tumors at the time of the primary PFS analysis in all randomized patients with PIK3CA-mutant tumors.

Data for patients without the occurrence 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 if no tumor assessment was performed after the baseline visit).

The two-sided log-rank test stratified by the three stratification factors will be used as the primary analysis to compare investigator-assessed PFS between the two treatment arms. The three stratification factors are: 1) visceral versus non-visceral, 2) sensitivity versus non-sensitivity to their most recently administered endocrine therapy, and 3) geographical regions (details in, Section 3.1). The Kaplan-Meier approach will be used to estimate median investigator-assessed PFS for each treatment arm. Cox proportional-hazards models stratified by the three stratification factors will be used to estimate the HR and its 95% CI. The results from the unstratified log-rank test will also be provided.

6.4.2 Secondary Efficacy Endpoints

Assuming that the primary endpoint PFS is statistically significant, the first two secondary endpoints are planned to be tested in the following hierarchical order:

- Overall ORR
- OS

6.4.2.1 Overall Objective Response Rate

The analysis of ORR will include only patients who have measurable disease per RECIST v1.1 at baseline as a secondary endpoint of the study and will be tested on the basis of a hierarchical testing procedure to preserve the type I error. That is, the ORR analysis will be conducted at at the significance level of two-sided 5% at the time that a statistically significant benefit is observed for the investigator-assessed PFS at either the interim efficacy or final PFS analysis.

An estimate of the response rate and its 95% CI will be calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms will be compared using the stratified Mantel-Haenszel test. Confidence intervals for the difference in ORRs between the two arms will be determined using the normal approximation to the binomial distribution.

6.4.2.2 Overall Survival

The analyses for OS will be conducted in all randomized patients with *PIK3CA*-mutant tumors as a secondary endpoint of the study and will be tested on the basis of a hierarchical testing procedure to preserve type I error. That is, the OS analysis will be tested only if both investigator-assessed PFS and ORR have reached their respective significance levels. The overall type I error for OS is preserved at two-sided 5%.

OS will be analyzed with patients grouped according to the treatment arm assigned at randomization. Data for patients who are alive at the time of the analysis data cutoff will be censored at the last date they were known to be alive. Data from patients without post-baseline information will be censored at the date of randomization.

The analyses will be conducted using the stratified two-sided log-rank test, and the results from the unstratified log-rank test will also be provided. The OS curve for each treatment arm will be estimated by the Kaplan-Meier methodology, and the HR and its 95% CI will be estimated by the Cox proportional-hazards models.

Three interim analyses and one final analysis for OS *were originally* planned in patients with *PIK3CA*-mutant tumors on the basis of the results from the cobas PIK3CA mutation test (see Table 12 and Table 13). *As a result of the completion of the primary PFS analysis, the Sponsor has decided to limit the additional OS follow-up to one additional analysis. This additional OS analysis coincides with the originally planned second OS interim analysis.*

1. The first interim OS analysis will be conducted at the time when both investigator-assessed PFS and ORR have reached their respective significance levels, so it could occur at the time of the interim efficacy or the final efficacy analysis for investigator-assessed PFS.
2. The second OS analysis will be conducted approximately 10 months after the first interim analysis.

Table 12 Analyses for OS if the First Interim OS Analysis Occurs at the Time of the Interim Efficacy Analysis of Investigator-Assessed PFS

	Estimated Timing (Clinical Data Cutoff)	OS Events	Two-Sided p-Value Boundary	Rejection HR Boundary [a]	Percentage Information
First OS IA	~21 months after FPI	~63	0.001	0.44	19%
Second OS *analysis*	~10 months after first OS IA	~134	0.010	0.65	41%

IA = interim analysis; FPI = first patient in; HR = hazard ratio; OS = overall survival; PFS = progression-free survival.

[a] Assuming exponential distributions for the OS event time of the two treatment arms.

Table 13 Analyses for OS if the First Interim OS Analysis Occurs at the Time of the Final Efficacy Analysis of Investigator-Assessed PFS

	Estimated Timing (Clinical Data Cutoff)	OS Events	Two-Sided p-Value Boundary	Rejection HR Boundary [a]	Percentage Information
First OS IA	~29 months after FPI	~118	0.001	0.53	36%
Second OS *analysis*	~10 months after first OS IA	~188	0.010	0.67	57%

IA = interim analysis; FPI = first patient in; HR = hazard ratio; PFS = progression-free survival.

[a] Assuming exponential distributions for the OS event time of the two treatment arms.

The stopping boundaries are computed using the generalized Haybittle-Peto boundaries with unequal p-values being used in the α-spending function and will be adjusted on the basis of the actual number of OS events observed at each interim OS analysis.

The timing of the analyses are based on an assumption of an annual loss-to-follow-up rate of 5%. The study team will be unblinded at the time when the iDMC recommends to stop the study and the Sponsor decides to stop the study, or at the time of the final PFS analysis if the study is not stopped early. Investigators and patients will remain blinded to individual patient-level treatment assignment until *approximately the end of August 2018, at which time unblinding is permitted at the discretion of the investigator or Sponsor*.

6.4.2.3 Clinical Benefit Rate

The analysis of CBR will be performed for patients with PIK3CA-mutant tumors with measurable disease per RECIST v1.1 at baseline and will be repeated for the group of patients with PIK3CA-mutant tumors regardless of measurable disease at baseline. An estimate of CBR and its 95% confidence interval will be calculated using the Blyth-Still-Casella method for each treatment arm. The clinical benefit rates in the treatment groups will be compared using the stratified Mantel-Haenszel test. Confidence intervals for the difference in clinical benefit rates between the two arms will be determined using the normal approximation to the binomial distribution.

6.4.2.4 Duration of Objective Response

The analysis of DOR will include only patients who achieved an objective response to study treatment, among patients with measurable disease per RECIST v1.1 at baseline.

DOR will be estimated using the Kaplan-Meier methodology, with patients grouped according to the treatment arm assigned at randomization. Comparisons between treatment arms using stratified and unstratified log rank test will be made for descriptive purposes. Because the determination of DOR is based on a nonrandomized subset of patients, formal hypothesis testing will not be performed.

6.4.2.5 BICR-Assessed PFS

While the primary efficacy endpoint is investigator-assessed PFS in patients with PIK3CA-mutant tumors, a blinded independent central review (BICR) of progression will be conducted in all patients based on RECIST v1.1 as described in a separate charter.

The BICR-assessed PFS in patients with PIK3CA-mutant tumors is not intended to provide an alternative means of definitive analysis but to show that there is no potential bias in the investigator assessment. The BICR-assessed PD date and events will be defined based on the BICR assesement only. The BICR-assessed PFS analysis will be identical to the investigator-assessed PFS analysis and will also be conducted in all randomized patients with PIK3CA-mutant tumors, with patients grouped according to the treatment arm assigned at randomization.

The Kaplan-Meier approach will be used to estimate median BICR-assessed PFS for each treatment arm. Cox proportional-hazards models stratified by the three stratification factors will be used to estimate the HR and its 95% CI.

6.5 SAFETY ANALYSES

Safety analyses will be performed for all randomized patients who receive at least one dose of taselisib or placebo or fulvestrant (the safety population), regardless of the *PIK3CA*-mutation status of their tumors and separately for the subgroups of patients with and without detectable *PIK3CA*-mutant tumors, with patients allocated to the treatment arm associated with the regimen actually received. Specifically, a patient will be

included in the taselisib + fulvestrant arm in the safety analyses if the patient receives any amount of taselisib, regardless of the initial treatment assignment at randomization.

Safety endpoints will include incidence, severity, and relationship to the study drugs; outcome and seriousness of adverse events; death; laboratory data; and vital signs.

Drug exposure will be summarized to include duration of treatment, number of doses, and intensity of dose.

Adverse events will be summarized by mapped term, appropriate thesaurus level, and toxicity grade according to NCI CTCAE v4.0. All adverse events occurring during or after the first study drug dose will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events, severe adverse events (Grade ≥ 3), adverse events of special interest, and adverse events leading to study drug discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity.

Deaths reported during the study treatment period and those reported during the safety follow-up period (that is, within 28 days after the last dose of treatment) after treatment discontinuation will be summarized by treatment arm.

Laboratory data with values outside the normal ranges will be identified. In addition, selected laboratory data will be summarized by treatment arm and grade.

Clinically significant changes in vital signs will be summarized by treatment arm and grade.

6.6 PHARMACOKINETIC ANALYSES

Taselisib plasma concentration versus time data will be tabulated and summarized. Additional analyses such as population PK analysis with covariate evaluation may be conducted, and data from other clinical trials may be pooled as appropriate. Exposure-response (i.e., efficacy, safety, and pharmacodynamic biomarkers) relationships may be explored. Additional analyses may be performed as appropriate.

6.7 PATIENT-REPORTED OUTCOME ANALYSES

HRQoL data will be captured using the following questionnaires: the EORTC QLQ-C30 and the modified breast cancer module, QLQ-BR23 (see Appendix 7).

The population for analysis will be defined as all randomized patients that have completed baseline and at least one post-baseline assessment. Summary statistics (mean, SD, median, 25th and 75th percentiles, and range) of linear transformed scores will be reported for selected subscales of the EORTC QLQ-C30 questionnaire and the modified BR23 (including oral mucositis and skin problems) according to the EORTC scoring manual guidelines for each assessment time point. The mean change of the

linear transformed scores from baseline (and 95% CI using the normal approximation) will also be assessed. Line charts depicting the mean changes (and standard errors) of items and subscales over time will be provided for each treatment arm from the baseline assessment. Only patients with a baseline assessment and at least one post-treatment assessment will be included in the analyses.

The HRQoL/global health scale (Items 29 and 30 of the EORTC QLQ-C30) will assess time-to-deterioration (TTD). Deterioration of HRQoL/GHS is defined as a decrease of 10 points or more from the baseline scale score with no subsequent increase above this threshold. A 10-point change is defined as the minimally important difference (Osoba et al. 1998). Data for patients who do not achieve a 10-point decrease will be censored at the last time PRO data are available. The Kaplan–Meier approach will be used to estimate median TTD for each treatment arm. Cox proportional hazard models stratified by the three stratification factors will be used to estimate the HR and its 95% CI. Data for patients without at least one post-baseline assessment will be censored at the date of randomization. Patients who had no definitive deterioration events will be censored at the time of the last available assessment prior to disease progression. Additional analyses may be conducted.

Completion rates for each PRO measure will be summarized at each timepoint by treatment arm.

6.8 EXPLORATORY ANALYSES

6.8.1 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.

6.8.2 Pharmacokinetic Assays

Plasma samples may be used for exploratory evaluation of safety and/or response biomarkers, potential taselisib-related metabolites, and/or determination of fulvestrant levels.

6.8.3 Pharmacogenetic Analysis

Blood samples may be used for the evaluation of genetic polymorphisms of drug metabolic enzymes, such as CYP3A4/5 and UGT1A1; transporters, such as OATP1B1 and BCRP; and genetic variants, which could contribute to potential drug-related safety assessments (including but not limited to HLA).

6.9 INTERIM ANALYSIS

6.9.1 Planned Interim Analysis

Until the primary PFS analysis has been completed, the iDMC will convene to review cumulative safety data approximately every 6 months. Data on serious adverse events,

death, and adverse events of special interest will be monitored by the iDMC approximately every 3 months.

One efficacy and one futility analysis for investigator-assessed PFS will be conducted in the patients with *PIK3CA*-mutant tumors when approximately 172 (60% of the information, expected at 21 months after the first patient is enrolled) investigator-assessed PFS events have occurred in patients with *PIK3CA*-mutant tumors. Approximately 320 patients with *PIK3CA*-mutant tumors and approximately 120 patients without detectable *PIK3CA*-mutant tumors will have been randomized into the study by the time of the interim analysis. The actual timing of the interim analysis and the number of patients randomized will depend on the accrual rate and actual accumulation of PFS events observed in the study.

The iDMC will review the efficacy data, while the Sponsor and investigators remain blinded to the treatment assignment until the iDMC recommends stopping the study for efficacy or futility at the specified interim analysis and the Sponsor decides to stop the study.

The iDMC may recommend stopping the study for efficacy at the interim efficacy analysis of investigator-assessed PFS, when the two-sided p-value $\leq 1.7 \times 10^{-5}$, with approximately 172 investigator-assessed PFS events at the interim efficacy analysis. The α-spending function specified as Gamma (-16), which allocates two-sided $\alpha = 1.7 \times 10^{-5}$ at the interim efficacy analysis, when approximately 172 PFS events are reached and preserves the two-sided 1% α-level at the final PFS analysis. The actual boundary will be adjusted based on the actual number of investigator-assessed PFS events at IA. Should the iDMC recommend stopping the study for efficacy at interim analysis and the Sponsor decides to stop the study, the study team will be unblinded, and the investigators and patients will remain blinded to individual patient-level treatment assignment until the final OS analysis.

The iDMC may recommend stopping the study for futility at the interim efficacy analysis of investigator-assessed PFS, when the observed PFS hazard ratio is above 0.85, which provides a probability of approximately 85% to stop the study if the true PFS hazard ratio is 1.0 (i.e., no treatment benefit). The purpose of the futility analysis is not to stop the study for a positive (significant) efficacy PFS outcome. Therefore, statistical significance level for the interim or final efficacy analysis of PFS does not need to be adjusted for this futility analysis. The overall type I error is under strong control.

Three interim analyses for OS *were originally* planned in patients with *PIK3CA*-mutant tumors on the basis of the cobas *PIK3CA* mutation test. *As a result of the completion of the primary PFS analysis, the Sponsor has decided to limit the additional OS follow-up to one additional analysis. This additional OS analysis coincides with the originally planned second OS interim analysis.* The timing, the expected number of deaths, and

the decision boundary at each analysis are described in Section 6.4.2.2. The type I error is under strong control by using the Generalized Haybittle-Peto method.

No formal interim analysis is planned for the patients without detectable *PIK3CA* mutations.

The responsibility, membership, and communication flow of the iDMC are specified in the iDMC Charter.

6.10 CHINA SUBPOPULATION ANALYSIS

After the global enrollment closes, additional Chinese patients may continue to be recruited into the China extension cohort. A total of up to 150 Chinese patients with detectable PIK3CA-mutant tumors may be enrolled as part of the global study population and the China extension cohort combined. The objective of this extension cohort is to assess the treatment effect of taselisib plus fulvestrant on efficacy and safety in the subpopulation of patients from China, including those enrolled originally during the global portion and the China extension cohort combined, and to investigate the consistency in treatment effect between the China subpopulation and global patients for the purpose of registration in China.

The analysis of PFS among Chinese patients will be performed when approximately 56 PFS events have occurred among the 150 Chinese patients. A total of 56 PFS events in the China subpopulation will provide approximate 85% probability of observing at least 50% of the risk reduction in the PFS expected to be observed in the global population. Data from patients in the China extension cohort will not be included in the analyses of the global phase of the study but instead will be combined with data from Chinese patients in the global phase of the study and summarized as China subpopulation analysis in a separate report.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

A contract research organization will be responsible for the 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 contract research organization will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

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

The 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 through use of an electronic device. The device will be designed for entry of data in a way that is attributable, secure, and accurate, in compliance with FDA regulations for electronic records (21 CFR Part 11). The electronic PRO device data are available for view access only via secure access. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

The eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and will have access to a manual for appropriate eCRF completion. The 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. The 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 on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification 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 study.

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, 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 investigational medicinal product (IMP), including eCRFs, electronic PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 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.

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 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 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).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Caregiver's 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.

The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens 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 allow any remaining specimens to be used for exploratory research. 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 9.6).

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.

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

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 (i.e., last patient, last visit).

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 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.

9.4 ADMINISTRATIVE STRUCTURE

This study is sponsored by F. Hoffman-La Roche Ltd. Approximately 200 study centers will participate in this study, globally, enrolling a total of approximately 600 patients as part of the global portion of the study unless the iDMC recommends stopping the study early and the sponsor decides to accept iDMC's recommendation. After the global enrollment closes, additional Chinese patients may continue to be recruited into the China extension cohort. A total of up to 150 Chinese patients whose tumors contain a detectable PIK3CA mutation may be enrolled as part of the global study population and

the China extension cohort combined. An IxRS will be used to manage site drug supply and to randomize patients to study drug.

Tumor tissue will be sent to a central laboratory for analysis of *PIK3CA*-mutation status. Serum samples of pharmacokinetics will be sent to a central laboratory for storage. Blood samples for exploratory biomarkers will be sent to a central laboratory for analysis and sample storage. Sample analysis will be performed by an external vendor or the Sponsor.

Until the primary PFS analysis has been completed, an iDMC, whose membership is independent of the Sponsor, will oversee safety monitoring and the results of the interim efficacy analyses for investigator-assessed PFS. The procedures of the iDMC conduct will be described in a separate Charter.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://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 studies 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 study results within 6 months after the availability of the respective clinical study report. In addition, for all clinical studies 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.

9.6 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 Assessments

	Screening [a]	Cycle 1		Cycle 2		Cycles ≥3	Cycles ≥3	Study Drug Discontinuation Visit [c] (within ≤28 days after last dose)	Post–Progressive Disease Assessment	Follow-Up [d] (every 3 months ±7 days)
Day (Window)	–28 to –1	1	15 (+2) [b]	1 (+2) [b]	15 (±2)	1 (±3)	15 (±3)			
Informed consent	x									
Medical history and demographic data [e]	x									
Concomitant medications [f]	x	x	x	x	x	x		x		
Adverse events [g]	x	x	x	x	x	x	x [h]	x		x [aa]
Vital signs [i]	x	x	x	x	x	x		x		
Oxygen saturation (pulse oximetry)	x	x	x	x	x	x		x		
Complete physical examination, weight [j]	x									
Limited physical examination, weight [k]		x	x	x	x	x		x		
ECOG Performance Status	x	x	x	x	x	x [aa]		x [aa]		
Single 12-lead ECG [z]	x	As clinically indicated						x		
Tumor assessment [l]	x	Every 8 weeks (±5 days) regardless of dose delay or early discontinuation until disease progression [aa]							x [aa]	x [aa]
Bone scan and/or skeletal X-rays [m]	x	Per clinical indication or to confirm a complete response [m]								

Appendix 1
Schedule of Assessments (cont.)

	Screening [a]	Cycle 1		Cycle 2		Cycles ≥3	Cycles ≥3	Study Drug Discontinuation Visit [c] (within ≤28 days after last dose)	Post–Progressive Disease Assessment	Follow-Up [d] (every 3 months ±7 days)
Day (Window)	−28 to −1	1	15 (+2) [b]	1 (+2) [b]	15 (±2)	1 (±3)	15 (±3)			
CBC with differential and platelets [n]	x	x	x	x	x	x		x		
Fasting blood chemistry [o]	x	x	x	x	x	x		x		
HbA_{1c}	x							x		
Coagulation (INR, aPTT [or PTT])	x	As clinically indicated Patients taking warfarin or its equivalent: twice in the first week of administration, then weekly for 3 weeks, and then as clinically necessary								
Fasting lipid profile [p]	x	x				x		x		
Urinalysis [q]	x	As clinically indicated								
Archival FFPE tumor tissue [r]	x									
Tumor biopsy sample at progression [s]		Collected following disease progression after the patient signs the optional informed consent [aa]								
Plasma sample: Somatic tumor mutations	See Appendix 2 [aa]									
Pharmacogenetic sample										
Blood sample for NGS										
Plasma sample: exploratory biomarkers										
Optional RCR sample (blood for DNA extraction)										
PRO assessments [t]		x		x		x [aa]		x [aa]	x [aa]	X [aa]

Appendix 1
Schedule of Assessments (cont.)

	Screening [a]	Cycle 1		Cycle 2		Cycles ≥3	Cycles ≥3	Study Drug Discontinuation Visit [c] (within ≤28 days after last dose)	Post–Progressive Disease Assessment	Follow-Up [d] (every 3 months ±7 days)
Day (Window)	−28 to −1	1	15 (+2) [b]	1 (+2) [b]	15 (±2)	1 (±3)	15 (±3)			
Fulvestrant administration [u]		x	x	x		x				
Taselisib/placebo, administration in the clinic [v]		x	x	x	x	x				
Pharmacokinetic assessments [w]		See Appendix 2 [aa]								
Drug accountability			x	x	x	x		x		
Anticancer therapies given after discontinuation of study treatment								x [aa]		X [aa]
Follow-up assessment for survival [x]										X [aa]

CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D = EuroQol 5-Dimension Questionnaire; FFPE = formalin-fixed paraffin-embedded; HbA_{1c} = glycosylated hemoglobin; MRI = magnetic resonance imaging; NGS = next-generation sequencing; PRO = patient-reported outcomes; QLQ-BR23 = Quality of Life Questionnaire Breast Cancer Module; QLQ-C30 = Quality of Life Questionnaire Core 30; RCR = Roche Clinical Repository.

Notes: Assessments scheduled on the day of study drug administration in the clinic (e.g., Cycle 2, Day 1) should be performed prior to study drug administration, unless otherwise noted. Visits are based on a 28-day cycle. If the timing of a protocol-mandated procedure coincides with a holiday and/or weekend that preclude the procedure within the allotted window, the procedure should be performed on the nearest following date. Patients should receive their first dose of study treatment on the day of randomization if possible, but no later than 5 business days after randomization.

[a] Results of screening tests or examinations performed as standard of care prior to obtaining informed consent and within 28 days prior to randomization may be used rather than repeating required tests. Note that standard of care tumor and laboratory assessments should be done within 28 days prior to Cycle 1, Day 1.

[b] The window for Cycle 1, Day 15 and Cycle 2, Day 1 assessment is +2 days since fulvestrant administration should not occur prior to Cycle 1, Day 15 or Cycle 2, Day 1 (Day 29).

[c] The visit at which disease progression is recorded may serve as the study drug discontinuation visit, provided that all tests required at the study drug discontinuation visit are performed. If study treatment had been interrupted for >28 days before the decision to permanently discontinue all study treatment and the study drug discontinuation visit can no longer occur within ≤ 28 days after the last dose of study treatment, the visit should be performed as soon as possible after permanent study drug discontinuation.

[d] Only serious adverse events considered to be related to study medication should be reported. *Until approximately the end of August 2018, patients* will also be followed for survival and subsequent anti-cancer therapies approximately every 3 months.

[e] Medical history includes clinically significant diseases within the previous 5 years before Cycle 1 Day 1, smoking history, breast cancer history (including tumor characteristics such as hormone receptor status, prior cancer therapies, surgeries, and procedures). Demographic data include age, sex, and self-reported race/ethnicity.

[f] *Until approximately the end of August 2018, concomitant* medications include prescription medication, over-the-counter preparations, and herbal or homeopathic remedies and supplements used within 7 days prior to the screening visit through the study drug discontinuation visit. After this visit, only medications administered for ongoing or new treatment-related adverse events will be collected. *After approximately the end of August 2018, concomitant medications include prescription medication, over-the-counter preparations, and herbal or homeopathic remedies and supplements used within 7 days prior to the screening visit through the study drug discontinuation visit or until 28 days after the last dose of study drug, whichever occurs later.*

[g] 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 28 days after the last dose of study drug. After this period, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug. 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, the patient withdraws consent*, or the patient is no longer followed for survival*. 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.

[h] *Until approximately the end of August 2018, phone* call from the site to the patient to assess adverse events as in footnote g. The rationale for this phone call is that some adverse events have a delayed onset (e.g., diarrhea), and follow-up that is more frequent than the visit, which is every 4 weeks, will be useful in management. *After approximately the end of August 2018, the phone call from the site to the patient is no longer required for patients continuing on single-agent fulvestrant.*

[i] Vital signs include measurements of respiratory rate, pulse, systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

[j] Complete physical examination should include the evaluation of head, eye, ear, nose, and throat and cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems and measurement of weight and height (height is measured at the screening visit only). Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

[k] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[l] Perform tumor assessments at screening (within 28 days prior to Cycle 1 Day 1) *and, until approximately the end of August 2018*, every 8 weeks (±5 days) from date of randomization, and when clinically indicated for all patients including those with bone-only disease. This schedule is to be maintained and will not be shifted for treatment delays. Screening assessments must include CT scans of the chest, abdomen, and pelvis; CT scans of the neck and brain imaging should be included if clinically indicated. A documented standard-of-care tumor assessment performed within 28 days before Cycle 1 Day 1 may be used for the screening assessment, provided it meets the above requirements. The same imaging method used at screening must be used throughout the study. Response assessments will be performed by the investigator, on the basis of physical examinations and imaging scans, through the use of RECIST, Version 1.1. *Until approximately the end of August 2018, patients* who are discontinued from study treatment for reasons other than disease progression will be asked to continue to have tumor assessments every 8 weeks (±5 days) until disease progression. *Until approximately the end of August 2018, patients* who are discontinued from study treatment because of disease progression will be asked to return for a repeat tumor assessment 4–6 weeks after experiencing disease progression. In addition, *until approximately the end of August 2018,* bone disease identified on bone imaging must be evaluated radiographically by CT scan, MRI, or X-ray. *Until approximately the end of August 2018, the* same modality used at screening should be used throughout the study. *After approximately the end of August 2018, subsequent tumor assessments may be conducted per local standard of care.*

[m] An isotope bone scan (e.g., technetium) and/or skeletal X-rays will be performed at screening and*, until approximately the end of August 2018,* should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the development of new bone lesions or for confirmation of complete response for all patients. For patients with bone-only disease not visible on CT or MRI scans or X-ray at baseline (see Section 4.5.5), *until approximately the end of August 2018,* bone scans should be repeated every 8 weeks (±5 days) from the date of randomization and when clinically indicated until disease progression. *After approximately the end of August 2018, subsequent tumor assessments may be conducted per local standard of care.*

[n] Includes RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, bands [optional], eosinophils, basophils, lymphocytes, and monocytes), and platelet count. Reporting the differential as absolute counts is preferred, but percent is accepted. Laboratory samples are required at screening (within 28 days prior to Cycle 1, Day 1). If screening laboratory samples are drawn within 2 days prior to Cycle 1, Day 1, they do not have to be repeated on Cycle 1, Day 1. All other predose laboratory samples may also be drawn within 2 days prior to the cycle visit.

[o] Fasting (≥8 hours) blood chemistry includes glucose, BUN (or urea), creatinine, sodium, potassium, magnesium, bicarbonate, chloride, calcium, phosphorus, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase. Laboratory samples are required at screening (within 28 days prior to Cycle 1, Day 1). If screening laboratory samples are drawn within 2 days prior to Cycle 1, Day 1, they do not have to be repeated on Cycle 1, Day 1. All other predose laboratory samples may also be drawn within 2 days prior to the cycle visit.

[p] Fasting (≥8 hours) lipid profile should be performed at screening (within 28 days prior to Cycle 1, Day 1), and on Day 1 of Cycles 1 and 3 and every 3 cycles thereafter and include total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, amylase, and lipase. If screening laboratory samples are drawn within 2 days prior to Cycle 1, Day 1, they do not have to be repeated on Cycle 1, Day 1. All other predose laboratory samples may also be drawn within 2 days prior to the cycle visit.

[q] Specific gravity, pH, glucose, protein, ketones, and blood.

[r] Archival tumor tissue blocks or a minimum of 20 (25 preferred) freshly cut unstained slides from the most recent tumor tissue will be collected at screening for molecular characterization of the tumor tissue including but not limited to PIK3CA mutation. If a tissue sample from the site(s) of metastasis was collected to meet enrollment criteria, a minimum of five additional formalin-fixed paraffin-embedded tissue slides of the primary lesion should be provided, if available.

[s] Tumor biopsy collection at the time of disease progression is not required for study participation but*, until approximately the end of August 2018,* is strongly recommended and will be collected for patients who sign the Optional Research Informed Consent Form.

[t] *Until approximately the end of August 2018, the* PRO questionnaires (EORTC QLQ-C30, modified QLQ-BR23) and EQ-5D will be completed by the patients at the investigational site during treatment. All questionnaires must be administered prior to any other study assessment(s), health care provider interaction, and administration of study drug, to ensure that the validity of the instrument is not compromised and that data quality meets regulatory requirements. *Until approximately the end of August 2018, patients* who are discontinued from study treatment for reasons other than disease progression will be asked to continue to complete the PRO assessments approximately every 8 weeks (±5 days) until disease progression. Additionally, *until approximately the end of August 2018,* all patients will also complete the PRO measures once at 4–6 weeks (±5 days) and once at 12 weeks (±7 days) after disease progression.

[u] Fulvestrant will be administered in the clinic (before administration of taselisib/placebo) as two intramuscular injections of 250 mg each on Days 1 and 15 of Cycle 1 and Day 1 of each subsequent 28-day cycle.

[v] Taselisib/placebo will be taken orally once daily beginning at Cycle 1, Day 1. Taselisib/placebo will be administered in the clinic on Cycle 1, Day 1 and Cycle 1, Day 15 and on each subsequent day that a cycle visit is scheduled, after the predose assessments and procedures, and at home on all non-clinic visit days. During clinic visits, taselisib/placebo will be administered after the fulvestrant injections (except for Cycle 2, Day 15). A sufficient number of taselisib/placebo tablets will be provided to last until the next visit, or, at the investigator's discretion, to last until the next administration of fulvestrant. Extra tablets may be dispensed if there is a reasonable possibility that the patient's next visit may be delayed (e.g., because of inclement weather or distance between the patient's home and study center). *Until approximately the end of August 2018, patients* will also receive a medication diary. Instruct the patient to record the time and date she takes each treatment dose in the diary and to return all unused tablets at each study visit, to assess compliance. Collect and review medication diary and unused tablets and assess compliance at each subsequent visit. *After approximately the end of August 2018, collect and review unused tablets and assess compliance at each subsequent visit.* At the study drug discontinuation visit, do not dispense any additional study drug tablets or provide a new medication diary.

[w] Taselisib plasma samples may be used for exploratory pharmacokinetics, metabolism, biomarker and/or safety analyses, which may include determination of fulvestrant concentration.

[x] *Until approximately the end of August 2018, all* patients who discontinue from the treatment phase will be followed for survival information unless the patient requests to be withdrawn from study-survival follow-up. Survival follow-up information will be collected via telephone calls, patient's medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, or study termination by the Sponsor.

[z] An ECG (12-lead) is required at screening and may be repeated during the study as clinically indicated. All ECG recordings should be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. 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. Clinically significant abnormalities observed during screening will be recorded on the General Medical History and Baseline Conditions eCRF. New or worsened clinically significant abnormalities will be recorded on the Adverse Event eCRF.

[aa] *Until approximately the end of August 2018.*

Appendix 2
Schedule for Collection of Pharmacokinetic and Exploratory Biomarker Samples

Study Visit	Timepoint	Sample Type
Pretreatment	≤7 days before first dose	Plasma (somatic tumor mutations) [a]
		Optional RCR Blood (for DNA extraction) [b]
Cycle 1, Day 1	Prior to taselisib/placebo administration	Plasma (somatic tumor mutations) [a, d]
		Plasma (exploratory biomarkers) [a]
		Pharmacogenetic blood sample [a]
		Blood for NGS [a, c]
	1–4 hours post-taselisib/placebo administration	PK plasma sample for taselisib
Cycle 1, Day 15	Prior to taselisib/placebo administration	Plasma (somatic tumor mutations) [a, d]
		Plasma (exploratory biomarkers) [a]
Cycle 2, Day 1 [e]	0–3 hours prior to taselisib/placebo and fulvestrant administration	PK plasma sample for taselisib
	2–6 hours post-taselisib/placebo and fulvestrant administration	PK plasma sample for taselisib
Cycle 3, Day 1 and Cycles 5, 7, 9, etc., Day 1	Prior to taselisib/placebo administration	Plasma (somatic tumor mutations) [a, d]
Cycle 6, Day 1 [e]	0–3 hours prior to taselisib/placebo and fulvestrant administration	PK plasma sample for taselisib [f]
SDDV	At visit	Plasma (somatic tumor mutations) [a, d]
		Plasma (exploratory biomarkers) [a]

NGS = next-generation sequencing; PK = pharmacokinetic; RCR = Roche Clinical Repository; SDDV = study drug discontinuation visit.

Notes: Predose blood samples may be drawn within 2 days prior to the cycle visit. *All samples in Appendix 2 are no longer required after approximately the end of August 2018.*

[a] Not applicable for a site that has not been granted approval by its local regulatory authorities.

[b] The optional RCR blood sample (for DNA extraction) requires an additional informed consent and can be collected at any time during the course of the study.

[c] A blood sample will also be collected as a source of normal DNA to determine whether or not sequence variants are somatic mutations or single nucleotide polymorphisms if approved by local regulatory authorities.

[d] Blood will be collected for ctDNA analysis prior to dosing at, Cycle 1, Days 1 and 15, prior to dosing on Day 1 of Cycles 3, 5, 7, 9, 11 etc., and SDDV

[e] The date and time of the previous taselisib/placebo dose prior to the Cycle 2 Day 1 and Cycle 6 Day 1 samples for PK analysis will need to be recorded.

[f] Back-up plasma sample at this timepoint may be used for determination of fulvestrant concentration as this is an exploratory objective.

Appendix 3
Mutations Detected by the cobas® *PIK3CA* Mutation Test

Exon	Mutation ID	Amino-Acid Change	cobas® Test Result
1	263 G>A	R88Q	R88Q
4	1035 T>A	N345K	N345K
7	1258 T>C	C420R	C420R
9	1624 G>A	E542K	E542K
9	1634 A>C	E545A	E545X
9	1635 G>T	E545D	E545X
9	1634 A>G	E545G	E545X
9	1633 G>A	E545K	E545X
9	1636 C>G	Q546E	Q546X
9	1636 C>A	Q546K	Q546X
9	1637 A>T	Q546L	Q546X
9	1637 A>G	Q546R	Q546X
20	3129 G>T	M1043I	M1043I
20	3140 A>T	H1047L	H1047X
20	3140 A>G	H1047R	H1047X
20	3139 C>T	H1047Y	H1047X
20	3145 G>C	G1049R	G1049R

Appendix 4
Eastern Cooperative Oncology Group Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (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 5
Inhibitors of PI3K/AKT/mTOR Signaling Pathway

Phosphatidylinositol 3-kinase (PI3K) inhibitors include but are not limited to the following:

- Idelalisib (GS-1101), pictilisib (GDC-0941), apitolisib (GDC-0980), taselisib (GDC-0032), buparlisib (BKM120), copanlisib (BAY80-6946), alpelisib (BYL719), MLN1117, IPI-145, GSK2636771, PF-04691502, BEZ235, LY294002, PIK-75, TGX-221, XL147, XL765, SF1126, PX-866, D-106669, GSK615

Mammalian target of rapamycin (mTOR) inhibitors include but are not limited to the following:

- Everolimus, temsirolimus, ridaforolimus, MLN0128

Protein kinase B (AKT) inhibitors include but are not limited to the following:

- MK-2206, ipatasertib (GDC-0068)

Appendix 6
Response Evaluation Criteria in Solid Tumors, V 1.1
Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1,[1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions and/or lymph nodes will be categorized as measurable or non-measurable as described below.

MEASURABLE TUMOR 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 no greater than 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 no greater than 5 mm). At baseline and at follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

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[1] 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.

[2] 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.

Appendix 6
Response Evaluation Criteria in Solid Tumors, V 1.1
Modified Excerpt from Original Publication (cont.)

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 non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, 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:

- Bone scan, positron emission tomography (PET) scan, or 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 as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

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

Appendix 6
Response Evaluation Criteria in Solid Tumors, V 1.1
Modified Excerpt from Original Publication (cont.)

Target Lesions: Specifications by Methods of Measurements

- Measurement of Lesions

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

- Method of Assessment

  The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during 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 $\geq$ 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, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

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, <u>if not, the patient should be considered not-evaluable from that point forward</u>. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality.

Appendix 6
Response Evaluation Criteria in Solid Tumors, V 1.1
Modified Excerpt from Original Publication (cont.)

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

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. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

BASELINE DOCUMENTATION 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 recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

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 ≥ 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. Nodal 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.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, 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").

RESPONSE CRITERIA

Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.
- Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

Special Notes on the Assessment of Target Lesions

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 nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Target Lesions That Become Too Small to Measure. During the study, all lesions (nodal and non-nodal) 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 measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, 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 BML (below measurable limit) should be ticked. (BML is equivalent to a "less than" sign.) (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 BML should also be ticked).

<u>To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and in that case BML should not be ticked.</u>

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

<u>Evaluation of Non-Target Lesions</u>

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

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

The appearance of one or more new lesions is also considered progression.

Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of 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 disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here 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-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, 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, or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. 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 partial or complete response. 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, then progression should be declared using the date of the initial scan.

(18)F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

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

- A negative FDG-PET scan at baseline with a positive[3] FDG-PET scan during the study is a sign of PD based on a new lesion.
- In the case of no FDG-PET scan at baseline and a positive FDG-PET scan during the study:

  If the positive FDG-PET scan during the study corresponds to a new site of disease confirmed by CT, this will be considered PD.

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

  If the positive FDG-PET scan during the study corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this will not be considered PD.

[3] A "positive" FDG-PET scan lesion means one that is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation-corrected image.

Appendix 6
Response Evaluation Criteria in Solid Tumors, V 1.1
Modified Excerpt from Original Publication (cont.)

EVALUATION OF RESPONSE

Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

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.

Appendix 6
Response Evaluation Criteria in Solid Tumors, V 1.1
Modified Excerpt from Original Publication (cont.)

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 only a subset of lesion measurements are made at an assessment, 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 lesion(s) 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.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess" except where this is clear evidence of progression, as this equates with the case being not evaluable at that timepoint.

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 1.

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.

Appendix 6
Response Evaluation Criteria in Solid Tumors, V 1.1
Modified Excerpt from Original Publication (cont.)

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 7
Patient-Reported Outcome Measure: QLQ-C30

ENGLISH

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.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): ____
Today's date (Day, Month, Year): 31 ____

		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

Appendix 7
Patient-Reported Outcome Measure: QLQ-C30 (cont.)

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 8
Patient-Report Outcome Measure: Modified QLQ-BR23

ENGLISH

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
44. Have you had skin problems (e.g. itchy, dry)?	1	2	3	4
45. Did itching of your skin bother you?	1	2	3	4
46. Have you had a sore mouth or tongue?	1	2	3	4
47. Have you had trouble swallowing?	1	2	3	4
During the past four weeks:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
48. To what extent were you interested in sex?	1	2	3	4
49. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
50. 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

Appendix 8
Patient-Report Outcome Measure: Modified QLQ-BR23 (cont.)

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
51. Did you have any pain in your arm or shoulder?	1	2	3	4
52. Did you have a swollen arm or hand?	1	2	3	4
53. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
54. Have you had any pain in the area of your affected breast?	1	2	3	4
55. Was the area of your affected breast swollen?	1	2	3	4
56. Was the area of your affected breast oversensitive?	1	2	3	4
57. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4

Appendix 9
Exploratory Health Economic Outcome Measure: EQ-5D

Health Questionnaire

English version for the US

Appendix 9
Exploratory Health Economic Outcome Measure: EQ-5D (cont.)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some 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 with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

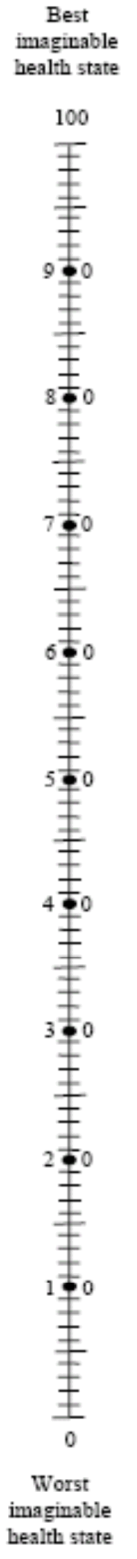
I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

Appendix 9
Exploratory Health Economic Outcome Measure: EQ-5D (cont.)

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE III, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED STUDY OF TASELISIB PLUS FULVESTRANT VERSUS PLACEBO PLUS FULVESTRANT IN POSTMENOPAUSAL WOMEN WITH ESTROGEN RECEPTOR-POSITIVE AND HER2-NEGATIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER WHO HAVE DISEASE RECURRENCE OR PROGRESSION DURING OR AFTER AROMATASE INHIBITOR THERAPY**

PROTOCOL NUMBER: GO29058/ NCT02340221

STUDY DRUG: Taselisib (RO5537381)

VERSION NUMBER: 2

IND NUMBER: 121658

EUDRACT NUMBER: 2014-003185-25

SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted], Ph.D.

DATE FINAL: 30 June 2015

DATE AMENDED: See electronic date stamp below.

STATISTICAL ANALYSIS PLAN APPROVAL

Name	Reason for Signing	Date and Time (UTC)
[redacted]	Company Signatory (Clinical)	03-Mar-2017 22:30:02

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

The major revisions to the Statistical Analysis Plan are as follows:

- An interim efficacy analysis for the primary efficacy endpoint investigator-assessed progression-free survival (PFS) was added. The timing and • -spending methods were added (Section 4.4.1 and Section 4.8).
- The stopping boundary for the interim futility analysis for the primary efficacy endpoint investigator-assessed PFS was updated (Section 4.4.1).
- An additional censoring rule required by the US Food and Drug Administration (FDA) was added and will be used as the primary efficacy analysis for investigator-assessed PFS for FDA submission (Section 4.4.1 and Section 4.7).
- The testing order of the secondary efficacy endpoints of overall objective response rate and overall survival, as well as the timing and stopping boundaries of the interim efficacy analyses for overall survival, were updated (Section 4.4.2 and Section 4.8).
- A secondary efficacy endpoint of blinded independent central review-assessed PFS was added (Section 4.4.2.5).
- Descriptions of analyses have been added to reflect the addition to the protocol of an extension cohort of patients from China who may be recruited beyond the planned primary analysis. Distinctions are made between analyses of the global study and the China subgroup (Section 1, Section 2.3, Section 2.5, and Section 5).
- Analyses were detailed for patient-reported outcomes that are captured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (QLQ-C30) and the modified breast cancer module QLQ-BR23 (Section 4.4.2.6 and Section 4.7).

Additional minor changes have been made to improve clarity and consistency.

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LIST OF APPENDICES

1. BACKGROUND

Study GO29058 is a Phase III, double-blind, multicenter, randomized, placebo-controlled study designed to evaluate the efficacy and safety of taselisib + fulvestrant compared with placebo + fulvestrant in postmenopausal women with estrogen receptor• positive and human epidermal growth factor 2 (HER2)-negative locally advanced or metastatic breast cancer (MBC) who have disease recurrence or disease progression during or after aromatase inhibitor therapy.

Approximately 600 patients will be enrolled in the global study, including 480 patients with detectable *PIK3CA*-mutant tumors and 120 patients without detectable *PIK3CA*-mutant tumors. Patients will be randomized in a 2:1 ratio to receive either fulvestrant + taselisib or fulvestrant + placebo. Patients with and without detectable *PIK3CA*-mutant tumors will be randomized separately.

The primary efficacy endpoint is investigator-assessed progression-free survival (PFS) in patients with detectable *PIK3CA*-mutant tumors, and the secondary efficacy endpoints are overall objective response rate (ORR), overall survival (OS), clinical benefit rate (CBR), duration of objective response (DOR), and blinded independent central review (BICR)-assessed PFS in patients with detectable *PIK3CA*-mutant tumors. The safety of taselisib and fulvestrant compared with placebo and fulvestrant will be evaluated in patients with detectable *PIK3CA*-mutant tumors and also in all randomized patients who receive at least one dose of any component of protocol treatment (i.e., study drug).

The purpose of this Statistical Analysis Plan (SAP) is to provide the analysis plan proposed for this study by the Sponsor, F. Hoffmann-La Roche Ltd. The SAP overrides the analyses described in the statistical section of the protocol. The analyses as described in the SAP will be used by the Sponsor for the purpose of regulatory submission.

The protocol was amended to include an additional cohort of patients from China who may be recruited after global enrollment closes (i.e., the China extension cohort). After the global enrollment closes, additional Chinese patients may continue to be recruited in a 2:1 randomized ratio into the China extension cohort. A total of up to 150 Chinese patients with detectable *PIK3CA*-mutant tumors may be enrolled as part of the global study population and the China extension cohort combined. The China extension cohort is for China registration purpose only and will be reported separately from the global study. The Clinical Study Report (CSR) for the global study will include only results from the patients enrolled in the global portion of the study.

2. STUDY DESIGN

2.1 PROTOCOL SYNOPSIS

The protocol synopsis is in Appendix 1. For additional details, see the schedule of assessments in Appendix 2.

2.2 OUTCOME MEASURES

The outcome measures are described in the protocol synopsis (Appendix 1).

2.3 DETERMINATION OF SAMPLE SIZE

The global study plans to enroll approximately 600 patients, including 480 patients with detectable *PIK3CA*-mutant tumors and 120 patients without detectable *PIK3CA*-mutant tumors (tumor status determined by the cobas• *PIK3CA* Mutation Test).

After the global enrollment closes, additional Chinese patients may continue to be recruited into the China extension cohort. A total of up to 150 patients with detectable *PIK3CA*-mutant tumors may be enrolled as part of the global study population and the China extension cohort combined (refer to the protocol for details).

The sample size of 480 patients with detectable *PIK3CA*-mutant tumors is determined on the basis of the power calculation for the PFS and the OS endpoints, whichever requires a larger sample size. In this case, the sample size is driven by OS.

Among the 480 patients with *PIK3CA*-mutant tumors, approximately 287 investigator-assessed PFS events will be required to detect a hazard ratio (HR) of 0.59 in PFS (3.1 months of improvement in median PFS) with 95% power at a two-sided significance level of 1%, assuming a median PFS of 4.5 months in the control arm (Mauriac et al. 2009; Johnston et al. 2013). One interim efficacy analysis of investigator-assessed PFS will be conducted at 60% of PFS information (see Section 4.8 for more details). The • -spending function is specified as Gamma (• 16), which allocates two-sided • $= 1.7 \bullet 10^{\bullet 5}$ at the interim efficacy analysis of PFS, when 172 investigator-assessed PFS events have occurred. The minimal detectable difference for PFS HR at final PFS analysis is 0.72 (i.e., 39% improvement in median PFS from 4.5 months in the control arm compared with 6.2 months in the treatment arm), when 287 investigator-assessed PFS events have occurred.

With the aforementioned sample size of 480 patients with *PIK3CA*-mutant tumors, the OS analyses in this population will require 330 deaths to detect an HR of 0.7 with at least 80% power at a two-sided significance level of 5%. Timeline for the analyses of OS is detailed in Section 2.4. OS will be tested only if both the investigator-assessed PFS and ORR have reached their respective significance levels.

The study plans to enroll 120 patients who do not have a detectable *PIK3CA*-mutant tumor, based on the cobas• *PIK3CA* Mutation Test, to estimate the clinical benefit in this population. For this group of patients, the focus is to estimate the benefit, and formal hypothesis testing will not occur. For example, If the observed HR in PFS is 1 (no evidence of benefit), the 90% CI will exclude a true HR < 0.72 (i.e., > 1.8-month improvement in median PFS). These analyses are exploratory.

In total, approximately 400 patients will be treated with the combination of taselisib + fulvestrant in this study (320 patients with detectable *PIK3CA*-mutant tumors and 80 patients without detectable *PIK3CA*-mutant tumors), which will enable the Sponsor to better characterize any rare but clinically significant safety events (e.g., for an adverse event with 4% frequency, there is a 96% probability to observe • 10 patients with such an adverse event based on 400 patients treated with taselisib + fulvestrant) to help enable the development of effective toxicity prevention and management guidelines for patients treated with the combination of taselisib and fulvestrant.

2.4 ANALYSIS TIMING FOR THE GLOBAL STUDY

Assuming a 12-month site ramp-up period and a total of 200 sites, the global study is expected to be fully enrolled with approximately 600 patients (480 patients with detectable *PIK3CA*-mutant tumors and 120 patients without detectable *PIK3CA*-mutant tumors) by 28 months from the first patient enrolled in the study (FPI).

One efficacy and futility interim analysis for investigator-assessed PFS will be conducted in patients with detectable *PIK3CA*-mutant tumors when approximately 172 investigator-assessed PFS events (approximately 60% of information) have occurred in patients with *PIK3CA*-mutant tumors, which is expected to be reached at approximately 21 months after FPI.

The primary efficacy analysis for PFS will be conducted when 287 PFS events are observed in patients with *PIK3CA*-mutant tumors. This is expected to be reached at approximately 29 months after FPI.

Three interim analyses (time driven) and one final analysis (event driven) for OS are planned in patients with *PIK3CA*-mutant tumors: 1) the first interim analysis will be conducted at the time when both investigator-assessed PFS and ORR have reached their respective significance levels, so it could occur at the time of the interim efficacy or the final efficacy analysis for investigator-assessed PFS (approximately 21 or 29 months after FPI, approximately 63 or 118 OS events or 19% or 36% of OS information will be observed, respectively); 2) the second interim analysis will be conducted approximately 10 months after the first interim analysis; 3) the third interim analysis will be conducted approximately 8 months after the second interim analysis. The final analysis will be conducted after approximately 330 deaths are observed (approximately 77 months after FPI). Details are described in Section 4.4.2.2.

The China extension cohort is for China registration purpose only and will be reported separately from the global study. The CSR for the global study will include only results from the patients enrolled in the global portion of the study.

2.5 ANALYSIS TIMING FOR THE CHINA SUBGROUP

The analysis of PFS among Chinese patients will be performed when approximately 56 PFS events have occurred among the 150 Chinese patients with detectable *PIK3CA*-mutant tumors. A total of 56 PFS events in the China subpopulation will provide approximate 85% probability of observing at least 50% of the risk reduction in the PFS that is expected to be observed in the global population.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Eligible and consented patients will be randomized to receive either taselisib + fulvestrant or placebo + fulvestrant based on a 2:1 randomization ratio. Patients with and without detectable *PIK3CA*-mutant tumors will be randomized separately using a permuted block randomization method.

Randomization will be stratified by the following criteria:

- Visceral versus non-visceral disease

  Visceral disease: metastatic disease in the lung, liver, adrenal glands, brain, heart, pericardium, pleura, peritoneum, or other end organs of the chest, abdomen, and pelvis

  Non-visceral disease: absence of metastatic disease in visceral organs. Pleural effusions and/or ascites, disease involving lymph nodes, and disease involving bone are not considered to be visceral disease.

- Sensitivity versus non-sensitivity to the most recently administered endocrine therapy

  Sensitive to most recently administered endocrine therapy:

  For patients with no endocrine treatment in the advanced or metastatic setting, at least 24 months of adjuvant endocrine therapy prior to disease recurrence

  Documented clinical benefit (complete response [CR], partial response [PR], or stable disease for • 24 weeks) to most recent endocrine treatment in the advanced or metastatic treatment setting

  Non-sensitive: not satisfying the criterion to be sensitive

- Geographical region with 3 levels

  Western Europe, United States, Canada, and Australia

  Asia

  Rest of the World

3.2 DATA MONITORING

An independent Data Monitoring Committee (iDMC) will monitor accumulating patient safety data for the global portion of the study. The iDMC will convene to review

cumulative safety data approximately every 6 months. The data on serious adverse events, death, and adverse events of special interest will be monitored by iDMC approximately every 3 months.

In addition, one efficacy and futility analysis for investigator-assessed PFS will be conducted in patients with *PIK3CA*-mutant tumors. The iDMC will review the data and may recommend stopping the study for efficacy or futility (details described in Section 4.8).

4. STATISTICAL METHODS

This section applies only to the global study. See Section 5 for the China subgroup analysis.

4.1 ANALYSIS POPULATIONS

4.1.1 Intent-to-Treat Population

The intent-to-treat (ITT) population includes all randomized patients regardless of whether they receive any amount of study treatment. Treatment assignment will be defined according to the treatment assigned at randomization by the interactive voice or Web response system (IxRS).

The ITT population will form the basis for efficacy analyses. The analyses for the primary and the secondary efficacy endpoints will be conducted in patients with *PIK3CA*-mutant tumors. These endpoints will also be evaluated in patients without detectable *PIK3CA*-mutant tumors as the exploratory analyses.

4.1.2 Safety Population

The safety population includes all randomized patients who receive at least one dose of taselisib or placebo or fulvestrant. Specifically, a patient will be included in the taselisib + fulvestrant arm in the safety analyses if the patient receives any amount of taselisib, regardless of the initial treatment assignment at randomization. The safety population will form the basis for safety analyses.

4.1.3 Pharmacokinetic Population

The pharmacokinetic population will include all patients who have received at least one dose of taselisib and provided valid (adequately documented dose time and pharmacokinetic sample time) pharmacokinetic assessments. The pharmacokinetic population at specific timepoints will vary, depending on the availability of results at confirmed dosing and pharmacokinetic assessment times.

4.2 ANALYSIS OF STUDY CONDUCT

Patient enrollment, duration of follow-up, and discontinuation from the study and discontinuation reasons will be summarized by treatment arm for all randomized patients. In addition, major protocol deviations, including violations of inclusion or exclusion

criteria, will be summarized by treatment arm. All the analyses will be performed separately for patients with and without detectable *PIK3CA*-mutant tumors.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

The evaluation of treatment group comparability between the two treatment arms will include summaries of demographics, baseline disease characteristics (including *PIK3CA* mutation status), and patient treatment history.

Descriptive summaries of continuous data will present the group mean, SD, median, minimum, and maximum. Descriptive summaries of discrete data will present the category counts as frequencies and percentages.

All the analyses will be performed separately for patients with and without detectable *PIK3CA*-mutant tumors.

4.4 EFFICACY ANALYSIS

The stratification factors collected from the IxRS will be used in all the stratified analyses.

4.4.1 Primary Efficacy Endpoint

PFS is defined as the time from randomization to disease progression as determined by the investigator with the use of Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) or death due to any cause, whichever occurs earlier. The primary PFS analysis will be conducted in all randomized patients with detectable *PIK3CA*-mutant tumors, with patients grouped according to the treatment arm assigned at randomization.

An interim efficacy analysis will be conducted for investigator-assessed PFS at the time of 172 investigator-assessed PFS events (expected 21 months after the first patient is enrolled), and the final efficacy analysis will be conducted at the time 287 investigator-assessed PFS events (expected 29 months after the first patient is enrolled) are observed in patients with *PIK3CA*-mutant tumors (see Table 1).

Table 1 Progression-Free Survival Analyses

	Estimated Timing (Clinical Data Cutoff)	PFS Events	Two-Sided p-Value Boundary	Rejection HR Boundary [a]	Percentage Information
PFS IA	~21 months after FPI	~172	$1.7 \cdot 10^{-5}$	0.5	60%
PFS FA	~29 months after FPI	~287	0.01	0.72	100%

FA = final analysis; FPI = first patient in; HR = hazard ratio; IA = interim analysis; PFS = progression-free survival.

[a] Assuming exponential distributions for the PFS event time of the two treatment arms.

The • -spending function is specified as Gamma (• 16), which allocates two-sided • $= 1.7 \cdot 10^{-5}$ at the interim efficacy analysis of investigator-assessed PFS, when 172 PFS events have occurred, and preserves the two-sided 1% • -level at the final PFS analysis. The exact boundary will be calculated on the basis of the exact number of PFS events observed at the interim analysis. The associated minimal detectable difference for the investigator-assessed PFS HR at the interim efficacy analysis is 0.5 (i.e., 100% improvement in median investigator-assessed PFS from 4.5 months in the control arm to 9 months in the treatment arm).

Data from patients who are lost to follow-up or without disease progression or death as of the clinical data cutoff date will be censored at the time of the last tumor assessment when the patient is known to be progression-free (i.e., an overall response other than "progressive disease" or "not evaluable") or at the time of randomization if there is no post-baseline tumor assessment or all post-baseline tumor assessments have overall responses of "not evaluable."

For the US Food and Drug Administration (FDA), the primary efficacy analysis for investigator-assessed PFS will be censored additionally for patients experiencing a progression event preceded by two or more missing tumor assessments before the disease progression (i.e., the duration between the date of first documented progressive disease [PD] deemed by investigator per RECIST v1.1 and the date of the last tumor assessment when the patient is known to be progression-free > 122 days, i.e., $2 \cdot 8 \cdot 7 + 10$, given that the protocol allows tumor assessments to be conducted every 8 weeks $\pm$ 5 days). These patients will be censored at the last tumor assessment prior to the missed visit that is known to be progression-free (i.e., an overall response other than "progressive disease" or "not evaluable") or at randomization if there is no post-baseline tumor assessment or all post-baseline tumor assessments have overall responses of "not evaluable" in between the randomization and the first documented PD per RECIST v 1.1.

The two-sided log-rank test stratified by the three stratification factors will be used as the primary analysis to compare investigator-assessed PFS between the two treatment arms. The three stratification factors are: 1) visceral versus non-visceral, 2) sensitivity versus non-sensitivity to their most recently administered endocrine therapy, and 3) geographical region. The Kaplan-Meier method will be used to estimate median investigator-assessed PFS for each treatment arm. Cox proportional hazards models stratified by the three stratification factors will be used to estimate the HR and its 95% CI. The results from the unstratified log-rank test will also be provided.

4.4.2 Secondary Efficacy Endpoints

Assuming that the primary endpoint PFS is statistically significant, the first two secondary endpoints are planned to be tested in the following order:

- Overall ORR
- OS

4.4.2.1 Overall Objective Response Rate

Overall ORR is defined as a CR or PR as determined by investigator assessment using RECIST v1.1.

The analysis of ORR will only include patients with detectable *PIK3CA*-mutant tumors who have measurable disease per RECIST v1.1 at baseline as a secondary endpoint of the study and will be tested on the basis of a hierarchical testing procedure to preserve the type I error. That is, the ORR analysis will be conducted at the significance level of two-sided 5% at the time that a statistically significant benefit is observed for the investigator-assessed PFS at either the interim efficacy or final PFS analysis.

An estimate of the response rate and its 95% CI will be calculated using the Blyth-Still-Casella method for each treatment arm. Response rates in the treatment arms will be compared using the stratified Mantel-Haenszel test. The CI for the difference in ORRs between the two treatment arms will be determined using the normal approximation to the binomial distribution. To be conservative, patients with no post-baseline tumor assessments or with post-baseline tumor assessments that have overall responses of “not evaluable” will be considered to be non-responders.

4.4.2.2 Overall Survival

OS is defined as the time from randomization to death from any cause. The analysis for OS will be conducted only in all randomized patients with detectable *PIK3CA*-mutant tumors as a secondary endpoint of the study and will be tested based on a hierarchical testing procedure to preserve type I error. That is, the OS will be tested only if both investigator-assessed PFS and ORR have reached their respective significance levels. The overall type I error for OS is preserved at two-sided 5%.

OS will be analyzed with patients grouped according to the treatment arm assigned at randomization. Data from patients who are alive at the time of the analysis data cutoff will be censored at the last date they are known to be alive. Data from patients without post-baseline information will be censored at the date of randomization.

The analyses will be conducted using the stratified two-sided log-rank test, and the results from the unstratified log-rank test will also be provided. The OS curve for each treatment arm will be estimated by the Kaplan-Meier method, and the HR and its 95% CI will be estimated by Cox proportional hazards models.

Three interim analyses (time driven) and one final analysis (event driven) for OS are planned in patients with detectable *PIK3CA*-mutant tumors (see Table 2 and Table 3):

- The first interim OS analysis will be conducted at the time when both investigator-assessed PFS and ORR have reached their respective significance levels, so it could occur at the time of the interim efficacy or the final efficacy analysis for investigator-assessed PFS.
- The second interim analysis will be conducted approximately 10 months after the first interim analysis.
- The third interim analysis will be conducted approximately 8 months after the second interim analysis.
- The final analysis will be conducted after approximately 330 deaths are observed (approximately 77 months after FPI).

Table 2 Interim Analyses for Overall Survival if the First Interim Overall Survival Analysis Occurs at the Time of the Interim Efficacy Analysis of Investigator-Assessed Progression-Free Survival

	Estimated Timing (Clinical Data Cutoff)	OS Events	Two-Sided p-Value Boundary	Rejection HR Boundary [a]	Percentage Information
First OS IA	~21 months after FPI	~63	0.001	0.44	19%
Second OS IA	~10 months after first OS IA	~134	0.010	0.65	41%
Third OS IA	~8 months after second OS IA	~188	0.045	0.75	57%
OS FA	~77 months after FPI	~330	0.007	0.74	100%

FA = final analysis; FPI = first patient in; HR = hazard ratio; IA = interim analysis; OS = overall survival; PFS = progression-free survival.

[a] Assuming exponential distributions for the OS event time of the two treatment arms.

Table 3 Interim Analyses for Overall Survival if the First Interim Overall Survival Analysis Occurs at the Time of the Final Efficacy Analysis of Investigator-Assessed Progression-Free Survival

	Estimated Timing (Clinical Data Cutoff)	OS Events	Two-Sided p-Value Boundary	Rejection HR Boundary [a]	Percentage Information
First OS IA	~29 months after FPI	~118	0.001	0.53	36%
Second OS IA	~10 months after first OS IA	~188	0.010	0.67	57%
Third OS IA	~8 months after second OS IA	~232	0.045	0.76	70%
OS FA	~77 months after FPI	~330	0.013	0.75	100%

FA = final analysis; FPI = first patient in; HR = hazard ratio; IA = interim analysis; OS = overall survival; PFS = progression-free survival.

[a] Assuming exponential distributions for the OS event time of the two treatment arms.

The stopping boundaries are computed using the generalized Haybittle-Peto boundaries with unequal p-values being used in the • -spending function and will be adjusted on the basis of the actual number of OS events observed at each interim OS analysis.

The timing of the analyses are based on an assumption of an annual loss-to-follow-up rate of 5%. The study team will be unblinded at the time when the iDMC recommends to stop the study and the Sponsor decides to stop the study or at the time of the final PFS analysis if the study is not stopped early. Investigators and patients will remain blinded to individual patient-level treatment assignment until the final analysis of OS.

4.4.2.3 Clinical Benefit Rate

Clinical benefit is defined as overall objective response (CR or PR) or no disease progression for • 24 weeks after randomization as determined by investigator tumor assessments using RECIST v1.1. The analysis of CBR will be performed for patients with detectable *PIK3CA*-mutant tumors with measurable disease per RECIST v1.1 at baseline and will be repeated for the group of patients with detectable *PIK3CA*-mutant tumors regardless of measurable disease at baseline. To be conservative, patients with no post-baseline tumor assessment or with post-baseline tumor assessments that have overall responses of “not evaluable” will be considered to not experience clinical benefit.

An estimate of CBR and its 95% CI will be calculated using the Blyth-Still-Casella method for each treatment arm. The CBRs in the treatment arms will be compared using the stratified Mantel-Haenszel test. The CI for the difference in CBRs between the two treatment arms will be determined using the normal approximation to the binomial distribution.

4.4.2.4 Duration of Objective Response

DOR is defined as the period measured from the date of the first occurrence of a CR or PR (whichever status is recorded first) until the first date that PD or death is documented. The analysis of DOR will only include patients with detectable *PIK3CA*-mutant tumors who achieve an objective response to study treatment among patients with measurable disease per RECIST v1.1 at baseline.

Data from patients who are lost to follow-up or without disease progression or death as of the clinical data cutoff date will be censored at the time of the last tumor assessment when the patient is known to be progression-free (i.e., an overall response other than "progressive disease" or "not evaluable").

DOR will be estimated using the Kaplan-Meier methodology, with patients grouped according to the treatment arm assigned at randomization. Comparisons between treatment arms using stratified and unstratified log-rank test will be made for descriptive purposes. Because the determination of DOR is based on a non-randomized subset of patients, formal hypothesis testing will not be performed.

4.4.2.5 Blinded Independent Central Review• Assessed Progression-Free Survival

While the primary efficacy endpoint is investigator-assessed PFS in patients with detectable *PIK3CA*-mutant tumors, a BICR of progression will be conducted for all patients based on RECIST v1.1 as described in a separate charter.

The BICR-assessed PFS in patients with detectable *PIK3CA*-mutant tumors is not intended to provide an alternative means of definitive analysis but to show that there is no potential bias in the investigator assessment. The BICR-assessed PD date and events will be defined based on the BICR assessment only. The BICR-assessed PFS analysis will be identical to the investigator-assessed PFS analysis and will also be conducted for all randomized patients with detectable *PIK3CA*-mutant tumors, with patients grouped according to the treatment arm assigned at randomization.

The Kaplan-Meier method will be used to estimate median BICR-assessed PFS for each treatment arm. Cox proportional hazards models stratified by the three stratification factors from IxRS will be used to estimate the HR and its 95% CI.

4.4.2.6 Patient-Reported Outcomes

Patient-reported outcomes (PROs) of health-related quality of life (HRQoL), treatment-related symptoms (e.g., oral mucositis, diarrhea, skin problems), and patient functioning will be captured using the following questionnaires: the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the modified breast cancer module QLQ-BR23 (refer to the protocol for the questionnaires).

Completion rates, i.e., complete • 1 questions on EORTC QLQ-C30 and modified QLQ-BR23 separately, will be summarized at each time point by treatment arm for patients with detectable *PIK3CA*-mutant tumors.

The population for the below PRO analyses will be defined as all randomized patients who have completed the baseline assessment (Cycle 1, Day 1) and • 1 post-baseline assessment. "Completed" means • 50% of the constituent items from the subscales and items answered.

Summary statistics (mean, SD, median, 25th and 75th percentiles, range) of linear transformed scores (Fayers et al. 2001) will be reported for selected subscales of the EORTC QLQ-C30 and the modified QLQ-BR23 or each assessment time point. The change in the linear transformed scores from baseline (Cycle 1, Day 1) for selected subscales for each assessment time point will be summarized with the aforementioned summary statistics. Proportion of the patients with single items for oral mucositis and skin problems (items 44-47 of the modified EORTC QLQ-BR23) will be summarized for each assessment time point for each single item.

The HRQoL or global health scale (Items 29 and 30 of the EORTC QLQ-C30) will be used to assess time-to-deterioration (TTD). Deterioration of HRQoL or global health scale score is defined as a decrease of • 10 points from the baseline score (Cycle 1, Day 1) with no subsequent increase above this threshold. A 10-point change is defined as the minimally important difference (Osoba et al. 1998). Data for patients who have no definitive deterioration events will be censored at the time of the last PRO assessment prior to disease progression. The Kaplan• Meier method will be used to estimate median TTD for each treatment arm. Cox proportional hazards models stratified by the three stratification factors from IxRS will be used to estimate the HR and its 95% CI.

If more than one answer is provided to a single question at one visit, the answer provided earlier will be counted in the analysis.

Additional sensitivity analyses investigating disease and treatment-related symptoms may be conducted.

4.4.3 Exploratory Analyses

The following efficacy endpoints will be evaluated in the randomized patients without detectable *PIK3CA*-mutant tumors: investigator-assessed PFS, ORR, OS, CBR, and DOR, based on the same analysis methods described in Sections 4.4.1 and 4.4.2.

4.4.4 Sensitivity Analyses

A subsequent anti-cancer therapy for purposes of the sensitivity analysis is defined as any non• protocol specified treatment that the patient receives that is intended to treat her MBC prior to documented PD. A sensitivity analysis of investigator-assessed PFS for patients with detectable *PIK3CA*-mutant tumors will be performed, which censors

patient data at the last tumor assessment prior to initiation of subsequent anti-cancer therapy before PD.

4.4.5 Subgroup Analyses

Subgroup analyses (forest plot) of PFS and OS will be performed based on the stratification factors, demographics, and baseline prognostic factors.

4.5 PHARMACOKINETIC, PHARMACODYNAMIC, AND BIOMARKER ANALYSES

Taselisib plasma concentration versus time data will be tabulated and summarized. Additional analyses such as population pharmacokinetic analysis with covariate evaluation and assessment of exposure-response (i.e., efficacy, safety, and pharmacodynamics biomarkers) relationships may be conducted as appropriate. The results of these exploratory analyses will be reported separately from the CSR.

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 from the CSR.

4.6 SAFETY ANALYSES

Safety analyses will be performed for the safety population, regardless of the *PIK3CA* mutation status of their tumors, and for the subgroup of patients with and without detectable *PIK3CA*-mutant tumors, with patients allocated to the regimen actually received.

Safety endpoints will include incidence and severity, outcome and seriousness of adverse events, death, laboratory data, and vital signs.

4.6.1 Exposure of Study Medication

Study treatment exposure (such as treatment duration, number of doses, dose reduction, and dose intensity) will be summarized for each treatment arm with descriptive statistics.

4.6.2 Adverse Events

Verbatim descriptions of adverse events will be mapped to MedDRA thesaurus terms and will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v4.0). Treatment-emergent adverse events (i.e., all adverse events that occurred on or after first dose of study drug and within 28 days after the last dose of study drug and related serious adverse events reported 28 days after the last dose of study drug) will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events, severe adverse events (Grade • 3), adverse events of special interest, and adverse events leading to study drug discontinuation, interruption, or reduction will be summarized accordingly. Multiple occurrences of the same event for a patient will be counted once at the maximum severity.

All deaths reported, deaths reported within (i.e., less than or equal to) 28 days of last dose of study drug, and deaths reported after 28 days of last dose of study treatment will be summarized separately by treatment arm, including the reasons for the deaths.

4.6.3 Laboratory Data

Selected laboratory data such as fasting glucose level, absolute neutrophil count, hemoglobin level, platelet count, lymphocyte count, serum creatinine level, and liver function test results (AST and ALT) with values outside the normal ranges will be summarized by treatment arm. For the selected laboratories, toxicity grade shift from baseline will be summarized by treatment arm.

4.6.4 Vital Signs

Change from baseline in vital signs will be summarized by treatment arm and grade.

4.7 MISSING DATA

For the analysis of OS, data from patients who are alive at the time of the analysis data cutoff will be censored at the last date they are known to be alive. Data from patients without post-baseline information will be censored at the date of randomization.

For the analyses of PFS and DOR, data from patients who are lost to follow-up or without disease progression or death as of the clinical data cutoff date will be censored at the time of the last tumor assessment when the patient is known to be progression-free (i.e., an overall response other than “progressive disease” or “not evaluable”) or at the time of randomization if there is no post-baseline tumor assessment or all post-baseline tumor assessments have overall responses of “not evaluable.”

For the FDA, the primary efficacy analysis for investigator-assessed PFS will be censored additionally for patients experiencing a progression event preceded by two or more missing tumor assessments before the disease progression (i.e., the duration between the date of first documented PD deemed by investigator per RECIST v1.1 and the date of the last tumor assessment when the patient is known to be progression-free $>$ 122 days). These patients will be censored at the last tumor assessment prior to the missed visits that is known to be progression-free (i.e., an overall response other than “progressive disease,” or “not evaluable”) or at randomization if there is no post-baseline tumor assessment or all post-baseline tumor assessments have overall responses of “not evaluable” in between the randomization and the first documented PD per RECIST v 1.1.

For the analysis of ORR, patients with measurable disease at baseline but with no post-baseline tumor assessment or post-baseline tumor assessments that all have overall responses of “not evaluable” will be categorized as non-responders.

For the analysis of CBR, patients with no post-baseline overall response or post-baseline tumor assessments that all have overall responses of “not evaluable” will be considered to not experience clinical benefit.

For the EORTC QLQ-C30 and the modified breast cancer module QLQ-BR23 questionnaires, if • 50% of the constituent items are completed, a prorated score will be computed consistent with the scoring manuals and validation papers. For subscales with < 50% of the items completed, the subscale will be considered to be missing. If the additional items of the modified breast cancer module QLQ-BR23 (including oral mucositis and skin problems) have not been completed, they will be considered missing.

For the analysis of deterioration of HRQoL or global health scale, patients who have no definitive deterioration events (i.e., a decrease of • 10 points from the Cycle 1, Day 1 scale score with no subsequent increase above this threshold) will be censored at the time of the last PRO assessment prior to disease progression.

4.8 INTERIM ANALYSES

The iDMC will convene to review cumulative safety data approximately every 6 months. Data on serious adverse events, death, and adverse events of special interest will be monitored by the iDMC approximately every 3 months.

One efficacy and futility analysis for investigator-assessed PFS will be conducted in patients with detectable *PIK3CA*-mutant tumors when approximately 172 investigator-assessed PFS events (approximately 60% of the information, expected at approximately 23 months after FPI) have occurred in patients with *PIK3CA*-mutant tumors. Approximately 320 patients with detectable *PIK3CA*-mutant tumors and approximately 120 patients without detectable *PIK3CA*-mutant tumors will have been randomized into the study by the time of the interim analysis. The actual timing of the interim analysis and the number of patients randomized will depend on the accrual rate and actual accumulation of PFS events observed in the study.

The iDMC will review the efficacy while the Sponsor and investigators remain blinded to the treatment assignment.

The iDMC may recommend stopping the study for efficacy at the interim efficacy analysis of investigator-assessed PFS, when the two-sided p-value • $1.7 • 10^{-5}$, with approximately 172 investigator-assessed PFS events at the interim efficacy analysis. The • -spending function is specified as Gamma (• 16), which allocates two-sided • $= 1.7 • 10^{-5}$ at the interim efficacy analysis when approximately 172 PFS events are reached and preserves the two-sided 1% • -level at the final PFS analysis. The actual boundary will be adjusted based on the actual number of investigator-assessed PFS events at the interim analysis. If the iDMC recommends stopping the study for efficacy at the interim analysis and the Sponsor decides to stop the study, the study team will be

unblinded, and the investigators and patients will remain blinded to individual patient-level treatment assignment until the final OS analysis.

The iDMC may recommend stopping the study for futility at the interim efficacy analysis of investigator-assessed PFS when the observed PFS HR is above 0.85, which provides a probability of 85% to stop the study if the true PFS HR is 1.0 (i.e., no treatment benefit). The purpose of the futility analysis is not to stop the study for a positive (significant) efficacy PFS outcome. Therefore, statistical significance level for the primary analysis of PFS does not need to be adjusted for this futility analysis to maintain the overall type I error control.

Three interim analyses for OS are planned in patients with detectable *PIK3CA*-mutant tumors based on the cobas® *PIK3CA* Mutation Test. The timing, expected number of deaths, and decision boundary at each interim analysis are described in Section 4.4.2.2. The type I error is under strong control by using the generalized Haybittle-Peto method (Haybittle 1971).

No formal interim analysis is planned for patients without detectable *PIK3CA*-mutant tumors.

The responsibility, membership, and communication flow of the iDMC are specified in the iDMC charter.

5. CHINA SUBGROUP ANALYSIS

The clinical data from the China extension cohort will not be included in the global analysis (efficacy and safety). The China extension cohort data will be combined with Chinese patients' data from the global study and will be summarized in a separate report for the China subgroup.

All analyses described in this section will include all data from the China subgroup collected up to the time approximately 56 PFS events have occurred among the 150 Chinese patients with detectable *PIK3CA*-mutant tumors as defined in Section 2.5.

The analysis populations will be equally defined as per Section 4.1 but will only be based on patients who are residents of the People's Republic of China. Analyses of study conduct will be performed as described in Section 4.2. Summaries of demographics, disease history, baseline disease characteristics, and patient treatment history will be produced as described in Section 4.3.

Data from patients who are lost to follow-up or without disease progression or death as of the clinical data cutoff date for the China subgroup analysis will be censored at the time of the last tumor assessment when the patient is known to be progression-free (i.e., an overall response other than "progressive disease" or "not evaluable") or at the time of randomization if there is no post-baseline tumor assessment or all post-baseline

tumor assessments have overall responses of “not evaluable.” The unstratified Cox proportional hazards model will be used to estimate investigator-assessed PFS HR between the two treatment groups and its 95% CI. An unstratified two-sided log-rank test will provide a comparison for investigator-assessed PFS in this subgroup in a descriptive manner. Plots of the Kaplan-Meier estimate for investigator-assessed PFS will be produced, including medians and confidence limits.

Safety data for the China subgroup will be analyzed as described in Section 4.6.

6. REFERENCES

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Mauriac L, Romieu G, Bines J. Activity of fulvestrant versus exemestane in advanced breast cancer patients with or without visceral metastases: data from the EFECT trial. Breast Cancer Res Treat 2009;117:69• 75.

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Appendix 1
Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED STUDY OF TASELISIB PLUS FULVESTRANT VERSUS PLACEBO PLUS FULVESTRANT IN POSTMENOPAUSAL WOMEN WITH ESTROGEN RECEPTOR-POSITIVE AND HER2-NEGATIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER WHO HAVE DISEASE RECURRENCE OR PROGRESSION DURING OR AFTER AROMATASE INHIBITOR THERAPY**
PROTOCOL NUMBER:	GO29058
VERSION NUMBER:	3
EUDRACT NUMBER:	2014-003185-25
IND NUMBER:	121658
TEST PRODUCT:	Taselisib (RO5537381, GDC-0032)
PHASE:	III
INDICATION:	ER-positive/HER2-negative locally advanced or metastatic breast cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Efficacy Objectives

The primary efficacy objective for this study is as follows:

- To compare the efficacy between taselisib + fulvestrant versus placebo + fulvestrant as measured by investigator-assessed progression-free survival (PFS) in patients with *PIK3CA*-mutant tumors

The secondary efficacy objectives for this study are as follows:

- To compare the efficacy between taselisib + fulvestrant versus placebo + fulvestrant as measured by overall survival (OS) in patients with *PIK3CA*-mutant tumors
- To compare the overall objective response rate (ORR) between taselisib + fulvestrant versus placebo + fulvestrant in patients with *PIK3CA*-mutant tumors, on the basis of tumor assessments made by the investigator
- To estimate the duration of objective response (DOR) within taselisib + fulvestrant versus placebo + fulvestrant in patients with *PIK3CA*-mutant tumors, on the basis of tumor assessments made by the investigator
- *To compare the clinical benefit rate (CBR) between taselisib +fulvestrant versus placebo +fulvestrant in patients with PIK3CA-mutant tumors, on the basis of tumor assessments made by the investigator*

Appendix 1
Protocol Synopsis (cont.)

- *To compare the efficacy between taselisib +fulvestrant versus placebo +fulvestrant as measured by PFS determined by blinded independent central review (BICR) in patients with PIK3CA-mutant tumors*

Safety Objective

The safety objective for this study is to evaluate the safety of taselisib + fulvestrant versus placebo + fulvestrant in patients with locally advanced or metastatic breast cancer (MBC) in all randomized patients who receive at least one dose of taselisib/placebo or fulvestrant, regardless of the *PIK3CA*-mutation status of their tumors, and separately in the subgroups of patients with and without detectable *PIK3CA*-mutant tumors.

Pharmacokinetic Objective

The pharmacokinetic objective for this study is to evaluate the pharmacokinetics of taselisib when taken with fulvestrant

Patient-Reported Outcome Objective

The patient-reported outcome (PRO) objective for this study is as follows:

- To evaluate and compare PROs of treatment-related symptoms, patient functioning, and health-related quality-of-life (HRQoL) as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the modified Breast Cancer Module (QLQ-BR23) between the taselisib + fulvestrant versus placebo + fulvestrant treatment arms

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate the PFS, ORR, *CBR,* and DOR of taselisib + fulvestrant versus placebo + fulvestrant in patients with locally advanced or MBC where a *PIK3CA* mutation was not detected
- To evaluate PFS, ORR, *CBR,* and DOR of taselisib + fulvestrant versus placebo + fulvestrant in patients with locally advanced or MBC whose tumor *PIK3CA*-mutation status is determined by plasma DNA analysis
- To explore the potential relationship between pharmacogenetic differences in drug-metabolizing enzymes, transporters, and other patient-specific covariates with pharmacokinetics and safety of taselisib when administered in combination with fulvestrant in patients with locally advanced or MBC
- To explore the potential taselisib exposure-response (efficacy and safety) relationship in patients with locally advanced or MBC receiving taselisib in combination with fulvestrant
- To explore fulvestrant concentrations in patients with locally advanced or MBC who receive fulvestrant alone or in combination with taselisib
- To evaluate predictive and prognostic plasma or tissue biomarkers associated with disease activity status or response to treatment
- To identify possible mechanisms of resistance to fulvestrant + taselisib through the comparative analysis of potential biomarkers in the pretreatment and post-progression biopsy tissue samples and in blood
- To assess health status as measured using the EuroQol 5-Dimension Questionnaire (EQ-5D) for health economic modeling

Appendix 1
Protocol Synopsis (cont.)

Study Design

Description of Study

Study GO29058 *(SANDPIPER)* is a Phase III, randomized, multicenter, international, double-blind, placebo-controlled clinical study designed to compare the efficacy, as measured by PFS, and safety of fulvestrant + taselisib with that of fulvestrant + placebo after recurrence or progression following treatment with an AI for patients with ER+, HER2-negative, *PIK3CA*-mutant, unresectable, locally advanced or MBC. *PIK3CA*-mutation status in all patients will be assessed by a central laboratory using the cobas® *PIK3CA* mutation test. In order to explore efficacy and differential benefit-risk in patients without a detectable *PIK3CA* mutation, 120 patients belonging to this category *are planned for enrollment.*

Study GO29058 will consist of a global study that will provide the evidence to determine the benefit-risk of taselisib plus fulvestrant in the target population; a possible extension cohort may continue to enroll only in China to meet local regulatory requirements.

In the global study, approximately 600 patients will be randomized in a 2:1 ratio to either fulvestrant + taselisib or fulvestrant + placebo *unless the independent Data Monitoring Committee (iDMC) recommends stopping the study early and the Sponsor accepts the iDMC's recommendation. Patients whose tumors contain a PIK3CA-mutation (n = 480) and patients whose tumors do not contain a detectable PIK3CA-mutation (n = 120) will be randomized separately. After the global enrollment closes, additional Chinese patients may continue to be recruited into the China extension cohort. A total of up to 150 Chinese patients with detectable PIK3CA-mutant tumors may be enrolled as part of the global study population and extension cohort combined. Patients enrolled as part of the China extension cohort will also be randomized in a 2:1 ratio to either fulvestrant + taselisib or fulvestrant + placebo.*

Number of Patients

Approximately 600 patients are planned for enrollment. *After the global enrollment closes, additional Chinese patients may continue to be recruited into the China extension cohort. A total of up to 150 Chinese patients with detectable PIK3CA-mutant tumors may be enrolled as part of the global study population and extension cohort combined.*

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

Disease-Specific Inclusion Criteria

- Women with histologically or cytologically confirmed invasive, ER+ breast cancer: metastatic or inoperable (not amenable to resection or other local therapy with curative intent) locally advanced breast cancer
- Patients for whom endocrine therapy (e.g., 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.
- Radiologic/objective evidence of recurrence or progression to the most recent systemic therapy for breast cancer
- Radiologic/objective evidence of breast cancer recurrence or progression while on or within 12 months of the end of adjuvant treatment with an AI, or progression while on or within 1 month of the end of prior AI treatment for locally advanced or MBC. The AI (letrozole, anastrozole, or exemestane) does not have to be the most recent treatment before randomization.
- Measurable disease via RECIST v1.1 or non-measurable, evaluable disease with at least one evaluable bone lesion via RECIST v1.1. Bone lesions that have been irradiated are not evaluable.

Appendix 1
Protocol Synopsis (cont.)

General Inclusion Criteria

- Able and willing to provide written informed consent and to comply with the study protocol
- Age • 18 years
- ECOG Performance Status of 0 or 1
- Postmenopausal status defined as one of the following:

  Age • 60 years

  Age < 60 years and postmenopausal as defined by documented follicle-stimulating hormone and estradiol in the postmenopausal ranges in addition to being amenorrheic for 12 months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression

  Prior bilateral oophorectomy (• 28 days prior to first fulvestrant treatment on Cycle 1 Day 1)
- Consent to provide a formalin-fixed paraffin-embedded (FFPE) tissue block (preferred) or a minimum of 20 (25 preferred) freshly cut unstained tumor slides from the most recently collected, available tumor tissue for *PIK3CA*-mutation testing and for other protocol-mandated exploratory assessments
- A valid cobas *PIK3CA* mutation result (per central testing) is required for all patients (e.g., patients with an "invalid" or "failed" *PIK3CA* mutation result are not permitted to enroll)

  After 120 patients whose breast cancers have a "wild-type" (mutation not detected result) *PIK3CA* status have been enrolled, all remaining enrolled patients must have a breast cancer sample that tests positive for *PIK3CA* mutation to be eligible.
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 28 days prior to Cycle 1 Day 1:

  ANC • 1500/• L (1.5 • 10^9/L)

  Platelet count • 100,000/• L (100 • 10^9/L)

  Hemoglobin • 9.0 g/dL (90 g/L)

  Total bilirubin • 1.5 • upper limit of normal (ULN) except in patients with previously documented Gilbert's syndrome, in which case total bilirubin • 3 mg/dL

  AST and ALT• 1.5 • ULN, with the following exceptions:

  Patients with documented liver metastases: AST and/or ALT • 5.0 • ULN

  Serum creatinine • 1.5 • ULN or creatinine clearance • 50 mL/min based on Cockcroft• Gault glomerular filtration rate estimation

$$\frac{(140 - \text{age}) \bullet (\text{weight in kg}) \bullet (0.85 \text{ if female})}{72 \bullet (\text{serum creatinine})}$$

  INR < 1.5 and aPTT (or PTT) < 1.5 • ULN; for patients requiring therapeutic anticoagulation therapy, a stable INR • 2.5
- Fasting glucose • 125 mg/dL (6.94 mmol/L)
- *For enrollment into the China extension cohort, residence in the People's Republic of China*

Exclusion Criteria

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

Disease-Specific Exclusion Criteria

- HER2-positive disease by local laboratory testing (IHC 3+ staining or in situ hybridization positive)
- Prior treatment with fulvestrant

- Prior treatment with a PI3K inhibitor, mTOR inhibitor (such as everolimus), or AKT inhibitor.
- Prior anti-cancer therapy within 2 weeks prior to Cycle 1 Day 1
- Prior radiation therapy within 2 weeks prior to Cycle 1 Day 1
- All acute treatment-related toxicity must have resolved to Grade • 1 or be deemed stable by the investigator
- Prior treatment with > 1 cytotoxic chemotherapy regimen for MBC
- Symptomatic hypercalcemia requiring continued use of bisphosphonate or denosumab therapy

  Use of bisphosphonate therapy or denosumab for other reasons (e.g., bone metastasis, osteoporosis, etc.) is allowed
- Concurrent hormone replacement therapy
- Known untreated or active CNS metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control); a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain will be performed at screening if required by the local health authority

  Patients with a history of treated CNS metastases are eligible, provided they meet all of the following criteria:

  Evaluable or measurable disease per inclusion criteria outside the CNS is present.

  Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

  No history of intracranial hemorrhage or spinal cord hemorrhage

  Minimum of 2 weeks between completion of radiotherapy and Cycle 1 Day 1 and recovery from significant (Grade • 3) acute toxicity with no ongoing requirement for • 10 mg of prednisone per day or an equivalent dose of other corticosteroid
- History of other malignancy within the previous 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or patients who have undergone potentially curative therapy with no evidence of disease and are deemed by the treating physician to be at low risk for recurrence

General Exclusion Criteria

- Type 1 or Type 2 diabetes mellitus requiring anti-hyperglycemic medications
- Clinically significant cardiac or pulmonary dysfunction, including the following:

  Current uncontrolled Grade • 2 hypertension or unstable angina

  Symptomatic congestive heart failure or serious cardiac arrhythmia requiring treatment, with the exceptions of atrial fibrillation and paroxysmal supraventricular tachycardia or a conduction abnormality that has been treated and for which the patient is no longer at risk for serious arrhythmia (e.g., Wolff-Parkinson-White syndrome treated with surgical ablation)
- Current dyspnea at rest or any requirement for supplemental oxygen therapy to perform activities of daily living
- History of malabsorption syndrome or other condition that would interfere with enteral absorption
- Inability or unwillingness to swallow pills or receive intramuscular injections
- Clinically significant history of liver disease, including cirrhosis, current alcohol abuse, or current known active infection with HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV)

Active infection is defined as requiring treatment with antiviral therapy or presence of positive test results for hepatitis B (hepatitis B surface antigen and/or total hepatitis B core antibody) or HCV antibody. Unless required by local regulations, patients are not required to have HIV, HBV, or HCV assessments at screening if these assessments have not been previously performed.

Patients who test positive for hepatitis B core antibody are eligible only if test results are also positive for hepatitis B surface antibody and polymerase chain reaction (PCR) is negative for HBV DNA.

Patients who are positive for HCV serology are only eligible if testing for HCV RNA is negative.

- History of inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis)
- Active bowel inflammation (e.g., diverticulitis)
- Immunocompromised status due to current known active infection with HIV or because of the use of immunosuppressive therapies for other conditions
- Need for current chronic corticosteroid therapy (• 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids)

  Stable use (i.e., no change in dose within 3 months prior to Cycle 1 Day 1) of inhaled corticosteroids is allowed.
- Pregnancy, lactation, or breastfeeding
- Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic or infectious disease)
- Major surgical procedure or significant traumatic injury within 28 days prior to Cycle 1 Day 1 or anticipation of the need for major surgery during the course of study treatment
- Inability to comply with study and follow-up procedures
- Inability to understand the local language(s) for which the EORTC QLQ-C30, the modified Breast Cancer module QLQ-BR23, and the EQ-5D questionnaires are available

Length of Study

The enrollment duration will be driven by enrollment of patients with *PIK3CA*-mutant tumors and is projected to be approximately 28 months (after first patient enrolled). The last PFS event (the 287th PFS event) for the *final* PFS analysis in patients with *PIK3CA*-mutant tumors is projected to occur approximately *29* months after the first patient is enrolled.

End of Study

The *global* study will be considered completed when approximately 330 deaths in patients with *PIK3CA*-mutant tumors have been reported and the final analysis of OS is completed or when the Sponsor decides to stop the study.

Outcome Measures

Efficacy Outcome Measures

The efficacy outcome measures for this study are as follows:

- *Investigator-assessed* PFS, defined as the time from randomization to the first occurrence of disease progression, as determined with the use of Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or death from any cause (whichever occurs earlier)
- Objective response (PR + CR) as determined by using RECIST v1.1
- OS, defined as the time from randomization to death from any cause
- Clinical benefit, defined as objective response or *no disease progression* lasting for • 24 weeks since randomization

- DOR, defined as the time from the first occurrence of a documented objective response to the time of the first documented disease progression, as determined by the investigator using RECIST v1.1, or death from any cause (whichever occurs earlier)
- *BICR-assessed PFS, defined as the time from randomization to the first occurrence of disease progression, as determined by the BICR with the use of RECIST v1.1, or death from any cause (whichever occurs earlier)*

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, type, and severity of adverse events (based on the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 [NCI CTCAE v4.0])
- Incidence, type, and severity of serious adverse events
- Incidence of adverse events leading to study treatment discontinuation, modification, or interruption
- Abnormal laboratory values
- Death and cause of death

Pharmacokinetic Outcome Measure

The pharmacokinetic (PK) outcome measure for this study is:

- Taselisib PK parameters including but not limited to plasma C_{max} and minimum plasma concentration under steady-state conditions within a dosing interval

Patient-Reported Outcome Measure

The PRO measure for this study is as follows:

- HRQoL, including treatment-related symptoms (e.g., oral mucositis, diarrhea, skin problems) and patient functioning, as measured by the EORTC QLQ–C30 and the modified QLQ-BR23 breast cancer module

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Correlation of efficacy with molecular markers related to the mechanism of action of taselisib and endocrine therapy that include the following:
    - Alterations in DNA and RNA, including DNA mutational status, RNA expression levels, DNA copy number and protein expression
    - Alteration in tumor tissue biomarkers including but not limited to PTEN
    - Assessment of PI3K pathway status (e.g., *PIK3CA* mutation status) in ctDNA from peripheral blood, as well as additional cancer related mutations (e.g., *ESR1*)
    - Cancer-related plasma biomarkers including assessment of cytokines and chemokines
- Association between genetic polymorphisms of drug metabolic enzymes or transporters and taselisib pharmacokinetics
- Fulvestrant concentration in the presence and absence of taselisib
- Genetic variants and association with drug-related safety assessments, including but not limited to HLA

Appendix 1
Protocol Synopsis (cont.)

Investigational Medicinal Products

Test Product

The test product for this study is taselisib. The taselisib tablet is a white to off-white, film coated, immediate release formulation of 2-mg strength. The taselisib 4-mg dose will be taken orally (PO) once a day (QD). Taselisib is formulated as 2-mg tablets, so patients will take two 2-mg tablets daily to receive a 4-mg dose. Taselisib will be administered in the clinic on Cycle 1 Day 1 and Cycle 1 Day 15 and on each subsequent day that a cycle visit is scheduled, after the predose assessments and procedures, and after the fulvestrant administration (except for Cycle 2 Day 15). Taselisib will be administered at home on all non-clinic visit days. Patients should take the taselisib dose at the same approximate time each day without regard to the timing of administration of food. If a dose is missed (not taken within 6 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.

Placebo

The taselisib placebo (corresponding to a 4-mg dose) will be two tablets taken PO QD. Taselisib placebo will be administered in the clinic on Cycle 1 Day 1 and Cycle 1 Day 15 and on each subsequent day that a cycle visit is scheduled, after the predose assessments and procedures, and after the fulvestrant administration (except for Cycle 2 Day 15). Taselisib placebo will be administered at home on all non-clinic visit days. Taselisib placebo should be taken at the same approximate time each day without regard to the timing of administration of food. If a dose is missed (not taken within 6 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.

Background Therapy

Fulvestrant will be supplied by the Sponsor per country-specific requirements. 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. Fulvestrant 500 mg will be administered in the clinic (before administration of taselisib or placebo) as two intramuscular injections of 250 mg each on Cycle 1 Days 1 and 15 and Day 1 of each subsequent 28-day cycle.

Non-Investigational Medicinal Products

None.

Statistical Methods

Primary Analysis

The primary efficacy endpoint is investigator-assessed PFS (PFS in this document refers to investigator-assessed PFS, unless stated otherwise). The primary efficacy analysis population will include all randomized patients with *PIK3CA*-mutant tumors. The primary efficacy endpoint, PFS, and the secondary efficacy endpoints will be analyzed in this population as the primary and the secondary objectives.

In addition, these efficacy endpoints, unless otherwise specified, will be analyzed in all randomized patients without detectable *PIK3CA*-mutant tumors at the same time as the analyses are conducted for the patients with *PIK3CA*-mutant tumors.

PIK3CA-mutant tumor status will be determined by the cobas *PIK3CA* mutation test of the patient's tissue sample.

The primary PFS analysis will be conducted in all randomized patients with *PIK3CA*-mutant tumors, with patients grouped according to the treatment arm assigned at randomization.

An interim efficacy analysis will be conducted *for investigator-assessed PFS at* the time *of 172 investigator-assessed* PFS events *(expected 21 months after the first patient is enrolled), and the final efficacy analysis will be conducted at the time 287 investigator-assessed PFS events (expected 29 months after the first patient is enrolled)* are observed in patients with

PIK3CA-mutant tumors. *The •-spending function is specified as Gamma (-16), which allocates two-sided • =1.7 • 10-5 at the interim efficacy analysis of investigator-assessed PFS, when 172 PFS events have occurred and preserves the two-sided 1% •-level at the final PFS analysis. The exact boundary will be calculated on the basis of the exact number of PFS events observed at the interim analysis. The associated minimal detectable difference for the investigator-assessed PFS hazard ratio at the interim efficacy analysis is 0.5 (i.e., 100% improvement in median investigator-assessed PFS from 4.5 months in the control arm to 9 months in the treatment arm).*

An exploratory analysis for *investigator-assessed* PFS will also be conducted in all randomized patients without detectable *PIK3CA*-mutant tumors at the time *of the primary PFS analysis in all randomized patients with PIK3CA-mutant tumors*.

Data for patients without the occurrence 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 if no tumor assessment was performed after the baseline visit).

Determination of Sample Size

The *global* study plans to enroll approximately 600 patients, including 480 patients with detectable *PIK3CA*-mutant tumors, and 120 patients without detectable *PIK3CA*-mutant tumors (tumor status determined by the cobas *PIK3CA* mutation test).

After the global enrollment closes, additional Chinese patients may continue to be recruited into the China extension cohort. A total of up to 150 patients with detectable PIK3CA-mutant tumors may be enrolled as part of the global study population and the China extension cohort combined.

The sample size of 480 patients with *PIK3CA*-mutant tumors is determined on the basis of the power calculation for the PFS and the OS endpoints, whichever requires a larger sample size. In this case, the sample size is driven by OS.

In 480 patients with *PIK3CA*-mutant tumors, approximately 287 investigator-assessed PFS events will be required to detect a hazard ratio of 0.59 in PFS (3.1 months of improvement in median PFS) with 95% power at the a two-sided significance level of 1%, assuming a median PFS of 4.5 months in the control arm (Mauriac et al. 2009; Johnston et al. 2013). *One interim efficacy analysis of investigator-assessed PFS will be conducted at 60% of PFS. The •-spending function specified as Gamma (-16), which allocates two-sided • =1.7 • 10-5 at the interim efficacy analysis of investigator-assessed PFS, when 172 investigator-assessed PFS events have occurred.* The minimal detectable difference for *investigator-assessed* PFS hazard ratio *at final PFS analysis* is 0.72 (i.e., 39% improvement in median investigator-assessed PFS from 4.5 months in the control arm compared with 6.2 months in the treatment arm), *when 287 investigator-assessed PFS events have occurred*.

With the aforementioned sample size of 480 patients with *PIK3CA*-mutant tumors, the OS analyses in this population will require 330 deaths to detect an hazard ratio of 0.7 in OS (11.1 months of improvement in median OS) with 80% power at a two-sided significance level of 5%, assuming a median OS of 26 months in the control arm based on the OS of 26.4 months in patients treated with 500 mg fulvestrant in the CONFIRM study, which investigated 500 mg fulvestrant versus 250 mg fulvestrant in a similar patient population (Di Leo et al. 2014).

The study plans to enroll 120 patients who do not have a detectable *PIK3CA*-mutant tumor, on the basis of the result of the cobas *PIK3CA* mutation test, to evaluate the clinical benefit in this population. If the observed hazard ratio in *investigator-assessed* PFS is 1 (no benefit), approximately 111 *investigator-assessed* PFS events will be observed at the analysis, and the 90% confidence interval will exclude a true hazard ratio < 0.72 (i.e., $>$ 1.8-month improvement in median PFS).

In total, approximately 400 patients will be treated with the combination of taselisib + fulvestrant in this study (320 patients with *PIK3CA*-mutant tumors and 80 patients without detectable *PIK3CA*-mutant tumors), which will enable the Sponsor to better characterize any rare but clinically significant safety events (e.g., for an adverse event with 4% frequency, there is 96% probability to observe • 10 patients with such adverse event on the basis of

400 taselisib + fulvestrant-treated patients) to help enable the development of effective toxicity prevention and management guidelines for patients treated with the combination of taselisib and fulvestrant.

Interim Analyses

The iDMC will convene to review cumulative safety data approximately every 6 months. Data on serious adverse events, death, and adverse events of special interest will be monitored by the iDMC approximately every 3 months.

One *efficacy and one* futility analysis for *investigator-assessed* PFS will be conducted in the patients with *PIK3CA*-mutant tumors when approximately 172 (60% of the information, expected at *21* months after the first patient is enrolled) investigator-assessed PFS events have occurred in patients with *PIK3CA*-mutant tumors. Approximately *320* patients with *PIK3CA*-mutant tumors and *approximately* 120 patients without detectable *PIK3CA*-mutant tumors will have been randomized into the study by the time of the *interim* analysis. The actual timing of the *interim* analysis and the number of patients randomized will depend on the accrual rate and actual accumulation of PFS events observed in the study.

The iDMC will review the efficacy data *, while the Sponsor and investigators remain blinded to the treatment assignment until the iDMC recommends stopping the study for efficacy or futility at the specified interim analysis and the Sponsor decides to stop the study.*

The iDMC may recommend stopping the study for *efficacy at the interim efficacy analysis of investigator-assessed PFS, when the two-sided p-value • 1.7 • 10^{-5}, with approximately 172 investigator-assessed PFS events at the interim efficacy analysis. The •-spending function specified as Gamma (-16), which allocates two-sided • = 1.7 • 10^{-5} at the interim efficacy analysis, when approximately 172 PFS events are reached and preserves the two-sided 1% •-level at the final PFS analysis. The actual boundary will be adjusted based on the actual number of investigator-assessed PFS events at IA. Should the iDMC recommend stopping the study for efficacy at interim analysis and the Sponsor decides to stop the study, the study team will be unblinded, and the investigators and patients will remain blinded to individual patient-level treatment assignment until the final OS analysis.*

The iDMC may recommend stopping the study for futility at the interim efficacy analysis of investigator-assessed PFS, when the observed PFS hazard ratio is above 0.*85*, which provides a probability of *approximately 85*% to stop the study if the true PFS hazard ratio is 1.0 (i.e., no treatment benefit). The purpose of the futility analysis is not to stop the study for a positive (significant) efficacy PFS outcome. Therefore, statistical significance level for the *interim or final efficacy* analysis of PFS does not need to be adjusted for this futility analysis. The overall type I error is under strong control.

Three interim analyses for OS are planned in patients with *PIK3CA*-mutant tumors on the basis of the cobas *PIK3CA* mutation test. The type I error is under strong control by using the Generalized Haybittle-Peto method.

No formal interim analysis is planned for the patients without detectable *PIK3CA* mutations.

The responsibility, membership, and communication flow of the iDMC are specified in the iDMC Charter.

Appendix 2
Schedule of Assessments

	Screening [a]	Cycle 1		Cycle 2		Cycles • 3	Cycles • 3	Study Drug Discontinuation Visit [c]	Post• Progressive Disease Assessment	Follow-Up [d]
Day (Window)	• 28 to • 1	1	15 (+2) [b]	1 (+2) [b]	15 (±2)	1 (±3)	15 (±3)	(within • 28 days after last dose)		(every 3 months ±7 days)
Informed consent	x									
Medical history and demographic data [e]	x									
Concomitant medications [f]	x	x	x	x	x	x		x		
Adverse events [g]	x	x	x	x	x	x	x [h]	x		x
Vital signs [i]	x	x	x	x	x	x		x		
Oxygen saturation (pulse oximetry)	x	x	x	x	x	x		x		
Complete physical examination, weight [j]	x									
Limited physical examination, weight [k]		x	x	x	x	x		x		
ECOG Performance Status	x	x	x	x	x	x		x		
Single 12-lead ECG [z]	x	As clinically indicated						x		
Tumor assessment [l]	x	Every 8 weeks (±5 days) regardless of dose delay or early discontinuation until disease progression							x	x
Bone scan and/or skeletal X-rays [m]	x	Per clinical indication or to confirm a complete response [m]								

Appendix 2
Schedule of Assessments (cont.)

	Screening [a]	Cycle 1		Cycle 2		Cycles • 3	Cycles • 3	Study Drug Discontinuation Visit [c]	Post• Progressive Disease Assessment	Follow-Up [d]
Day (Window)	• 28 to • 1	1	15 (+2) [b]	1 (+2) [b]	15 (±2)	1 (±3)	15 (±3)	(within • 28 days after last dose)		(every 3 months ±7 days)
CBC with differential and platelets [n]	x	x	x	x	x	x		x		
Fasting blood chemistry [o]	x	x	x	x	x	x		x		
HbA_{1c}	x							x		
Coagulation (INR, aPTT [or PTT])	x	As clinically indicated Patients taking warfarin or its equivalent: twice in the first week of administration, then weekly for 3 weeks, and then as clinically necessary								
Fasting lipid profile [p]	x	x				x		x		
Urinalysis [q]	x	As clinically indicated								
Archival FFPE tumor tissue [r]	x									
Tumor biopsy sample at progression [s]		Collected following disease progression after the patient signs the optional informed consent								
Plasma sample: Somatic tumor mutations	See Appendix 2 in the protocol									
Pharmacogenetic sample										
Blood sample for NGS										
Plasma sample: exploratory biomarkers										

Appendix 2
Schedule of Assessments (cont.)

	Screening [a]	Cycle 1		Cycle 2		Cycles • 3	Cycles • 3	Study Drug Discontinuation Visit [c] (within • 28 days after last dose)	Post• Progressive Disease Assessment	Follow-Up [d] (every 3 months ±7 days)
Day (Window)	• 28 to • 1	1	15 (+2) [b]	1 (+2) [b]	15 (±2)	1 (±3)	15 (±3)			
Optional RCR sample (blood for DNA extraction)										
PRO assessments [t]		x		x		x		x	x	x
Fulvestrant administration [u]		x	x	x		x				
Taselisib/placebo, administration in the clinic [v]		x	x	x	x	x				
Pharmacokinetic assessments [w]		See Appendix 2 in the protocol								
Drug accountability			x	x	x	x		x		
Anticancer therapies given after discontinuation of study treatment								x		x
Follow-up assessment for survival [x]										x

CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D = EuroQol 5-Dimension Questionnaire; FFPE = formalin-fixed paraffin-embedded; HbA_{1c} = glycosylated hemoglobin; MRI = magnetic resonance imaging; NGS = next-generation sequencing; PRO = patient-reported outcomes; QLQ-BR23 = Quality of Life Questionnaire Breast Cancer Module; QLQ-C30 = Quality of Life Questionnaire Core 30; RCR = Roche Clinical Repository.

Appendix 2
Schedule of Assessments (cont.)

Notes: Assessments scheduled on the day of study drug administration in the clinic (e.g., Cycle 2, Day 1) should be performed prior to study drug administration, unless otherwise noted. Visits are based on a 28-day cycle. If the timing of a protocol-mandated procedure coincides with a holiday and/or weekend that preclude the procedure within the allotted window, the procedure should be performed on the nearest following date. Patients should receive their first dose of study treatment on the day of randomization if possible, but no later than 5 business days after randomization.

[a] Results of screening tests or examinations performed as standard of care prior to obtaining informed consent and within 28 days prior to randomization may be used rather than repeating required tests. Note that standard of care tumor and laboratory assessments should be done within 28 days prior to Cycle 1, Day 1.

[b] The window for Cycle 1, Day 15 and Cycle 2, Day 1 assessment is +2 days since fulvestrant administration should not occur prior to Cycle 1, Day 15 or Cycle 2, Day 1 (Day 29).

[c] The visit at which disease progression is recorded may serve as the study drug discontinuation visit, provided that all tests required at the study drug discontinuation visit are performed. *If study treatment had been interrupted for >28 days before the decision to permanently discontinue all study treatment and the study drug discontinuation visit can no longer occur within • 28 days after the last dose of study treatment, the visit should be performed as soon as possible after permanent study drug discontinuation.*

[d] Only serious adverse events considered to be related to study medication should be reported. Patients will also be followed for survival and subsequent anti-cancer therapies approximately every 3 months.

[e] Medical history includes clinically significant diseases within the previous 5 years before Cycle 1 Day 1, smoking history, breast cancer history (including tumor characteristics such as hormone receptor status, prior cancer therapies, surgeries, and procedures). Demographic data include age, sex, and self-reported race/ethnicity.

[f] Concomitant medications include prescription medication, over-the-counter preparations, and herbal or homeopathic remedies and supplements used within 7 days prior to the screening visit through the study drug discontinuation visit. After this visit, only medications administered for ongoing or new treatment-related adverse events will be collected.

[g] 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 28 days after the last dose of study drug. After this period, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior treatment with study drug. 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.

Appendix 2
Schedule of Assessments (cont.)

[h] Phone call from the site to the patient to assess adverse events as in footnote g. The rationale for this phone call is that some adverse events have a delayed onset (e.g., diarrhea), and follow-up that is more frequent than the visit, which is every 4 weeks, will be useful in management.

[i] Vital signs include measurements of respiratory rate, pulse, systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

[j] Complete physical examination should include the evaluation of head, eye, ear, nose, and throat and cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems and measurement of weight and height (height is measured at the screening visit only). Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

[k] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[l] Perform tumor assessments at screening (within 28 days prior to Cycle 1 Day 1), every 8 weeks (±5 days) from date of randomization, and when clinically indicated for all patients including those with bone-only disease. This schedule is to be maintained and will not be shifted for treatment delays. Screening assessments must include CT scans of the chest, abdomen, and pelvis; CT scans of the neck and brain imaging should be included if clinically indicated. A documented standard-of-care tumor assessment performed within 28 days before Cycle 1 Day 1 may be used for the screening assessment, provided it meets the above requirements. The same imaging method used at screening must be used throughout the study. Response assessments will be performed by the investigator, on the basis of physical examinations and imaging scans, through the use of RECIST Version 1.1. Patients who are discontinued from study treatment for reasons other than disease progression will be asked to continue to have tumor assessments every 8 weeks (±5 days) until disease progression. Patients who are discontinued from study treatment because of disease progression will be asked to return for a repeat tumor assessment 4• 6 weeks after experiencing disease progression. In addition, bone disease identified on bone imaging must be evaluated radiographically by CT scan, MRI, or X-ray. The same modality used at screening should be used throughout the study.

[m] An isotope bone scan (e.g., technetium) and/or skeletal X-rays will be performed at screening and should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the development of new bone lesions or for confirmation of complete response for all patients. For patients with bone-only disease not visible on CT or MRI scans *or X-ray at baseline)*, bone scans should be repeated every 8 weeks (±5 days) from the date of randomization and when clinically indicated until disease progression.

[n] Includes RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, bands [optional], eosinophils, basophils, lymphocytes, and monocytes), and platelet count. Reporting the differential as absolute counts is preferred, but percent is accepted. Laboratory samples are required at screening (within 28 days prior to Cycle 1, Day 1). If screening laboratory samples are drawn within 2 days prior to Cycle 1, Day 1, they do not have to be repeated on Cycle 1, Day 1. All other predose laboratory samples may also be drawn within 2 days prior to the cycle visit.

Appendix 2
Schedule of Assessments (cont.)

[o] Fasting (• 8 hours) blood chemistry includes glucose, BUN (or urea), creatinine, sodium, potassium, magnesium, bicarbonate, chloride, calcium, phosphorus, total protein, albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase. Laboratory samples are required at screening (within 28 days prior to Cycle 1, Day 1). If screening laboratory samples are drawn within 2 days prior to Cycle 1, Day 1, they do not have to be repeated on Cycle 1, Day 1. All other predose laboratory samples may also be drawn within 2 days prior to the cycle visit.

[p] Fasting (• 8 hours) lipid profile should be performed at screening (within 28 days prior to Cycle 1, Day 1), and on Day 1 of Cycles 1 and 3 and every 3 cycles thereafter and include total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, amylase, and lipase. If screening laboratory samples are drawn within 2 days prior to Cycle 1, Day 1, they do not have to be repeated on Cycle 1, Day 1. All other predose laboratory samples may also be drawn within 2 days prior to the cycle visit.

[q] Specific gravity, pH, glucose, protein, ketones, and blood.

[r] Archival tumor tissue blocks or a minimum of 20 (25 preferred) freshly cut unstained slides from the most recent tumor tissue will be collected at screening for molecular characterization of the tumor tissue including but not limited to *PIK3CA* mutation. If a tissue sample from the site(s) of metastasis was collected to meet enrollment criteria, a minimum of five additional formalin-fixed paraffin-embedded tissue slides of the primary lesion should be provided, if available.

[s] Tumor biopsy collection at the time of disease progression is not required for study participation but is strongly recommended and will be collected for patients who sign the Optional Research Informed Consent Form.

[t] The PRO questionnaires (EORTC QLQ-C30, modified QLQ-BR23) and EQ-5D will be completed by the patients at the investigational site during treatment. All questionnaires must be administered prior to any other study assessment(s), health care provider interaction, and administration of study drug, to ensure that the validity of the instrument is not compromised and that data quality meets regulatory requirements. Patients who are discontinued from study treatment for reasons other than disease progression will be asked to continue to complete the PRO assessments approximately every 8 weeks (±5 days) until disease progression. Additionally, all patients will also complete the PRO measures once at 4• 6 weeks (±5 days) and once at 12 weeks (±7 days) after disease progression.

[u] Fulvestrant will be administered in the clinic (before administration of taselisib/placebo) as two intramuscular injections of 250 mg each on Days 1 and 15 of Cycle 1 and Day 1 of each subsequent 28-day cycle.

Appendix 2
Schedule of Assessments (cont.)

[v] Taselisib/placebo will be taken orally once daily beginning at Cycle 1, Day 1. Taselisib/placebo will be administered in the clinic on Cycle 1, Day 1 and Cycle 1, Day 15 and on each subsequent day that a cycle visit is scheduled, after the predose assessments and procedures, and at home on all non-clinic visit days. During clinic visits, taselisib/placebo will be administered after the fulvestrant injections (except for Cycle 2, Day 15). A sufficient number of taselisib/placebo tablets will be provided to last until the next visit, or, at the investigator's discretion, to last until the next administration of fulvestrant. Extra tablets may be dispensed if there is a reasonable possibility that the patient's next visit may be delayed (e.g., because of inclement weather or distance between the patient's home and study center). Patients will also receive a medication diary. Instruct the patient to record the time and date she takes each treatment dose in the diary and to return all unused tablets at each study visit, to assess compliance. Collect and review medication diary and unused tablets and assess compliance at each subsequent visit. At the study drug discontinuation visit, do not dispense any additional study drug tablets or provide a new medication diary.

[w] Taselisib plasma samples may be used for exploratory pharmacokinetics, metabolism, biomarker and/or safety analyses, which may include determination of fulvestrant concentration.

[x] All patients who discontinue from the treatment phase will be followed for survival information unless the patient requests to be withdrawn from study-survival follow-up. Survival follow-up information will be collected via telephone calls, patient's medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, or study termination by the Sponsor.

[z] An ECG (12-lead) is required at screening and may be repeated during the study as clinically indicated. All ECG recordings should be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. 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. Clinically significant abnormalities observed during screening will be recorded on the General Medical History and Baseline Conditions eCRF. New or worsened clinically significant abnormalities will be recorded on the Adverse Event eCRF.