Title: An Open-Label Phase 2 Study of MLN0128 (A TORC1/2 Inhibitor) in Combination With Fulvestrant in Women With ER-Positive/HER2-Negative Advanced or Metastatic Breast Cancer That Has Progressed During or After Aromatase Inhibitor Therapy

MLN0128 in Combination With Fulvestrant in Women With Advanced or Metastatic Breast Cancer After Aromatase Inhibitor Therapy

NCT Number: NCT02756364

Protocol Approve Date: 02 October 2017

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

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- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

PROTOCOL

An Open-Label Phase 2 Study of MLN0128 (A TORC1/2 Inhibitor) in Combination With Fulvestrant in Women With ER-Positive/HER2-Negative Advanced or Metastatic Breast Cancer That Has Progressed During or After Aromatase Inhibitor Therapy

MLN0128 in Combination With Fulvestrant in Women With Advanced or Metastatic Breast Cancer After Aromatase Inhibitor Therapy

Sponsor: Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
40 Landsdowne Street
Cambridge, MA 02139 USA
Telephone: +1 (617) 679-7000

Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium", "sponsor", or "Takeda".

Study Number: C31006

IND Number: 126,346 **EudraCT Number:** 2015-003612-20

Compound: MLN0128 (TAK-228)

Date: 02 October 2017 **Amendment Number:** 3

Amendment History:

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
10 February 2016	Initial Protocol	Not applicable	Global
30 March 2016	1	Nonsubstantial	Global
07 March 2017	2	Substantial	Global
02 October 2017	3	Substantial	Global

1.0 ADMINISTRATIVE

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event (SAE) reporting information is presented in Section 11.0, as is information on reporting product complaints.

Takeda Development Center, Inc. (TDC) sponsored investigators, per individual country requirements, will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	North America	Europe
SAE reporting	See Section 11.2	See Section 11.2

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, fulvestrant package insert, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 11.0 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B–Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

1.3 Protocol Amendment 3 Summary of Changes

Rationale for Amendment 3

This document describes the changes in reference to the protocol incorporating Amendment No. 03. The primary reason for this amendment is to update those sections affected by new nonclinical data for MLN0128 metabolism by specific cytochrome P450 (CYP) isoforms. The study's exclusion criteria, list of prohibited concomitant medications, list of relevant CYP inhibitors and inducers, and dietary restrictions related to CYP inhibitors and inducers have been updated accordingly. The number of study sites, recommendations for initiation of crossover treatment, and guidance for fasting serum glucose post-dose collection have also been updated.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

For specific descriptions of text changes and where the changes are located, see Appendix J.

Changes in Amendment 03

1. Remove the exclusion criterion relating to treatment with strong CYP inhibitors or inducers.
2. Update the list of concomitant medications prohibited during the study.
3. Update the list of relevant CYP inhibitors and inducers.
4. Remove dietary restrictions related to CYP inhibitors and inducers.
5. Update the number of study sites.
6. Update the recommendations for initiation of crossover treatment.
7. Update guidance for fasting serum glucose post-dose collection on non-dosing days.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Millennium Pharmaceuticals, Inc.	**Compound:** MLN0128 (TAK-228)	
Title of Protocol: An Open-Label Phase 2 Study of MLN0128 (A TORC1/2 Inhibitor) in Combination With Fulvestrant in Women With ER-Positive/HER2-Negative Advanced or Metastatic Breast Cancer That Has Progressed During or After Aromatase Inhibitor Therapy.	**IND No.:** 126,346	**EudraCT No.:** 2015-003612-20
Study Number: C31006	**Phase:** 2	

Study Design:

This phase 2, open-label, randomized, 3-arm study is designed to evaluate the efficacy and safety of the combination of fulvestrant+daily MLN0128 compared with single-agent fulvestrant, and the combination of fulvestrant+weekly (QW) MLN0128 compared with single-agent fulvestrant in the treatment of postmenopausal women with advanced or metastatic estrogen receptor (ER) positive, human epidermal growth factor receptor-2 (HER2) negative breast cancer that has progressed during or after aromatase inhibitor (AI) therapy. Patients who meet all eligibility criteria will be stratified according to the presence or absence of visceral metastasis (defined as all lesions not included in the following list: breast, skin, subcutaneous tissue, lymph node or bone), previous sensitivity to hormonal therapy, and previous exposure to cyclin-dependent kinase (CDK) 4/6 inhibitors and will be randomized 1:1:1 to 1 of 3 treatment arms:

- Arm A: Single-agent fulvestrant.
- Arm B: Combination of fulvestrant+daily MLN0128.
- Arm C: Combination of fulvestrant+weekly MLN0128.

A safety and tolerability assessment will be performed for the first 6 evaluable patients in Arm C treated with fulvestrant+30 mg weekly MLN0128. After the sixth evaluable patient completes Cycle 1, a review will be performed: if ≤1 dose-limiting toxicity (DLT; see Section 9.3) occurs, the MLN0128 dose for this treatment arm will remain the same (ie, 30 mg weekly MLN0128, in combination with fulvestrant); if ≥2 DLTs occur, all patients subsequently randomized to this treatment arm will receive a starting dose of 20 mg weekly MLN0128 in combination with fulvestrant. For any patients initially assigned to the 30 mg weekly starting dose, the MLN0128 dose may be decreased if necessary per the dose modification criteria in Section 9.4.

Safety assessments (including adverse events [AEs], serious adverse events, laboratory assessments, vital signs, electrocardiograms, Eastern Cooperative Oncology Group [ECOG] performance status, and weight) will be performed throughout the treatment period, including the End-of-Treatment (EOT) visit, to evaluate the safety and tolerability of MLN0128. Radiological tumor evaluations will be used to evaluate disease response according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (Version 1.1) [1].

CCI [redacted]

Patients will receive study medication(s) until disease progression (progressive disease [PD]), unacceptable toxicity, or withdrawal of consent. Patients who discontinue study treatment for reasons other than PD will continue to have progression-free survival (PFS) follow-up visits every 2 months for the first 6 months after the EOT Visit and then every 3 months, until PD or start of another anticancer therapy, whichever occurs first. After PD or start of another anticancer therapy, patients will be followed for survival every 6 months.

Patients in the single-agent fulvestrant arm who have confirmed PD may be allowed to receive crossover treatment with fulvestrant+MLN0128.

Primary Objectives:

- To compare the PFS of patients treated with the combination of fulvestrant+daily MLN0128 versus patients treated with single-agent fulvestrant.
- To compare the PFS of patients treated with the combination of fulvestrant+weekly MLN0128 versus patients treated with single-agent fulvestrant.

Secondary Objectives:

- To compare secondary efficacy endpoints in patients treated with the combination of fulvestrant+daily MLN0128 versus patients treated with single-agent fulvestrant.
- To compare secondary efficacy endpoints in patients treated with the combination of fulvestrant+weekly MLN0128 versus patients treated with single-agent fulvestrant.
- To assess the safety and tolerability of the combination of fulvestrant+MLN0128.
- To collect plasma concentration-time data with sparse pharmacokinetic (PK) sampling (combination fulvestrant+MLN0128 treatment arms [Arm B and Arm C] only) to contribute to future population PK analysis.

Subject Population: Postmenopausal women with advanced or metastatic ER-positive/HER2-negative breast cancer that has progressed during or after AI therapy. Enrollment will be managed to ensure that approximately 40% of enrolled patients have previously received a CDK4/6 inhibitor in combination with an AI.

Number of Subjects: Approximately 153 patients (51 per treatment arm).	**Number of Sites:** Approximately 65 study centers in the United States and Europe.
Dose Level(s): • Arm A, single-agent fulvestrant: fulvestrant, 500 mg intramuscularly (IM), on Cycle 1 Days 1 and 15 (loading regimen), and then on Day 1 of each subsequent 28-day treatment cycle. • Arm B, combination of fulvestrant+daily MLN0128: fulvestrant as above plus MLN0128, 4 mg orally (PO) every day (QD) of a 28-day treatment cycle. • Arm C, combination of fulvestrant+weekly MLN0128: fulvestrant as above plus MLN0128, 30 mg PO QW of a 28-day treatment cycle.	**Route of Administration:** • Fulvestrant: IM. • MLN0128: PO.
Duration of Treatment: Patients will receive study medication(s) until PD, unacceptable toxicity, or withdrawal of consent.	**Period of Evaluation:** Patients who discontinue study treatment for reasons other than PD will continue to have PFS follow-up visits every 2 months for the first 6 months after the EOT Visit, and then every 3 months until PD or start of another anticancer therapy (whichever occurs first). After PD or start of another anticancer therapy, patients will be followed for survival every 6 months.

Main Criteria for Inclusion:

Postmenopausal women with local histological confirmation of ER-positive/HER2-negative metastatic or advanced breast cancer; measurable extra-osseous lesion, or measurable bone lesion (lytic or mixed); ECOG status of 0 or 1; PD during or after prior AI therapy, defined as recurrence during or within 12 months after discontinuation of adjuvant therapy or defined as PD during or within 1 month after discontinuation in the metastatic setting; adequate bone marrow, coagulation, hepatic, cardiac, renal, and metabolic function.

Main Criteria for Exclusion:

Prior therapy with mechanistic target of rapamycin (mTOR) inhibitors, phosphoinositide-3-kinase (PI3K) inhibitors, dual PI3K-mTOR inhibitors, serine/threonine-specific protein kinase (AKT; also known as protein kinase B)

inhibitors, or fulvestrant; prior treatment with >1 line of chemotherapy for metastatic breast cancer; experienced PD on >2 endocrine therapies for metastatic breast cancer; significant previous or existing cardiac conditions; other comorbidities of interest (including poorly controlled diabetes mellitus, significant pulmonary disease).

Main Criteria for Evaluation and Analyses:

The primary endpoint for this study is PFS. Secondary endpoints for this study are overall survival (OS), time to progression (TTP), objective response rate (ORR), clinical benefit rate (CBR) with stable disease (SD) of any duration, CBR with SD duration of at least 6 months, and the number and percentage of patients with treatment-emergent AEs.

Statistical Considerations:

The primary endpoint, PFS, is defined as the time from the date of randomization to the date of first documentation of progression or death due to any cause, whichever occurs first. For a patient whose disease has not progressed and is last known to be alive, or started alternate therapy prior to PD, PFS will be censored at the last response assessment that is SD or better. The Kaplan-Meier method will be used to analyze the distribution of PFS for each treatment arm. The primary hypothesis is to be tested at the 0.10 significance level (2-sided). The p-values from a stratified log-rank test and hazard ratios (HRs) will be presented for each pair-wise comparison.

Secondary efficacy endpoints include OS, ORR, TTP, CBR with SD of any duration, and CBR with SD duration of at least 6 months. OS is defined as the time from the date of randomization to the date of death. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive. OS will be analyzed using similar methods as the primary endpoint of PFS.

ORR is defined as the proportion of patients who achieve a best response of complete response (CR) or partial response (PR) according to RECIST 1.1 criteria [1]. CBR is defined as the proportion of patients who achieve a best response of CR, PR, or SD. The CBR will also be presented for a best response of CR, PR, and SD of at least 6 months. A stratified Cochran-Mantel-Haenszel test will be used to compare ORR and CBR between treatment arms. The Mantel-Haenszel estimate of the odds ratio and the associated 95% confidence intervals (CIs) will be presented for each pair-wise comparison.

TTP is defined as the time from the date of randomization to the date of first documentation of progression. For a patient whose disease has not progressed, TTP will be censored at the last response assessment that is SD or better. TTP will be analyzed using similar methods as the primary endpoint of PFS.

Sample Size Justification: Assuming that the median PFS is 4 months for single-agent fulvestrant and that the combination of fulvestrant+MLN0128 (administered either QD or QW) can improve the median PFS to 8 months (HR of 0.5), then a total of 72 PFS events are needed for each pair-wise comparison. Each treatment arm will require 51 patients (1:1:1 randomization allocation). The calculations are based on a power of 90%, 2-sided alpha of 10%, and a dropout rate of 10% due to either lost to follow-up or withdrawal of consent.

The sample size for the study assumes the accrual duration will be approximately 14 months. The final analysis for the pair-wise comparison of PFS between fulvestrant+daily MLN0128 and fulvestrant, and between fulvestrant+weekly MLN0128 and fulvestrant, is estimated to occur approximately 20 months after the first patient is randomized.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Clinical Study Supplier List (or equivalent).

3.2 Principal Investigator/Coordinating Investigator

The sponsor will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AE	adverse event
AI	aromatase inhibitor
AKT	serine/threonine-specific protein kinase (also known as protein kinase B)
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Oncology
AST	aspartate aminotransferase
CAP	College of American Pathologists
CBR	clinical benefit rate
CDK	cyclin-dependent kinase
CI	confidence interval
CR	complete response
CT	computed tomography
CTC	circulating tumor cell
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer QLQ Questionnaire, version 3.0
EORTC QLQ-BR23	European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire
EOT	End-of-Treatment
ER	estrogen receptor
FBG	fasting blood glucose
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEICAM	Grupo Español de Investigación en Cáncer de Mama
GI	gastrointestinal
HDPE	high-density polyethylene
HbA1c	glycosylated hemoglobin
HER2	human epidermal growth factor receptor-2
Hgb	hemoglobin
HR	hazard ratio
HRQL	health-related quality of life

ICH	International Conference on Harmonisation
IEC	independent ethics committee
IM	intramuscular; intramuscularly
IRB	institutional review board
IRT	interactive response technology
IV	intravenous; intravenously
MedDRA	Medical Dictionary for Regulatory Activities
MLN0128	also known as TAK-228 and INK-128
MRI	magnetic resonance imaging
mTOR	mechanistic target of rapamycin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PD	progressive disease, disease progression
PFS	progression-free survival
PgR	progesterone receptor
PI3K	phosphoinositide-3-kinase
PIK3CA	phosphoinositide-3-kinase, catalytic alpha polypeptide
PK	pharmacokinetic(s)
PO	per os (orally administered)
PPI	proton pump inhibitor
PR	partial response
PRO	patient-reported outcome
PTE	pretreatment event
PTEN	phosphatase and tensin homolog
QD	daily, once per day
QD x3	3 times, daily dosing
QD x5	5 times, daily dosing
QTc	corrected QT interval
QW	weekly, once per week
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SERD	selective estrogen receptor downregulator
SERM	selective estrogen receptor modulator
SmPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reactions
TAK-228	also known as MLN0128
TEAE	treatment-emergent adverse event

TORC1	target of rapamycin complex 1
TORC2	target of rapamycin complex 2
TTP	time to progression
ULN	upper limit of the normal range
US	United States
USPI	United States prescribing information
WHO	World Health Organization

3.4 Corporate Identification

Millennium	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
Takeda	Millennium Pharmaceuticals, Inc, TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

4.1.1 Disease Under Treatment: Breast Cancer

Breast cancer is the most frequent cancer diagnosis in women and is the leading cause of cancer-related deaths in women in Europe and the second leading cause of cancer-related deaths in women in the United States. The American Cancer Society estimates that approximately 232,340 women in the US will receive a new diagnosis of breast cancer in 2013 [2,3]. According to GLOBOCAN 2012, the incidence of breast cancer across Europe in 2012 was 458,718 (http://globocan.iarc.fr/pages/fact_sheets_population.aspx, accessed 19 November 2015). Approximately 39,620 women in the United States and 131,347 women in Europe were predicted to die from their disease in 2013.

Breast cancer is a heterogeneous disease with different histologies, prognoses, natural history, responses to treatment, and molecular characteristics [4-6]. Breast cancer can be classified into 3 major categories or subtypes: hormone receptor-positive tumors that express estrogen receptor (ER), or progesterone receptors (PgRs), or both; tumors that over-express the receptor for human epidermal growth factor receptor-2 (HER2); and basal epithelial-like or "triple-negative tumors" that do not express hormone receptors or HER2 [4,7]. Approximately 66% to 75% of breast cancers are hormone receptor-positive tumors [4,6,8-10].

Standard therapy for ER-positive tumors in postmenopausal women, both in the adjuvant and metastatic disease settings, consists of single-agent antiestrogen therapy. Antiestrogen therapy for postmenopausal women with hormone receptor-positive breast cancer involves the sequential use of selective ER modulators (SERMs; eg, tamoxifen), nonsteroidal or steroidal aromatase inhibitors (AIs) either as single agents or in combinations, and selective ER downregulators (SERDs; eg, fulvestrant) [10]. A combination therapy of the steroidal AI letrozole plus the cyclin-dependent kinase 4/6 (CDK4/6) inhibitor palbociclib is an additional treatment option for postmenopausal women as initial endocrine-based therapy in the metastatic setting [11,12].

Resistance to antiestrogen treatment occurs commonly in patients and is an important therapeutic limitation. Approximately 30% of patients with metastatic disease have primary resistance to initial endocrine therapy and develop progressive disease (PD) within 6 months after initiation of antiestrogen therapy [10,13]. Many other patients may initially respond to hormonal therapy but then develop secondary resistance, defined as PD occurring more than 6 months after initiation of antiestrogen therapy [10,13]. The resistant tumors have not completely lost estrogen dependence and may respond to an additional or alternative antiestrogen therapy, such as the SERD fulvestrant, or to a combination of antihormonals plus agents directed against cellular targets that mediate endocrine resistance [14,15]. However, the duration of response or remission after subsequent, alternative therapy is often shorter than that achieved with earlier therapy [15].

4.1.2 Study Drug: MLN0128

4.1.3 Nonclinical Experience

MLN0128 (also known as TAK-228 and INK-0128) is an orally available, potent, and highly selective ATP-competitive inhibitor of mechanistic target of rapamycin (mTOR) kinase that exhibits dual specificity against both target of rapamycin complexes 1 and 2 (TORC1 and TORC2 [TORC1/2]). MLN0128 is a second-generation mTOR inhibitor that targets the kinase domain of the mTOR enzyme to suppress TORC1 and TORC2 functions. Currently the only mTOR inhibitor drugs available are the derivatives of rapamycin, called rapalogs, which are allosteric inhibitors that target only the TORC1 complex.

MLN0128 selectively and potently inhibited the mTOR kinases (1 nM) in in vitro studies, but relative to mTOR inhibition, MLN0128 had >100-fold less potency on class I (phosphoinositide-3-kinase [PI3K] isoforms α, β, ɣ, δ), class II (PI3KC2α and PI3K2Cβ), and class III (VPS34) PI3K family members. MLN0128 inhibited (>80%) the biochemical activity of 5 kinases (mTOR, DNA-PK, PDGFRα, Flt3, and CK1 epsilon kinases) out of a panel of 222 protein kinases. Out of a panel of 402 distinct kinases, MLN0128 inhibited the ligand binding of only 10 receptor and intracellular protein kinases (ACVR1, BMPR1B, CSF1R, CSNK1D, CSNK1E, DDR1, MEK1, MEK2, PDGFRα, and RIPK2). MLN0128 also displayed potent cellular inhibition of both the TORC1 and TORC2 pathway with cellular pharmacodynamic concentration producing 50% inhibition concentration values of less than 10 nM.

MLN0128, administered orally (PO) in multiple human tumor xenograft mouse models, inhibited angiogenesis and tumor growth by inhibiting mTOR signaling at plasma concentrations associated with in vitro inhibition of mTOR in a dose- and time-dependent manner. These effects display a clear pharmacokinetic (PK)-to-pharmacodynamic relationship [16]. MLN0128 inhibits both the phosphorylation of S6 and 4E-BP1, the downstream substrates of TORC1, and selectively inhibits serine/threonine-specific protein kinase (AKT) phosphorylation at Serine 473 (S473), as evidenced by decreased pAKT, the downstream substrate of TORC2 [16-18]. MLN0128 inhibits mTOR signaling and has demonstrated anticancer activity against a number of human solid tumor cell-line xenograft mouse models, including phosphatase and tensin homolog (PTEN) mutant endometrial, breast, and renal cell carcinomas.

4.1.3.1 Clinical Experience with MLN0128

The first-in-human, phase 1 study of single-agent MLN0128 is currently ongoing in patients with advanced solid malignancies (Study INK128-001). In the dose-escalation phase of this study, 4 dosing schedules were studied: daily dosing (QD) (31 patients), 3 times daily dosing (QD×3) (33 patients), 5 times daily dosing (QD)×5 (22 patients), and weekly dosing (QW) (30 patients). Based on the safety profile, PK/pharmacodynamics, and preliminary efficacy during the dose-escalation phase, MLN0128 dosing regimens of 5 mg QD and 40 mg QW were selected for further evaluation in the expansion phase in patients with renal cell carcinoma, endometrial cancer, or bladder cancer. The QW schedule started at 40 mg but was subsequently reduced to 30 mg due to poor long-term tolerability requiring high rates of dose modification and interruption. As of a

March 2015 data cutoff, the top 5 drug-related adverse events (AEs) by frequency were fatigue (67%), nausea (61%), hyperglycemia (59%), vomiting (49%), and stomatitis (46%), consistent with other agents that inhibit the PI3K/AKT/mTOR pathway. Preliminary signs of antitumor activity have been seen in an assessment of 70 evaluable patients with bladder, endometrial, and renal cell carcinoma that have been treated with MLN0128 either on daily or once weekly dosing schedules. Three partial responses (PRs) and 5 patients with stable disease (SD) ≥6 months were observed among patients treated with daily MLN0128 compared to 1 complete response (CR), 2 PRs, and 3 patients with SD ≥6 months observed in patients treated with weekly MLN0128 [19].

Another phase 1 study of single-agent MLN0128 has been completed in patients with relapsed or refractory multiple myeloma or Waldenström macroglobulinemia (Study INK128-002). The AE profile observed in this study was also consistent with other drugs of the same class, and while there was some preliminary antitumor activity in this patient population, further development in this indication is not being evaluated at this time [20]. A combination study evaluating the use of MLN0128 in combination with paclitaxel with or without trastuzumab in patients with advanced solid tumors (Study INK128-003) has been completed. MLN0128 was generally well tolerated in combination with weekly paclitaxel while exhibiting promising preliminary therapeutic activity.

The effect of MLN0128 on the corrected QT interval (QTc) in patients with advanced solid tumors has been tested in the ongoing, single-arm, designated QTc study (Study C31002). Study C31002 has completed enrollment and the primary analysis of the effect of a single dose of 40 mg MLN0128 on the QT/QTc interval in patients with advanced solid tumors has been concluded. The study results indicate that treatment with MLN0128 is not associated with clinically meaningful effects on the overall electrocardiographic safety profile.

Milled MLN0128 is being investigated either as a single agent or in combination with paclitaxel in an additional phase 1 study in patients with advanced solid tumors (Study MLN0128-1004). Study MLN0128-1004 also investigates the effects of food on MLN0128 exposures. In addition, combinations of milled MLN0128 with MLN1117 (an oral PI3Kα inhibitor) are being evaluated in a phase 1b study in adult patients with advanced nonhematologic malignancies (Study C32001), and combinations of milled MLN0128 with exemestane or fulvestrant are being evaluated in patients with ER-positive/HER2-negative breast cancer (Study C31001; see Section 4.1.3.2).

4.1.3.2 Preliminary Data in Women With ER-Positive/HER2-Negative Breast Cancer With MLN0128 in Combination With Exemestane or Fulvestrant

The ongoing phase 1b/2 Study C31001 examines the safety and efficacy of daily MLN0128 given in combination with exemestane or fulvestrant therapy in postmenopausal women with ER-positive/HER2-negative advanced or metastatic breast cancer that has progressed on treatment with everolimus in combination with exemestane or fulvestrant. The completed phase 1b portion of the study tested combination doses of MLN0128 from 3 to 5 mg QD. As of November 2015, 9 patients received treatment with MLN0128 plus fulvestrant and 15 patients received MLN0128 plus exemestane. Of 23 disease-evaluable patients, 3 achieved a PR (all treated in combination with fulvestrant) and 13 had SD. The clinical benefit rate (CBR) at 6 months was 75% in the fulvestrant-treated patients and 40% in the exemestane-treated patients. Four patients were

ongoing. Based on the available preliminary data, the most common (occurring in ≥50% of patients) drug-related AEs included fatigue, nausea, diarrhea, pruritus, and stomatitis.

The observed safety profile of MLN0128 in combination with either exemestane or fulvestrant was generally consistent with that of single-agent MLN0128. Per protocol, cohort safety reviews were conducted with the investigators during phase 1b, and 4 mg was selected as the starting dose of MLN0128 for the phase 2 portion of the study. As of 09 November 2015, 14 patients have been enrolled in the phase 2 part of the study.

4.1.3.3 Risk-Benefit Assessment for the Use of MLN0128 in ER-Positive/HER2-Negative Breast Cancer

The most common treatment-emergent AEs (TEAEs) observed with MLN0128 are consistent with the pharmacodynamic mechanism of mTOR inhibition that is also seen with rapalogs (TORC1 inhibition) or other dual TORC1/2 inhibitors. The TEAEs observed across the MLN0128 single-agent studies include diarrhea, fatigue, vomiting, rash, mucosal inflammation, asthenia, dysgeusia, thrombocytopenia, stomatitis, blood creatinine increased, hyperglycemia, nausea, anorexia, and decreased appetite. Further details are provided in the current version of the Investigator's Brochure.

During this study, risk mitigation strategies include, but are not limited to, strict application of the study inclusion and exclusion criteria, frequent monitoring of clinical and laboratory results, guidelines for prophylaxis and management of potential toxicities, criteria for dose modification, and regular monitoring of AEs and serious adverse events (SAEs) by the sponsor.

Nonclinical data supporting the potential benefits of MLN0128 as an anticancer therapy are summarized in Section 4.1.3. Observed indications of clinical activity of the combination of fulvestrant+MLN0128 are presented in Section 4.1.3.2.

4.2 Rationale for the Proposed Study

Approximately 70% of breast cancers express hormone receptors, either PgR or ER [8]. Historically, single-agent endocrine therapy has been the cornerstone of treatment for patients with ER/PgR-positive advanced breast cancer. Tamoxifen, a SERM that exhibits antagonistic activity against the ER in breast tissue, and nonsteroidal AIs such as letrozole and anastrozole, which block the conversion of androgenic steroids into estrogenic steroids, have routinely been used in succession in the adjuvant and/or the first-line setting of advanced and/or metastatic ER/PgR-positive breast cancer. In fact, a lack of complete cross-resistance between steroidal and nonsteroidal AIs has been demonstrated in several trials [21,22].

An alternate second-line or subsequent antihormonal treatment option is the SERD fulvestrant, which is currently indicated for the treatment of postmenopausal women with metastatic hormone receptor-positive breast cancer following the failure of antiestrogen therapy. Fulvestrant provides a distinct mechanism of action from AIs by directly targeting ER for proteasomal degradation, which downregulates E2F transcription and thereby the proliferation signal.

Preclinical data suggest that breast cancer cells critically rely on PI3K-mTOR signaling for survival after complete abrogation of ER signaling [23]. Data from a study with fulvestrant administered 500 mg monthly to patients with recurrent hormone receptor-positive/HER2-negative breast cancer indicate significant antitumor activity after both antiestrogen and AI failure [24].

Acquired resistance to antihormonal therapy remains a major clinical problem in the treatment of patients with ER/PgR-positive breast cancer [25]. Preclinical and clinical research focused on mechanisms of resistance has confirmed that various signal transduction pathways are activated in breast cancer cells to escape the effect of endocrine therapy. In particular, activation of the PI3K/mTOR pathway was identified as a key adaptive change driving acquired resistance to endocrine therapy. In addition, a strong link between proliferative properties and the emergence of hormone-independent breast cancer cells has been identified [26,27]. These results suggested that simultaneous inhibition of ER and either PI3K/mTOR signaling or cell cycle regulation could prevent or delay the emergence of hormone-independent breast cancer cells.

A strategy of targeting both ER and mTOR was tested in the BOLERO-2 study through the addition of everolimus (an mTOR inhibitor) to the steroidal AI exemestane. The combination significantly improved progression-free survival (PFS) in women with advanced ER-positive/HER2-negative breast cancer after failure of treatment with letrozole or anastrozole [28] and led to the US Food and Drug Administration (FDA) approval of everolimus in this setting in 2012. Of note, the BOLERO-2 study primarily included patients whose disease recurred during or soon after antihormonal therapy, a population that was thought to be more sensitive to combined ER/mTOR inhibition than patients who are naive to endocrine therapy or who progress after a long treatment-free interval. The HORIZON trial, in which women without prior antihormonal therapy were treated either with single-agent letrozole or with the combination of letrozole plus the rapalog temsirolimus, failed to show improvement in PFS with the combination (median PFS=9 months for both groups; hazard ratio [HR] 0.90) [29].

In February 2015, a combination of the nonsteroidal AI letrozole plus the CDK4/6 inhibitor palbociclib was approved by the FDA for the treatment of postmenopausal women with ER-positive/HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. The results of the PALOMA-1 study on which this approval was based demonstrated that the addition of palbociclib to letrozole significantly improved PFS (20.2 vs 10.2 months; HR 0.488) in advanced ER-positive/HER2-negative breast cancer [12].

Another potentially beneficial combination is the ER-targeted SERD fulvestrant+everolimus (an mTOR inhibitor that targets the TORC1 complex). This combination has shown efficacy in postmenopausal women after failure of AI treatment similar to that of the combination of tamoxifen with everolimus (median time to progression [TTP] 7.4 months) [30]. Furthermore, the combination of fulvestrant and a dual TORC1/TORC2 inhibitor induced significantly higher rates of tumor cell death when compared to the combination of fulvestrant+everolimus [27,31], suggesting synergistic effects on tumor cell death through a more complete inhibition of mTOR-related survival signaling in the presence of complete ER abrogation by fulvestrant. These

data suggest that by simultaneously targeting both the ER and survival pathways, there is a synergistic effect on tumor cell death.

Collectively, these data suggest that the combination of fulvestrant+MLN0128 may improve the outcome of patients with ER-positive breast cancer that has progressed on antiestrogen directed antihormonal therapy. The goal of this study is to test the hypothesis that dual TORC1/2 inhibition in combination with fulvestrant has the potential to overcome endocrine therapy resistance in ER-positive breast cancer through the inhibition of growth and survival of tumor cells as well as the emergence of resistant cells following therapy with AI or AI combined with CDK4/6 inhibitors.

RATIONALE FOR SELECTED DOSES AND SCHEDULES OF MLN0128

The selected doses and schedules of 4 mg QD (Arm B) and 30 mg MLN0128 QW (Arm C) to be given in combination with fulvestrant are based on the findings from 3 studies:
Studies INK128-001, MLN0128-1004, and C31001.

Study INK128-001 was the first-in-human study of MLN0128. Study INK128-001 was an open-label study designed to determine the maximum tolerated dose and to identify dose-limiting toxicity (DLT) for oral administration of single-agent unmilled MLN0128 and to characterize the safety and tolerability of escalating doses of MLN0128 in patients with advanced solid tumors. In this study, 116 patients with advanced solid tumors received single-agent MLN0128 (2 to 40 mg via 4 dosing schedules) in the dose escalation phase.

Doses of 40 mg QW, 30 mg QW, and 5 mg QD were further evaluated in an additional 82 patients in the expansion phase, where 30 mg QW and 5 mg QD were selected as the recommended phase 2 doses and schedules of MLN0128 for further development.

Weekly Dosing

Scale-up manufacturing of MLN0128 required the introduction of a physical milling step to control particle size distribution of MLN0128 drug substance. With the introduction of milled MLN0128, the recommended dose to be used in Arm C of this study (30 mg milled MLN0128 QW) was further confirmed in Study MLN0128-1004 (Table 4.a). A total of 14 patients were enrolled and assigned, sequentially, to 2 QW dosing cohorts. PK, safety, and tolerability were assessed.

Table 4.a DLT Observed With Weekly MLN0128 in Study MLN0128-1004

Dose of Milled MLN0128	Number of Evaluable Patients	DLTs Observed in Cycle 1
20 mg QW	6	None
30 mg QW	6	None

DLT=dose-limiting toxicity, QW=once weekly.

As none of the patients in either dose cohort experienced DLT in Cycle 1, a dose of 30 mg MLN0128 QW was selected for further development. No clinically meaningful differences in PK

of MLN0128 were noted between the unmilled MLN0128 (Study INK128-001) and milled MLN0128 (Study MLN0128-1004) when given QW. The tolerability of 30 mg milled MLN0128 QW in combination with fulvestrant will be tested in a safety lead-in of 6 patients in Arm C of this study (as detailed in Section 7.1.2).

Daily Dosing

The recommended phase 2 dose of 4 mg milled MLN0128 QD in combination with either exemestane or fulvestrant was determined in the phase 1b dose finding portion of Study C31001 (see Section 4.1.3.2). In the phase 1b portion of the study, 12 patients were initially dosed in a safety lead-in with 5 mg QD of the unmilled MLN0128 material in combination with either fulvestrant or exemestane (6 patients each). No DLTs were observed during Cycle 1 of treatment; however, 6 of the 12 patients did require dose reductions in Cycles 2 and 3 (2 patients each), and 1 patient each in Cycles 4 and 7. In order to evaluate the safety of milled MLN0128 material, escalation cohorts of 3 and 4 mg QD of the milled material were tested in combination: 6 patients at the 3 mg dose (3 in combination with exemestane and 3 with fulvestrant) and 6 patients at the 4 mg dose (all with exemestane). Of the 6 patients treated with 4 mg MLN0128 in combination with exemestane, 1 patient experienced a DLT of nausea and diarrhea. After review of the data with the investigators, including events occurring outside of the DLT evaluation period, it was agreed to stop escalation and move forward with 4 mg QD in the phase 2 portion of the study (in combination with either exemestane or fulvestrant), as well as in Study C31006 (in combination with fulvestrant).

5.0 STUDY OBJECTIVES

5.1 Primary Objectives

The primary objectives are:

- To compare the PFS of patients treated with the combination of fulvestrant+daily MLN0128 versus patients treated with single-agent fulvestrant.
- To compare the PFS of patients treated with the combination of fulvestrant+weekly MLN0128 versus patients treated with single-agent fulvestrant.

5.2 Secondary Objectives

The secondary objectives are:

- To compare secondary efficacy endpoints in patients treated with the combination of fulvestrant+daily MLN0128 versus patients treated with single-agent fulvestrant.
- To compare secondary efficacy endpoints in patients treated with the combination of fulvestrant+weekly MLN0128 versus patients treated with single-agent fulvestrant.
- To assess the safety and tolerability of the combination of fulvestrant+MLN0128.
- To collect plasma concentration-time data with sparse PK sampling (combination fulvestrant+MLN0128 treatment arms [Arm B and Arm C] only), to contribute to future population PK analysis.

5.3 Health-Related Quality of Life Objective

The health-related quality of life (HRQL) objective is:

- To assess the HRQL and symptoms, as measured by the European Organization for Research and Treatment of Cancer QLQ Questionnaire, version 3.0 (EORTC QLQ-C30) and the EORTC QLQ Breast Cancer-Specific Questionnaire (EORTC QLQ-BR23), among the 3 treatment arms.

5.4 Exploratory Objectives

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6.0 STUDY ENDPOINTS

6.1 Primary Endpoint

The primary endpoint is:

- PFS.

6.2 Secondary Endpoints

The secondary endpoints are:

- Overall survival (OS).
- TTP.
- Objective response rate (ORR); defined as CR+PR per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 [1].
- CBR; defined as CR+PR+SD with SD of any duration, and CBR with SD duration of at least 6 months.
- The number and percentage of patients with TEAEs.

6.3 Health-Related Quality of Life Endpoints

The HRQL endpoints are:

- Changes from Baseline in functional and symptom scores, and global health status and quality of life score from the EORTC QLQ-C30 questionnaire.
- Changes from Baseline in functional and symptom scales from the EORTC QLQ-BR23 questionnaire.

6.4 Exploratory Endpoints

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7.0 STUDY DESIGN

7.1 Overview of Study Design

7.1.1 Enrollment and Randomization

This is an open-label, randomized, 3-arm, multicenter, phase 2 study of the efficacy and safety of the combination of fulvestrant+daily MLN0128 compared with single-agent fulvestrant, and the combination of fulvestrant+weekly MLN0128 compared with single-agent fulvestrant, in the treatment of postmenopausal women with advanced or metastatic ER-positive/HER2-negative breast cancer that has progressed during or after AI therapy. Patients who provide written informed consent and meet all eligibility criteria will be randomized 1:1:1 to 1 of 3 treatment arms via the interactive response technology (IRT):

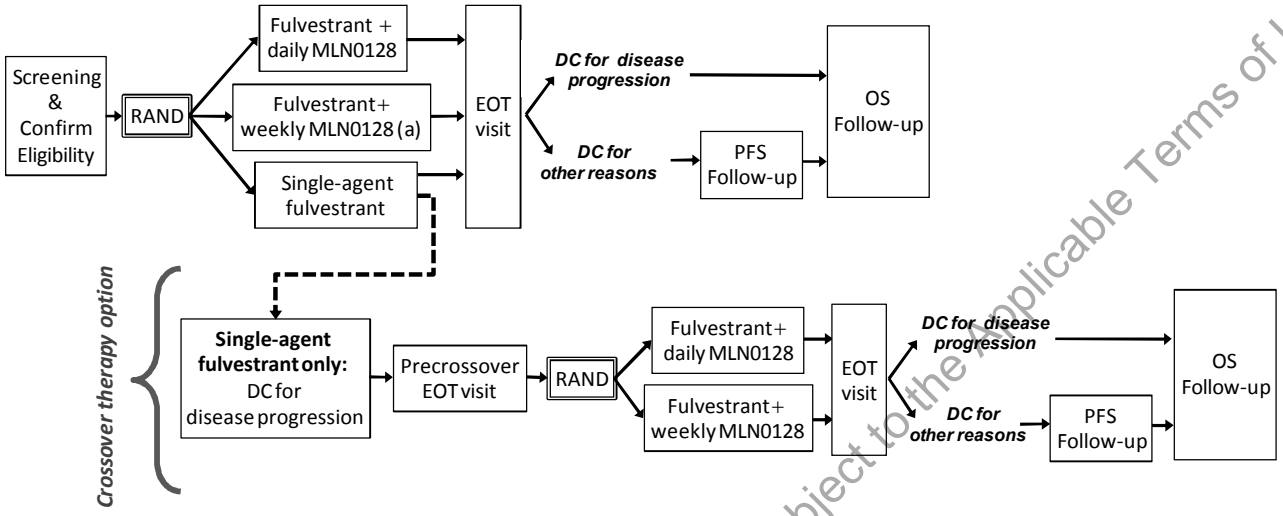
- Arm A, single-agent fulvestrant: fulvestrant, 500 mg intramuscularly (IM), on Cycle 1 Days 1 and 15 (loading regimen), and then on Day 1 of each subsequent 28-day cycle.
- Arm B, combination of fulvestrant+daily MLN0128: fulvestrant as above and MLN0128, 4 mg PO QD continuously.
- Arm C, combination of fulvestrant+weekly MLN0128: fulvestrant as above and MLN0128, 30 mg PO QW continuously.

Patients will be stratified at randomization according to the presence or absence of visceral metastasis, previous sensitivity to hormonal therapy, and previous exposure to CDK 4/6 inhibitors. Visceral metastasis is defined as all lesions not included in the following list: breast, skin, subcutaneous tissue, lymph node or bone. Previous sensitivity to hormonal therapy is defined as at least 24 months of endocrine therapy before recurrence in the adjuvant setting (ie, in patients who have not received previous endocrine therapy in the metastatic setting) or a response or stabilization for at least 24 weeks of the most recent endocrine therapy for advanced/metastatic disease.

Enrollment will be managed via the IRT to ensure that approximately 40% of enrolled patients have previously received a CDK4/6 inhibitor in combination with an AI. Enrollment of non-CDK4/6 pretreated patients may be stopped in the case that 60% or greater of enrollment has occurred with only non-CDK4/6 pretreated patients.

Enrollment is defined as being randomized to a treatment arm. The first dose of study drug must be administered within 5 days after randomization on study. Patients will receive study medication(s) in 28-day cycles. The study design is displayed in Figure 7.a.

Figure 7.a C31006 Study Design



DC=discontinuation, EOT=End-of-Treatment, OS=overall survival, PFS=progression-free survival, RAND=randomization.
(a) The weekly dose of 30 mg MLN0128 will be tested in a safety lead-in of 6 patients in this study (as detailed in Section 7.1.2) to ensure safety and tolerability of the combination with fulvestrant.

7.1.2 Weekly MLN0128 Dose Confirmation (Arm C)

This will be the first study in which weekly MLN0128 will be combined with fulvestrant. Therefore, a safety and tolerability assessment will be performed for patients treated with fulvestrant+weekly MLN0128 (30 mg) after the first 6 DLT-evaluable patients have completed 1 cycle (ie, Cycle 1 Day 28). Patients will be considered evaluable for DLT assessment if they have completed all scheduled study visits during the first cycle and have received at least 3 (75%) of the 4 planned doses of MLN0128 in combination with fulvestrant in Cycle 1. The 30 mg starting dose for weekly MLN0128 will be confirmed or adjusted based on the DLTs observed (see Section 9.3 for DLT definitions):

- If ≤1 DLT occurs, the MLN0128 dose for this treatment arm will remain the same (ie, 30 mg weekly MLN0128, in combination with fulvestrant).
- If ≥2 DLTs occur, all patients subsequently randomized to this treatment arm will receive a starting dose of 20 mg weekly MLN0128, in combination with fulvestrant. The starting dose reduction will be documented in formal written communication to all study sites.

DLTs will be assessed and collected in the database for the first 6 evaluable patients in Arm C only (fulvestrant+weekly MLN0128). DLTs are not applicable to patients in Arm A or Arm B at any time in the study, or to patients in Arm C who are not included in the safety and tolerability assessment, or to cross-over patients. Enrollment of patients into the study will continue while this safety and tolerability assessment is conducted. For any patients initially assigned to the 30 mg

QW starting dose, the MLN0128 dose may be decreased if necessary per the dose modification criteria in Section 9.4.

7.1.3 Study Evaluations (All Treatment Arms)

Safety assessments (including AEs, SAEs, laboratory assessments, vital signs, electrocardiograms (ECGs), Eastern Cooperative Oncology Group [ECOG] performance status, and weight) will be performed throughout the treatment period, including the End-of-Treatment (EOT) Visit, to evaluate the safety and tolerability of MLN0128. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective date 14 June 2010 [32].

HRQL will be assessed via the EORTC QLQ-C30 and EORTC QLQ-BR23 instruments throughout the treatment period, including the EOT Visit.

Radiological tumor evaluations (computed tomography [CT] scan with intravenous [IV] contrast or magnetic resonance imaging [MRI] as clinically indicated) of the chest, abdomen, and pelvis will be used to evaluate disease response according to RECIST guidelines (Version 1.1) [1]. Radiographic tumor evaluations will be performed by the investigator at the time points specified in the Schedule of Events.

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Blood samples will be collected (from patients in the combination fulvestrant+MLN0128 treatment arms [Arm B and Arm C] only) to contribute data to an overall population plasma PK analysis, in combination with data from the other clinical studies of MLN0128.

Patients will receive study medication(s) until PD, unacceptable toxicity, or withdrawal of consent. Patients who discontinue study medication will complete an EOT Visit 30 to 40 days after the last dose of study drug. The EOT Visit should be conducted before the initiation of subsequent anticancer therapy, even if it occurs sooner than 30 days after the last dose of study drug. Patients who discontinue study treatment for reasons other than PD will continue to have PFS follow-up visits every 2 months (±1 week) for the first 6 months after the EOT Visit and then every 3 months (±1 week), until PD or start of another anticancer therapy, whichever occurs first. After PD or start of another anticancer therapy, patients will be followed for survival every 6 months (±1 week).

7.1.4 Potential for Crossover Treatment

Patients in the single-agent fulvestrant arm (Arm A) who have radiographically confirmed PD may be allowed to receive crossover treatment with the combination of fulvestrant+MLN0128 (see Figure 7.a). Once documented PD has been confirmed, patients referred for crossover will

complete the Precrossover EOT Visit as soon as possible (see the Schedule of Events for details). Patients must meet all applicable study eligibility criteria at the time of crossover (eg, the exclusion for prior fulvestrant therapy would not apply), and eligibility for crossover will be confirmed by the sponsor's project clinician (or designee). Eligible patients will then be randomized via the IRT in a 1:1 ratio to either fulvestrant+daily MLN0128 or fulvestrant+weekly MLN0128.

It is recommended that crossover treatment begin within 28 days (+10 days) after documented disease progression (imaging date of PD), with the goal of maintaining the ongoing schedule of fulvestrant therapy (ie, dosing every 28 days). Whenever possible, MLN0128 should be initiated at the next scheduled dose of fulvestrant but only when the patient has completed the precrossover screening requirements and is eligible to continue. If the crossover treatment cannot begin within 28 days (+10 days) after documented PD, contact the medical monitor.

Patients may receive crossover treatment until they experience PD on crossover treatment, unacceptable toxicity, they withdraw consent, or they are no longer considered by the investigator to be deriving clinical benefit from the crossover treatment.

Only the data collected during the study treatment in the initial single-agent fulvestrant arm will be included in the planned efficacy and safety analyses for the study. After crossover treatment begins, safety and efficacy data will be collected (as detailed in the Schedule of Events) and presented separately.

7.1.5 Potential for Single-Agent MLN0128 Dosing

If fulvestrant is discontinued for a patient in either combination arm (Arm B or Arm C), the patient may continue receiving MLN0128 at their current dose if, after discussion between the investigator and sponsor, it is determined that the patient would derive benefit from continued treatment with single-agent MLN0128 and there are no safety concerns.

7.2 Number of Patients

Approximately 153 patients (51 patients per treatment arm) will be enrolled in this study from approximately 65 study centers in North America and Europe. A patient is considered to be enrolled in the study when she has been randomized into a treatment arm.

7.3 Duration of Study

Patients will receive study medication(s) until PD, unacceptable toxicity, or withdrawal of consent. Patients who discontinue study medication will complete an EOT Visit 30 to 40 days after the last dose of study drug. The EOT Visit should be conducted before the initiation of subsequent anticancer therapy, even if it occurs sooner than 30 days after the last dose of study drug. Patients who discontinue study treatment for reasons other than PD will continue to have PFS follow-up visits every 2 months (±1 week) for the first 6 months after the EOT Visit and then every 3 months (±1 week), until PD or start of another anticancer therapy, whichever occurs first. After PD or start of another anticancer therapy, patients will be followed for OS every 6 months (±1 week).

The accrual duration will be approximately 14 months. A final analysis of PFS will be performed after the required number of events has been observed which is expected approximately 20 months after the first patient is randomized. The study will be closed approximately 20 months after the first patient is randomized, or when the last patient discontinues study treatment.

8.0 STUDY POPULATION

8.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Female patients aged 18 years or older who are postmenopausal. Postmenopausal is defined as:
   - Aged ≥55 years and 1 year or more of natural amenorrhea prior to Screening, or
   - Aged <55 years and 1 year or more of amenorrhea prior to Screening, with a follicle-stimulating hormone level >40 mIU/mL and an estradiol level of <20 pg/mL, or
   - Surgical menopause with bilateral oophorectomy.

     Note: Ovarian radiation or treatment with a luteinizing hormone-releasing hormone agonist (goserelin acetate or leuprolide acetate) is not permitted for induction of ovarian suppression.
2. Histologically proven diagnosis of breast cancer with evidence of metastatic disease or locoregional recurrence, not amenable to resection or radiation therapy with curative intent.
3. Histological confirmation and documentation of ER-positive status (≥1% positive stained cells) by local laboratory testing utilizing an assay consistent with local standards.
4. Histological or cytological confirmation and documentation of HER2-negative status by local laboratory testing using criteria in the American Society of Oncology (ASCO)/College of American Pathologists (CAP) Clinical Practice Guideline update [33].
5. Measureable disease defined as either of the following:
   - At least 1 extra-osseous lesion that can be accurately measured in at least 1 dimension. The lesion must measure ≥20 mm with conventional imaging techniques or ≥10 mm with spiral CT or MRI. Lymph nodes must be ≥1.5 cm in the short axis to be considered measurable.
   - Bone lesions (lytic or mixed [lytic plus sclerotic]) in the absence of measurable disease as defined above.

     Note: Patients with sclerotic/osteoblastic bone lesions only, in the absence of measurable disease, are not eligible.
6. PD during prior AI therapy defined as:
   - Recurrence during or within 12 months after completion or discontinuation of adjuvant therapy or
   - Progression during or within 1 month after the end of therapy in the metastatic setting.

     Note: AI is not required to be the most recent therapy, but progression on AI and progression on most recent therapy are both required for eligibility.

7. Patients who have a history of brain metastasis are eligible for the study provided that all of the following criteria are met:
   - Brain metastases have been treated.
   - No evidence of PD for ≥3 months before the first dose of study drug.
   - No hemorrhage after treatment.
   - Off dexamethasone treatment for ≥4 weeks before the first dose of study drug.
   - No ongoing requirement for dexamethasone or antiepileptic drugs.
8. ECOG performance status of 0 or 1 (refer to Appendix D).
9. Clinical laboratory values as specified below within 4 weeks before the first dose of study drug:
   - Bone marrow reserve consistent with absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L; platelet count $\geq 100\times10^9$/L; hemoglobin (Hgb) ≥9 g/dL
   - Total bilirubin ≤1.5 × the upper limit of the normal range (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5×ULN (≤5×ULN if liver metastases are present).
   - Creatinine clearance ≥40 mL/min based on Cockcroft-Gault estimate (refer to Appendix E) or based on a 12- or 24-hour urine collection.
   - Fasting serum glucose ≤130 mg/dL and fasting triglycerides ≤300 mg/dL.
10. Ability to swallow oral medications, willingness to perform mucositis prophylaxis, and suitable venous access for the study-required blood sampling.
11. Voluntary written consent must be given by the patient (or the patient's legally acceptable representative) before performance of any study-related procedure that is not part of standard medical care, with the understanding that consent may be withdrawn at any time without prejudice to the patient's future medical care.

8.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Prior therapy with mTOR, PI3K, or dual PI3K-mTOR inhibitors, AKT inhibitors, or fulvestrant.
2. Prior treatment with >1 line of chemotherapy for metastatic breast cancer or for locoregional recurrence that was not amenable to resection or radiation therapy with curative intent.
3. Experienced PD on >2 endocrine therapies for metastatic breast cancer or for locoregional recurrence that was not amenable to resection or radiation therapy with curative intent.

4. Life-threatening metastatic visceral disease (defined as extensive hepatic involvement or symptomatic pulmonary lymphangitic spread). Patients with discrete pulmonary parenchymal metastases are eligible, provided their respiratory function is not compromised as a result of disease.
5. Other clinically significant comorbidities, such as uncontrolled pulmonary disease, active central nervous system disease, active infection, or any other condition that could compromise the patient's participation in the study.
6. History of any of the following within the last 6 months before the first dose of study drug:
   - Ischemic myocardial event, including angina requiring therapy and artery revascularization procedures.
   - Ischemic cerebrovascular event, including transient ischemic attack and artery revascularization procedures.
   - Requirement for inotropic support (excluding digoxin) or serious (uncontrolled) cardiac arrhythmia (including atrial flutter/fibrillation, ventricular fibrillation, or ventricular tachycardia).
   - Placement of a pacemaker for control of rhythm.
   - New York Heart Association Class III or IV heart failure (see Appendix F).
   - Pulmonary embolism.
7. Significant active cardiovascular or pulmonary disease, including:
   - Uncontrolled hypertension (ie, either systolic blood pressure >180 mm Hg or diastolic blood pressure >95 mm Hg).
   - Pulmonary hypertension.
   - Uncontrolled asthma or oxygen saturation <90% by arterial blood gas analysis or pulse oximetry on room air.
   - Significant valvular disease; severe regurgitation or stenosis by imaging independent of symptom control with medical intervention; or history of valve replacement.
   - Medically significant (symptomatic) bradycardia.
   - History of arrhythmia requiring an implantable cardiac defibrillator.
   - Baseline prolongation of QTc (eg, repeated demonstration of QTc interval >480 msec, or history of congenital long QT syndrome, or torsades de pointes).
8. Diagnosed with or treated for another malignancy within 2 years before the first dose of study drug, or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are *not* excluded if they have undergone complete resection.

9. Receipt before the first dose of study drug of any of the following:
    - Any investigational agent within 4 weeks.
    - Chemotherapy within a period of time that is less than the cycle length used for that treatment (eg, within 3 weeks for fluorouracil, doxorubicin, or epirubicin or within 1 week for weekly chemotherapy).
    - Previous endocrine therapy is permitted without any window.
    - Radiotherapy within 2 weeks. All acute toxic effects, except toxicities not considered a safety risk for the patient at the investigator´s discretion, must be resolved to Grade <1 per NCI CTCAE version 4.0.
    - Major surgery or other anticancer therapy not previously specified within 4 weeks. All acute toxic effects, except toxicities not considered a safety risk for the patient at the investigator´s discretion, must be resolved to Grades <1 per NCI CTCAE version 4.0.
10. Chronic concomitant therapy with bone-targeting agents (eg, bisphos, denosumab) for the prevention of bone metastases. Concomitant treatment with bone-targeting agents is permitted for treatment of osteoporosis or management of existing bone metastases if initiated at least 4 weeks before the first dose of study drug.
11. Requirement for chronic use of systemic corticosteroids (either IV or oral steroids). Inhalers and low-dose replacement therapy are allowed.
12. Requirement for daily or chronic use of a proton pump inhibitor (PPI). All patients are required to stop taking PPIs at least 7 days before receiving the first dose of study drug.
13. Manifestations of malabsorption due to prior gastrointestinal (GI) surgery, GI disease, or for an unknown reason that may alter the absorption of MLN0128.
14. Poorly controlled diabetes mellitus defined as glycosylated hemoglobin (HbA1c) >7%; patients with a history of transient glucose intolerance due to corticosteroid administration may be eligible if all other inclusion/exclusion criteria are met.
15. Known human immunodeficiency virus infection.

9.0 STUDY DRUG

9.1 Study Drug Administration: Fulvestrant Plus MLN0128

All protocol-specific criteria for administration of study drug (MLN0128 or fulvestrant) must be met and documented prior to the first dose of study drug. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

For all treatment arms, fulvestrant (500 mg) will be administered IM, according to the current US Prescribing Information (USPI) or the current Summary of Product Characteristics (SmPC), on Cycle 1 Days 1 and 15 (loading regimen), and then on Day 1 of each subsequent 28-day cycle. Fulvestrant will be administered at the study site by appropriately trained clinical staff, under the supervision of the investigator or identified subinvestigator(s).

For Arm B, daily MLN0128 will be administered on an empty stomach. It is recommended that each dose of MLN0128 be given PO with 8 ounces (240 mL) of water. Patients should be instructed to refrain from eating and drinking (except for water and prescribed medications) for 2 hours before and 1 hour after each dose.

For Arm C, weekly MLN0128 will be administered with a light meal. Examples of a light meal are provided in Table 9.a. Patients should begin consuming the light meal no more than 30 minutes before taking the weekly dose of MLN0128. It is recommended that each dose of MLN0128 be given PO with 8 ounces (240 mL) of water.

Table 9.a Examples of a Light Meal

	Low-Fat Breakfast	**Light Snack**
Nutritional information	Approximately 330 calories, with 9 g of fat	Approximately 100 to 300 calories, with 1.5 g of fat
Example	2 slices of toast with 1 teaspoon of low-fat margarine, 1 teaspoon of jelly, and 8 oz of skimmed milk	3.63 oz pudding cup or 1 slice of toast with 1 teaspoon of jelly and 8 oz of skimmed milk

Patients should be instructed to take MLN0128 at approximately the same time on each scheduled dosing day and not to take more than the prescribed dose at any time. Patients should swallow the MLN0128 capsules whole and not chew, open, or manipulate the capsules in any way before swallowing. If a patient does not take their MLN0128 dose within 12 hours after the scheduled dosing time (for patients in Arm B) or within 24 hours after the scheduled dosing time (for patients in Arm C), then the dose should be skipped and considered a missed dose. Patients should record any missed doses in their dosing diary (see Dosing Diary Arm A and Dosing Diary Arm B) and resume drug administration at the next scheduled time with the prescribed dosage. Patients should be instructed not to take their MLN0128 dose at home on days they have a study visit at the clinic. The MLN0128 dose should be taken at the clinic after the required procedures are performed as described in the Schedule of Events.

If severe emesis or mucositis prevents the patient from taking scheduled doses, that dose will be skipped. If emesis occurs after MLN0128 ingestion, the dose will not be readministered, and patients should resume dosing at the next scheduled time with the prescribed dosage. Patients should record the occurrence of the emesis in their patient dosing diary. Under no circumstance should a patient repeat a dose or double-up doses.

9.2 Reference/Control Therapy: Single-Agent Fulvestrant

Fulvestrant (500 mg) will be administered IM, according to the current USPI or SmPC, on Cycle 1 Days 1 and 15 (loading regimen), and then on Day 1 of each subsequent 28-day cycle. Fulvestrant will be administered at the study site by appropriately trained clinical staff, under the supervision of the investigator or identified subinvestigator(s).

9.3 Definitions of DLT (Weekly MLN0128 Dose Confirmation)

Dose-limiting toxicities are defined according to the AE profile observed during the first 28 days of study drug administration as described below. Occurrence of DLTs in the first 6 evaluable patients in the combination fulvestrant+weekly MLN0128 treatment arm (Arm C) will be reviewed to evaluate the safety and tolerability of 30 mg weekly MLN0128 in combination with fulvestrant (see Section 7.1.2):

- If ≤1 DLT occurs, the MLN0128 dose for this treatment arm will remain the same (ie, 30 mg weekly MLN0128 in combination with fulvestrant).
- If ≥2 DLTs occur, all patients subsequently randomized to this treatment arm will receive a starting dose of 20 mg weekly MLN0128 in combination with fulvestrant. The starting dose reduction will be documented in formal written communication to all study sites.

Toxicity will be evaluated according to the NCI CTCAE, Version 4.03, effective 14 June 2010 [32]. A DLT will be defined as any of the following events that are considered by the investigator to be at least possibly related to treatment with weekly MLN0128 in combination with fulvestrant:

- Grade 3 or higher nonhematologic toxicity, despite adequate treatment, except for the following:
  - Grade 3 hyperglycemia lasting ≤14 days (all patients should receive optimal antiglycemic treatment, including insulin).
  - Grade 3 rash lasting ≤3 days (all patients should receive topical steroid treatment, oral antihistamines, and oral steroids, if necessary).
- Grade 4 neutropenia lasting >7 days in the absence of growth factor support.
- Grade 4 neutropenia of any duration accompanied by fever ≥38.5°C and/or systemic infection.
- Any other ≥Grade 4 hematologic toxicity.
- Inability to administer at least 75% of planned doses of MLN0128 within Cycle 1 due to study drug-related toxicity.

- Any clinically significant occurrence that the investigator and sponsor agree would place patients at an undue safety risk.

9.4 Dose Modification Guidelines

This section describes dose modification guidelines for MLN0128. Any dose modifications for fulvestrant should follow the guidelines provided in the current USPI or SmPC for fulvestrant.

MLN0128 should be administered QD or QW in 28-day cycles, and dosing should continue unless the patient has a Grade 3 or higher MLN0128-related event. In the case of multiple less severe AEs occurring together for which, in the investigator's judgment, the patient would benefit from a dose modification (ie, reduction or delay), dose modification may be considered. General guidelines for MLN0128 dose interruption and dose reduction are provided in Section 9.4.1 and Section 9.4.2. Detailed dose modification requirements for specific clinical events are provided in Section 9.8.

Dose modifications (including dose interruption, reduction, or discontinuation) for fulvestrant, if necessary, should be based on the current fulvestrant SmPC or USPI, local institution standards, and the investigator's best clinical judgement. In the single-agent fulvestrant arm (Arm A): if fulvestrant is discontinued for a patient in the single-agent fulvestrant arm due to PD, the patient may be eligible for crossover treatment as described in Section 7.1.4; if fulvestrant is discontinued due to safety concerns or intolerability, the patient will complete the EOT Visit and be followed for PFS/OS as described in Section 10.7. If fulvestrant is discontinued for a patient in either of the combination treatment arms (Arm B or Arm C), the patient may be eligible to continue receiving MLN0128 at their current dose as described in Section 7.1.5. If MLN0128 is discontinued for a patient in either of the combination treatment arms (Arm B or Arm C), the patient will complete the EOT Visit and be followed for PFS/OS as described in Section 10.7.

9.4.1 MLN0128 Dose Interruption

Administration of MLN0128 should be withheld (for up to 3 weeks) for treatment-related toxicities that are Grade 3 or higher despite supportive treatment per standard clinical practice. MLN0128 may resume treatment at a lower dose (as detailed in Section 9.4.2) if the toxicity resolved to baseline level or Grade 1 (or Grade 2 for hyperglycemia or rash, as detailed in Sections 9.8.1 and 9.8.4, respectively). If the event does not resolve to baseline level or Grade 1 within 3 weeks, MLN0128 will be discontinued permanently and the patient will complete the EOT Visit and be followed for PFS/OS as described in Section 10.7.

The following nonhematologic toxicities attributed to MLN0128 would not require dose interruption:

- Grade 3 or higher nausea and/or emesis in the absence of optimal antiemetic prophylaxis. Optimal antiemetic prophylaxis is defined as an antiemetic regimen that employs both a 5-hydroxytryptamine antagonist and a corticosteroid given in standard doses and according to standard schedules.
- Grade 3 or higher diarrhea that occurs in the absence of optimal supportive therapy.

- Grade 3 fatigue.

9.4.2 MLN0128 Dose Reduction

As detailed in Section 9.4.1, MLN0128 administration should be withheld for treatment-related AEs that are Grade 3 or higher despite supportive treatment per standard clinical practice. If the event resolves to Grade 1 or to baseline values within 3 weeks of interrupting treatment, then the patient may resume study treatment at a dose reduced by 1 level (Table 9.b). If a patient does not tolerate the reduced dose, then the investigator and the project clinician should discuss whether the patient would benefit from a further dose reduction.

Table 9.b Dose Reductions for MLN0128

Dose Level	Daily Dose Regimen	Weekly Dose Regimen
0	4 mg QD	30 mg QW
–1	3 mg QD	20 mg QW
–2	2 mg QD	15 mg QW
–3	2 mg, 5 days on and 2 days off per week	10 mg QW

QD=once daily, QW=once weekly.

When a dose reduction of MLN0128 is required, no re-escalation of dose will be permitted.

9.4.3 Discontinuation of MLN0128

If MLN0128 administration is delayed for more than 3 weeks (21 consecutive days) due to study drug-related toxicity despite supportive treatment per standard clinical practice, or more than 3 dose reductions of study drug are required in a patient, MLN0128 will be permanently discontinued and the patient will complete the EOT Visit and be followed for PFS/OS as described in Section 10.7.

9.5 Excluded Concomitant Medications and Procedures

9.5.1 Excluded Concomitant Medications and Procedures for Single-Agent Fulvestrant Treatment Arm (Arm A)

Refer to the current fulvestrant USPI or SmPC for excluded medications for patients receiving single-agent fulvestrant in this study.

In addition, these specific exclusions also apply to Arm A (single-agent fulvestrant):

- Other investigational agents including mTOR, PI3K, dual PI3K-mTOR, and AKT inhibitors.
- Other anticancer therapies, including chemotherapy, immunotherapy, radioimmunotherapy, targeted agents, radiation, or surgery. Patients can have palliative radiation or surgery during the study for pre-existing lesions.

9.5.2 Excluded Concomitant Medications and Procedures for Combination MLN0128 Plus Fulvestrant Treatment Arms (Arm B and Arm C)

Refer to the current fulvestrant USPI or SmPC for excluded medications for patients receiving fulvestrant in this study.

In addition, the following medications, therapies, and procedures are prohibited during the study for patients receiving combination treatment:

- Other investigational agents including mTOR, PI3K, dual PI3K-mTOR, and AKT inhibitors.
- Other anticancer therapies, including chemotherapy, immunotherapy, radioimmunotherapy, targeted agents, radiation, or surgery. Patients can have palliative radiation or surgery during the study for pre-existing lesions.
- Systemic corticosteroids (either IV or oral steroids), unless necessary for treatment of a study drug-related AE (eg, rash). Inhalers and low-dose replacement therapy are allowed.
- Strong cytochrome P450 (CYP) 1A2 inhibitors and CYP inducers should be administered with caution and at the discretion of the investigator (see Appendix G for a list of these agents).
- Concomitant administration of any PPI is not permitted during the study. All patients are required to stop taking PPIs at least 7 days before receiving the first dose of study drug. Examples of PPIs include omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole.
- Histamine H2 receptor antagonists may be allowed if needed, provided that the histamine H2 receptor antagonist is not taken within 12 hours before or within 6 hours after study drug administration. Patients receiving histamine H2 receptor antagonists before enrollment must stop using these medications for at least 24 hours before their first dose of study drug. Examples of histamine H2 receptor antagonists include ranitidine, famotidine, and nizatidine. Cimetidine, a moderate CYP1A2 inhibitor, is not recommended as a first choice H2 receptor antagonist (see Appendix G).
- Administration of neutralizing antacids and calcium preparations is permitted except from 4 hours before until 2 hours after study drug administration. Some antigas preparations may also have antacid properties and should also not be permitted from 4 hours before until 2 hours after study drug administration.

9.6 Permitted Concomitant Medications and Procedures (All Treatment Arms)

All prescription and over-the-counter medications, including influenza vaccines, taken by a patient from the first dose of study drug through 30 days after the last dose will be recorded on the designated electronic case report form (eCRF).

Prophylactic use of antiemetic, antinausea, and antidiarrheal medications is encouraged, and these may be administered before the first dose of study drug, as needed throughout the study before each dosing, and as clinically indicated per standard practice.

Concomitant treatment with bone-targeting agents (eg, bisphos, denosumab) is permitted for treatment of osteoporosis or management of existing bone metastases if initiated at least 4 weeks before administration of the first dose of study drug. To minimize confounding factors that may contribute to assessment of potential drug-related toxicities, the dosage of any ongoing bone-targeting agents should not be changed, and no new bone-targeting agents should be initiated during Screening (within 4 weeks before the first dose of study drug) or during Cycle 1.

Other medications considered necessary for the safety and well being of the patient may be administered at the discretion of the investigator. Any concomitant medications added or discontinued during the study should be recorded on the eCRF.

9.7 Precautions and Restrictions

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with study drug. Examples of live vaccines include the intranasal influenza, measles, mumps, rubella, oral polio, Bacillus Calmette-Guerin, yellow fever, varicella, and TY21a typhoid vaccines.

No dietary restrictions will be imposed on study patients. Patients are required to fast for glucose monitoring (refer to Section 9.8.1 and Section 10.4.16). Patients receiving daily MLN0128 in Arm B should refrain from eating or drinking for 2 hours before and 1 hour after each dose (per Section 9.1). 9.1).

Patients who show evidence of hyperglycemia during the study should be encouraged to follow a low carbohydrate diet.

Patients should be encouraged to drink at least 20 ounces of fluids a day, especially on days requiring fasting (per protocol), with administration of IV fluids in the clinic as indicated to avoid dehydration.

9.8 Management of Clinical Events

Detailed MLN0128 dose modification and prevention/prophylaxis guidelines for specific clinical events are provided in the following sections. General guidelines for MLN0128 dose interruption and dose reduction are provided in Section 9.4.1 and Section 9.4.2.

9.8.1 Management of Hyperglycemia

On the basis of the clinical experience in MLN0128 trials, most episodes of hyperglycemia observed occurred within the first 60 days after initiation of treatment with MLN0128 and have been either Grade 1 or Grade 2, and have responded quickly to oral metformin. Hyperglycemia has not been dose-limiting since the institution of a standard regimen for early treatment of hyperglycemia.

All patients developing hyperglycemia during the study should have their glucose closely monitored by study staff. The investigator may choose to continue close monitoring of patients who develop Grade 1 hyperglycemia (fasting glucose >ULN ≤160 mg/dL) or, alternatively,

consider initiating treatment with an oral hypoglycemic agent, such as metformin. All patients with ≥Grade 2 hyperglycemia (fasting glucose >160 mg/dL) must be treated aggressively with oral hypoglycemic agents and/or insulin as clinically indicated. The investigator should consult an endocrinologist, if needed, to aid in optimizing the patient's hyperglycemia treatment plan.

It is recommended that patients be initially treated with a fast-acting insulin sensitizer such as metformin at 500 mg PO QD, and titrate up to a maximum of 1000 mg PO twice daily as needed. Concurrent addition to metformin of DPP-4 inhibitors (eg, sitagliptin or vildagliptin) and/or insulin should also be considered. Oral sulfonylureas (eg, glipizide or glyburide) should be used with caution, due to the higher risk of inducing hypoglycemia in patients. The dose of oral hypoglycemic agents should be adjusted in patients with renal insufficiency. In addition, patients should be encouraged to follow a low carbohydrate diet once hyperglycemia is first observed.

If any fasting serum glucose reading performed at the site indicates hyperglycemia (>ULN or ≥110 mg/dL), the study staff should first confirm that the patient was fasting at the time of blood specimen collection (ie, nothing by mouth for at least 8 hours before collection). To aggressively manage the hyperglycemia per standard clinical practice, the following guidelines (Table 9.c) are provided to aid the investigator in initiating antiglycemic therapies.

Table 9.c Management of Hyperglycemia

Grade	Description	Treatment	MLN0128 Dose Modification
1	FBG>ULN–160 mg/dL.	Continue close monitoring of blood glucose. Initiate oral hypoglycemic agent.	None
2	FBG>160–250 mg/dL.	Initiate oral hypoglycemic agent and/or insulin if not well controlled on oral agent.	None
≥3	FBG>250 mg/dL.	Initiate oral hypoglycemic agent and/or insulin.	Hold drug until ≤Grade 2. Resume MLN0128 based on timing of recovery: • ≤1 week: resume MLN0128 at same dose. • >1 but ≤2 weeks: resume MLN0128 with the dose reduced by 1 level (a). • >2 weeks: discontinue MLN0128 treatment permanently.

Prevention/Prophylaxis:

- Follow fasting serum glucose levels during clinic visits.
- Monitor home glucometer test results.
- Check HbA1c levels every 3 months during therapy.
- Recommend lifestyle modifications, as appropriate (balanced diet, limited alcohol consumption, increased physical activity).
- Most episodes of Grade 1 and 2 hyperglycemia respond quickly to oral metformin. Early initiation of therapy is recommended to prevent higher grade hyperglycemia.
- FBG levels ≥150 mg/dL by glucometer should be followed by closer monitoring of serum glucose and possible intervention.

FBG=fasting blood glucose, HbA1c=glycosylated hemoglobin, ULN=upper limit of the normal range.
(a) Refer to Table 9.b.

9.8.2 Management of Hyperlipidemia

Guidance on MLN0128 dose modification for patients with hyperlipidemia is provided in Table 9.d.

Table 9.d Management of Hyperlipidemia

Grade	Description	Treatment	MLN0128 Dose Modification
1	Cholesterol: >ULN-300 mg/dL Triglycerides: >150-300 mg/dL	None	None
2	Cholesterol: >300-400 mg/dL Triglycerides: >300-500 mg/dL	Treat hyperlipidemia according to standard guidelines. Triglycerides ≥500 mg/dL should be treated urgently due to risk of pancreatitis.	Maintain dose if tolerable. If toxicity becomes intolerable, interrupt MLN0128 dosing until recovery to ≤Grade 1. Resume MLN0128 at same dose.
3	Cholesterol: >400-500 mg/dL Triglycerides: >500-1000 mg/dL	Same as for Grade 2	Hold dose until recovery to ≤Grade 1, then resume MLN0128 with the dose reduced by 1 level. (a)
4	Cholesterol: >500 mg/dL Triglycerides: >1000 mg/dL	Same as for Grade 2	Same as for Grade 3
Prevention/Prophylaxis: • Lifestyle modifications, as appropriate (balanced diet, limited consumption of alcoholic beverages, increased physical activity).			

ULN=upper limit of the normal range.
(a) Refer to Table 9.b.

9.8.3 Management of Oral Mucositis

Guidance for the prevention and management of oral mucositis is provided in Table 9.e. Mucositis prophylaxis is strongly recommended for all patients while receiving MLN0128.

Table 9.e Management of Oral Mucositis

Grade	Description	Treatment	MLN0128 Dose Modification
1	Asymptomatic or mild symptoms.	Nonalcoholic mouth wash or 0.9% salt water rinse; consider topical corticosteroids at earliest signs of mucositis.	None
2	Moderate pain not interfering with oral intake; modified diet indicated.	Topical analgesic mouth treatments; topical corticosteroids; initiate antiviral or antifungal therapy, if indicated.	Maintain dose if tolerable. If toxicity becomes intolerable, interrupt MLN0128 dosing until recovery to ≤Grade 1. Resume MLN0128 at same dose.
3	Severe pain interfering with oral intake.	Same as for Grade 2; consider intralesional corticosteroids.	Hold dose until recovery to ≤Grade 1, then resume MLN0128 with the dose reduced by 1 level. (a)
4	Life-threatening consequences.	Same as for Grade 2; consider intralesional corticosteroids.	Discontinue MLN0128 treatment permanently.

Prevention/Prophylaxis:

- Initiate a nonalcoholic mouth wash or 0.9% salt water rinses 4-6 times per day with start of therapy before signs of mucositis develop.
- Avoid using agents containing hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

(a) Refer to Table 9.b.

9.8.4 Management of Rash

Patients who develop Grade 4 rash should permanently discontinue MLN0128, unless they derive clinical benefit, in which case they may be retreated at a reduced dose level after recovery to ≤Grade 1 severity. Grade 4 rash is defined as rash acneiform/papulopustular with papules and/or pustules covering any percent body surface area, which may or may not be associated with symptoms of pruritus or tenderness, and are associated with extensive superinfection with IV antibiotics indicated; life threatening consequences (NCI CTCAE Version 4.03, effective date 14 June 2010 [32]).

Guidance for management of rash is provided in Table 9.f.

Table 9.f Management of Rash

Grade	Description	Treatment	MLN0128 Dose Modification
≤2	Macules/papules covering ≤30% body surface area with or without symptoms.	Consider treatment with topical steroid cream/ointment and/or oral antihistamines.	None
3	Macules/papules covering >30% body surface area with or without symptoms.	Consider treatment with topical steroid cream/ointment, oral antihistamines, and/or pulsed steroids.	Hold until ≤Grade 2; resume MLN0128 based on timing of recovery: • ≤3 weeks: resume MLN0128 with the dose reduced by 1 level. (a) • >3 weeks: discontinue MLN0128 treatment.
4	Rash acneiform/ papulopustular with papules and/or pustules covering any percentage of body surface area, which may or may not be associated with symptoms of pruritus or tenderness, and are associated with extensive superinfection with IV antibiotics indicated; life threatening consequences.		Permanently discontinue MLN0128, unless patient is deriving clinical benefit, in which case resume at a reduced dose level (a) after recovery to ≤Grade 1 severity.

Prevention/Prophylaxis:

- Rash should be managed aggressively. The investigator should consider consulting a dermatologist or other specialist, if needed.
- A skin biopsy at the site of rash should be considered as soon as possible after the initial episode.

IV=intravenous.
(a) Refer to Table 9.b.

9.8.5 Management of Nausea and/or Vomiting

Patients who experience ≥Grade 3 nausea or vomiting for >72 hours despite optimal therapy may resume MLN0128 at a dose reduced by 1 level.

Guidance for the management of nausea and/or vomiting is provided in Table 9.g.

Table 9.g Management of Nausea and/or Vomiting

Grade	Description	Treatment	MLN0128 Dose Modification
≤2	Loss of appetite with or without decreased oral intake; 1-5 episodes of vomiting within 24 hours.	Maximize antiemetic therapy; consider IV fluid hydration.	None
≥3	Inadequate oral intake; ≥6 episodes of vomiting within 24 hours.	Maximize antiemetic therapy; initiate tube feeding, IVF, or TPN.	If experienced for ≤72 hours, hold MLN0128 until ≤Grade 1, then resume MLN0128 without dose modification. If experienced for >72 hours despite optimal therapy, hold MLN0128 until ≤Grade 1, then resume MLN0128 with the dose reduced by 1 level.
Prevention/Prophylaxis: • Prophylactic use of antiemetic, antinausea, and antidiarrheal medications is encouraged, and these may be administered before each dose of MLN0128 as needed throughout the study.			

IV=intravenous, IVF=intravenous fluids, TPN=total parenteral nutrition.

9.8.6 Management of Noninfectious Pneumonitis

Guidance for the management of pneumonitis is provided in Table 9.h.

Table 9.h Management of Noninfectious Pneumonitis

Grade	Description	Treatment	MLN0128 Dose Modification
1	Asymptomatic: Radiographic findings only.	Rule out infection and closely monitor.	None
2	Symptomatic: Not interfering with activities of daily living.	Rule out infection and consider treatment with corticosteroids until symptoms improve to ≤Grade 1.	Hold MLN0128 treatment: When symptoms ≤Grade 1, resume MLN0128 with the dose reduced by 1 level. (a) If no recovery within 4 weeks, then discontinue MLN0128 treatment permanently.
3	Symptomatic: Interfering with activities of daily living; Requires administration of oxygen.	Rule out infection and consider treatment with corticosteroids until symptoms improve to ≤Grade 1.	Hold MLN0128 treatment until symptoms resolve to ≤Grade 1. Consider re-initiating MLN0128 treatment with a dose reduction. (a) If toxicity recurs at Grade 3, discontinue MLN0128 treatment permanently.
4	Life-threatening: Ventilatory support indicated.	Rule out infection and consider treatment with corticosteroids.	Discontinue MLN0128 treatment permanently.

(a) Refer to Table 9.b.

9.8.7 Management of Other Nonhematologic Toxicities

Guidance on dose adjustment for patients with other nonhematologic toxicities, specifically fatigue, asthenia, and weakness, is provided in Table 9.i.

Table 9.i Management of Asthenia, Weakness, and Fatigue

Grade	Description	Treatment	Dose Modification
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Initiate appropriate medical therapy and monitor.	If tolerable, then no adjustment is required.
2	Moderate; minimal, local or noninvasive intervention indicated.	Initiate appropriate medical therapy and monitor.	If tolerable, no adjustment required. If toxicity becomes intolerable, hold MLN0128 treatment until symptoms resolve to ≤Grade 1, then re-initiate at same dose.
≥ 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated.		Hold MLN0128 treatment until symptoms resolve to ≤Grade 1. Re-initiate MLN0128 treatment with a dose reduction. (a)

(a) Refer to Table 9.b.

9.9 Blinding and Unblinding

This is an open-label study.

9.10 Description of Investigational Agents

MLN0128 will be supplied as capsules for oral administration. MLN0128 is available in 3 dose strengths (1, 3, and 5 mg of MLN0128). The capsules contain milled drug substance, microcrystalline cellulose, and magnesium stearate. All 3 dose strengths are formulated into size 2 hard-gelatin capsules, and each dose strength is differentiated by color:

- 1 mg MLN0128 capsules: white opaque.
- 3 mg MLN0128 capsules: Swedish orange opaque.
- 5 mg MLN0128 capsules: gray opaque.

Fulvestrant is a commercially available drug supplied as a solution for IM injection and will be procured or distributed according to the Pharmacy Manual. Please refer to the most recent USPI or SmPC for more information regarding fulvestrant.

9.11 Preparation, Reconstitution, and Dispensation

MLN0128 will be provided in 60 cc high-density polyethylene (HDPE) bottles with polypropylene, child-resistant caps and induction seal. MLN0128 will be dispensed with dosing

instructions for home use, including the requirement that capsules are stored in their original containers and that capsules be swallowed whole and not opened, chewed, or manipulated in any way. Materials provided by the sponsor should be dispensed to patients with clear administration instructions from the investigator.

MLN0128 is an anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling MLN0128 capsules.

Refer to the fulvestrant USPI or SmPC for details regarding the preparation, reconstitution, and dispensation of fulvestrant.

9.12 Packaging and Labeling

MLN0128 will be provided by Millennium and will be handled at the investigative site as open-label material. MLN0128 capsules are packaged in 60 cc HDPE bottles with polypropylene, child-resistant caps and an induction seal. For all 3 dose strengths, each bottle contains 30 capsules and will have a label containing pertinent study information, country-specific requirements, and a caution statement.

While the patient is enrolled in the study, fulvestrant may be supplied either by the site from commercial sources (US sites) or provided by Millennium (ex-US sites). When provided by Millennium, fulvestrant will be appropriately labeled in compliance with local and regional regulations.

9.13 Storage, Handling, and Accountability

Upon receipt at the investigative site, MLN0128 should be stored in the original bottles until use and stored at room temperature from 15°C to 30°C (59°F to 86°F). All temperature excursions will be reported to the sponsor for assessment and authorization for continued use. All investigational supplies must be stored in a secure area with controlled access and will be stored in original packaging. All MLN0128 should be used before the retest expiry date.

Refer to the current fulvestrant USPI or SmPC for details regarding the storage and handling of fulvestrant.

A drug dispensing log, including records of drug received from the sponsor and drug dispensed to the patients, will be provided and kept at the study site. Storage area temperature conditions must be monitored and recorded daily. A daily temperature log will also be kept at the study site.

Because MLN0128 is an investigational agent, it should be handled with due care. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful if inhaled, ingested, or absorbed through the skin. Gloves and protective clothing should be worn during the clean-up operation. The area should be ventilated and the spill site washed after material pick-up is complete. The spilled material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations. In case of contact with the powder (eg, from a broken capsule), the skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious

amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified.

Patients will receive instructions for home storage and administration of MLN0128.

Patients will be instructed to return any unused study drug in the original packaging along with their completed patient dosing diary at the appropriate visits per the Schedule of Events.

Please refer to the Investigator Site File for additional instructions.

10.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

10.1 Study Personnel and Organizations

The contact information for the project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country (where applicable), the IRT provider, and the study monitoring team may be found in the Investigator Site File. A full list of investigators is available in the sponsor's investigator database.

10.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/independent ethics committee (IEC).

10.3 Treatment Group Assignments

Patient eligibility will be established before randomization into the study. Patient eligibility will be confirmed by the sponsor's project clinician (or designee) before randomization by the investigator into the study. A centralized randomization IRT will be used for treatment group assignment.

Enrollment will be managed via the IRT to ensure that approximately 40% of enrolled patients have previously received CDK4/6 inhibitors in combination with an AI. Enrollment of non-CDK4/6 pretreated patients may be stopped in the case that 60% or greater of enrollment has occurred with only non-CDK4/6 pretreated patients.

Patients who meet the eligibility criteria will be stratified according to the presence or absence of visceral metastasis, previous sensitivity to hormonal therapy, and previous exposure to CDK4/6 inhibitors. Visceral metastasis is defined as all lesions not included in the following list: breast, skin, subcutaneous tissue, lymph node, or bone. Previous sensitivity to hormonal therapy is defined as at least 24 months of endocrine therapy before recurrence in the adjuvant setting (ie, in patients who have not received previous endocrine therapy in the metastatic setting) or a response or stabilization for at least 24 weeks of the most recent endocrine therapy for advanced/metastatic disease. Patients will be randomized 1:1:1 to 1 of 3 treatment arms (51 patients per arm):

- Arm A: Single-agent fulvestrant.
- Arm B: Combination of fulvestrant+daily MLN0128.
- Arm C: Combination of fulvestrant+weekly MLN0128.

Patients in the single-agent fulvestrant arm (Arm A) who have PD may be allowed to receive crossover treatment with the combination of fulvestrant+MLN0128, as detailed in Section 7.1.4. A centralized randomization IRT will be used to randomize crossover patients in a 1:1 ratio to either fulvestrant+daily MLN0128 or fulvestrant+weekly MLN0128. Patients who discontinue fulvestrant in either of the combination treatment arms (Arm B or Arm C) may be eligible to continue receiving MLN0128 at their current dose as described in Section 7.1.5. If MLN0128 is discontinued for a patient in either of the combination treatment arms (Arm B or Arm C), the patient will complete the EOT Visit and be followed for PFS/OS as detailed in Section 10.7.

10.4 Study Procedures

Patients will be evaluated at scheduled visits over the following study periods: Screening, Treatment, EOT, and PFS/OS Follow-Up. Unless otherwise noted, evaluations during the Screening period are to be conducted within 28 days before administration of the first dose of study drug. Evaluations during the Treatment Period must occur before study drug administration on that day. Tests and procedures should be performed on schedule for all visits but occasional changes are allowable (±2 days) for holidays, vacations, and other administrative reasons, starting after the completion of Cycle 2 Day 1.

All EOT evaluations should occur within 30 to 40 days after the last dose of study drug, or before the start of subsequent antineoplastic therapy (or crossover treatment if applicable; see Section 7.1) if that occurs earlier than 30 days after the last dose.

Refer to the Schedule of Events for timing of assessments. Additional details are provided as necessary in the sections that follow.

10.4.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

10.4.2 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during Screening.

10.4.3 Medical History

During Screening Period, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it.

10.4.4 Enrollment

Enrollment is defined as being randomized to a treatment arm.

Enrollment will be managed via the IRT to ensure that approximately 40% of enrolled patients previously received CDK4/6 inhibitors in combination with an AI.

10.4.5 Patient Height and Weight

Height will be measured only during Screening. Body weight will be measured at the visits specified in the Schedule of Events.

10.4.6 Physical Examination

A physical examination will be completed per standard of care at the times specified in the Schedule of Events.

10.4.7 Vital Signs

Vital sign measurements, including diastolic and systolic blood pressure, heart rate, and temperature will be measured at the visits specified in the Schedule of Events.

10.4.8 ECOG Performance Status

Performance status will be assessed according to the ECOG scale (see Appendix D) at the time points specified in the Schedule of Events.

10.4.9 ECG

A single, 12-lead ECG will be performed predose on Day 1 of every cycle and during the EOT Visit. When the timing of an ECG coincides with blood samples, the ECG should be completed first. Additional ECGs may be obtained as clinically indicated.

10.4.10Disease Assessment

10.4.10.1 CT Scan or MRI

Patients will undergo CT scan (with contrast) as appropriate to monitor and assess PD, using RECIST guidelines (Version 1.1), where measureable disease is defined as at least 1 extra-osseous lesion that can be accurately measured in at least 1 dimension [1]. An MRI may be performed for patients who are allergic to CT contrast or for patients with specific disease sites that cannot be adequately imaged by CT scan. Anatomical measurements (summed across target lesions) will be collected at Baseline and at each subsequent evaluation using an imaging modality consistent with that used at Screening. Objective assessments will be performed at each time point specified in the Schedule of Events. When possible, the same qualified physician will interpret results to reduce variability.

In the absence of measurable disease at Baseline, the following will be considered PD among patients with bone-only disease:

- The appearance of 1 or more new lytic lesions in bone.
- The appearance of any extra-osseous lesions.
- Unequivocal progression of existing bone lesions.

All images will be collected and quality controlled by a sponsor-specified central imaging vendor. Radiographic images will be maintained at the site, and test results and physicians' findings will be filed in patient source documents. The sponsor may request electronic images for those patients who demonstrate a response.

10.4.10.2 Bone Scan

A bone scan will be required for all patients during Screening (within 21 days before the first dose of study drug), and thereafter at the discretion of the investigator to monitor representative areas.

10.4.10.3 Health-related Quality of Life Assessments

The HRQL instruments, EORTC QLQ-C30 and EORTC QLQ-BR23, will be administered as specified in the Schedule of Events, and they must be completed before other assessments are performed or study drug is administered.

The EORTC QLQ-C30 incorporates 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning); 1 global health status scale; 3 symptom scales (fatigue, nausea and vomiting, and pain); and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). (See Appendix H.) The time recall period for this instrument is 1 week (the past week). The EORTC QLQ-C30 is a reliable and valid measure of HRQL in patients with cancer [34]. The instrument consists of a brief (30-item) questionnaire that has been validated and used in many countries.

The EORTC QLQ-BR23 is an instrument specific to breast cancer that was designed to be used in conjunction with the EORTC QLQ-C30. The questionnaire comprises 23 items on issues relevant to patients with breast cancer that are not, or not sufficiently, covered by the core questionnaire. The EORTC QLQ-BR23 instrument incorporates 2 functional scales (body image and sexual functioning), 3 symptom scales (arm symptoms, breast symptoms, and systemic side effects), and single items related to sexual enjoyment, distress by hair loss, and future perspective (see Appendix I). The recall period for this instrument is 1 week (the past week), except for items related to sexual function (recall period of 4 weeks). The instrument has been validated in many languages and among patients varying in disease stage and treatment modality [35].

10.4.11Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient from the first dose of study drug through 30 days after the last dose of study drug will be recorded on the eCRF. See Section 9.5 and Section 9.6 for a list of medications and therapies that are prohibited and/or allowed during the study.

10.4.12AEs

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedule of Events. Refer to Section 11.0 for details regarding definitions, documentation, and reporting of pretreatment events (PTEs), AEs, and SAEs.

10.4.13Patient Diary Instruction and Review

At the beginning of each cycle, patients in Arms B and C will receive a diary in which to record their dosing and fasting blood glucose (FBG) testing results. The study center staff will check the patient's diary versus the patient's supply of remaining study drug at each study visit to ensure compliance with dosing. Patients who are not compliant with the dosing schedule may be withdrawn from the study.

10.4.14Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally.

Blood specimens for analysis of the clinical chemistry, hematology, and coagulation parameters shown in Table 10.a and urine specimens for analysis of the parameters shown in Table 10.b will be obtained as specified in the Schedule of Events.

Table 10.a Clinical Chemistry, Hematology, and Coagulation Tests

Hematology and Coagulation	Chemistry	
Hematocrit (Hct)	Albumin	Gamma glutamyl transferase (GGT)
Hemoglobin (Hgb)	Alkaline phosphatase (ALP)	Glucose
Leukocytes with differential	ALT	Glycosylated hemoglobin (HbA1c) (a)
Neutrophils (ANC)	Amylase	Lactate dehydrogenase (LDH)
Platelets (count)	AST	Magnesium
Activated partial thromboplastin time (aPTT)	Bilirubin (total and direct) (b)	Phosphate
	Blood urea nitrogen (BUN) or Urea	Potassium
Prothrombin time/international normalized ratio (PT/INR)	Calcium (total)	Protein (total)
	Carbon dioxide (CO_2) or bicarbonate	Sodium
	Chloride	Urate
	Creatinine	

(a) Assessed only at the time points specified in the Schedule of Events.
(b) Direct bilirubin will be measured only if total bilirubin is altered.

Table 10.b Clinical Urinalysis Tests

Urinalysis (a)	
Bilirubin	Occult blood
Color	pH
Glucose	Protein
Ketones	Specific gravity
Leukocytes	Turbidity
Nitrite	Urobilinogen

(a) The use of test strips is permitted.

For Screening, creatinine clearance must be ≥40 mL/min based either on Cockroft-Gault estimate or based on a 12- or 24-hour urine collection.

Prospective monitoring for hyperlipidemia will be managed through fasting lipid testing. Sampling for the fasting lipid profile (Table 10.c) will be obtained at the times specified in the Schedule of Events.

Table 10.c Fasting Lipid Profile

Fasting Lipid Profile	
Cholesterol (total)	High-density lipoprotein cholesterol
Triglycerides	Low-density lipoprotein cholesterol

Fasting serum glucose will be measured in the clinic at the time points specified in the Schedule of Events. Patients are required to fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours before the assessment) for each of these measurements. For patients receiving single-agent fulvestrant in Arm A or fulvestrant+MLN0128 QW in Arm C, the fasting serum glucose may be assessed as part of the predose chemistry panel. After fasted sampling is complete, patients receiving fulvestrant+MLN0128 QW in Arm C should consume a light meal prior to dosing (Section 9.1). For patients receiving fulvestrant+MLN0128 QD in Arm B, a separate sample must be taken approximately 2 hours after study drug administration, with patients continuing to fast until that sample is taken.

In-home glucose monitoring is not required on days when fasting glucose is measured in the clinic.

10.4.15In-Home Daily FBG Monitoring (Combination Arms Only)

In addition to obtaining fasting serum glucose levels at the clinic visits as outlined in the Schedule of Events, all patients in the combination fulvestrant+MLN0128 treatment arms (Arm B and Arm C) will be given a glucometer to monitor their daily FBG levels at home. The level should be collected daily, predose on dosing days, and at approximately the same time each day. Before checking their blood glucose levels, patients should fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours before the assessment). After fasted testing is complete, patients in Arm C should consume a light meal prior to MLN0128 dosing (Section 9.1).

On Cycle 1 Day 1, the patient will be provided an in-home glucometer. Patients will be trained on proper use of the glucometer and instructed to collect a daily fasting glucose level every morning (predose on dosing days), starting on Cycle 1 Day 2. Patients will be instructed to bring the glucometer with them to each study visit so that the data collected can be reviewed and recorded in the source documents. Investigators will be responsible for reviewing the home glucose monitoring logs for hyperglycemia.

The patient will be instructed to contact the site immediately if the value is abnormal (ie, ≥150 mg/dL) for further instructions on the management of their hyperglycemia. Hyperglycemia observed during home glucose monitoring should be confirmed in the clinic.

If no irregularities in the FBG level are observed during a minimum of 2 consecutive months, then the frequency of in-home FBG testing can be reduced to a minimum frequency of once weekly, depending on the investigator's judgement and approval. Patients will continue to notify the investigator of FBG levels that exceed 150 mg/dL and, if blood glucose levels are not well controlled, or if the patient requires either oral hypoglycemic agents or insulin to control blood glucose levels, then the frequency of in-home testing of FBG levels will be reinstated to daily.

See also Section 9.8.1.

10.4.16Biomarker Measurements in Blood

CCI [redacted]

CCI [redacted]

10.4.18Banked Tumor Specimen Measurements

CCI [redacted]

CCI

[redacted]

10.4.19PK Measurements (Combination Arms Only)

Blood sampling to characterize the PK of MLN0128 will be performed for patients randomized to the combination fulvestrant+MLN0128 treatment arms (Arm B and Arm C, including patients who receive crossover treatment), at the times indicated in the Schedule of Events. When the timing of a PK blood sample coincides with vital sign or ECG measurements, the vital sign or ECG measurement should be obtained before the PK blood sample. Details on the collection, storage, processing, handling, and shipping of PK samples are in the CCI Central Laboratory Manual.

PK data for MLN0128 will be combined with similar data from other studies for future population PK analysis. The results of the population PK analysis will not be presented in the clinical study report and may be presented in a separate population PK analysis report at a later time.

10.5 Completion of Study Treatment

Patients will be considered to have completed treatment if they discontinue study drug for any of the reasons outlined in Section 10.7.

10.6 Completion of Study

Patients will be considered to have completed the study if they withdraw from the study for any of the reasons outlined in Section 10.8.

10.7 Discontinuation of Treatment With Study Drug

Treatment with study drug may be discontinued for any of the following reasons:

- AE.
- Protocol deviation.
- PD.
- Symptomatic deterioration.
- Study terminated by sponsor.
- Withdrawal by patient.
- Lost to follow-up.

- Other (eg, investigator's decision to initiate a different therapy, patient noncompliance with study requirements).

Patients must discontinue study drug if they experience PD or unacceptable toxicity.

Once study drug has been discontinued, all study procedures outlined for the EOT Visit will be completed as specified in the Schedule of Events. The primary reason for study drug discontinuation will be recorded on the eCRF.

Note that some patients may discontinue study drug for reasons other than PD. These patients will remain in the study for post-treatment assessments as outlined in the Schedule of Events and Section 10.10.

10.8 Withdrawal of Patients From Study

A patient may be withdrawn from the study for any of the following reasons:

- Lost to follow-up.
- Study terminated by sponsor.
- Withdrawal by patient.
- Death.
- Other.

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database. Data on survival may be obtained from publically available databases and sources.

10.9 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

Patients will receive a sufficient quantity of MLN0128 for each treatment cycle and a diary in which to record their dosing. The study center staff will check the patient's dosing diary versus the patient's supply of remaining study drug at each study visit to ensure proper compliance with dosing. Patients who are not compliant with the dosing schedule may be withdrawn from the study.

10.10 Post-Treatment Follow-up Assessments (Progression-Free Survival and Overall Survival)

After the EOT Visit (or, for crossover patients, after their second and final EOT Visit), patients will be followed for PFS and OS. Patients who discontinue study treatment for reasons other than PD will continue to have PFS follow-up visits every 2 months (±1 week) for the first 6 months after the EOT Visit, then every 3 months (±1 week) until PD or start of another anticancer therapy for treatment of disease under study, whichever occurs first. After PD or the start of another

anticancer therapy, patients will be followed for OS every 6 months (±1 week). OS follow-up will continue until approximately 20 months after the first patient is randomized, or when the last patient discontinues study treatment. Survivor information and death details may be collected by methods that include, but are not limited to, telephone, e-mail, mail, or retrieved from online or other databases (eg, Social Security indexes). In addition, the start of any other anticancer therapy for treatment of disease under study will be collected. Refer to the Schedule of Events for appropriate assessments during posttreatment follow-up.

NOTE: Any SAEs occurring after the EOT Visit that are considered related to study drug must be reported to Takeda Global Pharmacovigilance department or designee. This includes deaths that the investigator considers related to study drug that occur during the posttreatment follow-up. Refer to Section 11.0 for details regarding definitions, documentation, and reporting of SAEs.

11.0 ADVERSE EVENTS

11.1 Definitions

11.1.1 PTE Definition

A PTE is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

11.1.2 AE Definition

AE means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from Baseline.

11.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 11.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.)
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home,

blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [32]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

11.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 11.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious PTEs (as defined in Section 11.1) must be reported (see Section 11.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Takeda, will be provided to each clinical study site. A sample of the SAE Form may be found in the Investigator Site File. Follow-up information on the SAE or serious PTE may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

PPD

Planned hospital admissions or surgical procedures for an illness or disease that existed *before the first dose of study drug* are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious PTEs, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Intensity for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [32].

Causality (relationship) to study drug administration will be determined by the investigator responding yes (Related) or no (Not Related) to this question: Is there a reasonable possibility that the AE is associated with the study drug?

11.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from first dose of study drug through 30 days after administration of the last dose of study drug and recorded on the eCRFs.
- Serious PTEs will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the informed consent form up to first dose of study drug, but will not be recorded on the eCRF.
- Related and unrelated SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded on the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

11.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

Reporting procedures for pregnancy and birth events are not applicable for this study as enrollment is restricted to postmenopausal women only.

11.5 Procedures for Reporting Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact the Medical Information Call Center / PPD and report the complaint. The contact information is as follows:

Medical Information Call Center: PPD

Phone:

Fax:

E-mail:

Hours:

Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to PPD (refer to Section 11.2).

11.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 calendar days for fatal and life-threatening events and 15 calendar days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

12.0 STUDY-SPECIFIC COMMITTEES

A Steering Committee, comprising Takeda clinical research and biostatistics representatives, study site investigators, and medical consultants from GEICAM will be responsible for performing the safety and tolerability assessment for the first 6 evaluable patients treated in Arm C. The purpose of this assessment is to confirm the weekly dose of 30 mg MLN0128 in combination with fulvestrant (see Section 7.1.2 for details). After this assessment is completed, the Steering Committee will be available to meet on an ad hoc basis to review study data as necessary.

13.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. If selected for coding, AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

13.1 Electronic Case Report Forms

Completed eCRFs are required for each randomized subject.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, contract research organization partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission from the sponsor.

13.2 Record Retention

The investigator agrees to keep the records stipulated in Section 13.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, and the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the

site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 Section 8 until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

14.0 STATISTICAL METHODS

14.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. The SAP will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

14.1.1 Analysis Sets

Full analysis set: all randomized patients. Patients will be analyzed according to the treatment assignment per the randomization schedule.

Safety analysis set: patients who receive at least 1 dose of study drug. Patients will be analyzed according to the treatment actually received.

Response-evaluable analysis set: patients who receive at least 1 dose of study drug, have measurable disease at Baseline, and have 1 postbaseline disease assessment.

14.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics (age, weight, height, and other parameters, as appropriate) will be summarized by treatment arm.

14.1.3 Efficacy Analysis

14.1.3.1 Primary Efficacy Endpoint

The primary endpoint is PFS, defined as the time from the date of randomization to the date of first documentation of progression or death due to any cause, whichever occurs first. For a patient whose disease has not progressed and is last known to be alive, or started alternate therapy prior to PD, PFS will be censored at the last response assessment that is SD or better. The primary efficacy analysis will be based on the full analysis set.

The Kaplan-Meier method will be used to analyze the distribution of PFS for each treatment arm. Kaplan-Meier survival curves, the 25th, 50th (median), and 75th percentiles, along with associated 2-sided 95% confidence intervals (CIs), HR along with associated 95% CI, and Kaplan-Meier estimates at relevant time points will be presented. The primary hypothesis is to be tested at the 0.10 significance level (2-sided). The p-values from a stratified log-rank test and HRs and will be presented for each pair-wise comparison.

14.1.3.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include OS, ORR, TTP, CBR with SD of any duration, and CBR with SD duration of at least 6 months.

OS is defined as the time from the date of randomization to the date of death. Patients without documentation of death at the time of analysis will be censored at the date last known to be alive. OS will be analyzed using similar methods as the primary endpoint of PFS in the full analysis set.

ORR is defined as the proportion of patients who achieve a best response of CR or PR. CBR is defined as the proportion of patients who achieve a best response of CR, PR, or SD. The CBR will also be presented for a best response of CR, PR and SD of at least 6 months. A stratified Cochran-Mantel-Haenszel test will be used to compare ORR and CBR between treatment arms. The Mantel-Haenszel estimate of the odds ratio and the associated 95% CIs will be presented for each pair-wise comparison.

TTP is defined as the time from the date of randomization to the date of first documentation of progression. For a patient whose disease has not progressed, TTP will be censored at the last response assessment that is SD or better. TTP will be analyzed using similar methods as the primary endpoint of PFS in the full analysis set.

14.1.4 PK Analysis

The sparse PK data are being collected to contribute to a future population PK analysis. These data may be combined with data from other studies in which the PK of MLN0128 is characterized for population PK analysis. The results of population PK analysis will be presented in a separate report.

CCI [redacted]

14.1.5 Pharmacodynamic Analyses/Biomarker Analyses

CCI [redacted]

14.1.6 Patient-Reported Outcomes

Patient-reported outcome (PRO) assessments of HRQL using the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires will be analyzed to determine if response to therapy and side effects of

therapy are accompanied by measurable changes in the PROs. Published scoring manuals and guidelines will be used to generate scale scores and handle missing data.

Descriptive statistics for baseline values, actual values, and the change from Baseline will be presented at each scheduled time point for each of the functional and symptom scores from the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires, and the global health status/QOL score from the EORTC QLQ-C30 questionnaire. All analyses will be based on the full analysis set. Differences between treatment arms in the EORTC QLQ-C30 and EORTC QLQ-BR23 scores will be evaluated. Longitudinal analysis of PRO scores will be performed using linear mixed models.

14.1.7 Safety Analysis

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from Baseline in the patient's vital signs, weight, and clinical laboratory results using the safety analysis set. Exposure to each study drug (ie, MLN0128 and fulvestrant) will be summarized and reasons for discontinuation will be tabulated. Safety will be summarized by treatment arm.

TEAEs that occur after administration of the first dose of study drug and through 30 days after the last dose of study drug will be tabulated. AEs will be tabulated according to the MedDRA dictionary and will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- The most commonly reported TEAEs.
- SAEs.

A listing of AEs resulting in study drug discontinuation will be provided. A listing of all deaths within 30 days after the last dose of study drug will also be provided.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from Baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time.

Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE grade from Baseline to the worst postbaseline value.

Concomitant medications will be coded using the WHO Drug Dictionary. The number and percentage of patients taking concomitant medications will be tabulated by WHO drug generic term in the safety analysis set.

ECG intervals (PR interval, QT interval, and QTc with Fridericia correction), QRS duration, and ventricular rate will be summarized at each scheduled time point, along with mean change from

Baseline to each post-treatment time point. The number and percentage of patients with ECG abnormalities will be summarized at each time point.

14.2 Interim Analysis and Criteria for Early Termination

No formal interim analysis is planned. Details on considerations and decision rules for early stopping for futility will be described in the SAP or a separate document.

14.3 Determination of Sample Size

The primary efficacy endpoint is PFS. Assuming that the median PFS is 4 months for fulvestrant [36] and that the combination of fulvestrant and MLN0128 (administered either QD or QW) can improve the median PFS to 8 months (HR of 0.5), then a total of 72 PFS events are needed for each pair-wise comparison. Each treatment arm will require 51 patients. The calculations are based on a power of 90%, 2-sided alpha of 10%, and a dropout rate of 10% due to either lost to follow-up or withdrawal of consent.

The accrual duration will be approximately 14 months. The final analysis for the pair-wise comparisons of PFS between fulvestrant+MLN0128 QD and fulvestrant, and between fulvestrant+MLN0128 QW and fulvestrant, is estimated to occur approximately 20 months after the first patient is randomized.

15.0 QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

15.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or IEC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form or equivalent should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

15.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 15.1.

16.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

16.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification, no protocol activities, including Screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

16.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

16.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 16.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

16.4 Publication, Disclosure, and Clinical Trial Registration Policy

16.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

16.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum, register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator's name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

16.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

16.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Events

Schedule of Events

	Screening (a)	Treatment							PC EOT (b)	EOT (c)	PFS/OS Follow-up
		Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5 and Beyond			
	D -28 to D -1	D1	D15	D1	D15	D1	D1	D1			
Informed consent	X								X		
Inclusion/exclusion criteria	X								X		
Demographics	X										
Medical history	X										
Height	X										
Weight	X	X		X		X	X	X	X	X	
Physical examination	X	X	X	X	X	X	X	X	X	X	
Vital signs (d)	X	X	X	X	X	X	X	X	X	X	
ECOG performance status	X	X		X		X	X	X	X	X	
12-lead ECG (single) (e)	X	X		X		X	X	X	X	X	
Radiographic tumor evaluation (f)	X	Every other cycle, starting with Cycle 2 (f)							X	X	X (g)
Bone scan (h)	X	As necessary to monitor representative areas, at the investigator's discretion.									
Subsequent cancer therapy										X	X (g)
Follow-up phone calls (OS)											X (g)
HRQL assessments (i)		X		X		X	X	X		X	
Monitoring of concomitant medications and procedures		Recorded from first dose of study drug through 30 days after the last dose of study drug									
AE reporting		Recorded from first dose of study drug through 30 days after the last dose of study drug									
		SAEs (j) will be reported from signing of the informed consent form through 30 days after the last dose of study drug.									

Footnotes are on last table page.

Schedule of Events (continued)

	Screening (a)	Treatment							PC EOT (b)	EOT (c)	PFS/OS Follow-up
		Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5 and Beyond			
	D -28 to D -1	D1	D15	D1	D15	D1	D1	D1			
MLN0128 administration (Combination arms only) (k)		According to treatment arm assignment: daily (Arm B) or weekly (Arm C; ie, Days 1, 8, 15, and 22 of each 28-day cycle)									
Fulvestrant administration (All treatment arms) (k)		Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, and then once every 4 weeks									
Patient dosing diary instructions/review		X		X		X	X	X		X	
Samples/Laboratory Assessments											
Hematology and chemistry (l)	X	X	X	X	X	X	X	X	X	X	
Coagulation (PT/INR, aPTT)	X	X		X		X	X	X	X	X	
Fasting lipid profile	X			X		X	X	X	X	X	
HbA1c	X					X		Q3C (m)	X		
Urinalysis (l)	X (n)								X (n)		
Fasting serum glucose (o)		X		X		X	X	X			
In-home FBG monitoring (p)		For patients in Arms B and C, daily from Cycle 1 Day 2 through last dose of study drug (may be decreased to once a week after the first 2 months, as detailed in Section 10.4.15). In-home glucose monitoring is not required on days when fasting glucose is measured in the clinic.									
CCI [redacted]											
CCI [redacted]											

Footnotes are on last table page.

Schedule of Events (continued)

	Screening (a)	Treatment							PC EOT (b)	EOT (c)	PFS/OS Follow-up
		Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5 and Beyond			
	D -28 to D -1	D1	D15	D1	D15	D1	D1	D1			
CCI [redacted]											
CCI [redacted]											
Blood sample for plasma PK (t)		X	X	X							

AE=adverse event, aPTT=activated partial thromboplastin time, CT=computed tomography, CTC=circulating tumor cell, ctDNA=circulating tumor DNA, D=day, DNA=deoxyribonucleic acid, ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, EOT=End-of-Treatment visit, FBG=fasting blood glucose, HbA1c=glycosylated hemoglobin, HRQL=health-related quality of life, INR=international normalized ratio, MRI=magnetic resonance scan, OS=overall survival, PC EOT=Precrossover End-of-Treatment visit, PT=prothrombin time, PFS=progression-free survival, PK=pharmacokinetic(s), PTE=pretreatment event, SAE=serious adverse event.

Tests and procedures should be performed on schedule, but occasional changes are allowable (±2 days) for holidays, vacations, and other administrative reasons, starting after the completion of Cycle 2 Day 1.

(a) Screening assessments are performed within 28 days before administration of the first dose of study drug. Screening assessments performed no more than 3 days before the first dose will qualify as baseline (Cycle 1 Day 1) assessments and need not be repeated, unless otherwise specified.

(b) Patients randomized to the single-agent fulvestrant arm who progress on study may be eligible for crossover treatment. It is recommended that crossover treatment begin within 28 days (+10 days) after documented disease progression (imaging date of PD), with the goal of maintaining the ongoing schedule of fulvestrant therapy (ie, dosing every 28 days). Whenever possible, MLN0128 should be initiated at the next scheduled dose of fulvestrant, but only when the patient has completed the precrossover screening requirements and is eligible to continue. If the crossover treatment cannot begin within 28 days (+10 days) after documented PD, contact the medical monitor.

(c) Patients will attend an EOT Visit 30 to 40 days after receiving their last dose of study drug, or at the start of subsequent anticancer therapy (including crossover treatment as described in Section 7.1), at which time patients will enter posttreatment follow-up. If subsequent anticancer therapy is required before 30 days after the last dose, the EOT Visit should be conducted before the initiation of subsequent anticancer therapy.
(d) Perform vital signs measurement prior to study drug administration. Vital sign measurements include blood pressure (diastolic and systolic), heart rate, and temperature.
(e) A single, 12-lead ECG will be performed predose on Day 1 of every cycle, and during the EOT Visit. When the timing of an ECG coincides with blood samples, the ECG should be completed first. Additional ECGs may be obtained as clinically indicated.
(f) Baseline CT scan (with contrast) or MRI of the chest, abdomen, and pelvis must be obtained within 21 days before the first dose of study drug. Starting at Cycle 2, CT scan (with contrast) or MRI will be performed at the end of every other cycle, within 7 days before Day 1 of the next cycle; for example, the Cycle 2 evaluation must be done within 7 days before Cycle 3 Day 1, the Cycle 4 evaluation must be done within 7 days before Cycle 5 Day 1, etc. For those patients who have documented radiographic PD, CT scan (with contrast) or MRI are not required at the EOT Visit. The same imaging modality (CT scan [with contrast] or MRI) will be used throughout the study.
(g) Patients who discontinue study treatment for reasons other than PD will continue to have PFS follow-up visits every 2 months (±1 week) for the first 6 months after the EOT Visit and then every 3 months (±1 week), until PD or start of another anticancer therapy, whichever occurs first. After PD or start of another anticancer therapy (including crossover treatment as described in Section 7.1), all patients will be followed only for survival every 6 months (±1 week).
(h) A bone scan will be required for all patients within 21 days before the first dose of study drug), and thereafter at the discretion of the investigator to monitor representative areas.
(i) HRQL instruments to be used are the EORTC QLQ-C30 and the EORTC QLQ-BR23, and must be completed before other assessments are performed or study drug is administered.
(j) Including serious PTEs; see Section 11.0.
(k) The first dose of study drug must be administered within 5 days after randomization on study. In Arm B, daily MLN0128 will be administered on an empty stomach; in Arm C, weekly MLN0128 will be administered with a light meal (see Section 9.1).
(l) Refer to Section 10.4.14 for a list of the required clinical laboratory assessments. Laboratory assessments may be performed within 24 hours before the required study visit. Safety laboratory results must be available and reviewed by the investigator before study drug administration. Electrolyte levels should be corrected as needed before study drug administration. Preassessment fasting is not required for on Cycle 1 Day 15 or Cycle 2 Day 15.
(m) Starting at Cycle 6, HbA1c and urinalysis will be assessed every 3 cycles (Cycle 6, Cycle 9, Cycle 12, etc).
(n) For Screening, creatinine clearance must be ≥40 mL/min based either on Cockroft-Gault estimate or based on a 12- or 24-hour urine collection.
(o) Fasting serum glucose will be measured in the clinic. Patients are required to fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours before the assessment) for each of these measurements. For patients receiving single-agent fulvestrant in Arm A or fulvestrant+MLN0128 QW in Arm C, the fasting serum glucose may be assessed as part of the predose chemistry panel. After fasted sampling is complete, patients receiving fulvestrant+MLN0128 QW in Arm C should consume a light meal prior to dosing (Section 9.1). For patients receiving fulvestrant+MLN0128 QD in Arm B, a separate sample must be taken approximately 2 hours after study drug administration, with patients continuing to fast until that sample is taken. The collection of the 2-hour postdose sample is not expected on the nondosing days. In-home glucose monitoring is not required on days when fasting glucose is measured in the clinic.
(p) Patients in the combination fulvestrant+MLN0128 treatment arms (Arm B and Arm C) will be given a glucometer to monitor daily fasting glucose levels at home and will be instructed to notify the study clinician any time the fasting glucose is abnormal (ie, ≥150 mg/dL). See Section 10.4.15 for further instructions.

(q) CCI [redacted].
(r) CCI [redacted]
(s) CCI [redacted]

(t) PK samples will be collected only from patients receiving MLN0128, including patients receiving crossover treatment, but not from patients randomized to single-agent fulvestrant. Samples will be collected at the times specified in the Treatment Arm B Sparse PK Sample Breakdown and Treatment Arm C Sparse PK Sample Breakdown. For all PK samples, the date and time of MLN0128 dosing and the date and time of PK sampling will need to be recorded.

Treatment Arm B Sparse PK Sample Breakdown

	MLN0128 Sparse PK Sampling (Plasma)		
	Cycle 1 Day 1 (a)	**Cycle 1 Day 15 (b)**	**Cycle 2 Day 1 (c)**
At time of clinic visit (anytime postdose)		X1	X1
Approximately 1 hour after prior PK sample collection		X1	X1
1 to 2 hours postdose (±15 min)	X1		

PK=pharmacokinetic(s), X#=the number of samples required (eg, 2 samples=X2).
This PK sampling schedule applies to subjects initially randomized to Arm B and those receiving crossover treatment in Arm B.
(a) The exact date and time of MLN0128 dosing on Cycle 1 Day 1 and the date/time of PK sampling must be recorded. Over the course of the study, a distribution of sampling times within the specified sampling windows is encouraged.
(b) On Cycle 1 Day 15, subjects will take their regularly scheduled doses of MLN0128 at home and will record the exact date/time of dose administration in their subject diaries. Subjects will then report to the clinic for the scheduled visit, during which they will provide PK samples. Over the course of the study, a distribution of clinic visit/sampling times (eg, morning through late afternoon) for this visit is encouraged.
(c) On Cycle 2 Day 1, subjects will take their regularly scheduled doses of MLN0128 in the clinic after completion of fasting serum glucose sampling. The exact date/time of dose administration and the date/time of PK sampling must be recorded. Over the course of the study, a distribution of clinic visit/sampling times (eg, morning through late afternoon) for this visit is encouraged.

Treatment Arm C Sparse PK Sample Breakdown

	MLN0128 Sparse PK Sampling (Plasma)		
	Cycle 1 Day 1 (a)	**Cycle 1 Day 15 (b)**	**Cycle 2 Day 1 (c)**
At time of clinic visit (anytime postdose)		X1	X1
Approximately 1 hour after prior PK sample collection		X1	X1
1 to 2 hours postdose (±15 min)	X1		
3 to 6 hours postdose (±30 min)	X2 (d)		

PK=pharmacokinetic(s), X#=the number of samples required (eg, 2 samples=X2).
This PK sampling schedule applies to subjects initially randomized to Arm C and those receiving crossover treatment in Arm C.
(a) Subjects should bring a light meal with them to this visit. Subjects will begin consuming the meal within 30 min prior to dosing, after which they will take their doses of MLN0128. The exact date/time of meal consumption, MLN0128 dosing, and PK sampling must be recorded. Over the course of the study, a distribution of sampling times within the specified sampling windows is encouraged.
(b) Subjects will take their regularly scheduled doses of MLN0128 at home with a light meal and will record the exact date/time of meal consumption and dose administration in their subject diaries. Subjects will then report to the clinic for the scheduled visit, during which they will provide PK samples. The date/time of PK sampling must be recorded. Over the course of the study, a distribution of clinic visit/sampling times (eg, morning through late afternoon) for this visit is encouraged.
(c) Subjects should bring a light meal with them to this visit. After completion of fasting serum glucose sampling, subjects will begin consuming the meal within 30 min prior to dosing, after which they will take their regularly scheduled doses of MLN0128. The exact date/time of meal consumption, MLN0128 dosing, and PK sampling must be recorded. Over the course of the study, a distribution of clinic visit/sampling times (eg, morning through late afternoon) for this visit is encouraged.
(d) Two samples will be taken no less than 1 hour apart within the specified window.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing Form FDA 1572:

- Conduct the study in accordance with the protocol.
- Personally conduct or supervise the staff who will assist in the protocol.
- Ensure that study-related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
- Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
- Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
- Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
- Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH, and local regulations, are met.
- Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
- Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

- Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
- Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
- Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.
- If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details, and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D ECOG Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

ECOG=Eastern Cooperative Oncology Group.
Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology 1982;5(6):649-55 [37].

Appendix E Cockcroft-Gault Equation

For women:

$$\text{Creatinine Clearance} = \frac{0.85\ (140\text{-age [years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine [mg/dL]})}$$

OR

$$\text{Creatinine Clearance} = \frac{0.85\ (140\text{-age [years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine [µmol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41. [38]

Appendix F New York Heart Association Classification of Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. Ninth Ed. Boston, MA: Little, Brown & Co; 1994:253-256. [39]

Appendix G List of Relevant Cytochrome P450 Inhibitors and Inducers

Moderate CYP1A2 Inhibitors		
Cimetidine	Methoxsalen	
Strong CYP1A2 Inhibitors		
Fluvoxamine	Ciprofloxacin	
Clinically Significant Enzyme Inducers		
Carbamazepine	Rifabutin	St. John's Wort
Phenobarbital	Rifampin	Phenytoin
T=Rifapentine		

Source: fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.
Note that these lists are not exhaustive.

Appendix H EORTC QLQ-C30 Version 3

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): |_|_|_|_|_|_|_|_|

	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

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 I EORTC QLQ-BR23

EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have a dry mouth?	1	2	3	4
32. Did food and drink taste different than usual?	1	2	3	4
33. Were your eyes painful, irritated or watery?	1	2	3	4
34. Have you lost any hair?	1	2	3	4
35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36. Did you feel ill or unwell?	1	2	3	4
37. Did you have hot flushes?	1	2	3	4
38. Did you have headaches?	1	2	3	4
39. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41. Did you find it difficult to look at yourself naked?	1	2	3	4
42. Have you been dissatisfied with your body?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
44. To what extent were you interested in sex?	1	2	3	4
45. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

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

Appendix J Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment No. 3 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Remove the exclusion criterion relating to treatment with strong CYP inhibitors or inducers.

The primary change occurs in Section 8.2 Exclusion Criteria:

Deleted text: ~~11. Treatment with strong cytochrome P450 (CYP) 3A4, CYP2C9, and/or CYP2C19 inhibitors and/or inducers within 1 week before the first dose of study drug (see Appendix G).~~

Rationale for Change:

This change, which removes enrollment restrictions for patients taking CYP3A4, CYP2C9, or CYP2C19 inhibitors and/or inducers in this study, was made due to updated data on MLN0128 metabolism by specific CYP isoforms.

Change 2: Update the list of concomitant medications prohibited during the study.

The primary change occurs in Section 9.5.2 Excluded Concomitant Medications and Procedures for Combination MLN0128 Plus Fulvestrant Treatment Arms (Arm B and Arm C):

Initial wording:

- Strong CYP3A4 and CYP2C19 inducers and/or inhibitors and moderate inhibitors of CYP2C9 (see Appendix G) should be administered only with caution and at the discretion of the investigator. Alternative treatments, if available, should be considered.

  …

- […] Examples of histamine H2 receptor antagonists include ranitidine, famotidine, nizatidine, and cimetidine.

Amended or new wording:

- Strong ~~CYP3A4 and CYP2C19 inducers and/or~~ **cytochrome P450 (CYP) 1A2** inhibitors **and CYP inducers** should be administered with caution and at the discretion of the investigator **(see** Appendix **G for a list of these agents).** ~~Alternative treatments, if available, should be considered. (Refer to Appendix G for a list of strong inhibitors and strong inducers of CYP2C9, CYP2C19, and CYP3A4.)~~

  …

- […] Examples of histamine H2 receptor antagonists include ranitidine, famotidine,**and** nizatidine~~, and c~~. **C**imetidine, **a moderate CYP1A2 inhibitor, is not recommended as a first choice H2 receptor antagonist (see**Appendix **G).**

Rationale for Change:

This change was made to update the recommendations on concomicant medication use during the study based on updated data on MLN0128 metabolism by specific CYP isoforms.

Change 3: Update the list of relevant CYP inhibitors and inducers.

The primary change occurs in Appendix G List of Relevant Cytochrome P450 Inhibitors and Inducers:

Description of the change:	The list of relevant CYP inhibitors and inducers was updated to remove sections listing strong CYP2C19 inhibitors and strong and moderate CYP3A4 inhibitors, to add a section listing strong and moderate CYP1A2 inhibitors, and to update the section listing clinically significant enzyme inducers.

Rationale for Change:

This change was made for consistency with updated data on MLN0128 metabolism by specific CYP isoforms**.**

Change 4: Remove dietary restrictions related to CYP inhibitors and inducers.

The primary change occurs in Section 9.5.2 Excluded Concomitant Medications and Procedures for Combination MLN0128 Plus Fulvestrant Treatment Arms (Arm B and Arm C):

Deleted text: ~~In addition to the above medications, consumption of grapefruit or grapefruit juice is not permitted during the study. Patients should not consume food or beverages containing the fruit or juice of grapefruits or Seville oranges within 7 days before the first dose of study drug and throughout the study (see Appendix G)~~

Rationale for Change:

This change was made for consistency with new data that removes the necessity for restrictions concerning CYP2C9 and 2C19.

The following sections also contain this change:

- Section 9.7 Precautions and Restrictions.
- Appendix G List of Relevant Cytochrome P450 Inhibitors and Inducers**.**

Change 5: Update the number of study sites.

The primary change occurs in Section 7.2 Number of Patients:

Initial wording:	Approximately 153 patients (51 patients per treatment arm) will be enrolled in this study from approximately 55 study centers in North America and Europe. A patient is considered to be enrolled in the study when she has been randomized into a treatment arm.
Amended or new wording:	Approximately 153 patients (51 patients per treatment arm) will be enrolled in this study from approximately ~~55~~ **65** study centers in North America and Europe. A patient is considered to be enrolled in the study when she has been randomized into a treatment arm.

Rationale for Change:

This change was made to ensure that enrollment was achieved within the timelines.

Section 2.0 STUDY SUMMARY also contains this change.

Change 6: Update the recommendations for initiation of crossover treatment.

The primary change occurs in Section 7.1.4 Potential for Crossover Treatment:

Initial wording:	Crossover treatment must begin within 28 days after documented PD. The ongoing schedule of fulvestrant therapy should be maintained (ie, dosing every 28 days), and MLN0128 should be initiated at the next scheduled dose of fulvestrant. This will be Cycle 1 Day 1 of the crossover treatment.
Amended or new wording:	**It is recommended that** ~~C~~crossover treatment ~~must~~ begin within 28 days (+10 days) days after documented **disease progression (imaging date of** PD**), with the goal of maintaining** ~~T~~**the** ongoing schedule of fulvestrant therapy ~~should be maintained~~ (ie, dosing every 28 days)~~, and~~**. Whenever possible,** MLN0128 should be initiated at the next scheduled dose of fulvestrant**, but only when the patient has completed the precrossover screening requirements and is eligible to continue. If the crossover treatment cannot begin within 28 days (+10 days) after documented PD, contact the medical monitor.** ~~This will be Cycle 1 Day 1 of the crossover treatment.~~

Rationale for Change:

This change was made to reflect updated dosing recommendations**.**

- Appendix A Schedule of Events also contains this change.

Change 7: Update guidance for fasting serum glucose post-dose collection on non-dosing days.

The primary change occurs in Appendix A Schedule of Events:

Description of the change	A sentence was added to footnote (o) to clarify that collection of the 2 hour post-dose sample is not expected on non-dosing days.

Rationale for Change:

This change was made to increase the ease and accuracy of recording data at the site level.

The following sections also contain this change:

- Appendix A Schedule of Events.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Pharmacology Approval	05-Oct-2017 14:20 UTC
	Biostatistics Approval	05-Oct-2017 16:13 UTC
	Clinical Approval	06-Oct-2017 18:16 UTC