Official Title: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Inavolisib Plus Palbociclib and Fulvestrant Versus Placebo Plus Palbociclib and Fulvestrant in Patients With PIK3CA-Mutant, Hormone Receptor-Positive, HER2-Negative, Locally Advanced or Metastatic Breast Cancer

NCT Number: NCT04191499

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STATISTICAL ANALYSIS PLAN

STUDY TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF INAVOLISIB PLUS PALBOCICLIB AND FULVESTRANT VERSUS PLACEBO PLUS PALBOCICLIB AND FULVESTRANT IN PATIENTS WITH PIK3CA-MUTANT, HORMONE RECEPTOR–POSITIVE, HER2-NEGATIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER**
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PLAN PREPARED BY:	[redacted] MMath

STATISTICAL ANALYSIS PLAN APPROVAL

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DATE FINAL:	See electronic date stamp on the last page of this document

STATISTICAL ANALYSIS PLAN VERSION HISTORY

This Statistical Analysis Plan (SAP) was developed based on Roche SAP model document 28 February 2022.

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
2	see electronic date stamp on last page of this document	Protocol v8, 08 March 2023
1	25 April 2023	Protocol v8, 08 March 2023

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

Key changes to the SAP, along with the rationale(s) for each change, are summarized below.

Section	Description of Change	Rationale for Change
4.3	Clarifying statistical testing procedure of key secondary efficacy endpoints	The order of fixed sequence testing of key secondary efficacy endpoints following primary endpoint was clarified with the specific procedure added
4.3.1.1 and 4.7.1	Clarifying the power of OS analyses	The power of OS analysis at pre-specified time points was clarified

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
BICR	blinded independent central review
BGPL	Biometrics Global Process Library
BMI	body mass index
BOR	best overall response rate
CBR	clinical benefit rate
CCOD	clinical cutoff date
CR	complete response
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAS	disease activity score
DMC	Data Monitoring Committee
DOR	duration of response
FAS	full analysis set
FEV	forced expiratory volume
GHS	global health status
HER2	human epidermal growth factor receptor 2
HR	Hazard ratio
HR-positive	hormone receptor-positive tumors
HRQoL	health-related quality of life
IA	interim analysis
ICE	Intercurrent events
ICH	International Council on Harmonization
iDMC	independent Data Monitoring Committee
IRF	Independent Review Facility
IxRx	interactive voice/web-based response system
LLoQ	lower limit of quantification
MDD	minimally detectable difference
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging

NCI	National Cancer Institute
NMPA	National Medical Products Administration
NPT	non-protocol anti-cancer therapy
ORR	overall response rate
OS	overall survival
PD	pharmacodynamic
PF	physical functioning
PFS	progression-free survival
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcomes
RECIST	response evaluation criteria in solid tumors
RF	role functioning
SAE	serious adverse events
SAP	Statistical Analysis Plan
SAS	safety analysis set
SMART	sequential multiple assignment randomized study
SMQs	standardized MedDRA queries
SRE	skeletal related event
TTCD	time to confirmed deterioration
VAS	visual analog scale

1. INTRODUCTION

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for study WO41554 (INAVO120). For detailed information on the study, refer to the study protocol. The analyses described in this SAP will supersede those specified in Protocol WO41554.

1.1 OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of inavolisib in combination with palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant in patients with *PIK3CA*-mutant, HR-positive, HER2-negative locally advanced or metastatic breast cancer whose disease progressed during treatment or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease. Specific primary and secondary objectives and corresponding endpoints for the study are outlined in Table 1 and Table 2. For details on exploratory objectives and endpoints, refer to Section 4.4

Table 1 Primary and Secondary Objectives and Corresponding Estimands

Primary Objective(s)	Estimand Definition
• Evaluate the efficacy of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant on the basis of progression free survival (PFS)	• Population: patients with *PIK3CA*-mutant, hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer whose disease progressed during treatment or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease, as defined in study protocol (refer to Protocol Section 4.1) • Endpoint: PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1 or death from any cause (whichever occurs first) • Treatment: o Experimental: inavolisib 9-mg tablet taken PO QD on Days 1−28 of each 28-day cycle, palbociclib 125-mg capsule or tablet taken PO QD on Days 1−21 of each 28-day cycle, and fulvestrant 500 mg administered by IM injection on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle

	○ Control: placebo tablet taken PO QD on Days 1−28 of each 28-day cycle, palbociclib 125-mg capsule or tablet taken PO QD on Days 1−21 of each 28-day cycle, and fulvestrant 500 mg administered by IM injection on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle • Intercurrent events (ICE) and handling strategies: ○ Start of non-protocol anticancer therapy prior to disease progression ○ Early discontinuation from study treatment for any reason prior to a PFS event ○ Handing of ICE: Following treatment policy the above ICE will be ignored and tumor assessment data collected after the ICE will be included in the primary PFS analysis • Population-level summary: hazard ratio for PFS
Secondary Objective(s)	**Estimand Definition**
• To evaluate the efficacy of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant on the basis of overall survival (OS)	• Population: As defined for the primary estimand for PFS • Endpoint: OS defined as time from randomization to death from any cause • Treatment: As defined for the primary estimand for PFS • Intercurrent events and handling strategies: ○ Start of non-protocol anticancer therapy prior to an OS event ○ Early discontinuation from study treatment for any reason prior to an OS event ○ Handling of ICE: Following treatment policy the above ICE will be ignored • Population-level summary: hazard ratio for OS

HER2 = human epidermal growth factor receptor 2; HRQoL = health-related quality of life; ICE = intercurrent events; IM = intramuscular; *PIK3CA* = Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PFS = progression-free survival; OS = overall survival; QD = once a day; RECIST = response evaluation criteria in solid tumors.

Table 2 Other Secondary Objectives and Endpoints

Other Secondary Objectives	Corresponding Endpoints
• Evaluate the efficacy of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant on the basis of	• Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions ≥4 weeks apart, as determined by the investigator according to RECIST v1.1 • Best overall response rate (BOR), defined as the proportion of patients with a CR or PR, as determined by the investigator according to RECIST v1.1 • Duration of response (DOR), defined as the time from the first occurrence of a CR or PR to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1 or death from any cause (whichever occurs first) • Clinical benefit rate (CBR), defined as the proportion of patients with a CR, PR, and/or stable disease (SD) for at least 24 weeks, as determined by the investigator according to RECIST v1.1 • Time to confirmed deterioration (TTCD) in pain, defined as the time from randomization to the first documentation of a ≥ 2-point increase from baseline on the "worst pain" item from the Brief Pain Inventory−Short Form (BPI-SF) held for at least two consecutive cycles, or an initial increase followed by death or treatment discontinuation within three weeks from the last assessment • TTCD in Physical Function, defined as the time from randomization to the first documentation of a ≥ 10-point decrease from baseline in the European Organisation for Research and Treatment of Cancer Quality of Life−Core 30 Questionnaire (EORTC QLQ-C30) Physical Function scale (items 1−5) held for at least two consecutive cycles, or an initial decrease followed by death or treatment discontinuation within three weeks from the last assessment

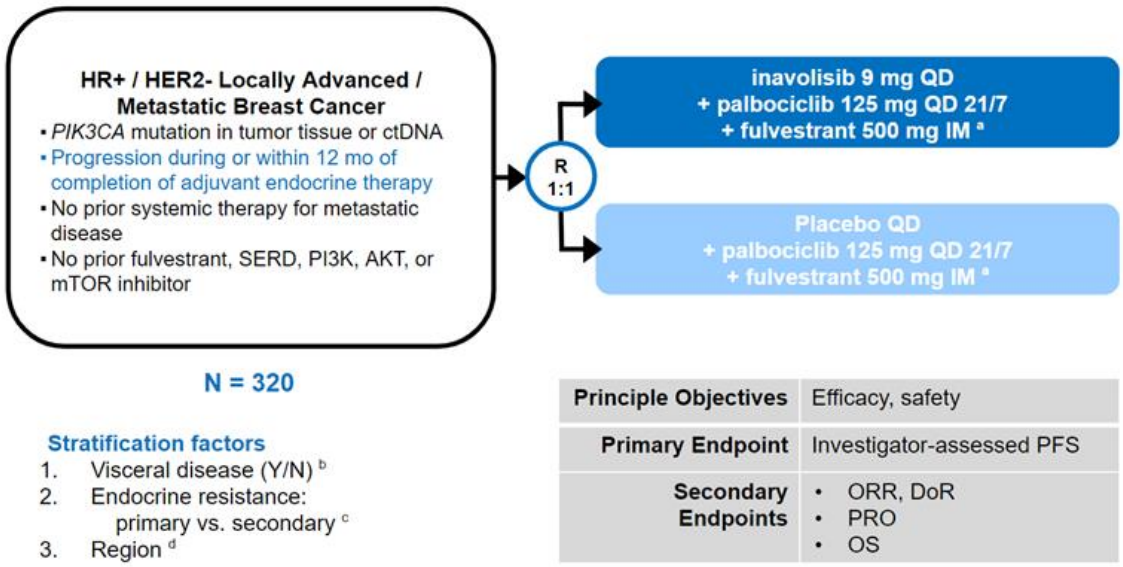
	• TTCD in Role Function, defined as the time from randomization to the first documentation of a ≥ 10-point decrease from baseline in the EORTC QLQ-C30 Role Function scale (items 6 and 7) held for at least two consecutive cycles, or an initial decrease followed by death or treatment discontinuation within three weeks from the last assessment • TTCD in global health status (GHS)/health-related quality of life (HRQoL), defined as the time from randomization to the first documentation of a ≥ 10-point decrease from baseline in the EORTC QLQ-30 GHS/HRQoL scale (items 29 and 30) held for at least two consecutive cycles, or an initial decrease followed by death or treatment discontinuation within three weeks from the last assessment
• To evaluate the safety of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant on the basis of	• Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0) • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results • Change from baseline in ECG parameters
• To characterize the pharmacokinetics of inavolisib, palbociclib, and fulvestrant, when administered in combination in this population, on the basis of	• Plasma concentration of inavolisib at specified timepoints • Plasma concentration of palbociclib at specified timepoints • Plasma concentration of fulvestrant at specified timepoints

BOR = best overall response; BPI-SF = Brief Pain Inventory−Short Form; CBR = clinical benefit rate; CR = complete response; DOR = duration of response; ECG = Electrocardiography; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life−Core 30 Questionnaire; GHS = global health status; HRQoL= health-related quality of life; NCI = National Cancer Institute; ORR = objective response rate; OS = overall survival; PK = pharmacokinetic; PR = partial response; RECIST = response evaluation criteria in solid tumors; SD = stable disease; TTCD = time to confirmed deterioration;.

1.2 STUDY DESIGN

The study schema is shown in Figure 1.

Figure 1 Study Schema



ctDNA = circulating tumor DNA; DOR = duration of response; HER2− = HER2-negative; HR+ = hormone-receptor positive; IM = intramuscular; mTOR = mammalian target of rapamycin; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PI3K = phosphatidylinositol 3-kinase; PRO = patient-reported outcome; QD = once daily; SERD = selective estrogen-receptor degrader

[a] Fulvestrant is administered on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle, or approximately every 4 weeks

[b] "Visceral" (Yes/No) refers to lung, liver, brain, pleural, and peritoneal involvement

[c] Primary endocrine therapy resistance is defined as relapse while on the first 2 years of adjuvant endocrine therapy. Secondary endocrine therapy resistance is defined as relapse while on adjuvant endocrine therapy but after the first 2 years or relapse within 12 months of completing adjuvant endocrine therapy (4th ESO–ESMO International Consensus Guidelines for ABC 4, Cardoso et al. 2018).

[d] Region is stratified by site location: i) North America/Western Europe, ii) Asia/Pacific, iii) Other.

Study WO41554 is a Phase III, randomized, double-blind, placebo-controlled, multicenter, global study designed to compare the efficacy, as measured by progression-free survival (PFS), and the safety of the triplet combination of inavolisib plus palbociclib and fulvestrant versus placebo plus palbociclib and fulvestrant in patients with *PIK3CA*-mutant, HR-positive, HER2-negative locally advanced or metastatic breast cancer whose disease progressed during treatment or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease.

Approximately 320 patients will be enrolled at approximately 200 global investigative sites.

Of the 320 patients, no more than 60 patients will be allowed to have a *PIK3CA* tumor mutation not confirmed by the central FoundationOne Liquid CDx assay. As such, at least 260 patients will have the presence of (one or more) *PIK3CA* mutation(s) confirmed by the central FoundationOne® Liquid CDx assay.

1.2.1 Treatment Assignment and Blinding

This is a randomized, double-blind study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from an interactive voice or web-based response system (IxRS).

Patients will be randomly assigned to one of two treatment arms: inavolisib plus palbociclib and fulvestrant or placebo plus palbociclib and fulvestrant. Randomization will occur in a 1:1 ratio using a permuted-block randomization method to ensure a balanced assignment to each treatment arm.

Randomization will be stratified according to the following factors:

- Visceral disease (yes or no)
- Endocrine resistance (primary or secondary according to ESMO ABC4 guidelines [Cardoso et al. 2018])
- Geographic region (North America/Western Europe, Asia, Other).

1.2.1.1 Blinding

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

While inavolisib pharmacokinetic (PK) samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, inavolisib PK assay results for these patients are generally not needed for the safe conduct or proper interpretation of the study data since those patients are expected to receive placebo and not inavolisib. Laboratories responsible for performing study drug PK assays will be unblinded to patient treatment assignments to identify appropriate samples for analysis. PK samples from patients assigned to the comparator arm will not be analyzed for

inavolisib PK concentration except by request (e.g., to evaluate a possible error in dosing).

To optimize timelines for delivery of PK-related analyses, unblinded PK data may be released to selected clinical pharmacology personnel at the clinical cutoff date, prior to study unblinding.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to patient unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

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

1.2.2 Blinded Independent Central Imaging Review

A blinded independent central review (BICR) of tumor assessment data will be performed to support the primary endpoint of investigator-assessed PFS. To facilitate BICR for PFS, all radiological data (e.g., computed tomography [CT] scan, magnetic resonance imaging [MRI], bone scan) and photographs for skin lesions obtained at baseline, during the treatment period, at the time of disease progression, and at the time of study treatment discontinuation (if not the same as disease progression) should be sent to a central imaging vendor (contracted by the Sponsor) within 2 weeks of imaging to enable retrospective BICR. Additional details about tumor assessment collections and readings will be outlined in a separate charter with the imaging vendor.

1.2.3 Data Monitoring

An external independent Data Monitoring Committee (iDMC) will be formed to evaluate safety and efficacy data from the first patient randomized until the time of the primary analysis of PFS and to conduct the interim analysis (see Protocol Section 6.9). The iDMC will monitor accumulating patient safety data approximately every 4 months during

the course of the study. The iDMC will include qualified personnel, all independent of the Sponsor, who are committed to preservation of the trial integrity and reaching valid conclusions as described in the iDMC guidance. The primary responsibilities of the iDMC will be to thoroughly review the available cumulative safety data and to make recommendations regarding modification of the conduct of study, enrollment hold, performance of additional interim safety analyses, changes to the inclusion/exclusion criteria or safety evaluation, or termination of the study if there is evidence of undue risk to the study participants.

The analyses will be conducted by an independent Data Coordinating Center and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

2. STATISTICAL HYPOTHESES AND SAMPLE SIZE DETERMINATION

2.1 STATISTICAL HYPOTHESES

The primary analysis will be a comparison of the Investigator-assessed PFS between the two treatment arms using a stratified log-rank test at an overall 0.05 significance level (two-sided).

The statistical hypothesis of this study is as follows:

- H0: PFS inavolisib plus palbociclib and fulvestrant = PFS placebo plus palbociclib and fulvestrant
- H1: PFS inavolisib plus palbociclib and fulvestrant ≠ PFS placebo plus palbociclib and fulvestrant

The null and alternative hypotheses will be tested at a two-sided 0.05 significance level. The primary trial objective is to demonstrate superiority of the experimental over the control treatment.

2.2 SAMPLE SIZE DETERMINATION

Estimates of the number of events required to demonstrate efficacy with regard to PFS are based on the following assumptions:

- Two-sided log-rank test at the 0.05 level of significance
- Eighty-five percent power to detect a hazard ratio for inavolisib plus palbociclib and fulvestrant versus placebo plus palbociclib and fulvestrant of 0.65, corresponding to an improvement of 5.9 months (from 11 to 16.9 months) in median PFS for the treatment arm over the control arm
- Exponential distribution of PFS
- An annual dropout rate of 15%

With these assumptions, 194 PFS events are required to achieve 85% power for the primary analysis. The 320 patients will be enrolled over approximately 43 months and the primary analysis is expected to occur approximately 50 months after the first patient randomized.

The minimal detectable difference for the PFS hazard ratio is 0.754 (i.e., an improvement of 3.6 months (from 11 to 14.6 months) in median PFS for the treatment arm over the control arm).

3. ANALYSIS SETS

The participant analysis sets for the purposes of analyses are defined in Table 3.

Table 3 Participant Analysis Sets

Participant Analysis Set	Description
FAS	All randomized participants; participants will be included in the analyses according to the treatment they were assigned.
SAS	All participants exposed to study treatment; participants will be analyzed according to the treatment that they actually received.
PK-evaluable	All randomized participants in the inavolisib arm who have at least one evaluable inavolisib plasma concentration.

FAS = full analysis set; SAS = safety analysis set; PK = pharmacokinetic

4. STATISTICAL ANALYSES

This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints. It also describes the sensitivity analysis related to the primary study estimand and any pre-specified subgroup analyses.

The analyses described in this SAP will supersede those specified in the protocol.

4.1 GENERAL CONSIDERATIONS

All efficacy analyses will be performed on the full analysis set population, unless otherwise specified. All safety analyses will be performed in the safety analysis set, unless otherwise specified.

Analyses of demographics and other baseline information will be based on full analysis set population. The baseline value of any variable will be defined as the last available data point prior to the first administration of study drug.

4.2 PRIMARY ENDPOINT ANALYSIS

The primary efficacy objective for this study is to evaluate the efficacy of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant on the

basis of the Investigator-assessed PFS endpoint as defined in Section 1.1 of SAP (see Table 1).

4.2.1 Definition of Primary Estimand

Following the estimand framework introduced in the ICH-E9 addendum (ICH 2020), the attributes of the estimand built around the primary endpoint are defined as follows:

- **Population**: patients with *PIK3CA*-mutant, hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer whose disease progressed during treatment or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease, as defined in study protocol (refer to Protocol Section 4.1)
- **Variable**: PFS, defined as the time from randomization to the first occurrence of disease progression as determined by the investigator and according to response evaluation criteria in solid tumors (RECIST) v1.1, or death from any cause (whichever occurs first)
- **Treatment**:
    - Experimental: inavolisib 9-mg tablet taken PO QD on Days 1−28 of each 28-day cycle, palbociclib 125-mg capsule or tablet taken PO QD on Days 1−21 of each 28-day cycle, and fulvestrant 500 mg administered by IM injection on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle
    - Control: placebo tablet taken PO QD on Days 1−28 of each 28-day cycle, palbociclib 125-mg capsule or tablet taken PO QD on Days 1−21 of each 28-day cycle, and fulvestrant 500 mg administered by IM injection on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28day cycle
- **Intercurrent events and handling strategies**:
    - Start of non-protocol anticancer therapy prior to disease progression
    - Early discontinuation from study treatment for any reason prior to a PFS event
    - Handling ICE: Following treatment policy, the above ICE will be ignored and tumor assessment data collected after the ICE will be included in the primary PFS analysis
- **Population-level summary**: Hazard ratio for PFS

4.2.2 Main Analytical Approach for Primary Endpoint

If participants have any intercurrent event(s), then the strategies defined as defined in Section 4.2.1 to handle the intercurrent events will be implemented. Data for participants without the occurrence of disease progression or death as of the clinical cutoff date (CCOD) will be censored at the time of the last tumor assessment prior to the CCOD (or at the time of randomization if no tumor assessment was performed after the baseline visit).

PFS will be compared between treatment arms using the two-sided stratified logrank test at the 0.05 level of significance.

The hazard ratio will be estimated using a stratified Cox proportional hazards model. The 95% CI for the hazard ratio will be provided. The stratification factors used will be the same as the randomization stratification factors (as entered in IxRS, Section 1.2.1). Results from an unstratified analysis (see Section 4.2.3) will also be provided as sensitivity analysis. For each treatment arm, Kaplan-Meier methodology will be used to estimate the median PFS, and the Brookmeyer-Crowley method will be used to construct the 95% CI for the median PFS. Kaplan-Meier curves will also be produced.

4.2.3 Sensitivity Analyses

The following sensitivity analysis to the primary estimand of the primary PFS after randomization will be performed:

- PFS assessed by Blinded Independent Central Review (BICR): To assess the concordance of PFS assessment by investigators' PFS analysis, as mentioned in Section 4.2.2, will be repeated based on BICR assessment. The BICR cannot evaluate patients if the baseline scans were missing hence, in such cases, data will be censored at randomization.
- PFS assessed by investigator based on unstratified analysis: To assess the impact of stratification (as entered in IxRS, see Protocol Section 6.4.1) the main analysis described in Section 4.2.2 will be repeated without stratification factors.
- PFS assessed by investigator in patients with *PIK3CA* mutation-positive status by the central test.
- Handling of missing scheduled tumor assessments: Patients who missed two or more scheduled assessments immediately prior to the date of disease progression as determined by investigator per RECIST v1.1 will be censored at the last tumor assessment prior to the missed visits.

4.2.4 Supplementary Analyses

Two supplementary analyses based on differing strategies of handling ICE (as outlined below) are planned for PFS. Note that the attributes of population, variables, and population level summary will remain the same as the primary estimand. The analysis for the supplementary estimands will be conducted only on the primary endpoint investigator assessed PFS.

- PFS assessed by investigator based on hypothetical strategy for use of any non-protocol anti-cancer therapy (NPT) prior to disease progression: To assess the impact of use of any NPT prior to disease progression, the analysis of investigator assessed PFS will be repeated with the ICE of use of any NPT handled using a hypothetical strategy. According to this strategy, patients who start NPT prior to disease progression will be censored at the time of the last

disease status assessment before the initiation of NPT. If patients start any NPT before starting study treatment, then the data of those patients will be censored at the time of randomization. Approaches to handle other ICE (Discontinuation of study treatment prior to disease progression) and analysis method will be the same as mentioned in Section 4.2.2.

- PFS assessed by investigator based on composite strategy for use of any NPT prior to disease progression: In addition to the above estimand, in this case a supplementary estimand for PFS will be estimated by following the composite strategy. According to composite strategy, use of any NPT prior to disease progression will be considered as a PFS event (progression) at the time of initiation of NPT. If patients start any NPT before starting study treatment then the data of those patients will be censored at the time of randomization. Approaches to handle other ICE (Discontinuation of study treatment prior to disease progression) and analysis method will be the same as mentioned in Section 4.2.2.

4.2.4.1 Subgroup Analyses for Primary Endpoint(s)

The generalizability of PFS after randomization results when comparing the addition of inavolisib to standard-of-care treatment with palbociclib plus fulvestrant will be investigated as a part of an exploratory analysis by estimating the treatment effect in subgroups based on the following baseline prognostic factors (including stratification factors):

- Age (<65, ≥65)
- Age (<65, ≥65 to <75, ≥75)
- Sex (Male, Female)
- Ethnicity (Hispanic or Latino; Not Hispanic or Latino)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander)
- Visceral disease (yes/no)
- Liver (yes/no)
- Number of organs of disease (<3 vs≥3)
- Region (North America/Western Europe; Asia; Other)
- Endocrine resistance (primary resistance, secondary resistance)
- Menopausal status at randomization (not post-menopausal, post-menopausal)
- ECOG (0, 1)
- Hormone receptor status (ER+/PR+, ER+/PR-, ER-/PR+)
- Prior treatment in the adjuvant/neo-adjuvant setting:
    - aromatase inhibitor only
    - tamoxifen only
    - aromatase inhibitor and tamoxifen

- an endocrine based combination with a CDK4/6 inhibitor
- prior (neo)-adjuvant chemotherapy (Yes/No)

Further prognostic factors may be considered for subgroup analyses as deemed appropriate. Un-stratified analysis results will be presented for subgroup analyses due to the potentially limited number of patients in each subgroup. Summaries of PFS by above subgroups will be provided in forest plots including estimates for HR and 95% CIs from unstratified Cox proportional hazard models.

4.3 SECONDARY ENDPOINT(S) ANALYSIS

The type I error-controlled secondary endpoints of this study will be tested hierarchically according to the following pre-specified and fixed order of endpoints only if the primary endpoint, PFS, is statistically significant at the primary PFS analysis:

1. Overall survival (OS)
2. Objective response rate (ORR)
3. Best overall objective response rate (BOR)
4. Clinical benefit rate (CBR)
5. Time to confirmed deterioration (TTCD) in pain
6. TTCD in physical functioning (PF)
7. TTCD in role functioning (RF)
8. TTCD in Global Health Status/Quality of Life (GHS/QoL).

To adjust for multiple statistical testing of the key secondary efficacy endpoints, thereby controlling the overall type I error rate at a two-sided significance level of 5%, the fixed-sequence testing procedure will be used, where each subsequent endpoint will be formally tested at a two-sided significance level of 0.05 only if all previously tested hypotheses are statistically significant.

The primary efficacy analysis population is used for all secondary endpoints unless otherwise specified.

4.3.1 Key Secondary Endpoint

4.3.1.1 Overall Survival

The secondary comparison of interest is the hazard ratio of OS.

OS is defined as the time from randomization to death from any cause. 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.

Analysis methodology is as outlined for the primary endpoint, PFS.

An interim analysis of OS will be performed at the time of the primary analysis of PFS. In addition to the fixed sequence testing approach described before, a group-sequential design (Lan-DeMets with O'Brien-Fleming stopping boundaries) will be used to control the overall type I error rate (Lan and DeMets 1983) for the OS interim analysis and a final (event-driven, after approximately 153 OS events) analysis of OS.

The median OS in the control arm is assumed to be 35 months and the median OS in the experimental treatment arm is assumed to be 50 months, equating to a hazard ratio of 0.7. At the time of the primary PFS analysis, on the basis of the above assumptions, 105 OS events are expected to have occurred and 153 OS events for the final analysis of OS are expected to have occurred 19 months later. With the above assumptions, the cumulative power at the interim and final OS analysis is 25% and 59%, respectively. This statistical analysis plan for OS has been designed to provide appropriate OS information and maturity to support the primary PFS endpoint. However, if appropriate, additional exploratory analyses of OS may be conducted after the final analysis at time points defined through study milestones such as Health Authority interactions.

Following the estimand framework (ICH 2020), the attributes of the estimand for the secondary endpoint are defined as follows:

- **Population**: As defined for the primary estimand in Section 4.2.1
- **Variable**: OS defined as time from randomization to death from any cause.
- **Treatment**: As defined for the primary estimand in Section 4.2.1
- **Intercurrent events and Handling strategy:**
    - Start of non-protocol anticancer therapy prior to OS. Following treatment policy, the ICE will be ignored.
    - Early discontinuation from study treatment for any reason prior to an OS event. Following treatment policy, the ICE will be ignored.
- **Population-level summary:** Hazard ratio for OS.

4.3.1.2 Objective Response Rate

Patients not meeting the criteria for ORR, including patients with no response assessments (for whatever reason) will be considered non-responders.

Following the estimand framework (ICH 2020), the attributes of the estimand for the secondary endpoint are defined as follows:

- **Population:** As defined for the primary estimand in Section 4.2.1.

- **Variable:** ORR, defined as the proportion of patients with a CR or PR on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1.
- **Treatment:** As defined for the primary estimand in Section 4.2.1
- **Intercurrent events and Handling strategy:**
    - As defined for the primary estimand in Section 4.2.1
    - **ICE Handling Strategy:** Following treatment policy, all the ICE's will be ignored and tumor assessment data collected after the ICE will be included in the ORR analysis.
- **Population-level summary:** Difference in proportion

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.

4.3.1.3 Best Overall Response

Patients not meeting the criteria for BOR, including patients with no response assessments (for whatever reason) will be considered non-responders.

Following the estimand framework (ICH 2020), the attributes of the estimand for the secondary endpoint are defined as follows:

- **Population:** As defined for the primary estimand in Section 4.2.1.
- **Variable:** BOR, defined as the proportion of patients with a CR or PR, as determined by the investigator according to RECIST v1.1.
- **Treatment**: As defined for the primary estimand in Section 4.2.1
- **Intercurrent events and Handling strategy:**
    - As defined for the primary estimand in Section 4.2.1
    - **ICE Handling Strategy**: Following treatment policy, all the ICE's will be ignored and tumor assessment data collected after the ICE will be included in the BOR analysis.
- **Population-level summary:** Difference in proportion

Analysis methodology is as outlined for ORR.

4.3.1.4 Clinical Benefit Rate

Patients not meeting the criteria for CBR, including patients with no response assessments (for whatever reason) will be considered non-responders.

Following the estimand framework (ICH 2020), the attributes of the estimand for the secondary endpoint are defined as follows:

- **Population:** As defined for the primary estimand in Section 4.2.1.
- **Variable:** CBR, defined as the proportion of patients with a CR, PR, and/or SD for at least 24 weeks, as determined according to RECIST v1.1.
- **Treatment:** As defined for the primary estimand in Section 4.2.1
- **Intercurrent events and Handling strategy:**
    - As defined for the primary estimand in Section 4.2.1
    - ICE Handling Strategy: Following treatment policy, all the ICE's will be ignored and tumor assessment data collected after the ICE will be included in the CBR analysis.
- **Population-level summary:** Difference in proportion

Analysis methodology is as outlined for ORR.

4.3.1.5 Duration of Objective Response

The analysis of DOR will include only patients who achieved an objective response.

Following the estimand framework (ICH 2020), the attributes of the estimand for the secondary endpoint are defined as follows:

- **Population:** All randomized patients who had an objective response
- **Variable:** DOR is defined as the time from the first occurrence of a PR or CR to the first occurrence of disease progression as determined by the investigator according to RECIST v1.1 or death from any cause (whichever occurs first)
- **Treatment:** As defined for the primary estimand in Section 4.2.1
- **Intercurrent events and Handling strategy:**
    - As defined for the primary estimand in Section 4.2.1
    - ICE Handling Strategy: Following treatment policy, all the ICE's will be ignored and tumor assessment data collected after the ICE will be included in the DOR analysis
- **Population-level summary:** Hazard ratio

Analysis methodology is as outlined for the primary endpoint, PFS. Data for patients without the occurrence of disease progression or death will be censored at the time of the last tumor assessment. 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.

4.3.2 Supportive Secondary Endpoint

4.3.2.1 Patient Reported Outcomes

To evaluate TTCD in pain, the "worst pain" item from the BPI-SF will be assessed. TTCD is defined as the time from randomization to the first documentation of a 2-point

increase from baseline in “worst pain” held for at least two consecutive cycles, or an initial increase followed by death or treatment discontinuation within three weeks from the last assessment. A 2-point change is defined as clinically meaningful (Mathias et al. 2010).

TTCD in physical function (PF), role function (RF), and global health status (GHS)/health-related quality of life (HRQoL) will be assessed. TTCD is defined as the time from randomization to the first documentation of a ≥10-point decrease from baseline in the specific scale held for at least two consecutive cycles, or an initial decrease followed by death or treatment discontinuation within three weeks from the last assessment:

- Physical Function (items 1 through 5)
- Role Function (items 6 and 7)
- Global Health Status (GHS)/Quality of Life (QoL) (items 29 and 30)

A ≥10-point change is defined as a clinically meaningful difference (Osoba et al. 1998) on all scales of the EORTC-QLQ-C30.

For both BPI-SF and EORTC-QLQ-C30, patients who do not have an observed deterioration at the time of the clinical data cutoff will be censored at the last non-missing assessment date. Patients without a post-baseline assessment will be censored at the time of randomization.

4.4 EXPLORATORY ENDPOINT(S) ANALYSIS

The exploratory efficacy objective for this study is to evaluate the efficacy of inavolisib in combination with palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant on the basis of the following endpoints:

- Time to end of next-line treatment (proxy for time to second objective disease progression [PFS2]), defined as the time from randomization to end or discontinuation of next-line treatment, or death from any cause (whichever occurs first). Data for patients without the occurrence of second objective disease progression or death and patients who have not started next-line treatment 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. Analysis methodology is as outlined for the primary endpoint, PFS in Section 4.2.2.
- Time to first Skeletal related event (SRE), defined as the time from randomization to the first occurrence of an SRE. An SRE is a pathologic fracture, radiation therapy to bone, cancer-related surgery to bone, or spinal cord compression. Data from patients without the occurrence of an SRE will be censored at the last valid visit. Data from patients without post-baseline information will be censored at the date of randomization. Analysis methodology is as outlined for the primary endpoint, PFS in Section 4.2.2.

- Mean scores and mean change from baseline in functional scores (physical, role, cognitive, emotional, and social), GHS/QoL, disease and treatment–related symptom scores.

Summary statistics (mean, standard deviation, median, 25th and 75th percentiles, and range) of scores will be reported for the "worst pain" item of the BPI-SF, as well as all linear transformed scores for scales (symptoms, functional domains, and GHS/QoL) of the QLQ-C30 and QLQ-BR23 questionnaires 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 analyzed for each treatment arm.

In the event of incomplete data for all questionnaire scales, if more than 50% of the constituent items are completed, a prorated score will be computed consistent with the scoring manuals and validation papers (see protocol). For scales with less than 50% of the items completed, the scale will be considered as missing in accordance with the EORTC scoring manual guidelines.

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

4.5 SAFETY ANALYSES

The safety analysis population consists of all patients who received at least one dose of study drug and is based on the treatment the patients actually received; that is, all patients who received at least one dose of inavolisib are included in the inavolisib plus palbociclib and fulvestrant group and all patients who received any palbociclib or fulvestrant (and no inavolisib) are included in the placebo plus palbociclib and fulvestrant group.

The safety objective for this study is to evaluate the safety of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant on the basis of the following endpoints:

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

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Additionally, a shift table of selected laboratory tests (e.g., FBG, HbA1C, liver enzymes) will be used to summarize the baseline and maximum post-baseline severity grade. Changes in vital signs and ECGs will be summarized.

4.5.1 Extent of Exposure

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) and dose intensity will be summarized with descriptive statistics.

4.5.2 Adverse Events

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All AEs will be coded using the current version of MedDRA (which is anticipated to be Version 26.0) at the time of database closure.

All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, selected AEs and adverse events leading to study treatment discontinuation or dose modification that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized accordingly. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

4.5.3 Additional Safety Assessments

4.5.3.1 Laboratory Data

Relevant laboratory values will be summarized by treatment arm over time, with NCI CTCAE v5.0 Grade 3 and Grade 4 values identified, where appropriate (e.g., Hy's law, AST/ALT elevation, FBG). Summary tables of clinically relevant shifts in NCI CTCAE v5.0 grades (Grades ≤ 2) at baseline to the worst post-baseline (Grade ≥3) value will be presented.

A Hy's law analysis will be provided: the finding of an elevated ALT or AST (>3× baseline value) in combination with either an elevated total bilirubin (> 2×ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law).

4.5.3.2 Vital Signs and ECGS

Changes in vital signs and ECGs will be summarized.

4.5.3.3 Exploratory Safety Analysis

The exploratory safety objective for this study is to evaluate tolerability of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant from the patient's perspective, on the basis of the following endpoints:

- Presence, frequency of occurrence, severity, and/or degree of interference with daily function of selected symptomatic treatment toxicities as assessed through use of the NCI PRO-CTCAE and the "bother from side effects" item

Change from baseline in symptomatic treatment toxicities, as assessed through use of the PRO-CTCAE and the “bother from side effects” item

4.5.3.4 Exploratory Analyses of PRO-CTCAE Data

PRO-CTCAE analyses will be descriptive, with a focus on characterizing the pattern of symptomatic treatment toxicities over the course of the study. The number and percentage of patients reporting each symptom and the change from baseline by category (frequency of occurrence, severity, interference) will be summarized at each assessment time point by treatment arm. For items that are rated on a 5-point Likert scale, the maximum post-baseline score and change from baseline will be summarized by treatment arm.

Results from these exploratory analyses will be presented separately from the safety analyses. PRO-CTCAE data will be analyzed at the item level in line with current NCI recommendations for data handling (Basch et al. 2014). Graphical representation of PRO-CTCAE data over time may also be provided. PRO-CTCAE data will be summarized over time. These analyses will also apply to the “bother from side effects of treatment” item. The proportion of missing data at each assessment time point will also be summarized to facilitate interpretation of data.

4.6 OTHER ANALYSES

4.6.1 Summaries of Conduct of Study

Study enrollment, duration, study treatment discontinuation, and study discontinuation, as well as reasons for study drug discontinuation and study discontinuation, will be listed and summarized overall and by treatment arm. Major protocol deviations, including major deviations with regard to inclusion and exclusion criteria, will also be listed and summarized overall and by treatment arm.

4.6.2 Summaries of Treatment Group Comparability

The evaluation of treatment group comparability between the treatment arms will include summaries of demographic and baseline characteristics, including stratification factors and patient treatment history. Continuous variables will be summarized using means, standard deviations, medians and ranges. Categorical variables will be summarized by counts and proportions.

4.6.3 Pharmacokinetic Analyses

The PK analysis population will consist of patients who received at least one dose of study drug and is based on the treatment patients actually received; that is, all patients who received at least one dose of inavolisib are included in the inavolisib plus palbociclib and fulvestrant group and all patients who received at least one dose of palbociclib and/or fulvestrant (and no inavolisib) are included in the palbociclib and fulvestrant group.

Individual and mean plasma concentrations of inavolisib, palbociclib, and fulvestrant versus time data will be tabulated and plotted. Inavolisib plasma concentration versus time data, together with information on dosing and patient characteristics, will be pooled and analyzed using a population PK (PopPK) analysis approach, as appropriate. Non-linear mixed-effect modeling will be used for the estimation of PopPK parameters for inavolisib. Covariates such as patient demographics (e.g., age, sex, body size) may be tested for significance on PK parameters of interest.

The PK data may be combined with the safety, efficacy, and biomarker data for exposure-response modeling as an exploratory objective. PopPK and exposure-response analyses may be reported in separate standalone reports. Additional PK analyses will be conducted as appropriate. A separate PK cut-off date may be established prior to the clinical cut-off date to ensure expedient sample analysis. An earlier PK cut-off date will only be applied when there is sufficient PK data available to adequately characterize PK.

The China-specific pharmacokinetic objective is to characterize the pharmacokinetics of inavolisib in all patients enrolled in China. PK parameters such as C_{max}, T_{max}, AUC, half-life, etc., will be derived from the plasma concentration–time profile of inavolisib from Chinese patients who provided intense PK sampling.

4.6.4 Biomarker Analyses

The exploratory biomarker objective is based on the relationship between biomarkers in blood, plasma, and tumor tissue and efficacy, safety, PK, or other biomarker endpoints. No formal statistical analysis of exploratory biomarkers will be performed. Data may be analyzed in the context of this study and in aggregate with data from other studies. Results may be presented in a separate report.

4.6.5 Health Status Utility

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant on the basis of the EQ-5D-5L. These data will be used in pharmacoeconomic models and reported separately from the CSR.

4.6.6 Analyses of China Subpopulation

A separate analysis will be performed for the China subpopulation, where data from all participants enrolled at sites in mainland China, Hong Kong and Taiwan will be combined and summarized. Results from these analyses will be summarized in a separate Clinical Study Report.

The efficacy objective of the China subpopulation analyses is to evaluate whether the efficacy of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant in the China subpopulation is consistent with the efficacy

observed in the global population. Therefore, no formal hypothesis testing will be performed for China subpopulation.

The China subpopulation analyses will be conducted at the same time as global population.

4.7 INTERIM ANALYSES

4.7.1 Planned Interim Analyses

An iDMC will convene to review cumulative safety data approximately every 4 months.

One interim analysis for futility of the primary endpoint has been conducted by iDMC after 75 PFS events (33% of information) were observed. The futility boundary was non-binding. The futility boundary (point estimate of PFS HR >1.1) has been chosen so that the probability of stopping for futility when the study would be positive at primary analysis was small (<3%).

As an additional safety monitoring measure, an interim safety review has been performed after the enrollment of the first 25 patients and treatment for at least three cycles.

One interim analysis will be performed for OS at the time of the primary PFS analysis. The type I error probability will be controlled by using a Lan-DeMets (O'Brien Fleming) α−spending function for the secondary endpoint, OS, at a 5% overall level of significance. The stopping boundaries used for the efficacy test will be calculated using the two-sided α-spending function approach described by Lan and DeMets 1983. This function generates stopping boundaries that closely resemble the O'Brien-Fleming boundaries (O'Brien and Fleming 1979) (see Table 4). Refer to Section 4.3.1.1 for details on OS assumption.

Table 4 Stopping Boundaries for Efficacy at the Interim or Final OS Analysis

Analysis	p-Value Stopping Boundary (Effect Scale)	Estimated Time from FPI (months)	Information Fraction	Power
First interim analysis	0.0132 (or HR 0.615)	50	68% (105/153)	25%
Final analysis	0.0460 (or HR 0.724)	69	100% (153/153)	59%

OS=overall survival

The actual boundaries will be calculated at the time of OS analysis based on the observed information fraction (i.e., actual number of events observed at time of analysis over the total planned target number of events).

5. SUPPORTING DOCUMENTATION

This section is not applicable, since there is no additional supporting document. For Synopsis, Schedule of assessments, PRO forms, etc. refer to study protocol.

6. REFERENCES

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