

Clinical Development

LEE011 (ribociclib)

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A Phase III randomized, double-blind, placebo-controlled study of LEE011 or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer

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List of abbreviations

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse Event
AI	Aromatase Inhibitor
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/SGPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/SGOT
ATC	Around the clock
AUC	Area under the curve
b.i.d.	<i>bis in diem</i> /twice a day
BC	Breast cancer
BIRC	Blinded independent review committee
BOR	Best overall response
BSEP	Bile export salt pump
CBC	Complete blood count
CBR	Clinical Benefit Rate
CCND1	Cyclin D1
CDK	Cyclin Dependent Kinase
CI	Caloric intake
CISH	Cytokine-inducible SH2-containing protein
C _{max}	Peak concentration
C _{min}	Minimum concentration
CNS	Central nervous system
CR	Complete response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CYP	Cytochrome P450
DDI	Drug drug interaction
DILI	Drug-induced liver injury
DLT	Dose Limiting Toxicity
DMC	Data monitoring committee
DOR	Duration of Response
E2F	E2F transcription factor
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment
ER	Estrogen Receptor
EWOC	Escalation with Overdose Control
FDG	Fluorodeoxyglucose
FFPE	Formalin-Fixed, Paraffin-Embedded
FISH	Fluorescence in situ hybridization

FMO3	Flavin containing monooxygenase 3
FSH	Follicle stimulating hormone
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLP	Glucagon-like peptide
GnRH	Gonadotropin-releasing hormone
hCG	Human chorionic gonadotropin
Hct	Hematocrit
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hormone Receptor
i.v.	intravenous(ly)
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	In situ hybridization test
INR	International normalization ratio
IRB	Institutional Review Board
ITT	Intent to Treat
IU	International Unit
IUD	Intra uterine device
LFT	Liver function test
LHRH	Luteinizing-hormone-releasing hormone
LLOQ	Lower Limit of Quantification
LVEF	Left ventricular ejection fraction
MDR1	Multidrug resistance 1
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multi gated acquisition scan
MXR	multixenobiotic resistance
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	Next generation sequencing
NSAI	Non-steroidal aromatase inhibitor
o.d.	<i>omnia die</i> /once a day
OFS	Ovarian follicular suppression
ORR	Overall Response Rate
OS	Overall survival
p.o.	<i>per os</i> /by mouth/orally
PD	Progressive disease
PFS	Progression free survival
P-gp	P-glycoprotein
PgR	Progesterone receptor
PhRMA	Pharmaceutical Research and Manufacturers of America
PI3K	Phosphatidylinositol 3-kinase
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
PK	Pharmacokinetics

PPS	Per protocol set
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PPS	Per protocol set
PR	Partial response
pRb	Retinoblastoma protein
PRO	Patient reported outcomes
PS	Performance status
PT	Prothrombin
PTEN	Phosphatase and tensin homolog
q.d.	Quaque die/everyday
QLQ	Quality of Life Questionnaire
QoL	Quality of Life
Rb	Retinoblastoma
RBC	Red blood cells
REB	Research Ethics Board
RP2D	Recommended phase two dose
s.c.	Subcutaneous(ly)
SAE	Serious Adverse Event
SC	Steering committee
SD	Stable disease
SERM	Selective ER Modulators
SISH	In situ hybridization test
SOP	Standard Operating Procedure
TBIL	Total bilirubin
TTR	Time to response
ULN	Upper limit of normal



Glossary of terms

Assessment	A procedure used to generate data required by the study
Biological Sample	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number (Subject No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints
Withdrawal of Consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

Protocol summary:

Study code	CLEE011E2301
Title	A Phase III randomized, double-blind, placebo-controlled study of LEE011 or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer.
Brief title	Study assessing the efficacy and safety of LEE011+ tamoxifen + goserelin or LEE011 + a NSAI + goserelin in premenopausal women with HR+, HER2-negative advanced breast cancer.
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	<p>Treatment of hormone receptor (HR) positive, HER2-negative breast cancer still represents an unmet medical need as it typically affects younger women who become resistant to standard hormonal treatment. The rationale for assessing the efficacy of LEE011 in combination with hormonal agents in a randomized Phase III study is based upon the role of the CDK4/6 pathway in HR+ breast cancer and the potential synergy when combined with hormonal agents such as tamoxifen or NSAIs.</p> <p>The purpose of this study is to compare the progression-free survival (PFS) between tamoxifen or a NSAI + goserelin + LEE011 and tamoxifen or a NSAI + goserelin + placebo in premenopausal women with HR+, HER2-negative advanced breast cancer.</p>
Primary Objective	To determine whether treatment with tamoxifen or a NSAI + goserelin + LEE011 prolongs PFS compared to treatment with tamoxifen or a NSAI + goserelin + placebo in premenopausal women with HR+, HER2-negative advanced breast cancer.
Secondary Objectives	<p>Key Secondary:</p> <p>To determine whether treatment with tamoxifen or a NSAI + goserelin + LEE011 prolongs overall survival (OS) compared to treatment with tamoxifen or a NSAI + goserelin + placebo in premenopausal women with HR+, HER2-negative advanced breast cancer.</p> <p>Other Secondary:</p> <ul style="list-style-type: none"> ● To evaluate the safety and tolerability of LEE011 in combination with either tamoxifen + goserelin or a NSAI + goserelin ● To evaluate the two treatment arms with respect to response rate (RR) and clinical benefit rate (CBR) ● To describe time to response (TTR) and duration of response (DOR) in each treatment arm ● To evaluate the two treatment arms with respect to time to deterioration of Eastern Cooperative Group (ECOG) performance status (PS) ● To evaluate patient reported outcomes for health-related quality of life in the two treatment arms
Study design	This is a randomized, phase III, double-blind, global trial comparing the combination of tamoxifen or a NSAI + goserelin + LEE011 to tamoxifen or a NSAI + goserelin + placebo in premenopausal women with HR+, HER2-negative advanced breast cancer. The study will consist of a 28 day screening phase, treatment phase and post-treatment phase which includes safety, efficacy, and survival follow up.

<p>Population</p>	<p>The study will include premenopausal women with HR+ advanced breast cancer. The investigator or designee must ensure that only patients who meet all of the following inclusion and none of the exclusion criteria are offered treatment in the study.</p>
<p>Inclusion criteria</p>	<p>Refer to Section 5.2 for details on inclusion criteria.</p> <ul style="list-style-type: none"> ● Patient is an adult, female ≥ 18 years old and < 60 years old at the time of informed consent and has signed informed consent before any trial related activities are conducted according to local guidelines. ● Confirmed negative serum pregnancy test (β-hCG) before starting study treatment or patient has had a hysterectomy ● Patient is pre-menopausal or peri-menopausal at the time of study entry. Premenopausal status is defined as either: <ul style="list-style-type: none"> ● Patient had last menstrual period within the last 12 months, <p>OR</p> <ul style="list-style-type: none"> ● If on tamoxifen or toremifene within the past 14 days, plasma estradiol and FSH must be in the premenopausal range per local normal range, <p>OR</p> <ul style="list-style-type: none"> ● In case of therapy induced amenorrhea, plasma estradiol and/or FSH must be in the premenopausal range per local normal range. ● Patients who have undergone bilateral oophorectomy are not eligible. <p>Perimenopausal status is defined as neither premenopausal nor postmenopausal (see exclusion criteria).</p> <ul style="list-style-type: none"> ● Patient has advanced (locoregionally recurrent or metastatic) breast cancer not amenable to curative therapy (e.g. surgery and/or radiotherapy). ● Patients who received (neo) adjuvant therapy for breast cancer are eligible. <ul style="list-style-type: none"> ● If the patient has never received any prior endocrine therapy OR if ≥ 12 months have elapsed since the patient's last dose of adjuvant therapy, then the patient is eligible to receive tamoxifen + goserelin OR a NSAI + goserelin for advanced breast cancer based on the investigators choice. ● If tamoxifen or fulvestrant was the last prior (neo) adjuvant therapy and the last dose was given < 12 months prior to randomization, then the patient is eligible to receive a NSAI (letrozole or anastrozole) + goserelin for advanced breast cancer. ● If letrozole, anastrozole, or exemestane was the last prior (neo) adjuvant therapy and the last dose was given < 12 months prior to randomization, then the patient is eligible to receive tamoxifen + goserelin for advanced breast cancer. ● Patients who received ≤ 14 days of tamoxifen or a NSAI (letrozole or anastrozole) with or without goserelin or goserelin ≤ 28 days for advanced breast cancer prior to randomization are eligible. Patients must continue treatment with the same hormonal agent + goserelin during the study. No treatment interruption is required for these patients prior to randomization. <p>Note: Patients who are receiving goserelin for reasons other than advanced breast cancer treatment are eligible (e.g endometriosis). Patients who received ≤ 28 days goserelin for advanced breast cancer are eligible.</p> <ul style="list-style-type: none"> ● Patients who have received up to 1 line of chemotherapy for advanced breast cancer and have been discontinued at least 28 days before randomization are eligible. <p>Note: If a cytotoxic chemotherapy regimen was discontinued for reasons other than disease progression and lasted less than 21 days, this regimen does not count as a prior line of chemotherapy.</p> <ul style="list-style-type: none"> ● Patient has a histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive and/or progesterone receptor positive breast cancer by local laboratory (based on most recently analyzed biopsy).

	<ul style="list-style-type: none"> ● Patient has HER2-negative breast cancer (based on most recently analyzed biopsy) defined as a negative in situ hybridization test or an IHC status of 0, 1+ or 2+. If IHC is 2+, a negative in situ hybridization (FISH, CISH, or SISH) test is required by local laboratory testing. ● Patient must have either: <ul style="list-style-type: none"> ● Measurable disease, i.e., at least one measurable lesion as per RECIST 1.1 criteria. <p>OR</p> <ul style="list-style-type: none"> ● If no measurable disease is present, then at least one <i>predominantly</i> lytic bone lesion must be present (patients with no measurable disease and only one predominantly lytic bone lesion that has been previously irradiated are eligible if there is documented evidence of disease progression of the bone lesion after irradiation). <ul style="list-style-type: none"> ● Patient has an ECOG PS 0 or 1. ● Patient has adequate bone marrow and organ function as defined by the following laboratory values (as assessed by central laboratory): <ul style="list-style-type: none"> ● Absolute neutrophil count $\geq 1.5 \times 10^9/L$ ● Platelets $\geq 100 \times 10^9/L$ ● Hemoglobin ≥ 9.0 g/dL ● Potassium, sodium, calcium (corrected for serum albumin), and magnesium within normal limits of the central laboratory ● INR ≤ 1.5 ● Serum creatinine < 1.5 mg/dL ● In absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be below $2.5 \times ULN$. If the patient has liver metastases, ALT and AST should be $< 5 \times ULN$ ● Total serum bilirubin $< ULN$; or total bilirubin $\leq 3.0 \times ULN$ with direct bilirubin $< 1.5 \times ULN$ of the central laboratory in patients with well documented Gilbert's Syndrome ● Patient must be able to swallow study therapy ● Patient must be able to communicate with the investigator and comply with the requirements of the study procedures ● Patient must be willing to remain at the clinical site as required by the protocol
<p>Exclusion criteria</p>	<p>Refer to Section 5.3 for details on exclusion criteria</p> <ul style="list-style-type: none"> ● Patient who has received a prior CDK4/6 inhibitor. ● Patient has a known hypersensitivity to any of the excipients of LEE011, tamoxifen, NSAID (letrozole or anastrozole), or goserelin. ● Patient is post-menopausal. Post-menopausal status is defined either by: <ul style="list-style-type: none"> ● Prior bilateral oophorectomy <p>OR</p> <ul style="list-style-type: none"> ● Age ≥ 60 <p>OR</p> <ul style="list-style-type: none"> ● Age < 60 and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) and FSH and estradiol in the postmenopausal range per local normal range. <p>Note: For women with therapy-induced amenorrhea, serial measurements of FSH and/or estradiol are needed to ensure menopausal status (NCCN Guidelines Version 3.2014).</p> <ul style="list-style-type: none"> ● Patients who currently have inflammatory breast cancer at screening.

	<ul style="list-style-type: none">● Patients who received any prior hormonal anti-cancer therapy for advanced breast cancer except for ≤ 14 days of tamoxifen or a NSAID or goserelin ≤ 28 days for advanced breast cancer prior to randomization.● Patient who has not had resolution of all acute toxic effects of prior anti-cancer therapy to NCI CTCAE version 4.03 Grade ≤1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion).● Patient has a concurrent malignancy or malignancy within 3 years of randomization, with the exception of adequately treated basal cell carcinoma, squamous cell skin carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer.● Patient with CNS metastases. Note: CNS involvement must be ruled out by assessments if a patient has any signs or symptoms indicating potential CNS metastases.● Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).● Patient has a known history of HIV infection (testing not mandatory).● Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, contraindicate patient participation in the clinical study (e.g., chronic pancreatitis, chronic active hepatitis, etc.).● Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality including any of the following:<ul style="list-style-type: none">● History of angina pectoris, symptomatic pericarditis, or myocardial infarction or coronary artery bypass graft (CABG) within 6 months prior to study entry.● Documented cardiomyopathy.● Left Ventricular Ejection Fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO).● Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)● Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:<ul style="list-style-type: none">● Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia● resting heart rate < 50 at rest, by the triplicate ECG● resting heart rate >90 at rest, by the triplicate ECG● Systolic blood pressure >160 or <90 mmHg.● On screening, inability to determine the QTcF interval on the ECG (ie: unreadable or not interpretable) or QTcF >450 msec (using Fridericia's correction). All determined by the average of the triplicate screening ECG, per central review.● Patient is currently receiving any of the following substances and cannot be discontinued 7 days prior to the start of the treatment:<ul style="list-style-type: none">● Known strong inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges.● Medications with a known risk to prolong the QT interval or induce Torsades de Pointes that cannot be discontinued or replaced by safe alternative medication (e.g. within 5 half-lives or 7 days prior to starting study drug).
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	<ul style="list-style-type: none">● Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5.● Additionally, for patients receiving tamoxifen: known strong inducers or inhibitors of CYP2D6.● Herbal preparations/medication and dietary supplements (except for vitamins).● Patient has had major surgery within 14 days prior to starting study drug or has not recovered from major side effects of surgery.● Patient is currently receiving warfarin or other Coumadin derived anti-coagulant, for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH), or fondaparinux is allowed.● Patient is currently receiving or has received systemic corticosteroids \leq 2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment. Note: The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular).● Patient is concurrently using other antineoplastic agents (except for patients who are receiving \leq 14 days of tamoxifen or a NSAID or goserelin \leq 28 days for advanced breast cancer prior to randomization).● Patient who has received radiotherapy \leq 4 weeks or limited field radiation for palliation \leq 2 weeks prior to randomization, and who has not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia) and/or if \geq 25% of the bone marrow was irradiated.● Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.● Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study treatment and for 21 days after stopping study medication. Highly effective contraception methods include:<ul style="list-style-type: none">● Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.● Total hysterectomy (surgical removal of the uterus and cervix) or tubal ligation (getting your “tubes tied”) at least six weeks before taking study treatment.● Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.● Combination of the following:<ol style="list-style-type: none">a. Placement of an intrauterine device (IUD) or intrauterine system (IUS)b. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository● Participating in a prior investigational study within 30 days prior to enrollment or within 5-half-lives of the investigational product, whichever is longer.● Not able to understand and to comply with study instructions and requirements.● Patient with symptomatic visceral disease or any disease burden that makes the patient ineligible for endocrine therapy per the investigator’s best judgment
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<p>Investigational and reference therapy</p>	<p>LEE011 or LEE011-matching placebo will be given orally once a day on days 1-21 of each 28 day cycle. Days 22-28 will be a “rest” period from LEE011 or LEE011-matching placebo. Tamoxifen or a NSAID will be given orally once a day on a continuous daily schedule (e.g., days 1-28 of each 28-day cycle). Goserelin will be given as an injectable subcutaneous implant on day 1 of every 28 day cycle. There will be no “rest” period in the tamoxifen or NSAID schedule.</p> <table border="1" data-bbox="553 464 1409 877"> <thead> <tr> <th data-bbox="553 464 760 548">Study treatments</th> <th data-bbox="760 464 1052 548">Pharmaceutical form and route of administration</th> <th data-bbox="1052 464 1182 548">Dose</th> <th data-bbox="1182 464 1409 548">Frequency and/or Regimen</th> </tr> </thead> <tbody> <tr> <td data-bbox="553 548 760 611">LEE011/Placebo</td> <td data-bbox="760 548 1052 611">Capsules for oral use</td> <td data-bbox="1052 548 1182 611">600 mg</td> <td data-bbox="1182 548 1409 611">Days 1-21 of each 28 day cycle</td> </tr> <tr> <td data-bbox="553 611 760 674">Tamoxifen*</td> <td data-bbox="760 611 1052 674">Tablets for oral use</td> <td data-bbox="1052 611 1182 674">20 mg</td> <td data-bbox="1182 611 1409 674">Days 1-28 of each 28 day cycle</td> </tr> <tr> <td data-bbox="553 674 760 737">Letrozole*</td> <td data-bbox="760 674 1052 737">Tablets for oral use</td> <td data-bbox="1052 674 1182 737">2.5 mg</td> <td data-bbox="1182 674 1409 737">Days 1-28 of each 28 day cycle</td> </tr> <tr> <td data-bbox="553 737 760 800">Anastrozole*</td> <td data-bbox="760 737 1052 800">Tablets for oral use</td> <td data-bbox="1052 737 1182 800">1 mg</td> <td data-bbox="1182 737 1409 800">Days 1-28 of each 28 day cycle</td> </tr> <tr> <td data-bbox="553 800 760 877">Goserelin</td> <td data-bbox="760 800 1052 877">Subcutaneous implant</td> <td data-bbox="1052 800 1182 877">3.6 mg</td> <td data-bbox="1182 800 1409 877">Day 1 of each 28 day cycle</td> </tr> </tbody> </table> <p>*Patients will be eligible to receive either tamoxifen or a NSAID (letrozole or anastrozole) based on prior (neo) adjuvant therapy received.</p> <p>The study drugs will be administered as a flat-fixed dose, and not by body weight or body surface area. All oral study treatment drugs must be administered together at approximately the same time each day and can be given with or without food.</p>	Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen	LEE011/Placebo	Capsules for oral use	600 mg	Days 1-21 of each 28 day cycle	Tamoxifen*	Tablets for oral use	20 mg	Days 1-28 of each 28 day cycle	Letrozole*	Tablets for oral use	2.5 mg	Days 1-28 of each 28 day cycle	Anastrozole*	Tablets for oral use	1 mg	Days 1-28 of each 28 day cycle	Goserelin	Subcutaneous implant	3.6 mg	Day 1 of each 28 day cycle
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Goserelin	Subcutaneous implant	3.6 mg	Day 1 of each 28 day cycle																						
<p>Efficacy assessments</p>	<ul style="list-style-type: none"> ● CT/ MRI every 8 weeks for the first 18 months, then every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, or subject/guardian decision. ● Brain CT or MRI as clinically indicated. ● Whole body bone scan at screening if not collected previously within 42 days (6 weeks) prior to randomization; as clinically indicated thereafter. ● Bone x-ray, CT or MRI (if bone lesion at screening) every 8 weeks for the first 18 months and then every 12 weeks thereafter. ● Skin color photography (if skin lesions at screening) every 8 weeks during the first 18 months and then every 12 weeks thereafter. ● CT/ MRI for any disease outside of the chest, abdomen, pelvis (if lesion identified at baseline) every 8 weeks for the first 18 months and then every 12 weeks thereafter. ● Survival status every 12 weeks (or earlier if required) regardless of treatment discontinuation reason. 																								
<p>Safety assessments</p>	<ul style="list-style-type: none"> ● Physical examinations ● ECOG performance status ● Height, weight, and vital signs ● 12 lead ECGs ● ECHO, MUGA scan ● Laboratory assessments including hematology, biochemistry, lipid panel, coagulation (via INR), [REDACTED] pregnancy and urinalysis 																								

<p>Other assessments</p>	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>Patient-reported outcomes: Patient questionnaires will be collected to assess health-related quality-of-life, health status, functioning, disease symptoms, side effects, [REDACTED], and activity impairment.</p> <ul style="list-style-type: none">• European Organization for Research and Treatment of Cancer's core quality of life questionnaire and breast cancer specific questionnaire (e.g., EORTC-QLQ-C30 and QLQ-BR23)• EuroQoL 5-level instrument (EQ-5D-5L)• [REDACTED] <p>[REDACTED]</p>
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Data analysis	<p>The primary objective for this study is to determine whether treatment with tamoxifen or a NSAID + goserelin + LEE011 prolongs PFS compared to treatment with tamoxifen or a NSAID + goserelin + placebo in premenopausal women with HR+, HER2-negative advanced breast cancer. The primary efficacy endpoint, PFS, will be determined based on local tumor assessment following RECIST 1.1 guidelines. The primary efficacy analysis will be the comparison of the distribution of PFS between the two treatment groups using a stratified (randomization strata per IRT) log-rank test at one-sided 2.5% level of significance.</p> <p>The primary PFS analysis will be performed after approximately 329 PFS events have been documented per local assessment. Distribution of PFS will be estimated using the Kaplan-Meier method. The median PFS along with 95% confidence intervals will be presented for each of the two treatment groups. The stratified Cox regression will be used to estimate the hazard ratio of PFS, along with 95% confidence interval. The treatment effect in terms of PFS within the subgroup of patients receiving tamoxifen and goserelin with LEE011/placebo, and within the subgroup receiving NSAID and goserelin with LEE011/placebo, will be estimated using separate Cox regression models; estimated hazard ratios with corresponding 95% CIs will be presented for each subgroup.</p> <p>The Full Analysis Set (FAS) will comprise all randomized patients. Following the intent to treat (ITT) principle, patients will be analyzed according to the treatment and strata they have been assigned to at the time of randomization. The FAS will be the primary population for all efficacy analyses. The safety set will consist of all patients who received at least one dose of the study treatment (tamoxifen and goserelin or NSAID and goserelin and LEE011/placebo). Patients will be analyzed according to treatment actually received..</p> <p>The key secondary objective in this study is to compare the two treatment groups with respect to OS. OS will be compared between the two treatment groups, provided the primary endpoint PFS is statistically significant favoring the test treatment arm (tamoxifen or a NSAID + goserelin + LEE011). A hierarchical testing procedure will be adopted in this study and the OS analyses will be performed only if the primary efficacy endpoint PFS is statistically significant. A maximum of three analyses are planned for OS: (1) at the time of the primary analysis for PFS, at which point a total of 123 (49%) deaths are expected); (2) after approximately 189 (75%) deaths have been documented; and (3) a final analysis for OS when 252 deaths are expected (expected approximately 40 months from date of first patient to be randomized).</p> <p>At the time of primary PFS analysis, both PFS and interim OS analyses will be performed by the Sponsor's clinical team. Investigators and patients will remain blinded to study treatment and all patients will continue to be followed for OS until the final OS analysis (or earlier if OS reaches statistical significance at any of the interim analyses).</p> <p>The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety assessments (e.g., electrocardiogram, vital signs) will be summarized by treatment group.</p>
Key words	HR-positive, HER2-negative, advanced breast cancer, LEE011, tamoxifen or NSAID, goserelin, CDK4/6, Phase III, ER-positive, PR-positive, premenopausal

Amendment 4 (24-Feb-2017)

Study CLEE011E2301 was initiated in November 2014 and enrollment is complete. The last patient was randomized on 01-Aug-2016 and 672 patients were randomized in total.

The purpose of this amendment is to:

- (i) Eliminate the efficacy interim analysis:

Elimination of the interim analysis will allow additional PFS events and longer follow-up for more robust treatment effect and PFS estimates, while not unduly delaying the readout of the study. Based on current events projection, it is expected that the cutoff date for the final PFS analysis (based on 329 PFS events) would occur approximately 3 months later than the cutoff for the currently planned interim analysis (based on 263 PFS events). An increase of 25% in the number of PFS events, together with an additional 3 months follow-up for all patients, is therefore warranted.

- (ii) Update the clinical safety and efficacy data for LEE011 in line with newly reported results of CLEE011A2301.

- (iii) Additional changes

- (i) The definition of the Safety set in the statistical analysis was updated to remove the requirement of a post-baseline safety assessment for inclusion in the Safety set. The updated definition, i.e. including all treated patients, reflects the current standard Novartis definition and a widely used definition in the industry.
- (ii) Interim summary PK data from anastrozole-treated patients may be used to support ongoing health authority interactions. This use of the data is described in the protocol together with a description of the corresponding safeguards to ensure trial integrity is maintained.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The changes being made to the protocol due to this amendment are incorporated in the following sections:

- Summary section of the protocol has been updated to maintain consistency with the main body of the protocol
- Section 1.1.3 updated current preclinical and clinical data supporting CDK4/6 pathway in breast cancer
- Sections 1.2.1.2 deleted study status of CLEE011A2301 as updated information has been provided in a later section.
- Section 1.4.1.1 added clinical safety and efficacy of LEE011 with newly reported results of CLEE011A2301
- Section 4.1 removed reference to IDMC review of efficacy data and interim analysis of PFS
- Section 4.2 removed efficacy interim analysis for primary PFS endpoint

- Section 4.3 removed reference to interim PFS analysis and updated reference of final PFS analysis to primary PFS analysis
- Section 7.2.1.1 corrected reference to Novartis guideline version 3.2
- Tables 7-9, 7-10, 7-11 corrected footnote c and d for unscheduled PK sample numbers
- Sections 8.2.2 and 8.4 replaced “Novartis Drug Safety and Epidemiology (DS&E)” with “Novartis Chief Medical Office and Patient Safety (CMO&PS)”
- Section 8.6 removed reference to IDMC review of efficacy data from the interim analysis; added description of use of interim PK data from anastrozole-treated patients to support health authority interactions
- Section 10 removed reference to interim PFS analysis
- Section 10.1.2 updated definition of Safety set
- Section 10.4.2 removed reference to interim PFS analysis and indicated timing of primary efficacy analysis at approximately 329 PFS events
- Section 10.4.4 clarified that the analysis of PFS as assessed by BIRC, implemented in protocol amendment 3, uses a sample-based/audit approach; [REDACTED]
- Section 10.5.1 updated the timing of OS analyses as a result of removing the PFS interim analysis
- Section 10.7.1 removed PFS interim analysis
- Section 10.7.2 updated number and timing of OS interim analyses as a result of removing the PFS interim analysis
- Section 10.8 removed the group sequential design aspects of the sample size calculation due to removal of PFS interim analyses (the sample size calculation itself, to the level of precision reported, is unchanged)
- Section 10.9.1 changed from 4-look to 3-look design for OS as a direct result of removing PFS interim analysis (the sample size calculation itself, to the level of precision reported, is unchanged)
- Section 10.9.2.1 corrected typographical errors in the half-width of 90% CI for the treatment difference; updated table numbers and references due to deletion of a table earlier in the section
- Section 11.5 updated Novartis guidelines for publication of study protocols and results
- Section 13 updated protocol references

Review requirements by IRB/IEC and Health Authorities

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

Summary of previous amendment(s)

Amendment 3 (24-Jun-2016)

Study CLEE011E2301 was initiated in November 2014 and enrollment is currently ongoing. As of June 13, 2016, 611 patients have been randomized in the study.

The purpose of this amendment is to:

- (i) Eliminate the planned futility analysis:

Since the start of Study CLEE011E2301, additional clinical data have been generated with LEE011 and other CDK 4/6 inhibitors that provide additional assurance of the activity of this compound and class in patients with breast cancer. In addition, Study CLEE011E2301 will be fully enrolled prior to the time of the originally planned futility analysis, negating the need for the originally planned interim futility analysis.

- (ii) Change the approach for Blinded Independent Review Committee (BIRC) assessment of PFS from a full read to an audit (sample) based approach:

For studies with local PFS as the primary endpoint, central PFS has generally been used as a secondary analysis in support of the treatment effect observed in the primary efficacy analysis. Although 100% central review of scans has been performed in many trials, there is a growing body of evidence that an audit based approach for central evaluation is sufficient ([Zhang et al 2012](#), [FDA ODAC 2012](#)). Therefore, the BIRC assessment of PFS is being changed from a full read to an audit based approach. Consequently, BIRC based PFS will no longer be a secondary endpoint but will be considered supportive of the primary.

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- (iv) The protocol appendix 3 has been updated to reflect the new Novartis guidance on the implementation of RECIST 1.1
- (v) Additional changes
- (i) The clinical pharmacokinetic section has been updated to reflect new data available
 - (ii) Palliative radiotherapy, previously only allowed for bone pain relief, is permitted provided it is not delivered to a target lesion
 - (iii) A sensitivity analysis has been added for ORR based on patients with measurable disease at baseline.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The changes being made to the protocol due to this amendment are incorporated in the following sections:

- Summary section of the protocol has been updated to maintain consistency with the main body of the protocol

- Section 1.2.1.5 addition of language regarding new pharmacokinetics data on LEE011
- Section 3, Table 3-1 removal of secondary objective to evaluate centrally assessed PFS, [REDACTED]
- Section 4.1 update of centrally assessed PFS from a secondary endpoint to supportive evidence of the primary endpoint
- Section 4.1, 4.2, and 4.3 removal of futility analysis
- [REDACTED]
- Table 6-5, to further clarify triplicate ECG measurements
- Section 6.4.1.4, to remove the requirement of palliative radiation solely for bone pain relief.
- [REDACTED]
- [REDACTED]
- Section 7.2.1.1 addition of language relating to audit-based central PFS assessment
- [REDACTED]
- Section 7.2.2.7.2 corrected reference to Table 6-6
- Section 8.6 removal of reference to futility analysis
- Section 9.3.6 addition of language describing audit-based BIRC assessment of PFS
- Sections 10, 10.4.2, 10.5.1, 10.7.1, 10.7.2, 10.8 removal of futility interim analysis and update of corresponding operating characteristics and sample size descriptions
- Section 10.4.4 addition of text describing supportive analysis of PFS based on audit-based BIRC assessment
- Section 10.5 and 10.5.2.1 removal of BIRC-assessed PFS from secondary objectives; addition of a sensitivity analysis in Section 10.5.2.1 for ORR based on patients with measurable disease at baseline
- [REDACTED]
- Section 10.8 addition of sample size calculation for audit size of sample-based BIRC assessment of PFS
- Section 13: addition of new protocol references.

Review requirements by IRB/IEC and Health Authorities

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

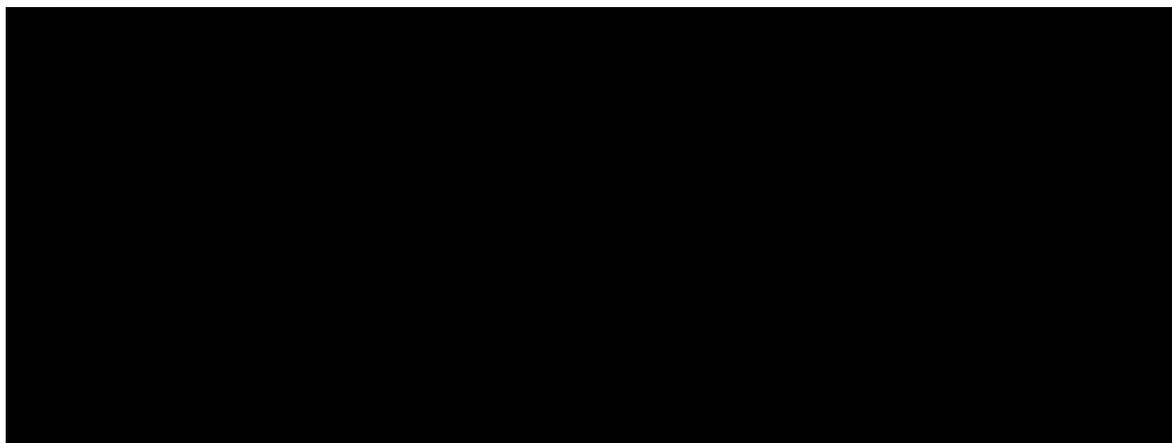
Amendment 2

Study CLEE011E2301 was initiated in November 2014 and enrollment is currently ongoing. As of February 08, 2016, 372 patients have been randomized in the study.

The purpose of this amendment is to:

(i) Update and clarify the safety monitoring of patients to be consistent across LEE011 clinical trials, and better characterize the QTc [REDACTED] effects including:

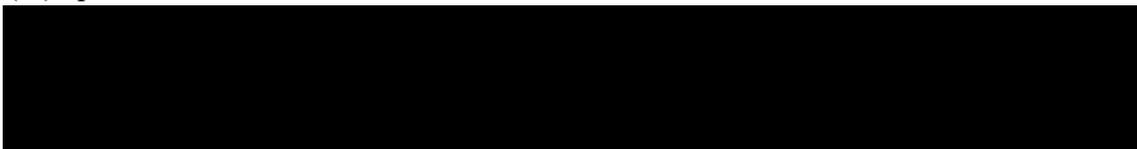
- (i) Management of QTcF prolongation: Potential risk of QT prolongation has been observed in patients treated with LEE011. Updates to inclusion and exclusion criteria, ECG monitoring and dose modification guidelines for QTcF prolongation have been made.



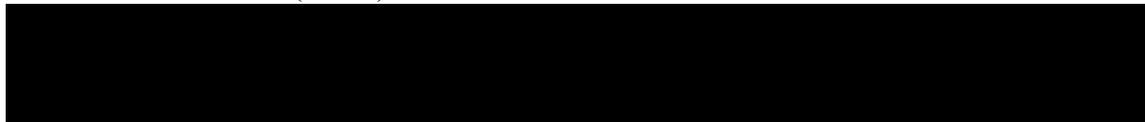
- (iii) Management of dose modification based on local laboratory results: Clarification has been provided that, in case of safety emergency, local laboratory results can be used to evaluate the need for potential study treatment dose modifications

(ii) Additional changes

- (i) List of prohibited concomitant medications has been updated based on recently released Novartis internal Oncology Clinical Pharmacology drug-drug interaction guidance (from 2015) and based on new data and recommendations from the latest version of LEE011 Investigator's Brochure.
- (ii) New information is provided on the safety pharmacology and toxicology
- (iii) Updated clinical trial information with the most recent data



- (v) Remove the requirement for a central radiology assessment by medical oncologist: Medical oncologist review has been replaced by a standard blinded independent review committee (BIRC) assessment



Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The changes being made to the protocol due to this amendment are incorporated in the following sections:

- Summary section of the protocol has been updated to maintain consistency within the main body of the protocol
- Section 1.1.3 Addition of most recent information on available therapeutic options
- Section 1.2 Addition of language to refer to most recent version of the LEE011 investigator brochure
- Section 1.4 Addition of language to refer to most recent version of the LEE011 investigator brochure
- Section 2.3 has been updated to incorporate most updated trial information
- 
- Section 5.2 Inclusion Criteria has been updated:
 - #2) Clarify that pregnancy test not needed in case of hysterectomy
 - #5) Remove prior neo adjuvant therapy washout requirements
 - #7) Phosphorus assessment has been removed from screening visit
 - #12) Bilirubin assessment lab ranges clarified
 - #13- #15) Added per program standard language
- Section 5.3 Exclusion Criteria have been updated:
 - #12) and #13) to clarify the exclusion criteria for patients with clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality and for patients currently receiving prohibited medications. Also updated heart rate parameters.
 - #20) Clarified contraception requirements
 - #23) Added exclusion 23 to state that patients with disease burden which makes them poor candidates for endocrine therapy are excluded
- Section 6.1 has been updated with timing recommendation on dosing schedule and meal conditions
- Section 6.3.1.4:
 - To clarify the use of local laboratory results for dose modifications
 - To add clarity on dose modification guidelines

- Section 6.3.1.5 and Section 6.3.1.6: Table 6-3, Table 6-4 and Table 6-5
 - Dose modifications have been updated to clarify actions to be taken [REDACTED] QTcF prolongation and all other toxicities, [REDACTED]
 - “Placebo” has been added in the table wording and baseline value has been modified to baseline grade based on CTCAE
- Section 6.4.1: wording around the use of corticosteroids has been updated
- Section 6.4.3: wording around the use of prohibited concomitant medications has been clarified
- Section 6.6.4 has been added to clarify the use of medications with a known risk of QT prolongation
- Section 7, Table 7-1:
 - Modification to the timeframe for the ECGO/MUGA now includes a +/- 7 day window
 - [REDACTED]
 - Clarify that the ECOG assessment will not be repeated at Cycle 1 Day 1 when done in the timeframe -7 to -1 at the screening visit
 - Clarify that the FSH, [REDACTED] and serum pregnancy test can be done within 28 days before randomization.
 - [REDACTED]
- Section 7.1.2 clarification on ICF process for patients who rescreen
- Section 7.1.5.1 update to the study treatment discontinuation language in the case of AEs
- Section 7.2.2.5:
 - Clarification on the use of local laboratory results
 - [REDACTED]
- [REDACTED]
- Section 7.2.2.7.1 and Table 7-5:
 - Electrocardiogram (ECG) was updated to include triplicate readings for each time point
 - Clarity was added on the unscheduled ECG management
- [REDACTED]
- [REDACTED]

- Table 7-13
 - [REDACTED]
 - Blood volume for circulating tumor DNA has been updated from 6mL to 20mL at Cycle 1 Day 1 and 6mL to 10mL at other applicable time points
 - Updated baseline tumor tissue collection language from strongly recommended to mandatory
- Section 7.2.4.1.1: Updated baseline tumor sample language from strongly recommended to mandatory
- [REDACTED]
- Section 8: implementation of new Serious Adverse Event (SAE) reporting instructions
- Section 9.3.6: medical oncologist review has been replaced by a standard blinded independent review committee (BIRC) review assessment
- [REDACTED]
- Section 13: new protocol references have been added
- Section 14.1 Appendix 1- Concomitant medications
 - Table 14-1 and Table 14-2 have been updated with the latest information available.

Review requirements by IRB/IEC and Health Authorities

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

Some changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 1

The purpose of this amendment is to:

(i) Further enhance and clarify safety monitoring of patients, including:

- (i) Management of QTc prolongation: More specific recommendations for cases of QTc prolongation have been included : addition of ECG assessments at the first day of each cycle, check and follow-up of electrolyte abnormalities until normalization, review of concomitant medications, and compliance with correct dose have been included with each grade. Additionally, if patient's have any QTcF values ≥ 481 ms at any time before Cycle 7 Day 1, then continued ECG monitoring is indicated for all subsequent cycles.

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- (iii) Management of grade 3 neutropenia: Clarification that re-initiation of LEE011/placebo after grade 3 neutropenia may occur at the same dose level if the neutropenia resolves in ≤ 7 days to better manage consistency regarding dose reductions.

(ii) Update the protocol requirements for consistency with the most recent preclinical information:

- (i) In the initial rat ADME study cited in previous IB version, thyroid had the highest exposure in albino animals only. As a precaution, thyroid function was monitored in all clinical study protocols. A most recent study (DMPK 1300792) using p.o. dosing in partially pigmented animals with a longer observation period showed the highest distribution to the melanin-containing structures and not to the thyroid gland. In addition, no clinically significant thyroid adverse events have been reported in clinical trials so far. Based on this information, the risk to thyroid gland is removed from the reference safety information for the compound and thyroid laboratory monitoring in clinical protocols are no longer mandated.
- (ii) In the 15-week rat toxicity study, kidney has been identified as an additional organ of toxicity for LEE011. In order to better characterize this potential side effect, as well as improve the management of the safety of the patients, monthly urinalysis has been added as well as blood urea nitrogen assessment with each chemistry panel.

(iii) Revise the treatment allocation in case of prior use of fulvestrant:

In the original protocol, patients who had a last dose of (neo)adjuvant fulvestrant (last dose given <12 months prior to randomization) were eligible to receive tamoxifen +goserelin on study. However, because fulvestrant is an estrogen receptor antagonist with a mechanism of action more similar to tamoxifen than to NSAIs, patients having received (neo)adjuvant fulvestrant (last dose was given < 12 months prior to randomization) will instead be eligible to receive a NSAID + goserelin on study instead of tamoxifen +goserelin.

(iv) Additional changes:

The assessment of PFS as per blinded independent review committee (BIRC) was changed from a supportive analysis of the primary endpoint to a secondary endpoint.

Updated language has been included in the protocol covering “Discontinuation of Clinical Trial Protocol Elements” in order to maintain consistency with Novartis protocol template language.

Additionally, Amendment 1 includes minor editorial changes, typographical error corrections, and additional clarifications to address investigators’ questions as described in the list of changes below. Lastly, minor changes to the evaluation schedule have been made to allow the screening period to be more efficiently managed.

Changes to the protocol:

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

The changes being made to the protocol due to this amendment are incorporated in the following sections:

- Summary section of the protocol has been updated to maintain consistency within the main body of the protocol.
- Section 1.2.1: Addition of language to refer to most recent version of the LEE011 Investigator Brochure.
- Section 3 Table 3-1: Addition of secondary objective which includes the evaluation of the two treatment arms with respect to centrally assessed PFS.
- Section 4.1: Revision with regard to prior use of fulvestrant – Patients with prior use of fulvestrant will be eligible to receive a NSAI + goserelin on study as opposed to tamoxifen. Section 4.1: Clarification added to mention that crossover between NSAIs (letrozole to anastrozole or vice versa) is not permitted.
- Section 4.2: Removal of “There is no intent to stop the study due to futility at this efficacy interim analysis.”
- Section 4.3: Clarification regarding the definition of end of study.
- Section 4.4: word “prematurely withdrawn patient” replaced by “discontinued or withdrawn patient.”
- Section 5.1: Addition of clarification on study population and introduction of a statement that potential patients should be eligible to receive endocrine therapy in order to enroll in this study.
- Section 5.2 Inclusion Criteria:
 - #2). Removal of “within 72 hrs” regarding the collection of a negative serum pregnancy test. A negative serum pregnancy test will be collected during the screening period (-14 to -1 days) in this amendment.
 - #3). Clarification of the definition of menopausal status: FSH and/or estradiol should be assessed per local normal range.
 - #5). Clarification of prior fulvestrant use as mentioned in Section 4.1

- #6). Clarification of prior goserelin use: patients who are receiving goserelin for reasons other than for advanced breast cancer treatment are eligible (e.g endometriosis). Patients who received ≤ 28 days goserelin for advanced breast cancer are eligible.
- #7). Addition of the note further describing 1 line of chemotherapy.
- #12). Revision of the eligibility regarding serum creatinine.
- Section 5.3 Exclusion Criteria:
 - #3). Clarification of the definition of menopausal status: FSH and/or estradiol should be assessed per local normal range.
 - #5). Clarification of prior goserelin use
 - #8). Further clarification regarding the exclusion of CNS metastases. CNS involvement must be ruled out by assessments if a patient has any signs or symptoms indicating potential CNS metastases.
 - #12). Addition of cardiac disease or history of dysfunction: Congenital long QT syndrome or a family history of long QT syndrome, and Bradycardia (heart rate <50 at rest), by ECG or pulse. In addition, the word “per central review” was added.
 - #13). Clarification regarding tamoxifen and the known strong inducers or inhibitors of CYP2D6. Additionally, dietary supplements were added as an exclusion criterion.
 - #17). Clarification of prior goserelin use.
 - #20). Additional language added to specify patients must be using highly effective methods of contraception 21 days after stopping study medication.
 - #21 and #22). Two additional exclusion criteria were added to comply with Novartis standard protocol language.
- Section 6.1.1: Addition of the word “placebo.”
- Section 6.1.1.1: Clarification of the timing and dosing of patients allowed after Cycle 3 Day 16. Addition of no herbal supplements and that multivitamins are permitted was also added.
- Figure 6-1: Revised per site guidance
- Section 6.1.4: Modified for better clarity
- Section 6.1.5: Modified for better clarity
- Section 6.3.1: Modified for better clarity
- Section 6.3.1.4: Modified to ensure patients receive 7 consecutive rest days of LEE011/placebo to avoid any inadvertent overdose.
- Section 6, Table 6-3: More detailed guidance regarding management of grade 3 neutropenia based on duration of adverse event prior to resolution: If resolved in ≤ 7 days, then maintain dose level. If resolved in > 7 days, then reduce LEE011/placebo dose to the next lower dose level.
- Section 6, Table 6-4: Addition of dose adjustment and management recommendations for hepatic toxicities. Additional follow-up guidance was also added under Section 6.3.1.4.1.

- Section 6, In Table 6-5: More specific guidance for electrolyte abnormalities with QTcF prolongations grade 1-4 was added: “If outside of the normal range, interrupt LEE011/placebo administration, correct with supplements or appropriate therapy, and repeat electrolytes until documented normalization of the electrolytes.”
- Section 6.3.1.4.1, renumbered as 6.3.1.4.3. Word “planned” changed to “ongoing” regarding the status of the human ADME study.
- Section 6.4: Modified for better clarity
 - Section 6.4.4: Additional clarification added regarding concomitant medication associated with menopausal status.
- Section 6.5.3, added the words “for safety reasons” and “safety reasons for” in order to align protocol and IRT language regarding the specific reasons for emergency patient unblinding.
- Section 7, to include Table 7-1, Table 7-2:
 - Minor modifications to screening windows
 - Further clarification of Cycle 1 Day 1 assessments
 - Removal of Thyroid T3 and TSH
 - Addition of monthly urinalysis collection
 - Further clarification of Local FSH and/or Estradiol for eligibility
 - Addition of “Fluid/Tissue Collection” in the Tumor Assessments, as clinically indicated.
 - Revision of window regarding whole body bone scan: change from within 28 days to within 42 days of randomization
 - Further clarification on ECG assessments
 - Removal of ECHO/MUGA after screening, and addition of ECHO/MUGA collection at End of Treatment (EOT).
 - Clarification of Serum Pregnancy test and Urine Pregnancy Test
 - Revision of collection to blood for circulating DNA
 - Clarification regarding study treatment discontinuation
 - Clarification regarding tumor assessment schedule following randomization
- Section 7.1.2: Minor modifications to reflect screening windows, removal of thyroid testing
- Section 7.1.5: Modified for better clarity on the definition of study treatment discontinuation.
- Section 7.1.6: Modified for better clarity regarding follow-up period.
- Section 7.1.8 has been added to better clarify patient withdrawal of consent and process to follow by investigators.
- Section 7.2.1: Modified for better clarity; revision of whole body bone scan screening window
- 
- Section 7.2.4: Modified for better clarity

- Table 7-14, 7-15: Screening window modified to reflect Table 7-1.
- Section 9.3.5 modified to clarify which local lab results to collect in the CRF
- Section 10.4.4, 10.5, 10.5.1, 10.5.2, 10.7.1, 10.7.2, Table 10-1: Revisions reflect the addition of secondary objective which includes the evaluation of the two treatment arms with respect to centrally assessed PFS and clarifications/corrections of typographical errors.
- Section 11.3: Removal of language indicating an additional consent form.
- Section 14 Appendix 1, Table 14-1, Table 14-2: Update to concomitant medications.

Review requirements by IRB/IEC and Health Authorities

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

Some changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

1 Background

1.1 Overview of epidemiology, disease pathogenesis and current treatment

1.1.1 Epidemiology

Breast cancer is the most common cancer in women worldwide. It is estimated that more than 1.7 million new cases of breast cancer occurred among women worldwide in 2012 ([GLOBOCAN 2012](#)). In 2014, an estimated 232,670 new cases will be diagnosed in women in the United States; of those, 133,310 will be in women < 65 years old. More than 40,000 deaths will occur in the United States in 2014 from breast cancer with 16,970 of those women being less than 65 years old. Fewer than 5% of breast cancers occur in women < 40 years old ([American Cancer Society 2014](#)), but it is still the leading cause of cancer death among women 20 to 59 years old ([Siegel 2014](#)). Death rates for breast cancer have steadily decreased in women since 1989, with larger decreases in younger women; from 2006 to 2010, rates decreased 3.0% per year in women under 50 years and 1.8% per year in women 50 and older. The decrease in breast cancer death rates represents improvements in early detection and treatment, and possibly decreased incidence ([American Cancer Society 2014](#)).

Breast cancer incidence varies between women of different ethnicities and in different geographic locations around the world. According to GLOBOCAN generated data from 2008, the Age Standardized Incidence Rates of breast cancer in women < 40 years old are highest in Europe, North America, Argentina, Japan, Brazil and China with 13.2, 9.8, 9.0, 7.4, 6.3, and 4.4 cases per 100,000 women per year, respectively. Some of the differences in rates may be due to local screening guidelines for women who are less than 40 years old ([Assi 2013](#)).

Invasive breast cancer is classified by the presence of estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) antigen for prognostic and treatment purposes. Seventy percent of invasive breast cancers in women > 45 years express ER and/or PgR and are termed hormone receptor positive (HR+). Compared with women aged > 45, those ≤ 45 years are slightly less likely to be ER-positive; ER-positivity may decrease to approximately 55% in women aged 20-39 years ([Li 2003](#)). Younger women are also more likely to have higher tumor grades, larger tumor sizes, and positive axillary lymph nodes. Approximately 20% of invasive breast cancers express HER2 and are termed HER2-positive (irrespective of ER and PgR expression). There are no differences in HER2 or PgR status between younger and older women with breast cancer ([Huang 2005](#)).

In 1983, the median survival time for premenopausal women with metastatic breast cancer was 35 months, with only 28% still alive at 5 years ([Falkson 1995](#)). Nineteen to twenty-five years later (2002 to 2008), the 6 year survival rate for women diagnosed with metastatic breast cancer was 24% in the United States ([American Cancer Society 2013](#)).

1.1.2 Treatment options for hormone receptor positive (HR+), HER2-negative premenopausal advanced breast cancer

Endocrine therapy remains the therapeutic backbone for the treatment of HR+, HER2 negative breast cancer. Based on current treatment guidelines ([NCCN breast cancer guidelines version](#)

3.2014), tamoxifen is a standard treatment option in premenopausal women with HR+, HER2-negative, advanced BC, in addition to ovarian function suppression (OFS) or anti-hormonal therapy with NSAI and OFS ([NCCN breast cancer guidelines version 3.2014](#)).

Tamoxifen is approved for the treatment of metastatic breast cancer in premenopausal women. It works by blocking the ER in the breast cancer cells, thereby preventing estrogen from binding. In women < 40 years of age with HR+ breast cancer, 5 years of adjuvant tamoxifen, with or without ovarian suppression, is considered the standard endocrine treatment and remains the first choice for endocrine therapy in the metastatic setting as well ([Christinat 2013](#)). The therapeutic benefits of tamoxifen are determined by the menopausal status and they are limited by the development of resistance. A prospective study of nearly 400 women demonstrated that menopausal status is a key factor that determined whether the disease would respond well to tamoxifen ([Ravdin 1992](#)). Premenopausal women with ER+ tumors had an overall response rate of only 24%, as compared with an 86% response rate among postmenopausal women whose tumors were strongly positive for estrogen and progesterone receptors. Despite the efficacy of endocrine therapy for HR+ advanced BC, approximately 30% of women with metastatic disease will have primary resistance to endocrine therapy, which is commonly defined as recurrence within the first 2 years on adjuvant endocrine therapy or as progressive disease within 6 months of treatment initiation for advanced disease. Furthermore, many patients with initial response to endocrine therapy will acquire secondary resistance, commonly defined as disease progression more than 6 months after endocrine therapy initiation ([Pritchard 2013](#), [Bachelot 2012](#), [Bedard 2008](#)). Almost 50% of ER-positive metastatic breast cancer patients do not respond to tamoxifen in the first-line setting, thereby demonstrating intrinsic resistance. Even if patients respond to tamoxifen initially, they all eventually develop acquired resistance and their disease progresses.

Tamoxifen may be given either alone or in combination with an ovarian function suppression (OFS) agent, such as goserelin, an approved agent for the palliative treatment of pre- and perimenopausal advanced breast cancer. Goserelin and tamoxifen may function through different pathways (those of estrogen withdrawal and estrogen receptor blockade, respectively), which might target different cell populations ([Davidson 2000](#)). The addition of luteinizing hormone-releasing hormone (LHRH) agonists such as goserelin to tamoxifen in premenopausal women will suppress the tamoxifen-induced stimulation of the pituitary-ovarian function and act in a similar way to an oophorectomy ([Zoladex® Prescribing Information](#)). Data assessing the combination of endocrine therapy in premenopausal women are limited. A meta-analysis (n = 506) of 4 randomized studies ([Boccardo 1994](#), [Jonat 1995](#), [Klijn 2000](#)) showed the combination of a LHRH agonist plus tamoxifen is superior to the LHRH agonist alone in premenopausal women with advanced breast cancer. The results of this study showed an improved hazard ratio (HR) favoring the combination in terms of response (HR, 0.67; 95% confidence interval [CI], 0.46-0.96) and survival (HR, 0.78; 95% CI, 0.63-0.96) after 6.8 years of median follow-up. Goserelin was the LHRH agonist used in 3 of the 4 studies ([Klijn 2001](#)).

Most premenopausal women with ER+ advanced breast cancer have received tamoxifen as adjuvant therapy; once breast cancer has relapsed new endocrine treatment options are required. According to current treatment guidelines ([NCCN breast cancer guidelines version 3.2014](#)), these patients can also receive ovarian ablation/suppression treatment and receive anti-hormonal treatment such as aromatase inhibitors (AIs) similar to what postmenopausal women

typically receive. AIs block the peripheral conversion of androgens to estrogens and reduce estrogen levels in tissue and plasma. Third generation non-steroidal AIs (NSAIs) are highly selective for the enzyme aromatase and are fairly well tolerated. Both anastrozole (Arimidex[®]) and letrozole (Femara[®]) are third generation NSAIs that reversibly bind aromatase. Exemestane (Aromasin[®]) is a third generation steroidal AI that irreversibly binds aromatase.

Based on the clinical benefit shown in postmenopausal patients, AIs in combination with ovarian function suppression (OFS) have been investigated in premenopausal patients with breast cancer in neoadjuvant, adjuvant and advanced settings. Results from the randomized phase III trials SOFT (Suppression of Ovarian Function Trial) and TEXT (Tamoxifen and EXemestane Trial) showed that adjuvant treatment with exemestane+OFS as compared with tamoxifen+OFS, significantly reduced recurrence in premenopausal women with HR+ early breast cancer. Results from both trials (N=5,738) showed statistically significant differences in disease free survival (DFS) at 5 years (91.1% in exemestane + OFS vs 87.3% in tamoxifen + OFS) and rate of freedom from breast cancer at 5 years (92.8% in exemestane+OFS vs 88.8% in tamoxifen+OFS) (Pagani 2014). Studies exploring the combination of third generation AIs and goserelin in metastatic premenopausal BC patients are shown below in Table 1-1. (Montagna 2013)

Table 1-1 Goserelin and third generation AIs in metastatic premenopausal BC patients

Study	N	AI+goserelin (G)	ORR (CR+PR) (%)	CB (CR+PR+SD) (%)	TTP (months)	First line endocrine therapy
(Forward 2004)	16	Anastrozole+G	6.2	75	N/R	No
(Cheung 2010)	36 13	Anastrozole+G Exemestane+G*	36 N/R	67 38	12 N/R	Yes No
(Carlson 2010)	35	Anastrozole+G	37	72	8.3	Yes
(Park 2010)	35	Letrozole+G	46	77	9.5	Yes
(Yao 2011)	52	Letrozole+G	21	71	10	Yes/No
(Roche 2009)	33	Anastrozole+G	55	64	13	Yes
(Nishimura 2012)	37	Anastrozole+G	19	62	7.2	Yes/No

ORR=Objective response rate, CR=Complete response, PR=Partial response, CB=Clinical benefit, SD=Stable disease, PD=Progressive disease, TTP=Time to progression, N/R=Not reported

*In study by Cheung et al, patients received treatment with exemestane after they received treatment with anastrozole.

Although data are limited ([Montagna 2013](#)), clinical benefit of the combination of AIs and OFS in premenopausal women with advanced ER+ breast cancer has been shown in small phase II studies with letrozole and anastrozole. In one study ([Cheung 2010](#)), patients received exemestane, but only after they had received anastrozole, so the effect of single-agent exemestane has not been well characterized. Lastly, novel therapeutic approaches targeting promising pathways should be explored to further improve efficacy in premenopausal women with advanced HR+ breast cancer.

1.1.3 Role of the CDK4/6 pathway in breast cancer

Cell cycle progression is directly regulated by cyclin-dependent serine-threonine protein kinases (CDKs). Extracellular growth and adhesion signals increase the level and function of cyclin D proteins within the cell. In turn, the cyclin D proteins associate with and activate CDK4 and CDK6 ([Musgrove et al 2011](#)). CDK4 and CDK6 phosphorylation leads to inactivation of the retinoblastoma protein (pRb) and thus releases E2F which in turn leads to the transcription initiation of proteins involved in cell cycle propagation and cell proliferation. The luminal A and B subtypes of breast cancer (85% of which are ER+/HER2-negative) have high rates of cyclin D/CDK activation; in the luminal A and B subtypes, cyclin D1 (CCND1) amplifications were observed in 29% and 58%, and CDK4 amplifications were observed in 14% and 25% respectively ([Holm et al 2012](#); [The Cancer Genome Atlas Network 2012](#)). Luminal A subtype tumors also have loss of CDKN2A, which encodes p16Ink4a, a CDK inhibitor ([Beroukhim et al 2010](#)). The luminal subtypes also maintain expression of Rb, which is essential for benefit from treatment with a CDK4/6 inhibitor ([Thangavel et al 2011](#)).

Dysregulation of cell cycle checkpoints is common in cancer. Modulating the cell cycle has always been an attractive therapeutic target in cancer, and previously published data have suggested that CDK4/6 inhibition may play a key role in the treatment of subsets of breast cancers. Patients with HR+ breast cancer exhibiting a gene expression signature of Rb loss had shorter recurrence-free survival following adjuvant tamoxifen ([Bosco et al 2007](#)). A tumor gene expression signature of E2F activation was associated with higher residual tumor cell proliferation following pre-surgical AI therapy. Therefore, activation of the CDK4/CDK6/E2F axis promotes endocrine resistance, and treatment with a CDK4/6 inhibitor or knockdown of CDK4 expression abrogates endocrine-resistant cell proliferation.

In conclusion, loss of cell cycle control is a hallmark of cancer, and aberrations in the cyclin/CDK/Rb pathway are common in breast cancer. Consequently, inhibition of this pathway at the level of CDK4/6 leads to reactivation of Rb and binding of E2F, thus leading to cell cycle arrest. Therefore, targeting the inhibition of this pathway is considered an attractive therapeutic strategy.

Additionally, preclinical and clinical data demonstrate that CDK4/6 inhibitors are active in advanced HR+ breast cancer. Palbociclib (PD 0332991) is a selective inhibitor of CDK4/6 that inhibits proliferation and induces apoptosis in preclinical models of endocrine-resistant breast cancer ([Miller et al 2011](#), [Thangavel et al 2011](#)). Preclinical data with palbociclib demonstrated synergy with tamoxifen in ER+ breast cancer cell lines; moreover, palbociclib enhanced sensitivity to tamoxifen in cell lines with conditioned resistance to ER blockade ([Finn et al 2009](#)).

Palbociclib in combination with fulvestrant for the treatment of patients with HR+ Her 2 advanced breast cancer who relapsed or progressed during prior endocrine therapy, resulted in prolonged progression free survival (median PFS was 9.5 months for palbociclib plus fulvestrant versus 4.6 months for the fulvestrant – placebo (HR 0.46; 95% CI: 0.36 - 0.59; P:<0.001)). In this study, women were eligible regardless of their menopausal status and up to 1 line of prior chemotherapy in the context of advanced disease was allowed and the relative difference in progression-free survival between palbociclib and placebo was similar in premenopausal or perimenopausal patients and postmenopausal patients (HR 0.50 and 0.45 respectively) (Cristofanilli M 2015).

Selective inhibitors of CDK4/6, such as palbociclib and ribociclib, inhibit proliferation and induce apoptosis in preclinical models of endocrine-resistant breast cancer (Miller et al 2011; Thangavel et al 2011; [ribociclib Investigators Brochure]). Both palbociclib and ribociclib demonstrated synergy with endocrine treatments in preclinical studies and efficacy in clinical studies in patients with HR-positive, HER2-negative advanced BC (Finn et al 2009; [ribociclib Investigators Brochure]). Addition of palbociclib to letrozole improved median progression-free survival (PFS) from 10.2 months to 20.2 months (hazard ratio 0.49, 95% CI: 0.32-0.75, p=0.0004) in a randomized, open-label, multicenter phase II study (Finn et al 2015) and from 14.5 to 24.8 months (hazard ratio 0.58, 95% CI: 0.46-0.72, p=0.0001) in a phase III study in systemic non-adjuvant treatment-naïve postmenopausal women with ER-positive, HER2-negative advanced BC (Finn et al 2016). In addition, in a phase III study in 521 patients with advanced HR-positive, HER2-negative BC that had relapsed or progressed during prior ET, addition of palbociclib to fulvestrant improved median PFS from 3.8 months to 9.2 months (hazard ratio 0.42; 95% CI: 0.32-0.56; p<0.001) (Turner et al 2015). Efficacy and safety of the combination of ribociclib and letrozole as first line treatment was evaluated in 668 postmenopausal women with HR-positive, HER2-negative advanced BC in a phase III study [CLEE011A2301]. Ribociclib significantly improved PFS (hazard ratio 0.56, 95% CI: 0.43-0.72, p = 0.00000329) (Hortobagyi et al 2016). Refer to the most recent [ribociclib Investigators Brochure] for more details.

Considering demonstrated efficacy of CDK4/6 inhibitors in the HR-positive, HER2-negative advanced BC, co-targeting the CDK4/6-Rb-E2F pathway with CDK4/6 inhibitors may be a viable strategy to enhance endocrine responsiveness and prevent or delay the development of acquired resistance.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

This study includes LEE011, tamoxifen, goserelin, anastrozole and letrozole as treatments.

1.2.1 Overview of LEE011

LEE011 is an orally bioavailable, highly selective small molecule inhibitor of CDK4/6 that potently induces G1 arrest with sub-micromolar IC₅₀'s in a variety of pRb-positive cancer cells. Please refer to the most recent [LEE011 Investigators Brochure] for more information.

1.2.1.1 Non-clinical experience

1.2.1.1.1 Nonclinical pharmacology

In Jeko-1 MCL cells that overexpress cyclin D1 as a result of the t(11;14) chromosomal translocation, LEE011 inhibits the phosphorylation of pRb at CDK4/6-specific sites with an average IC₅₀ of 60 nM. In nude rats bearing Jeko-1 subcutaneous xenografts, LEE011 demonstrates dose-dependent target inhibition in the tumors. LEE011 doses that induce >75% inhibition of pRb phosphorylation in this model are associated with complete tumor regression.

LEE011 also inhibits the growth of many other tumor cell types *in vitro* and *in vivo*, including liposarcoma, melanoma, rhabdoid cancer, and carcinomas of the esophagus, breast, lung and pancreas. Regardless of the various genetic aberrations that may be present in the cancer cells, the anti-tumor activity of LEE011 requires the presence of functional pRb. Refer to [LEE011 Investigators Brochure] for more details.

Preclinical data with LEE011 in a primary model of ER+ breast cancer demonstrated synergy when given in combination with letrozole, showing complete and sustained inhibition of tumor growth (Figure 1-1).

1.2.1.1.2 Safety pharmacology and toxicology

In vivo cardiac safety studies demonstrated a signal for QT prolongation with the potential to induce incidences of premature ventricular contractions (PVCs) at higher exposure levels.

The effects of LEE011 on the bone marrow (hypocellularity), lymphoid system (lymphoid depletion), intestinal mucosa (atrophy), skin (atrophy), bone (decreased bone formation) and testes (atrophy) are considered to be related to the pharmacological inhibition of cell replication in these tissues due to CDK4/6 inhibition.

An increased number of ovarian corpora lutea was observed in a single female dog in the 4-week toxicity study at the highest dose tested (20 mg/kg/day) and this effect could also be related to the pharmacology of LEE011 (arrest of estrous cycle).

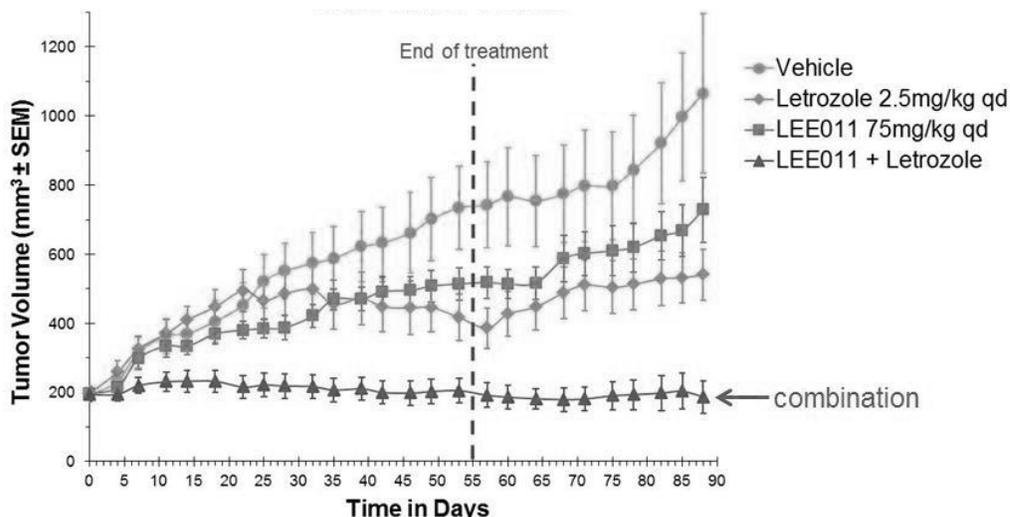
The liver, bile system and gall bladder (proliferative changes, cholestasis, sand-like gallbladder calculi and inspissated bile) and the kidney (concurrent degeneration and regeneration of tubular epithelial cells) were identified as additional target organs of toxicity which are not likely related to the primary pharmacology of LEE011.

Inflammatory changes in the lungs of dogs were considered secondary to aspiration of test article and are indicative of the irritant potential of the formulated test-article in the respiratory tract. Correlating hematological and/or biochemistry changes were seen for the effects described in the bone marrow, lymphoid system and liver.

Generally all changes demonstrated either reversibility or a clear tendency towards reversibility. In the rat, there was no evidence of teratogenicity however LEE011 was embryofetotoxic. Data

from a rabbit embryofetal development study, shows that LEE011 is teratogenic in the rabbit in the absence of maternal toxicity.

Figure 1-1 LEE011 in combination with letrozole in an ER+ primary breast cancer model



Mean tumor volumes in mice treated at clinically relevant doses for 56 days with LEE011 (75 mg/kg qd) alone; letrozole (2.5 mg/kg qd) alone; LEE011 (75 mg/kg qd) plus letrozole (2.5 mg/kg qd); or vehicle. The combination arm shows complete inhibition of tumor growth that was sustained for more than 30 days of post-treatment observation.

1.2.1.1.3 Nonclinical pharmacokinetics and metabolism

The pharmacokinetics (PK) of LEE011 was investigated in mouse, rat, dog and monkey. LEE011 showed high clearance (CL) in the mouse, rat, dog and monkey. The volume of distribution was large across species and the terminal elimination half-life (T_{1/2}) was moderate in rodents and monkey (~2 to 5 h) and longer in dog (18 h). Bioavailability was low to moderate in rat (37%) and cynomolgus monkey (17%); moderate in mouse (65%) and dog (64%). Following oral administration, time to reach maximal plasma concentrations (T_{max}) occurred between 2 to 4 h across species. Gender dependent toxicokinetics were observed in rats with higher exposure to LEE011 in males as compared to females and higher exposure to the metabolite, LEQ803. Plasma protein binding was moderate in all species (unbound fraction (f_u) in human: 30%).

In a rat ADME (absorption, distribution, metabolism and excretion) study, extensive distribution of [³H] LEE011 and its metabolites was observed. In pigmented rats, radioactivity was specifically found in melanin-containing structures; the highest exposure to total radiolabeled components was observed in eye ciliary body, eye choroid, meninges, tactile hair and hair follicles. Radioactivity was not detected in the brain. LEQ803 (N-demethylation) was a prominent metabolite found in mouse, rat, dog, monkey and human hepatocytes. This metabolite retains some pharmacologic activity and interacts with human Ether-a-go-go Related Gene (hERG) channels in vitro.

Results from the ADME (male rats) study showed that 3H-components were predominantly excreted with bile (61.4% of dose). Minor urinary excretion was observed (5.9% of dose after p.o.). The majority of the administered dose (87.3%) was excreted within 24 h via urine, feces (enteric secretion) and bile.

In vitro, LEE011 was a reversible inhibitor of cytochrome P450 (CYP) enzymes CYP1A2, CYP2E1 and CYP3A4 and a time-dependent inhibitor of CYP3A4. LEE011 may inhibit CYP3A4 under therapeutic conditions. No induction of CYP1A2, CYP2B6 or CYP3A4 was observed. The *in vitro* inhibitory potency of LEE011 observed for the transporters OATP1B1 (organic anion transporting polypeptide 1B1), BCRP (breast cancer resistance protein), OCT1 (organic cation transporter 1), OCT2, MATE1 (multidrug and toxin extrusion protein 1), MATE2K and BSEP (bile salt export pump) may translate into clinically relevant inhibition at therapeutic doses. Elimination of LEE011 is dominated by oxidative metabolism mainly via CYP3A4 with a minor contribution by flavin-containing monooxygenase 3 (FMO3). The elimination of LEE011 may be affected by co-administered drugs that inhibit or induce CYP3A4. Although LEE011 is a substrate of the P-glycoprotein (P-gp) efflux transporter, this process is likely not clinically relevant due to the high passive permeability of LEE011.

1.2.1.2 Clinical experience of LEE011

LEE011 is currently being investigated in patients as a single agent in 3 phase I studies, in 2 phase II studies and in combination in 15 studies: 12 phase Ib/II studies and 3 randomized phase III studies. Four studies were closed for enrollment: a randomized phase II study; a phase I dose finding study; a phase I study in malignant rhabdoid tumors and neuroblastomas; and a phase Ib/II study in BRAF mutant melanoma. LEE011 is also being investigated in 4 clinical pharmacology studies: 3 clinical pharmacology studies in healthy subjects have been completed. Details on ongoing studies can be found in the [LEE011 Investigator Brochure, Section 5.1 and Section 5.2].

In single agent trials, a total of 199 patients have been treated: 157 in study [CLEE011X2101] as of 15-Jun-2015 (in a Caucasian population, including 85 in the dose escalation), 17 in [CLEE011X1101] as of 28-Jan-2015 (in Japanese patients, all in the dose escalation) and 32 in [CLEE011X2102] as of 9-Apr-2015 (in patients under the age of 21 years, all in the dose escalation). Please refer to the [LEE011 Investigator Brochure] for more details.

The combination of LEE011 (600 mg) with letrozole (2.5 mg once daily) is being evaluated in an ongoing studies [CLEE011A2201], [CLEE011A2115C] and [CLEE011A2301].

1.2.1.3 Clinical safety of LEE011

As of 15-Jun-2015, 157 patients have been treated with single agent LEE011 in the first-in-human (FIH) phase I study; 85 patients have been treated in the initial dose escalation part for the 3 week on/1 week off regimen and 47 patients in the dose expansion part of the study; 18 patients were enrolled for the continuous dosing regimen with LEE011 and, 7 patients were enrolled in the liquid formulation cohort.

Patients with advanced solid tumors or lymphomas were treated with increasing doses of LEE011 orally, once daily (qd) for 21 days followed by a 1-week rest (28-day cycle). Doses ranging from 50 mg to 1200 mg were evaluated on this schedule. Treatment has been

discontinued in 120 (90%) patients; the primary reasons for treatment discontinuation were: disease progression (106 [80%] patients); AEs (7 [5%] patients); death (2 [1.5%] patients); withdrawal of consent (3 [2%] patient); and loss to follow up (1 [1%] patient).

The most frequently reported AEs ($\geq 10\%$), regardless of grade, causality and LEE011 dose were: nausea (52.3%); fatigue (40.9%); diarrhea (37.1%); vomiting (35.6%); neutropenia (34.1%); anemia (32.6%); decreased appetite (23.5%), thrombocytopenia (23.5%); white blood cell count decrease (22.7%); leukopenia (22%); constipation (21.2%); dyspnea (20.5%); asthenia (19.7%); cough (18.2%); hyperglycemia (17.4%); headache, hypoalbuminemia (16.7% each); ECG QT prolonged (15.9%); abdominal pain, back pain, lymphocyte count decrease, pyrexia (15.2% each); AST increase, blood creatinine increased, dizziness, lymphopenia (14.4% each), peripheral edema (13.6%), neutrophil count decreased (12.9%); ALT increase; pain in extremity (12.1% each) and hypocalcemia (11.4%).

For either continuous or intermittent dosing, the onset of neutropenia (most frequently Grade 2) typically occurs by Day 15, reaching a nadir in the third or fourth week with recovery during the week of drug holiday for the three weeks on/one week off schedule. Some patients require additional time for recovery (7 to 14 days). QT changes become evident in the first cycle by Day 8 and later (once steady state is reached), are associated with the maximum drug levels between 1 to 8 h post-dose, and remain stable or improve in subsequent cycles.

As of 15-Jun-2015, asymptomatic Grade 2 QTcF prolongation was observed with increasing frequency when increasing the dose, starting at 600 mg: ten patients (13.5%) in the 600 mg cohort, three patients (21%) in the 750 mg cohort, four patients (31%) in the 900 mg cohort, and two patients (67%) in the 1200 mg cohort. Four patients (5.4%) at 600 mg and two patients (15%) at 900 mg had asymptomatic QTcF prolongation that resulted in a QTcF interval of 500 ms or more. As compared to baseline value, QTcF prolongation was at least 30 msec in 2 patients (50%) at 250mg, 2 (40%) at 350 mg and 400 mg, 59 (79.7%) at 600 mg, 11 (78.6%) at 750 mg, 11 (85%) at 900 mg and 2 (67%) at 1200 mg; and at least 60 msec in 23%, 0%, 39% and 67% of patients at 600 mg, 750 mg, 900 mg and 1200 mg, respectively. One grade 1 atrioventricular block of first degree was reported as related to LEE011 given at the dose of 140 mg. No other cardiac abnormalities were observed as related adverse events in any patient.

There have been no deaths related to study drug reported on study [CLEE011X2101]. The following serious adverse events shown in Table 1-2 have been reported with a suspected causal relationship in study [CLEE011X2101] as of 6-Aug-2015. For a complete list of AEs, all grades and Grade 3/4 that are suspected to be related to LEE011 refer to the [LEE011 Investigator Brochure].

Table 1-2 Serious adverse events with a suspected causal relationship with LEE011 single agent

Serious suspected adverse events which have occurred with LEE011 (single agent)	
System Organ Class Preferred Term	Preferred Term
Blood and lymphatic system disorders	Anaemia, Febrile neutropenia, Neutropenia, Thrombocytopenia
Gastrointestinal disorders	Diarrhoea, Nausea, Pancreatitis
General disorders and administration site conditions	Generalized oedema
Infections and infestations	Herpes simplex
Investigations	Blood creatinine increased, Electrocardiogram QT prolonged

Refer to [LEE011 Investigators Brochure] for more details.

1.2.1.4 Clinical efficacy of LEE011

Preliminary anti-tumor activity of LEE011 from an ongoing Phase I trial [CLEE011X2101] was assessed across all dose levels (50 mg – 1200 mg). Out of 114 evaluable subjects, 3 partial responses were observed at the 600 mg dose level; one each in BRAF/NRAS wild type with CCND1 amplified melanoma, and head and neck acinar carcinoma with CDKN2A loss (both on the 3 weeks on/1 week off regimen), and ER+/HER2, PIK3CA mutant, CCND1 amplified breast cancer (on the continuous daily dosing regimen) LEE011 [Investigator Brochure]. Stable disease (SD) was the best overall response in 41 (37%) patients. Stable disease ≥ 4 cycles and ≥ 6 cycles was observed in 26 (24%) and 17 (15%) patients, respectively. Six patients with SD ≥ 4 cycles received treatment for >1 year, of these 2 patients, were on study for >2 years (Jeffrey R Infante ASCO 2014 abstract 2528).

Refer to the [LEE011 Investigators Brochure] for the most recent details.

1.2.1.5 Clinical pharmacokinetics of LEE011

The pharmacokinetics of LEE011 have been evaluated following single and repeat daily doses in the ongoing single agent, phase I study in patients with advanced solid tumors or lymphomas [CLEE011X2101]. Following oral administration of LEE011, peak plasma concentrations (C_{max}) are achieved at approximately 1-4 hours post-dose. LEE011 plasma exposure (C_{max} and AUC_{0-24h}) demonstrates slightly over-proportional increases across the dose range tested (50 to 1200 mg). Steady-state is generally reached by Day 8 and the mean effective T_{1/2} based on accumulation ratio (i.e., T_{1/2}, acc) ranged from 12.3 to 42.9 hours across the dose range tested.

The mean accumulation ratio (R_{acc}) calculated from AUC_{0-24h} at steady-state and AUC_{0-24h} after a single dose across the studied doses ranged from 1.35 to 3.11. At the recommended dose for future development (600 mg), steady-state plasma C_{max} (n=56) ranges from 606-6170 ng/mL (geometric mean = 1790 ng/mL or 4.1 μ M), median T_{max} (n=72) is 2.1 h, and AUC_{0-24h} (n=53) ranges from 6770-90600 ng*h/mL (geometric mean = 23600 h*ng/mL). At this dose, inter-patient variability in C_{max} and AUC is 62% and 66%, respectively, as assessed by geometric mean percent coefficient of variation (% CV). At the 600 mg dose level, LEQ803, an active metabolite of ribociclib, accounted for approximately 8% (geometric mean) of ribociclib AUC_{0-24h} after single and multiple doses.

In the human ADME study [CLEE011A2102], a single oral dose of 600 mg [¹⁴C]LEE011 was administered to 6 healthy male subjects. The majority of the administered dose was excreted in feces (69.1%), with a minor amount excreted in urine (22.6%). Absorption was estimated to be approximately 58.8%. Ribociclib accounted for approximately 23% of the total radioactivity in plasma, based on AUC_{inf}. Metabolites M1 (glucuronidation of M15), M4 (LEQ803, N-demethylation) and M13 (CCI284, N-hydroxylation) were the most abundant metabolites in plasma, representing an estimated 7.78%, 8.60% and 9.39% of total [¹⁴C]AUC_{0-48h}, and 17.9%, 19.8% and 21.6% of ribociclib AUC_{0-48h}, based on metabolite profiles.

In a food effect study [CLEE011A2111] in 24 healthy subjects, a single dose of LEE011 (600 mg) was administered as drug-in-capsule (DiC) with a high-fat, high-calorie meal and under fasted conditions. Compared to the fasted state, oral administration of a single 600 mg dose of LEE011 DiC with a high-fat, high calorie meal decreased the rate of absorption resulting in a 23% decrease in C_{max} (geometric mean ratio: 0.775; 90% confidence interval [CI]: 0.700, 0.858) and a median difference in T_{max} of 2 hours. However, there was no effect on the extent of absorption as the overall exposure (AUC_{inf}) was unaffected under fed conditions (geometric mean ratio: 0.994; 90% CI: 0.925, 1.070). A similar trend was observed for LEQ803, an active metabolite of LEE011, with a decrease in C_{max} (32%), a delay in median T_{max}, and no substantial effect on overall exposure. Results from this study indicate the DiC can be taken without regard to meals.

A DDI study with ritonavir (a strong CYP3A4 inhibitor) and rifampicin (a strong CYP3A4 inducer) was conducted in 48 healthy subjects [CLEE011A2101]. Compared to LEE011 alone, ritonavir (100 mg bid for 14 days) increased LEE011 C_{max} and AUC_{inf} by 1.7-fold and 3.2-fold, respectively, following a single oral dose of 400 mg LEE011. C_{max} and AUC_{last} for LEQ803 decreased by 96% and 98%, respectively. These results demonstrated that concurrent use of strong CYP3A4 inhibitors may markedly increase LEE011 exposure and are prohibited.

Compared to LEE011 alone, rifampicin (600 mg daily for 14 days) decreased LEE011 C_{max} and AUC_{inf} by 81% and 89%, respectively, following a single oral dose of 600 mg LEE011. LEQ803 C_{max} increased 1.7-fold and AUC_{inf} decreased by 27%, respectively. These results demonstrated that concurrent use of strong CYP3A4 inhibitors or strong CYP3A4 inducers may markedly decrease LEE011 exposure and are prohibited. A DDI cocktail study with midazolam (a sensitive CYP3A4 substrate) and caffeine (a sensitive CYP1A2 substrate) conducted in 25 healthy subjects [CLEE011A2106] indicated that LEE011 (400 mg) is a moderate inhibitor of CYP3A4, but did not have a substantial effect on CYP1A2 substrates in humans. PK data indicated that compared to midazolam and caffeine alone, multiple doses of LEE011 (400 mg qd for 8 days) increased midazolam C_{max} and AUC_{inf} by 2.1-fold and 3.8-fold, respectively. The effect of multiple doses of LEE011 on caffeine was minimal, with C_{max} decreased by approximately 10% and AUC_{inf} increased slightly by 20%. Based on these data, LEE011 (400 mg) is a moderate CYP3A4 inhibitor (\geq 2-fold but $<$ 5-fold increase in AUC). Concurrent use of sensitive CYP3A4 substrates with a narrow therapeutic index is prohibited. LEE011 (400 mg) did not have a substantial effect on CYP1A2 in humans; therefore concurrent use of CYP1A2 substrates is not expected to lead to clinically significant DDIs.

Refer to the [LEE011 Investigators Brochure] for more details.

1.3 Overview of tamoxifen

Tamoxifen has been used for over 30 years to treat both pre- and postmenopausal women with HR+ breast cancer. Its antitumor effects are thought to be due to its anti-estrogenic activity, mediated by competitive inhibition of estrogen binding to ER (Osborne 1996). Adjuvant therapy with tamoxifen for 5 years resulted in a 34% reduction in the annual breast cancer death rate, with an absolute reduction in mortality of 9.2% at 15 years (Early Breast Cancer Trialists' Collaborative Group 2005).

The recommended dose for treatment of breast cancer is 20 mg daily (Tamoxifen Prescribing Information). Tamoxifen is generally well tolerated and side effects are mainly attributable to estrogen deprivation. However, in some tissues, tamoxifen acts as an estrogen agonist, and these estrogenic effects may be beneficial or detrimental, depending on the target organ. For example, tamoxifen has favorable effects on bone health, lipid metabolism and the cardiovascular system, but long-term tamoxifen use is also associated with serious, potentially life-threatening adverse events, including invasive endometrial cancer and thromboembolic disease (Perez 2007).

Following oral administration of a single dose of tamoxifen (20 mg), T_{max} was achieved approximately 5 hours post-dose and concentrations declined with a terminal elimination T_{1/2} of approximately 5-7 days. Steady-state is achieved for tamoxifen in approximately 4 weeks, while for its metabolite, N-desmethyltamoxifen, steady-state is achieved in approximately 8 weeks (Tamoxifen Prescribing Information). Tamoxifen metabolism is complex and extensive after oral administration. Tamoxifen is a substrate of CYP3A4/5, CYP2D6, and CYP2C9 and an inhibitor of P-glycoprotein (P-gp) (Tamoxifen Prescribing Information). Tamoxifen is predominantly metabolized by CYP3A4/5 to N-desmethyltamoxifen. A minor route of metabolism occurs via CYP2D6 to form the pharmacologically active metabolite, 4-hydroxytamoxifen. These metabolites are further metabolized to several secondary metabolites, one of which is the pharmacologically active metabolite, 4-hydroxy-desmethyltamoxifen (endoxifen), formed mainly via CYP2D6 from N-desmethyltamoxifen. The two pharmacologically active metabolites, 4-hydroxytamoxifen and endoxifen, are 30- to 100-fold more potent than tamoxifen in terms of ER binding affinity and effects on breast cancer cell proliferation and gene expression (Johnson 2004). In breast cancer patients, endoxifen plasma concentrations are 5- to 10-fold higher than 4-hydroxytamoxifen (Lien 1990; Stearns 2003), suggesting that endoxifen may contribute significantly to the overall response to tamoxifen therapy. However, it is also likely that the combined pharmacologic activity of tamoxifen and its active metabolites contribute to the clinical efficacy of tamoxifen (Johnson 2004).

Formation of the pharmacologically active metabolites (4-hydroxytamoxifen and endoxifen) occurs predominantly through CYP2D6 (Stearns 2003). Reduced CYP2D6 activity, either through genetic polymorphisms of the enzyme or through concomitant administration of drugs that are CYP2D6 inhibitors, could lead to reduced exposure to endoxifen (Hoskins 2009; Stearns 2003). In addition, inhibition or induction of CYP3A4 may affect the metabolism of tamoxifen. Based on the prescribing information of tamoxifen, no dose adjustment is required for CYP2D6 poor metabolizers or for individuals taking medications that are strong inhibitors or inducers of CYP3A4. CYP2D6 poor metabolizer status has been

associated with poorer invasive disease-free survival in tamoxifen treated patients in a number of studies, though not in others ([Province 2014](#)). The value of CYP2D6 genotyping in tamoxifen therapy is therefore still under investigation.

For information on tamoxifen and management of potential tamoxifen related adverse events refer to the Tamoxifen SmPC or Prescribing Information.

1.4 Overview of non-steroidal aromatase inhibitors (NSAIs): letrozole and anastrozole

1.4.1 Overview of letrozole

Letrozole (Femara[®]) is a nonsteroidal competitive inhibitor of the aromatase enzyme system with demonstrated efficacy in the treatment of postmenopausal patients with HR+ breast cancer. Letrozole acts by inhibiting in a highly selective fashion the conversion of adrenal androgens to estrogens, which is the primary source of estrogens in postmenopausal women. Letrozole is a highly selective inhibitor of aromatase that induces a 75% to 95% decrease of estrogen levels after two weeks of treatment using daily doses of 0.1 to 5 mg, with no significant clinical and laboratory toxicities or changes in levels of other hormones of the endocrine system as shown in early phase I ([Lipton 1995](#); [Trunet 1996](#)). It is indicated for the adjuvant treatment of postmenopausal women with HR+ early breast cancer as well as the extended adjuvant treatment of patients who have received 5 years of tamoxifen therapy. It is also indicated for the treatment of advanced HR+ breast cancer, both in the first-line setting as well as in patients who have disease progression following anti-estrogen therapy. Letrozole was compared with tamoxifen in a phase III trial in the first line setting in ER+/HER2+ breast cancer. Letrozole was superior to tamoxifen for time to progression (median, 9.4 v. 6.0 months) and median OS trended superior for letrozole (median, 34 versus 30 months) but this difference was not statistically significant ([Mouridsen 2001](#)).

Letrozole is administered orally once daily at a dose of 2.5 mg and is rapidly and completely absorbed from the gastrointestinal tract. Concomitant intake of food has no effect on the extent of letrozole absorption and only a minor effect on the rate of absorption, which is considered to be of no clinical relevance. The terminal elimination half-life of letrozole is 2 days and steady-state plasma concentration with daily dosing at the standard dose is reached in 2-3 weeks. Letrozole is metabolized via CYP3A4 to a pharmacologically-inactive carbinol metabolite (4,4'-methanol-bisbenzotrile) and renal excretion of the glucuronide conjugate of this metabolite is the major pathway of letrozole clearance. In addition, CYP2A6 forms the carbinol metabolite as well as its ketone analog ([Femara[®] Prescribing Information Novartis](#)).

The most frequently reported adverse events that were significantly different from placebo for letrozole in the adjuvant and extended adjuvant setting include hot flashes, arthralgia/arthritis and myalgia. In the first line setting, the most frequently reported adverse events include musculoskeletal pain (bone/back pain and arthralgia), hot flashes, nausea and dyspnea and incidences of adverse events were similar for tamoxifen in this setting. In general, the observed adverse reactions are mild to moderate in nature ([Femara[®] Prescribing Information Novartis](#)).

Letrozole, when given as neoadjuvant treatment to women with unresectable hormone receptor positive early breast cancer, was associated with significantly higher response rate than

tamoxifen (60% versus 48%, $P=0.004$) and a higher percentage of patients underwent breast conservative surgery (48% versus 36%, $P=0.036$) (Ellis 2001).

For information on letrozole and management of letrozole related adverse events refer to the Femara® SmPC or Prescribing Information.

1.4.1.1 Clinical data with the combination of LEE011 and letrozole

Study [CLEE011X2107] is an ongoing multicenter phase Ib/II dose escalation/expansion study of LEE011 and BYL719 in combination with letrozole in adult patients with advanced ER+ breast cancer. Patients must be postmenopausal with metastatic or locally advanced ER+, HER2-negative breast cancer. Dose escalation is to occur in cohorts of 3-6 patients within one of the three treatment arms:

- Letrozole (2.5 mg daily) plus LEE011 (Arm 1)
- Letrozole (2.5 mg daily) plus BYL719 (Arm 2)
- Letrozole (2.5 mg daily) plus LEE011 and BYL719 (Arm 3)

In the dose escalation phase, patients may have received any number of prior lines of hormonal treatment and less than or equal to one prior line of chemotherapy in the metastatic or locally advanced setting. Selection criteria include: absolute neutrophil count (ANC) $> 1 \times 10^9$ g/dL, platelets $> 100 \times 10^9$ /L, hemoglobin > 9 mg/dL, total bilirubin and creatinine $< 1.5 \times$ ULN, and AST/ALT $< 3 \times$ the upper limit of normal (or $\leq 5 \times$ in the presence of liver metastases).

As of 2-Mar-2015, 98 patients have been enrolled to one of the following dose combinations:(1) LEE011 (600 mg) + letrozole (2.5 mg), $n=41$; (2) alpelisib (300 mg) + letrozole (2.5 mg), $n=21$; and (3) LEE011 + alpelisib + letrozole (2.5 mg), $n=36$. The median age of patients treated with LEE011 + letrozole was 58 (range: 38–76) years, all the patients were female, and the distribution of ECOG performance status of 0/1 at baseline was 24/17 patients, respectively. Among the 41 patients treated with LEE011 + letrozole, 23 were discontinued from the study (22 due to progressive disease, 1 due to adverse events) and 18 patients were still ongoing. The most frequent AE, regardless of grade, causality, was neutropenia (70.7%) and a total of two patients experienced dose limiting toxicities (DLTs) (Grade 4 neutropenia).

As of 15-May-2014, preliminary PK data for letrozole (2.5 mg qd) in the presence of LEE011 (600 mg, qd, 3 weeks on/1 week off) on Day 1 and on Day 21 are summarized below. Mean C_{max} and AUC_{0-24h} for LEE011 on Day 1 and at steady-state (Day 21) in the presence of letrozole are comparable to those observed for single agent LEE011 CLEE011X2101 as shown in Table 1-3.

Mean C_{max} and AUC_{0-24h} for letrozole on Day 1 and at steady-state (Day 21) in the presence of LEE011 are compared to the historical single agent data for letrozole as shown in Table 1-4.

Table 1-3 Preliminary pharmacokinetic data for LEE011 with and without letrozole

LEE011 (600 mg)	Single Dose or Day 1 ^a		Repeat Doses ^a	
	C _{max} (ng/mL)	AUC _{0-24h} (h*ng/mL)	C _{max} (ng/mL)	AUC _{0-24h} (h*ng/mL)

With letrozole (2.5 mg) ^b	1180 ± 664(1030) [n=13]	11900 ± 4550 (11000) [n=12]	2080 ± 800 (1930) [n=10]	27600 ± 12300 (2500) [n=8]
Without letrozole ^c	1200 ± 718 (1030) [n=62]	11800 ± 7120 (10100) [n=60]	2100 ± 1290 1790) [n=47]	29200 ± 19300 (24500) [n=43]
^a Values are mean ± SD (geometric mean) [n] ^b Preliminary data (data cut-off: 15-May-2014) on Day 1 and Day 21 from combination study with letrozole (CLEE011X2107) ^c Preliminary data (data cut-off: 28-Mar-2014) on Day 1 and Day 18 or 21 from single agent study with LEE011 (CLEE011X2101)				

Table 1-4 Preliminary pharmacokinetic data for letrozole with and without LEE011

Letrozole (2.5 mg)	Single Dose or Day 1		Repeat doses	
	Cmax (ng/mL)	AUC0-24h (h*ng/mL)	Cmax (ng/mL)	AUC0-24h (h*ng/mL)
With LEE011 (600 mg) ^a	22.4 ± 5.66 (21.8) [n=13]	352 ± 71.1(346) [n=12]	95.3 ± 45.1(88) [n=10]	1720 ± 581 (1640) [n=9]
Without LEE011 ^b	39.3 ± 9.47 [n=20] ^c	559 ± 191 [n=12] ^e 465 ± 88 [n=12] ^e	133 ± 69.5 [n=24] ^d	2547 ± 1388 [n=24] ^d
	37.3 ± 10.9 [n=20] ^c		186 ± 59.1 [n=12] ^e	3709 ± 1182 [n=12] ^e
	30.5 ± 11.2 [n=27] ^d		152 ± 52.8 [n=10] ^e	3297 ± 1268 [n=10] ^e
	43.2 ± 16.1 [n=12] ^e			2677 ± 1073 [n=14] ^f
	32.4 ± 5.50 [n=10] ^e			
^a Values are mean ± SD (geometric mean) [n] for preliminary data (data cut-off: 15-May-2014) on Day 1 and Day 21 from study (CLEE011X2107) ^b Values are mean ± SD for letrozole published data with some values back-calculated from molar concentrations ^c Filipe et al. 2008 ; single dose in healthy volunteers (two different formulations) ^d Pfister et al. 2001 ; single vs multiple dose in breast cancer patients (8 weeks) ^e Tanii et al. 2011 ; population PK after 2 or 4 weeks administration in Japanese postmenopausal women ^f Dowsett et al. 1999 ; multiple dose in postmenopausal women with breast cancer (6 weeks)				

The safety and efficacy profile of ribociclib in combination with letrozole was investigated in a randomized clinical trial of ribociclib and letrozole versus placebo and letrozole [CLEE011A2301] in 668 treatment-naïve postmenopausal women with HR-positive, HER2-negative, advanced BC. Most common treatment-emergent AEs reported in the ribociclib arm in this study occurring in >30% of patients were neutropenia (74.3%), nausea (51.5%), infections (50.3%), fatigue (36.5%), diarrhea (35.0%), alopecia (33.2%) and leukopenia (32.9%). The most common grade 3 or 4 AEs reported in ≥5 % of patients in the ribociclib arm were neutropenia (59.3%), leukopenia (21.6%), hypertension (9.9%), increased alanine aminotransferase (9.3%), lymphopenia (6.9%) and increased aspartate aminotransferase (5.7%). Febrile neutropenia occurred in 1.5% of the patients in the ribociclib arm. Four patients (1.2%) met the biochemical and clinical criteria for Hy's Law with 3 reported as treatment-related and all 4 returning to normal values after treatment discontinuation. Eleven patients (3.3%) presented on treatment QTcF prolongation >480 msec. Serious AEs were reported in 21.3% of patients in the ribociclib arm with 7.5% of serious AEs deemed by investigators as treatment-related. There were 3 fatal events in the ribociclib arm (disease progression, sudden death, unknown cause) with 1 AE (sudden death) reported as treatment-related in a patient that had grade 3 hypokalemia and grade 2 QTcF prolongation [REDACTED]. Neutropenia, QT interval prolongation and hepatobiliary toxicity are considered to be important identified risks for

ribociclib which appear to be manageable and reversible with adequate monitoring, interruption and/or reduction of ribociclib dosing.

Ribociclib improved PFS (hazard ratio 0.56, 95% CI: 0.43-0.72, $p=0.00000329$). The investigator-reported overall response rate was 40.7% (95% CI: 35.4%-46.0%) in the ribociclib arm and 27.5% (95% CI: 22.8%-32.3%) in the placebo arm ($p=0.000155$) in the full analysis set; and 52.7% (95% CI: 46.6%, 58.9%) and 37.1% (95% CI: 31.1%, 43.2%) ($p=0.00028$) in patients with measurable disease at baseline ([Hortobagyi et al 2016](#)).

Refer to the most recent [ribociclib Investigators Brochure] for additional details of the safety and efficacy profile of ribociclib in combination with letrozole.

1.4.2 Overview of anastrozole

Anastrozole (Arimidex[®]) is a selective non-steroidal aromatase inhibitor. It significantly lowers serum estradiol concentrations and has no detectable effect on formation of adrenal corticosteroids or aldosterone. Anastrozole is indicated for adjuvant treatment of postmenopausal women with early HR+ breast cancer and first line and second line treatment of postmenopausal women with advanced HR+ breast cancer.

Anastrozole is administered orally once daily at a dose of 1 mg. Absorption of anastrozole is rapid and C_{max} typically occurs within 2 hours of dosing under fasted conditions. The mean C_{max} of anastrozole decreased by 16% and the median T_{max} was delayed from 2 to 5 hours when anastrozole was administered 30 minutes after food. Plasma concentrations approach steady-state levels after approximately 7 days of once daily dosing. The major circulating metabolite of anastrozole lacks pharmacologic activity. Anastrozole inhibited reactions catalyzed by CYP1A2, 2C8/9, and 3A4 *in vitro* with K_i values which were approximately 30 times higher than the mean steady-state C_{max} values observed following a 1 mg daily dose. Anastrozole had no inhibitory effect on reactions catalyzed by CYP2A6 or 2D6 *in vitro*. Hepatic metabolism accounts for approximately 85% of anastrozole elimination. Renal elimination accounts for approximately 10% of total clearance. The mean elimination half-life of anastrozole is 50 hours. ([Arimidex[®] Prescribing Information](#)). Current treatment guidelines consider there is no compelling evidence showing meaningful efficacy or toxicity differences between the AIs letrozole, anastrozole and exemestane ([NCCN breast cancer guidelines version 3.2014](#))

For information on anastrozole and management of anastrozole related adverse events refer to the Arimidex[®] SmPC or Prescribing Information.

1.5 Overview of goserelin

Goserelin (Zoladex[®]) is a synthetic decapeptide analog of gonadotropin releasing hormone (GnRH) indicated for prostatic carcinoma, endometriosis, endometrial thinning, and advanced breast cancer. Goserelin is administered subcutaneously every 28 days at a dose of 3.6 mg. Following subcutaneous administration of goserelin (3.6 mg for 2 months), T_{max} was 12-15 days post-dose in males and 8-22 days post-dose in females. The metabolism of goserelin is not CYP-mediated; rather it is metabolized by hydrolysis of C-terminal amino acids. More than 90% of a radiolabeled dose was excreted in the urine, with approximately 20% of the dose in urine accounted for by unchanged goserelin. The adverse events occurring in > 20% of women included hot flushes, headache, sweating, acne, emotional lability, depression, decreased libido, vaginitis, breast atrophy, seborrhea and peripheral edema (Zoladex[®] Prescribing Information).

For information on goserelin and management of goserelin related adverse events refer to the Zoladex[®] SmPC or Prescribing Information.

1.6 Potential for drug-drug interactions

No combinations of LEE011 and tamoxifen + goserelin or LEE011 and a NSAID + goserelin have been evaluated in the clinic to date.

1.6.1 Potential for a drug-drug interaction between LEE011 and tamoxifen

The prescribing information for tamoxifen suggests that tamoxifen may affect the metabolism of co-administered drugs. A significant increase in anticoagulant effect may occur when tamoxifen is co-administered with coumarin-type anticoagulants. These medications should be avoided if possible, otherwise careful monitoring of prothrombin time is recommended. In addition, tamoxifen has been shown to reduce letrozole plasma concentrations following co-administration (Tamoxifen Prescribing Information).

Tamoxifen could potentially affect the metabolism of co-administered drugs that are substrates for CYP3A4 since *in vitro* data indicate tamoxifen is a reversible and time-dependent inhibitor of CYP3A4 (Zhao et al 2002) as well as an inducer of CYP3A4 (Desai et al 2002). LEE011 is mainly metabolized by CYP3A4 with a minor contribution by FMO3 based on *in vitro* data. Clinical drug interactions studies of tamoxifen and drugs that are mainly metabolized by CYP3A4 (e.g., gefitinib, palbociclib) resulted in no significant changes in exposure in the presence of steady-state levels of tamoxifen when compared with exposures when given alone (Cantarini et al 2005, Hoffman et al 2014). Therefore, based on these *in vivo* data, tamoxifen is not expected to affect LEE011 PK due to CYP-mediated interactions.

Tamoxifen is also an inhibitor of P-gp (Tamoxifen Prescribing Information) and could potentially affect substrates of this transporter. However, since LEE011 is a low-affinity substrate of P-gp with moderate permeability, LEE011 PK is not expected to be significantly affected by inhibition of P-gp by tamoxifen.

LEE011 may increase the exposure of co-administered drugs that are substrates for CYP3A4 due to time-dependent inhibition of the enzyme. *In vitro* studies indicate LEE011 is a reversible ($K_i = 35 \mu\text{M}$) and time-dependent inhibitor ($K_I = 5.06 \mu\text{M}$, $k_{\text{inact}} = 0.0245 \text{ min}^{-1}$) of CYP3A4. Tamoxifen is a substrate of CYP3A4/5, CYP2D6, and CYP2C9 (Nolvadex[®] Prescribing Information). *In vitro*, troleandomycin and ketoconazole (CYP3A4 inhibitors) reduced the

formation of N-desmethyltamoxifen (Stearns 2003); however the clinical significance is unknown. No clinical studies have been conducted to evaluate the effect of a strong inhibitor of CYP3A4/5 on the PK of tamoxifen. However, the effect of co-administration of strong CYP3A4/5 inducers (e.g., rifampicin, aminoglutethimide) with tamoxifen has been evaluated and resulted in reduced concentrations of tamoxifen and its metabolites (Lien 1990; Binkhorst 2012). Based on this information, a potential DDI with co-administration of LEE011 cannot be fully excluded.

Simcyp modeling was conducted using *in vitro* and clinical data to estimate the magnitude of the potential DDI between tamoxifen and LEE011. A loading dose of tamoxifen (160 mg) followed by 20 mg tamoxifen daily was simulated to rapidly achieve steady-state levels of tamoxifen, after which LEE011 was added to the model at 600 mg dose daily for 21 days. At steady-state for both compounds, LEE011 (600 mg) was predicted to increase the exposure (AUC) of tamoxifen (20 mg) by 1.9- to 2.5-fold. Conversely, the modeling predicted a weak effect of tamoxifen on LEE011 exposure at steady-state, consistent with clinical observations from DDI studies with tamoxifen and CYP3A4 substrates (Cantarini et al 2005, Hoffman et al 2014). The effect of LEE011 on the formation of the active metabolites of tamoxifen are unknown, therefore tamoxifen metabolites will be monitored in patients (as described in Section 7).

1.6.2 Potential for drug-drug interaction between LEE011 and NSAIs (letrozole, anastrozole)

Letrozole and anastrozole are not expected to affect the metabolism of LEE011, which is mainly metabolized by CYP3A4 with a minor contribution by FMO3 based on *in vitro* data. Letrozole inhibits CYP2A6 ($K_i = 4.6 \mu\text{M}$) and CYP2C19 ($K_i = 42 \mu\text{M}$) *in vitro* (Jeong 2009); (Femara® Prescribing Information), but is not an inhibitor of CYP3A4 or FMO3 and is therefore not expected to affect LEE011 metabolism. See Section 1.4.1.1 for preliminary clinical PK data for the combination of LEE011 (600 mg) and letrozole (2.5 mg).

Anastrozole inhibits reactions catalyzed by CYP1A2, CYP2C8/9, and CYP3A4 based on *in vitro* data, with K_i values that are approximately 30-fold higher than the mean steady-state C_{max} values observed following 1 mg daily dosing of anastrozole. Anastrozole has no inhibitory effect on reactions catalyzed by CYP2A6 or CYP2D6 *in vitro*. Based on *in vitro* and *in vivo* results, it is unlikely that co-administration of anastrozole at 1 mg will affect other drugs as a result of CYP-mediated inhibition. (Arimidex® Prescribing Information).

LEE011 may increase the exposure of co-medications due to time-dependent inhibition of CYP3A4. *In vitro* studies indicate LEE011 is a reversible inhibitor of CYP3A4 ($K_i = 35 \mu\text{M}$) and a time-dependent inhibitor of CYP3A4 ($K_I = 5.06 \mu\text{M}$, $k_{\text{inact}} = 0.0245 \text{ min}^{-1}$). Letrozole is metabolized via CYP3A4 and CYP2A6 (Femara® Prescribing Information) and hence letrozole concentrations could be affected by co-administration with LEE011. Preliminary PK data for the combination of LEE011 (600 mg) and letrozole (2.5 mg) from a limited number of patients indicate LEE011 and letrozole exposures are within the range of values observed for single agent LEE011 (Table 1-3) and letrozole (Table 1-4), respectively, and the combination is safe and tolerable (see Section 1.4.1.1).

Anastrozole is metabolized by N-dealkylation, hydroxylation and glucuronidation. Anastrozole metabolism occurs mainly via CYP3A4 and UGT1A4 based on *in vitro* data ([Kamdem et al 2010](#)). Therefore, anastrozole metabolism could be affected by coadministration of LEE011. However, anastrozole has been studied up to doses of 10 mg/day and all doses evaluated were well tolerated with no serious adverse events attributed to anastrozole ([Plourde 1995](#)). Therefore, LEE011 at 600 mg in combination with anastrozole at 1 mg is expected to be well tolerated in this study.

1.6.3 Low potential for drug-drug interactions with goserelin

The metabolism of goserelin is not CYP-mediated; rather hydrolysis of C-terminal amino acids is the major clearance mechanism. No formal clinical DDI studies have been conducted or reported with goserelin. Based on the available information, goserelin is not expected to affect the metabolism of nor be affected by co-administered drugs ([Zoladex[®] Prescribing Information](#)).

2 Rationale

2.1 Study rationale and purpose

Endocrine treatment is a standard treatment option for premenopausal women with advanced breast cancer. Patients commonly receive tamoxifen, either alone or in combination with an OFS agent, such as goserelin, which is approved for the palliative treatment of premenopausal and perimenopausal advanced breast cancer. Patients with advanced breast cancer may also receive OFS in combination with a hormonal treatment other than tamoxifen, such as AIs, similar to what postmenopausal women typically receive. Despite several treatment options, resistance to endocrine therapy and disease progression occur. There is a need for new therapeutic options targeting additional molecular pathways involved in breast cancer pathogenesis. This study will investigate LEE011 in combination with the two most accepted endocrine treatment options, therefore giving patients and treating physicians a choice of endocrine therapy.

Dysregulation of cell cycle checkpoints is common in cancer, including breast cancer. Preclinical data suggests that CDK4/6 inhibition may play a key role in the treatment of subsets of breast cancer by, for example, abrogating endocrine-resistant cell proliferation. Therefore, the addition of a CDK4/6 inhibitor such as LEE011 to standard endocrine therapy (tamoxifen and goserelin or letrozole/anastrozole and goserelin) is a promising therapeutic approach that will be explored in this study.

Letrozole and anastrozole are the two AIs that will be included in the study because they are the AIs that have been most widely studied in the postmenopausal setting.

2.2 Rationale for the study design

This is a randomized, placebo-controlled two-arm study with the objective to evaluate the effect of adding LEE011 to tamoxifen and goserelin or a NSAI and goserelin in premenopausal patients with advanced breast cancer. The randomized, double-blind, placebo-controlled, multicenter, parallel group design is the gold standard design for phase III trials as it minimizes allocation bias, balancing both known and unknown prognostic factors in the assignment of treatments.

Randomization is stratified by the following factors:

1. Lung or liver metastases: (yes versus no)
2. Prior chemotherapy for advanced disease: (yes versus no)
3. Endocrine combination partner (tamoxifen and goserelin versus NSAI (letrozole or anastrozole) and goserelin)

The first two stratification factors are selected because of their well-recognized prognostic value and the third factor is selected to balance randomization within the two endocrine therapy groups.

2.3 Rationale for dose and regimen selection

The LEE011 dose and regimen selected for this study is 600 mg QD 21 days on/7 days off. In the FIH study of single agent LEE011 in adult patients with solid tumors [CLEE011X2101], the MTD of LEE011 was 900 mg QD with a 3 weeks on/1 week off schedule. The recommended dose for future development was 600 mg QD with a 3 weeks on/1 week off schedule, which showed an acceptable safety profile, lower risk for QTcF prolongation, adequate exposure, and preliminary evidence of disease stabilization with single agent. In the phase III study of LEE011/placebo (600 mg) combined with letrozole (2.5 mg once daily) in postmenopausal women with advanced breast cancer HR+ HER-2 negative [CLEE011A2301] the most recent DMC took place on October 7, 2015 and reviewed safety of 664 patients recommending to continue the study without changes.

The marketed drugs used in this study will be administered at doses according to their approved label. Based on available data, there is low probability of DDIs between LEE011 and other study treatments (Section 1.6), so approved doses will be used in this study.

The standard dose and regimen of tamoxifen will be used in this study (20 mg daily). Tamoxifen has been studied in metastatic melanoma patients at doses up to 240 mg daily (McClay 2001) and 320 mg daily (O'Day 2001) in combination with standard therapies, without reported dose-limiting toxicities (DLT). At tamoxifen doses of 280 mg daily with cisplatin, the DLT was primarily hematologic (thrombocytopenia and septic neutropenia) and gastrointestinal. There were no episodes of thrombosis, except in patients with central venous catheters (McClay 2001; O'Day 2001). The combination of LEE011 (600 mg) with the well-established tamoxifen dose of 20 mg daily and goserelin, even in the event of a potential increase in tamoxifen exposure, is expected to be generally well tolerated.

The standard daily doses of NSAIs will be used in this study (2.5 mg letrozole or 1 mg anastrozole). Letrozole has been used in the clinic at doses up to 7.5 mg/day and studied at doses up to 12.5 mg/day. The observed toxicity at these higher dose levels was similar to that

at the dose level of 2.5 mg (Pritts 2011; Dixon 2001). Preliminary results from patients treated with the combination of LEE011 at 600 mg and letrozole at 2.5 mg suggest that the combination is tolerable. Anastrozole has been studied up to doses of 10 mg/day and all doses evaluated were well tolerated with no serious adverse events attributed to anastrozole (Plourde 1995). Therefore, LEE011 at 600 mg in combination with anastrozole at 1 mg is expected to be well tolerated in this study.

The standard dose of goserelin of 3.6 mg subcutaneously every 28 days will be used in this study as goserelin is not expected to affect the metabolism of nor be affected by co-administration of other drugs.

2.4 Rationale for choice of combination drugs

Expression of the ER and/or PgR is one of the most important prognostic factors in invasive breast cancer and is detected in approximately 70% of cases. Estrogen deprivation therapy is the core treatment modality in patients with HR+ advanced breast cancer. Endocrine therapy options for premenopausal women with ER+ advanced breast cancer (locally advanced, recurrent, or metastatic breast cancer) include selective ER modulators (SERM; e.g. tamoxifen, raloxifene), and luteinizing hormone-releasing hormone agonists (LHRHa; e.g. goserelin). Blocking estrogen signaling with tamoxifen has been the main approach in treatment for premenopausal women with ER+ breast cancer for over 35 years. Current guidelines also recommend treating premenopausal women with advanced HR+ breast cancer with an ovarian function suppression treatment and following treatment recommendations for post-menopausal women, such as non-steroidal AIs (NCCN breast cancer guidelines version 3.2014).

Ovarian suppression of estrogen release with LHRH agonists such as goserelin is effective in preventing relapse in premenopausal women with early stage ER+ breast cancer (Klijn 2001). A meta-analysis of four randomized trials of combined tamoxifen and a LHRH agonist versus LHRH agonists alone demonstrated that the combination was superior to the LHRH agonist alone in premenopausal women with advanced breast cancer (see Section 1.1.2).

Overexpression of cyclin D1 is seen in the majority of breast cancers, likely activating the CDK4/CDK6/E2F axis and promoting endocrine resistance. Therefore, using a CDK4/6 inhibitor to block this activity may enhance efficacy of current treatment strategies (Yu 2006). Preclinical data with CDK4/6 inhibitors including LEE011 suggest a synergistic effect when the CDK4/6 pathway is inhibited in combination with anti-endocrine treatment (Section 1.1.3). Therefore, a combination approach of endocrine therapy and CDK4/6 inhibitors is a promising therapeutic approach in this patient population.

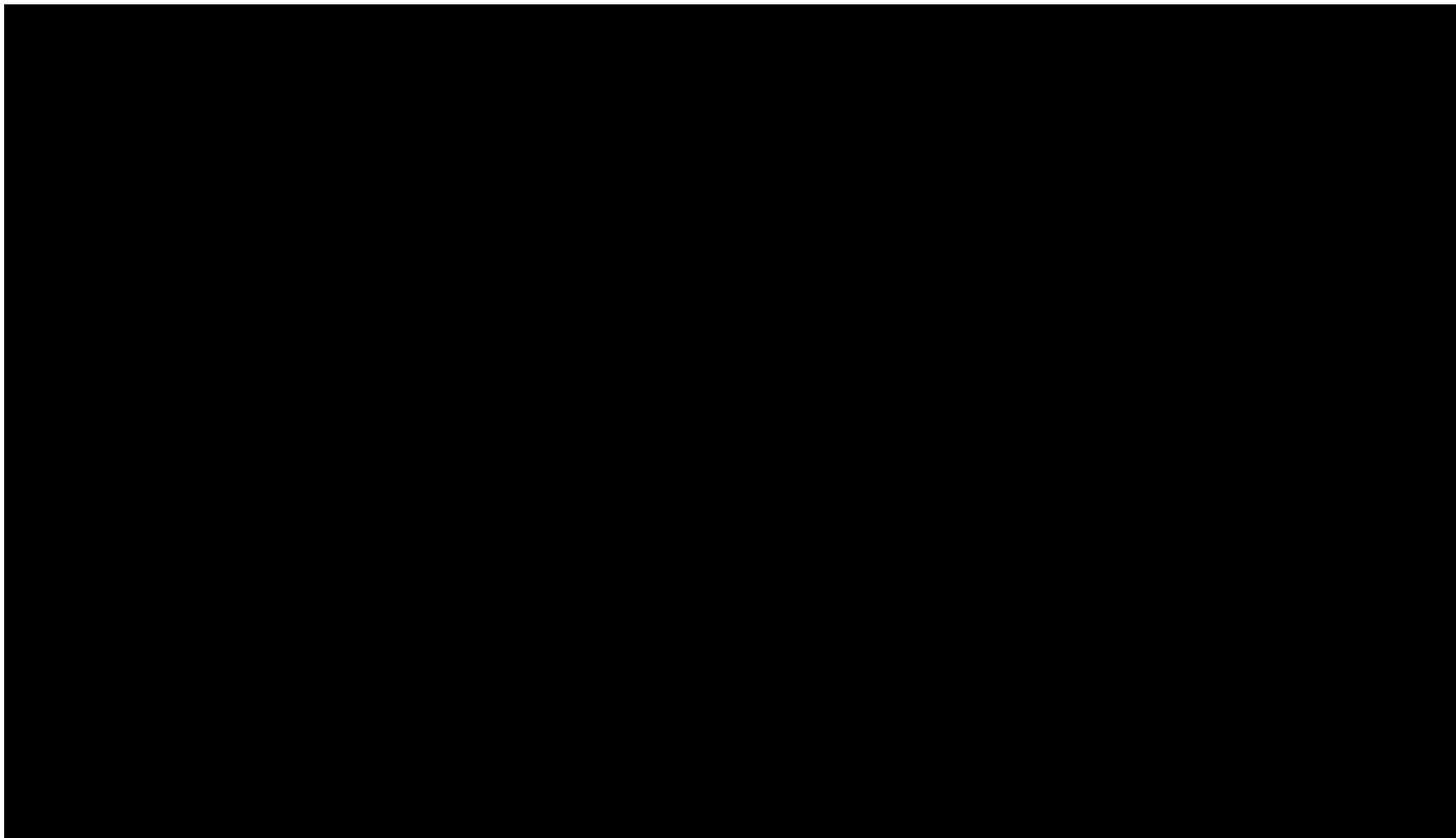
Additionally, clinical data from a Phase II open-label randomized trial of letrozole with or without palbociclib, a CDK4/6 inhibitor, showed that post-menopausal women treated with the combination achieved a statistically significant improvement in median progression PFS compared to women who received letrozole alone (20.2 months and 10.2 months, respectively) and that the combination was well tolerated (Finn 2014). These data, although using another investigational agent belonging to the same class as LEE011, also support the investigation of the combination of the class of CDK4/6 inhibitors with hormonal agents such as letrozole and others.

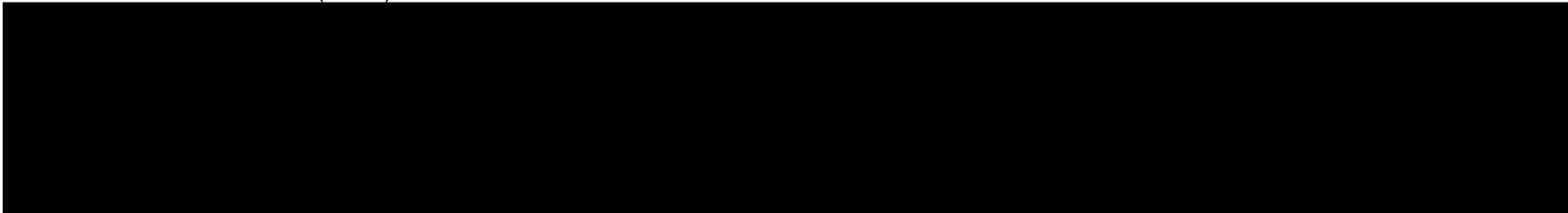
3 Objectives and endpoints

Objectives and related endpoints are described in [Table 3-1](#) below.

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
<p>Primary</p> <p>To determine whether treatment with tamoxifen or a NSAI + goserelin + LEE011 prolongs PFS compared to treatment with tamoxifen or a NSAI + goserelin + placebo in premenopausal women with HR+, HER2-negative advanced breast cancer</p>	<p>The primary endpoint is PFS per local assessment and RECIST 1.1</p>	<p>Refer to Section 10.4</p>
<p>Key secondary</p> <p>To determine whether treatment with tamoxifen or a NSAI + goserelin + LEE011 prolongs OS compared to treatment with tamoxifen or a NSAI + goserelin + placebo in premenopausal women with HR+, HER2-negative advanced breast cancer.</p>	<p>OS</p>	<p>Refer to Section 10.5.1</p>
<p>Other secondary</p> <p>To evaluate the safety and tolerability of LEE011 in combination with tamoxifen + goserelin or a NSAI + goserelin.</p>	<p>Frequency/ severity of adverse events, lab abnormalities</p>	<p>Refer to Section 10.5</p>
<p>To evaluate the two treatment arms with respect to response rate and clinical benefit rate (CBR).</p>	<p>ORR as defined by RECIST 1.1. CBR, defined as percentage of patients with CR, PR per RECIST 1.1 or SD lasting 24 weeks or longer</p>	
<p>To describe time to response (TTR) and duration of response (DOR) in each treatment arm.</p>	<p>Time to response and duration of response per RECIST 1.1</p>	
<p>To evaluate the two treatment arms with respect to time to deterioration of ECOG PS</p>	<p>Time to definitive deterioration of the ECOG PS from baseline</p>	
<p>To evaluate patient reported outcomes for health-related quality of life in the two treatment arms.</p>	<p>Time to 10% deterioration in the global health status/QOL scale score of the EORTC QLQ-C30 Change from baseline in the global health status/QOL scale score of the EORTC QLQ-C30</p>	





4 Study design

4.1 Description of study design

This is a phase III randomized, double-blind, placebo-controlled global study comparing the combination of tamoxifen or a NSAI (letrozole or anastrozole) + goserelin + LEE011 to tamoxifen or a NSAI (letrozole or anastrozole) + goserelin + placebo in premenopausal women with HR+, HER2-negative advanced breast cancer. The study will consist of a 28-day screening phase, treatment phase which includes safety follow up, and post-treatment phase which includes the efficacy and survival follow up described in [Figure 4-1](#).

Approximately 660 patients will be randomly assigned to one of the below treatment arms in 1:1 ratio:

- a. Tamoxifen (20 mg orally once daily) + goserelin (3.6 mg subcutaneously every 28 days) or NSAI (letrozole 2.5 mg orally once daily or anastrozole 1 mg orally once daily) + goserelin (3.6 mg subcutaneously every 28 days) + LEE011 (600 mg orally once daily on days 1 to 21 in a 28 day cycle).
- OR,
- b. Tamoxifen (20 mg orally once daily) + goserelin (3.6 mg subcutaneously every 28 days) or NSAI (letrozole 2.5 mg orally once daily or anastrozole 1 mg orally once daily) + goserelin (3.6 mg subcutaneously every 28 days) + placebo (orally once daily on days 1 to 21 in a 28 day cycle).

Randomization will be stratified by the presence of liver and/or lung metastases (yes versus no), prior chemotherapy for advanced disease (yes versus no), and Endocrine combination partner (tamoxifen and goserelin versus NSAI (letrozole or anastrozole) and goserelin).

Treatment with tamoxifen or NSAI in this study will be based on the patient's prior (neo) adjuvant therapy for breast cancer:

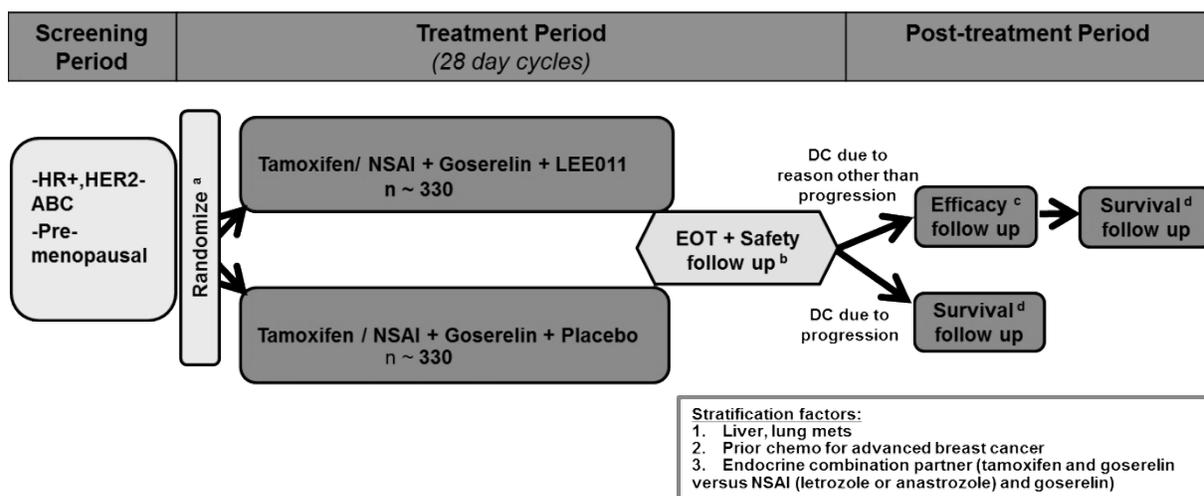
- If the patient has not received any prior endocrine therapy **OR** if ≥ 12 months have elapsed since the patient's last dose of (neo) adjuvant therapy, then the patient is eligible to receive tamoxifen + goserelin **OR** a NSAI + goserelin for advanced breast cancer based on the investigator's choice.
- If tamoxifen or fulvestrant was the last prior (neo) adjuvant therapy and the last dose was given < 12 months prior to randomization, then the patient is eligible to receive a NSAI (letrozole or anastrozole) + goserelin for advanced breast cancer.
- If letrozole, anastrozole, or exemestane was the last prior (neo) adjuvant therapy and the last dose was given < 12 months prior to randomization, then the patient is eligible to receive tamoxifen + goserelin for advanced breast cancer.
- The choice of which NSAI (letrozole or anastrozole) to be used on study is left to the investigator's choice.

PFS, as assessed by the local radiologists/investigators and using RECIST 1.1 criteria will be the primary endpoint. PFS as assessed through blinded independent central review will be used for supportive evidence of the primary efficacy endpoint.

An independent data monitoring committee (IDMC) will be constituted and will monitor safety data as outlined in Section 8.6. A Steering Committee (SC) will be established, comprising of investigators and Novartis personnel participating in the trial, to ensure transparent management of the study according to the protocol through recommending and approving modifications as outlined in Section 8.7.

If the study proceeds after a positive effect on PFS is declared (i.e. at the primary analysis of PFS), crossover to the experimental arm from the control arm is not permitted and investigators and patients will remain blinded to study treatment; all patients will continue to be followed for OS until the final OS analysis (or earlier if OS reaches statistical significance at any of the interim analyses). In addition, crossover from tamoxifen to a NSAI, or vice versa, is not permitted in this study. Crossover between NSAIs (letrozole to anastrozole or vice versa) is also not permitted in this study.

Figure 4-1 Study design



- a. Treatment with tamoxifen or NSAI will be based on the patient’s prior hormonal adjuvant therapy.
- b. After discontinuation of study treatment, all patients will be followed for safety for at least 30 days except in case of death, loss to follow-up or withdrawal of consent.
- c. Efficacy follow up is through tumor assessment and for selected patient reported outcomes every 8 weeks during the first 18 months and every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, or subject/guardian decision.
- d. Survival follow-up will be done every 12 weeks until at least 252 deaths have been documented.

4.1.1 Screening phase

Premenopausal women with HR+, HER2-negative advanced breast cancer will be screened for eligibility during the period up to 28 days immediately prior to starting the combination of tamoxifen or a NSAI + goserelin + LEE011 or tamoxifen or a NSAI + goserelin + placebo on study Day 1. During this time, the inclusion and exclusion criteria will be assessed and all screening assessments, laboratory tests, and procedures will be performed. Requested tissue

will be retrieved, if available. Results of all screening/baseline evaluations must be reviewed by the investigator or his/her designee prior to patient enrollment into the study in order to assure that all inclusion and exclusion criteria have been satisfied.

All study patients must be thoroughly informed about all aspects of the study, including the study agents, visit schedule, required evaluations, and all regulatory requirements for informed consent. The signed informed consent must be obtained to participate in this study prior to the performance of any study-related activities. If the patient is unable to read, an impartial witness should be present during the entire informed consent discussion.

Eligibility will be determined according to the inclusion/exclusion criteria as described in [Section 5](#). A list of procedures to be performed at the time of screening is summarized in [Table 7-1](#). Patients must meet all eligibility criteria to be considered for enrollment in the study.

4.1.2 Treatment phase

Patient eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded to the Interactive Response Technology (IRT) system. Please refer and comply with detailed guidelines in the IRT manual. IRT system will confirm the inclusion of eligible patients and randomly assign patients to one of the two treatment arms in a 1:1 ratio (see [Section 4.1](#)).

Patients may continue study treatment until disease progression, occurrence of unacceptable toxicity, withdrawal of consent by the patient, patient is lost to follow-up, or the sponsor terminates the study. Patients will be followed for survival regardless of treatment discontinuation for any reason, and regardless of achieving the primary endpoint, until the planned number deaths for final OS analysis have been documented (except if consent is withdrawn or patient is lost to follow-up).

4.1.3 Safety follow-up

After discontinuation of study treatment, all patients will be followed for safety for at least 30 days except in case of death, loss to follow-up or withdrawal of consent. For details please refer to [Section 7](#).

4.1.4 Efficacy follow-up

Patients who discontinue treatment for reasons other than disease progression will continue to be followed every 8 weeks for efficacy (i.e., tumor assessments and selected patient reported outcomes) during the first 18 months and every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, or subject/guardian decision. If a patient starts a new antineoplastic treatment without withdrawing consent, the patient should continue to be followed for efficacy according to above specified protocol schedule until disease progression, death, withdrawal of consent, loss to follow-up, or subject/guardian decision. For further details please refer to [Table 7-1](#) and [Section 7](#).

4.1.5 Survival follow-up

All patients will be followed for survival once they discontinue study treatment and efficacy evaluations until the final number of OS events have been reached or the study is stopped for

other reasons. Survival follow-up will be conducted every 12 weeks or earlier if a survival update is required to meet safety or regulatory needs. Survival information can be obtained by clinical visits or telephone calls until death, the patient is lost to follow-up, or the patient withdraws consent for survival follow-up.

During the survival follow up, in addition to vital status, all subsequent anti-neoplastic therapies initiated after study treatment discontinuation will be collected along with the start/end date and date of disease progression on subsequent therapies [REDACTED]

4.2 Timing of interim analyses and design adaptations

There is no planned efficacy interim analysis for the primary PFS endpoint. Interim analyses for OS will be conducted if PFS is statistically significant as detailed in [Section 10.5.1](#) and [Section 10.7.2](#).

4.3 Definition of end of the study

The end of treatment (EOT) for a given patient is defined as when the patient permanently discontinues all study treatment and all the end of treatment procedures are completed. The end of study (EOS) for a given patient is defined as when the patient discontinues from follow-up assessments as detailed in [Table 7-1](#).

If the primary endpoint, PFS, is statistically significant at the primary PFS analysis, data collection will continue during survival follow-up and End of Study will be declared after the final number of OS events are reached (or earlier if OS reaches statistical significance at any of the interim analyses for OS) and after all patients have completed the safety follow-up period (30 days after treatment discontinuation).

If the primary endpoint, PFS, is not statistically significant at the primary PFS analysis then End of Study will be declared after all patients have discontinued all components of study therapy and completed the safety follow-up period (30 days after treatment discontinuation).

Patients continuing to derive benefit from study treatment at the end of the study in the opinion of the investigator will be able to continue receiving trial therapy on a separate protocol. Alternatively Novartis will provide study treatment to the investigator as per local regulations.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in [Section 7.1.5](#) for a discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

The study will include pre-menopausal women with HR+, HER2-negative, advanced breast cancer who received no prior hormonal therapy for advanced breast cancer and are eligible for endocrine therapy. The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

Written informed consent must be obtained prior to any screening study-related procedures.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Patient is an adult, female ≥ 18 years old and < 60 years old at the time of informed consent and has signed informed consent before any trial related activities are conducted and according to local guidelines.
2. Confirmed negative serum pregnancy test (β -hCG) before starting study treatment or patient has had a hysterectomy.
3. Patient is premenopausal or perimenopausal at the time of study entry.
 - Premenopausal status is defined as either:
 - Patient had last menstrual period within the last 12 months,**OR**
 - If on tamoxifen or toremifene within the past 14 days, plasma estradiol and FSH must be in the premenopausal range per local normal range,**OR**
 - In case of therapy induced amenorrhea, plasma estradiol and/or FSH must be in the premenopausal range per local normal range.
 - Patients who have undergone bilateral oophorectomy are not eligible.
 - Perimenopausal status is defined as neither premenopausal nor postmenopausal (see exclusion criteria 3).
4. Patient has advanced (locoregionally recurrent or metastatic) breast cancer not amenable to curative therapy (e.g. surgery and/or radiotherapy).
5. Patients who received **(neo) adjuvant therapy** for breast cancer are eligible:
 - If the patient has never received any prior endocrine therapy **OR** if ≥ 12 months have elapsed since the patient's last dose of adjuvant therapy, then the patient is eligible to receive tamoxifen + goserelin **or** a NSAI + goserelin for advanced breast cancer based on the investigator's choice.
 - If tamoxifen or fulvestrant was the last prior (neo) adjuvant therapy and the last dose was given < 12 months prior to randomization, then the patient is eligible to receive a NSAI (letrozole or anastrozole) + goserelin for advanced breast cancer.
 - If letrozole, anastrozole, or exemestane was the last prior (neo) adjuvant therapy and the last dose was given < 12 months prior to randomization, then the patient is eligible to receive tamoxifen + goserelin for advanced breast cancer.

6. Patients who received ≤ 14 days of tamoxifen or a NSAI (letrozole or anastrozole) with or without goserelin or goserelin ≤ 28 days for advanced breast cancer prior to randomization are eligible. Patients must continue treatment with the same hormonal agent + goserelin during the study. No treatment interruption is required for these patients prior to randomization.

Note: Patients who are receiving goserelin for reasons other than for advanced breast cancer treatment are eligible (e.g endometriosis). Patients who received ≤ 28 days goserelin for advanced breast cancer are eligible.

7. Patients who have received up to 1 line of chemotherapy for advanced breast cancer and have been discontinued 28 days before randomization are eligible.

Note: If a cytotoxic chemotherapy regimen was discontinued for reasons other than disease progression and lasted less than 21 days, this regimen does not count as a prior line of chemotherapy.

8. Patient has a histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive and/or progesterone receptor positive breast cancer by local laboratory (based on most recently analyzed biopsy).
9. Patient has HER2-negative breast cancer (based on most recently analyzed biopsy) defined as a negative in situ hybridization test or an IHC status of 0, 1+ or 2+. If IHC is 2+, a negative in situ hybridization (FISH, CISH, or SISH) test is required by local laboratory testing.

10. Patient must have either:

- Measurable disease, i.e., at least one measurable lesion as per RECIST 1.1 criteria.

OR

- If no measurable disease is present, then at least one *predominantly* lytic bone lesion must be present (patients with no measurable disease and only one predominantly lytic bone lesion that has been previously irradiated are eligible if there is documented evidence of disease progression of the bone lesion after irradiation).

11. Patient has ECOG PS 0 or 1.

12. Patient has adequate bone marrow and organ function as defined by the following laboratory values (as assessed by central laboratory):

- Absolute neutrophil count $\geq 1.5 \times 10^9/L$.
- Platelets $\geq 100 \times 10^9/L$.
- Hemoglobin ≥ 9.0 g/dL.
- Potassium, sodium, calcium (corrected for serum albumin), and magnesium within normal limits of the central laboratory or corrected to within normal limits with supplements before the first dose of study medication
- INR ≤ 1.5 .
- Serum creatinine < 1.5 mg/dL.
- In absence of liver metastases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be below $2.5 \times ULN$. If the patient has liver metastases, ALT and AST should be $< 5 \times ULN$.

- Total serum bilirubin < ULN; or total bilirubin $\leq 3.0 \times$ ULN with direct bilirubin <1.5 x ULN of the central laboratory in patients with well documented Gilbert's Syndrome.
13. Must be able to swallow study therapy
 14. Subjects must be able to communicate with the investigator and comply with the requirements of the study procedures.
 15. Must be willing to remain at the clinical site as required by the protocol visit evaluation schedule.

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Patient who has received a prior CDK4/6 inhibitor.
2. Patient has a known hypersensitivity to any of the excipients of LEE011 or goserelin or hormonal treatment assigned (tamoxifen or a NSAID (letrozole or anastrozole)).
3. Patient is postmenopausal. Postmenopausal status is defined either by:
 - Prior bilateral oophorectomy
 - OR
 - Age ≥ 60
 - OR
 - Age <60 and amenorrhea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression) and FSH and estradiol in the postmenopausal range per local normal range.
 - If taking tamoxifen or toremifene, and age <60, then FSH and plasma estradiol level in postmenopausal ranges per local laboratory normal range.
4. Patients who currently have inflammatory breast cancer at screening.
5. Patients who received any prior hormonal anti-cancer therapy for advanced breast cancer, except for ≤ 14 days of tamoxifen or NSAID or goserelin ≤ 28 days for advanced breast cancer prior to randomization.
6. Patient who has not had resolution of all acute toxic effects of prior anti-cancer therapy to NCI CTCAE version 4.03 Grade ≤ 1 (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion).
7. Patient has a concurrent malignancy or malignancy within 3 years of randomization, with the exception of adequately treated basal cell skin carcinoma, squamous cell skin carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer.
8. Patient with CNS metastases.

Note: CNS involvement must be ruled out by assessments if a patient has any signs or symptoms indicating potential CNS metastases.

9. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of the study drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
10. Patient has a known history of HIV infection (testing not mandatory).
11. Patient has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, contraindicate patient participation in the clinical study (e.g., chronic pancreatitis, chronic active hepatitis, etc.).
12. Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality, including any of the following:
 - History of angina pectoris, symptomatic pericarditis, myocardial infarction, or coronary artery bypass graft (CABG) within 6 months prior to study entry
 - Documented cardiomyopathy
 - Left Ventricular Ejection Fraction (LVEF) < 50% as determined by Multiple Gated acquisition (MUGA) scan or echocardiogram (ECHO)
 - Clinically significant cardiac arrhythmias (e.g., ventricular tachycardia), complete left bundle branch block, high-grade AV block (e.g., bifascicular block, Mobitz type II and third degree AV block)
 - Long QT syndrome or family history of idiopathic sudden death or congenital long QT syndrome, or any of the following:
 - Risk factors for Torsades de Pointe (TdP) including uncorrected hypokalemia or hypomagnesemia, history of cardiac failure, or history of clinically significant/symptomatic bradycardia
 - resting heart rate < 50 at rest, by the triplicate ECG
 - resting heart rate >90 at rest, by the triplicate ECG
 - Systolic blood pressure >160 or <90 mmHg
 - On screening, inability to determine the QTcF interval on the ECG (ie: unreadable or not interpretable) or QTcF >450 msec (using Fridericia's correction). All as determined by the average of the triplicate screening ECG, per central review.
13. Patient is currently receiving any of the following substances and cannot be discontinued 7 days prior to the start of the treatment:
 - Known strong inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, pummelos, star-fruit, and Seville oranges.
 - Medications with a known risk to prolong the QT interval or induce Torsades de Pointes that cannot be discontinued or replaced by safe alternative medication (e.g. within 5 half-lives or 7 days prior to starting study drug).
 - Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5.
 - Additionally, for patients receiving tamoxifen: known strong inducers or inhibitors of CYP2D6.
 - Herbal preparations/medications and dietary supplements (except for vitamins).

14. Patient has had major surgery within 14 days prior to starting study drug or has not recovered from major side effects.
15. Patient is currently receiving warfarin or other Coumadin derived anti-coagulant, for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin (LMWH), or fondaparinux is allowed.
16. Patient is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting study drug, or who have not fully recovered from side effects of such treatment.

Note: The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular).

17. Patient is concurrently using other antineoplastic agents (except for patients who are receiving ≤ 14 days of tamoxifen or NSAID or goserelin ≤ 28 days for advanced breast cancer prior to randomization).
18. Patient who has received radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to randomization, and who has not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia) and/or if $\geq 25\%$ of the bone marrow was irradiated.
19. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
20. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during dosing of study treatment and for 21 days after stopping study medication. Highly effective contraception methods include:
 - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
 - Total hysterectomy or tubal ligation at least six weeks before taking study treatment.
 - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
 - Combination of the following:
 - a. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
 - b. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository
21. Participation in a prior investigational study within 30 days prior to enrollment or within 5-half lives of the investigational product, whichever is longer.
22. Not able to understand and to comply with study instructions and requirements.
23. Patient with symptomatic visceral disease or any disease burden that makes the patient ineligible for endocrine therapy per the investigator's best judgment

6 Treatment

6.1 Study treatment

For this study, the term “investigational drug” refers to Novartis study drug LEE011. The other drugs to be used in this study are tamoxifen, letrozole, anastrozole, and goserelin. Study treatment in this study refers to the triple combination of the investigational drug, LEE011/placebo, and tamoxifen/NSAI and goserelin. Refer to [Section 4](#) for the criteria determining treatment with tamoxifen or NSAI.

Novartis will supply LEE011/placebo as 200 mg hard gelatin capsules as individual patient supply packaged in bottles. Tamoxifen, letrozole, anastrozole and goserelin will be procured locally as they are commercially available drugs in each participating country according to local practice and regulation. Storage conditions are described in the medication label. Tamoxifen, letrozole, anastrozole, and goserelin should be used in accordance with the locally approved label (SmPC). Medication labels will comply with the legal requirements of each country and be printed in the local language.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.1.1 Dosing regimen

LEE011 or LEE011 placebo will be given orally once daily on days 1-21 of each 28 day cycle. Days 22-28 will be a “rest” period from dosing with LEE011 or LEE011 placebo. Tamoxifen, letrozole, and anastrozole will be given orally once daily on a continuous daily schedule (e.g., days 1-28 of each 28 day cycle). Goserelin will be given as an injectable subcutaneous implant on day 1 of every 28 day cycle. There will be no “rest” in the tamoxifen, letrozole, or anastrozole schedule.

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
LEE011/placebo	Capsules for oral use	600 mg	Days 1-21 of each 28 day cycle
Tamoxifen	Tablets for oral use	20 mg	Daily (all days of every cycle without interruption.)
Letrozole	Tablets for oral use	2.5 mg	Daily (all days of every cycle without interruption.)
Anastrozole	Tablets for oral use	1 mg	Daily (all days of every cycle without interruption.)
Goserelin	Subcutaneous implant	3.6 mg	Day 1 of each 28 day cycle

The study drugs will be administered as a flat-fixed dose, and not by body weight or body surface area. All study treatment drugs must be administered together at approximately the same time each day. All oral study treatment drugs can be administered with or without food.

The investigator or responsible site personnel should instruct the patient to take the study drugs as per protocol (promote compliance). Patients will be instructed to return unused study drugs to the site at discontinuation or completion of treatment. The site personnel will ensure that the

appropriate dose of each study drug is administered and that the drug accountability is performed.

6.1.1.1 General dosing guidelines

The study treatments should be taken as follows:

- LEE011/placebo is dosed orally for the first 21 days out of a 28 day cycle while tamoxifen, letrozole, or anastrozole are dosed orally daily (28 days out of the 28 day cycle). Goserelin is continuously released via a subcutaneous implant injected on Day 1 of each 28 day cycle.
- Patients should be instructed to take the study treatment of LEE011/placebo capsules and one tablet of tamoxifen or letrozole or anastrozole together with a large glass of water (~250 mL) at the same time each day. For the first cycle, patients must take LEE011/placebo in the morning due to PK assessments. Once the PK assessments have been completed, patients can determine if they prefer morning or early afternoon dosing, but should maintain a consistent time regardless of AM or PM dosing. Evening doses are strongly **not recommended**.
- In general, study treatment may be taken without regard to meals. Please see [Section 6.1.1.2](#) below for additional guidelines for scheduled visit days.
- Patients should be instructed to swallow the capsules and tablets whole and not to chew, crush or open them.
- Goserelin implant should be administered as a subcutaneous injection every 28 days using an aseptic technique under the supervision of a physician. Administration technique should be in accordance with the locally approved label (SmPC).
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse events section of the eCRF.
- Any doses that are missed (not taken within 6 hours of the intended time) should be skipped and should not be replaced or made up on a subsequent day.
- Patients must avoid consumption of grapefruit, grapefruit hybrids, pummelos, star-fruit, Seville oranges or products containing the juice of each during the entire study and preferably for an additional 7 days before the first dose of study medications and during the study, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.
- No herbal or dietary supplements are permitted.
- Multivitamins are permitted.

6.1.1.2 Additional dosing guidelines for scheduled visit days

On days with fasting, (overnight fasting defined as at least 8-12 hours) biochemistry and/or lipid profile samples as outlined in [Table 7-1](#) and [Figure 6-1](#), the following additional guidelines should be followed:

reason other than disease progression may continue on tamoxifen or a NSAID per investigator's discretion until disease progression, unacceptable toxicity, death or discontinuation from study treatment due to any other reason and continue to be followed for safety and/or efficacy.

6.1.5 Treatment duration

Patients may continue study treatment until disease progression (radiologically documented according to RECIST 1.1), or until discontinuation of study treatment due to any other reason (see [Section 7.1.5](#)).

6.2 Dose escalation guidelines

Not applicable.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, LEE011/placebo dose adjustments are permitted in order to allow the patient to continue the study treatment.

Dose reductions are not permitted for goserelin, tamoxifen or NSAIDs.

Any changes to the dose or interruption of dosing must be recorded on the Dosage Administration Record eCRF. All patients will be followed for AEs and for SAEs for 30 days following the last dose of study drug.

6.3.1.1 Tamoxifen

The established clinical dose of tamoxifen (20 mg/day) will be used in each arm and no dose modification of tamoxifen is planned in this study.

For information on tamoxifen and management of tamoxifen related adverse events refer to the Tamoxifen SmPC or Prescribing Information.

6.3.1.2 Non-steroidal aromatase inhibitors (NSAIDs)

The established clinical dose of letrozole (2.5 mg/day) and anastrozole (1 mg/day) will be used in each arm and no dose modification of letrozole or anastrozole is planned in this study.

For information on NSAIDs (letrozole or anastrozole) and management of related adverse events refer to the Femara[®] or Arimidex[®] SmPC or Prescribing Information.

6.3.1.3 Goserelin

The established clinical dose of goserelin (3.6 mg subcutaneous injection every 28 days) will be used in each arm and no dose modification of goserelin is planned in this study.

For information on goserelin and management of goserelin related adverse events refer to the Zoladex[®] SmPC or Prescribing Information.

6.3.1.4 LEE011/placebo

Management of severe or intolerable adverse reactions requires temporary dose reduction and/or interruption of LEE011 therapy. Refer to [Table 6-2](#) for guidance.

Table 6-2 Dose modification guideline

	LEE011/placebo	
	Dose	Number of capsules & strength
Starting dose	600 mg	3 x 200 mg capsules
First dose reduction	400 mg	2 x 200 mg capsules
Second dose reduction	200 mg	1 x 200 mg capsules

Recommendations for dose reduction, interruption or discontinuation of LEE011 in the management of adverse reactions are summarized in [Table 6-3](#), [Table 6-4](#), [Table 6-5](#), and [Table 6-6](#).

Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment. However, for events requiring a discontinuation in [Table 6-3](#), [Table 6-4](#), [Table 6-5](#) and [Table 6-6](#) or listed in [Section 7.1.5.1](#), treatment must be discontinued.

If a patient inadvertently doses on a rest day (e.g. days 22-28 of any given cycle), LEE011/placebo will be interrupted to ensure 7 consecutive rest days and avoid overdose. The visit schedule will not be adjusted.

Unscheduled local laboratory assessments may be performed if medically indicated to document a (potential) adverse event or when the treating physician cannot wait for central laboratory results for decision making (e.g. dose modifications). In this particular situation, if possible, the blood sample obtained at the same time point should be submitted to the central laboratory for analysis in parallel with local analysis.

The results of the local laboratory will be recorded in the eCRF if any the following criteria are met:

- A treatment decision was made based on the local results, or
- There are no concomitant central results available, or
- Local lab results document an adverse event not reported by the central lab, or
- Local lab results document an adverse event where the severity is worse than the one reported by the central lab

For assessment of patients' eligibility to the study, only laboratory results from the central laboratory will be used.

Table 6-3 LEE011/placebo dose adjustment and management recommendations for hematological adverse reactions

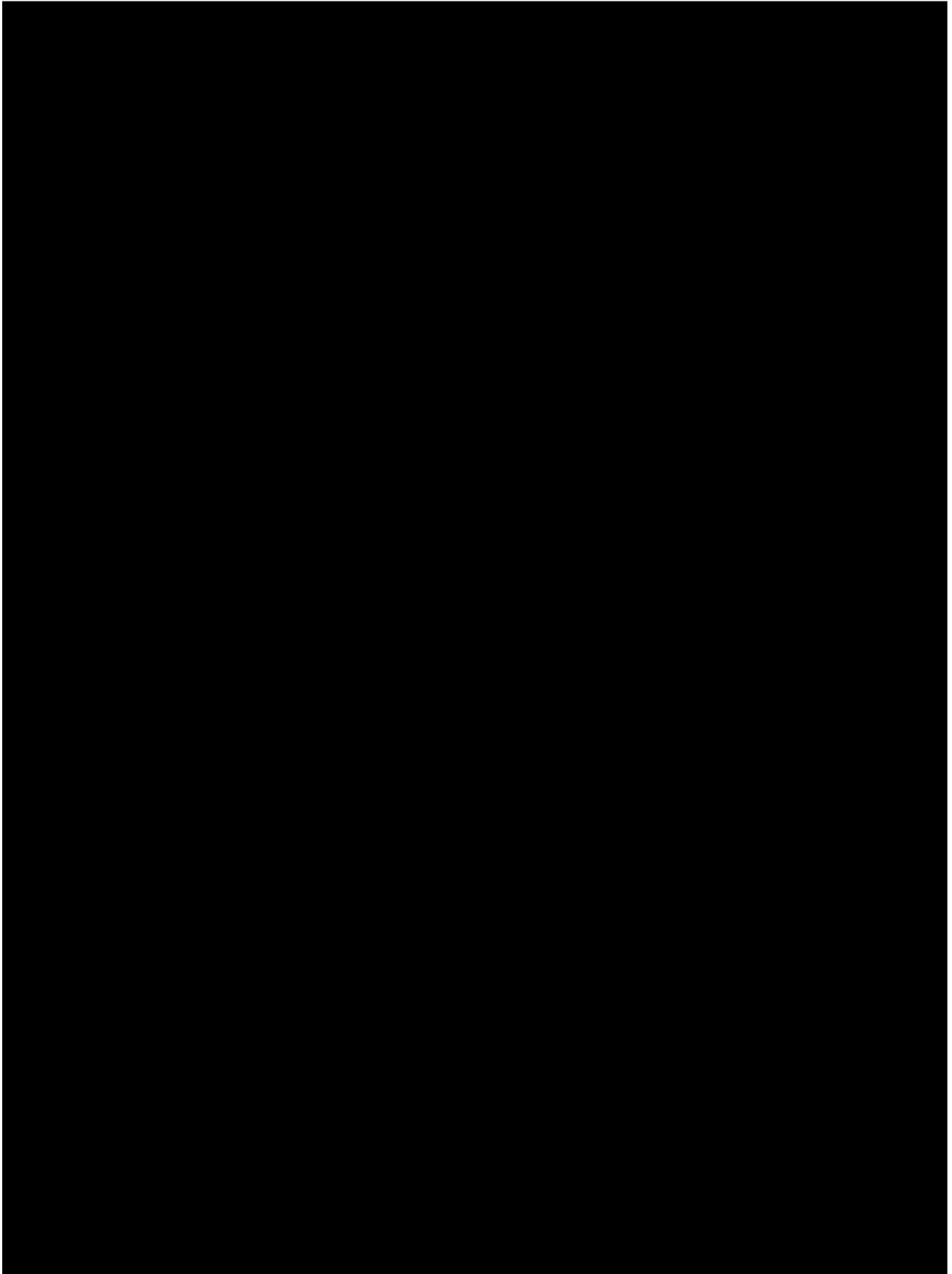
Toxicity	Grade	Dose Adjustment and Management Recommendations
Thrombocytopenia	1 ≥75 x 10 ⁹ /L	No dose adjustment required.
	2 ≥50 x 10 ⁹ /L – <75 x 10 ⁹ /L	Dose interruption until recovery to grade ≤1. Re-initiate LEE011/placebo at the same dose.
	3 ≥25 x 10 ⁹ /L - <50 x 10 ⁹ /L	Dose interruption until recovery to grade ≤1. Re-initiate LEE011/placebo at the same dose level. <ul style="list-style-type: none"> ● If toxicity recurs at grade 3: temporary dose interruption until recovery to grade ≤1 and reduce LEE011/placebo to the next lower dose level.
	4 <25 x 10 ⁹ /L	Dose interruption until recovery to grade ≤1. Re-initiate LEE011/placebo at the next lower dose level. <ul style="list-style-type: none"> ● If toxicity recurs at grade 4: discontinue LEE011/placebo.
Absolute neutrophil count (ANC)	1 ≥1.5 x 10 ⁹ /L	No dose adjustment required.
	2 ≥1.0 - <1.5 x 10 ⁹ /L	No dose adjustment required.
	3 ≥0.5 - <1.0 x 10 ⁹ /L	Dose interruption until recovery to >1.0 x 10 ⁹ /L. Re-initiate LEE011/placebo at the same dose level. <ul style="list-style-type: none"> ● If toxicity recurs at grade 3: temporary dose interruption until recovery to > 1.0 x 10⁹/L. ● If resolved in ≤ 7 days, then maintain dose level. ● If resolved in > 7 days, then reduce LEE011/placebo dose to the next lower dose level.
	4 <0.5 x 10 ⁹ /L	Dose interruption until recovery to > 1.0 x 10 ⁹ /L. Re-initiate LEE011/placebo at the next lower dose level. <ul style="list-style-type: none"> ● If toxicity recurs at grade 4: temporary dose interruption until recovery to >1.0 x 10⁹/L and reduce LEE011/placebo at the next lower dose level.
Febrile neutropenia	3 ANC <1.0 x 10 ⁹ /L with [a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour]	Dose interruption until improvement of ANC ≥ 1.0 x 10 ⁹ /L and no fever. Restart at the next lower dose level. <ul style="list-style-type: none"> ● If febrile neutropenia recurs, discontinue LEE011/placebo.
	4 Life-threatening consequences; urgent intervention indicated	Discontinue LEE011/placebo.

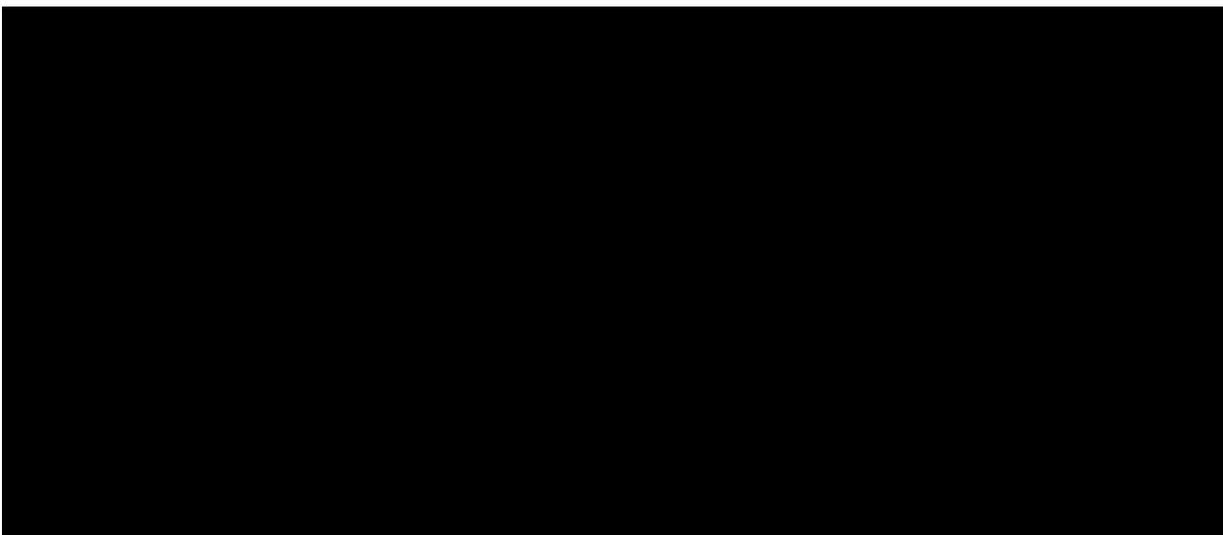
Toxicity	Grade	Dose Adjustment and Management Recommendations
Anemia (Hemoglobin)	1 ≥10.0 – LLN g/dL	No dose adjustment required.
	2 ≥8.0 – <10.0 g/dL	No dose adjustment required.
	3 <8.0 g/dL	Dose interruption until recovery to grade ≤ 2. Re-initiate LEE011/placebo at the same dose.
	4 Life-threatening consequences; urgent intervention indicated	Discontinue LEE011/placebo.

Table 6-4 LEE011/placebo dose adjustment and management recommendations for hepatic toxicities

HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)	
TOTAL BILIRUBIN without ALT/AST increase above baseline value	
Grade 1 (> ULN – 1.5 x ULN) (confirmed 48-72h later by repeat testing)	Maintain dose level with LFTs monitored bi-weekly
Grade 2 (> 1.5 – 3.0 x ULN)	Dose interruption of LEE011/placebo <ul style="list-style-type: none"> • If resolved to ≤ grade 1 in ≤ 21 days, then maintain dose level • If resolved to ≤ grade 1 in > 21 days or toxicity recurs, then reduce 1 dose level • Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption • If toxicity recurs after two dose reductions, discontinue LEE011/placebo
Grade 3 (> 3.0 – 10.0 x ULN)	Dose interruption of LEE011/placebo. <ul style="list-style-type: none"> • If resolved to ≤ grade 1 in ≤ 21 days, lower 1 dose level of LEE011/placebo • Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption • If resolved to ≤ grade 1 in > 21 days or toxicity recurs, discontinue LEE011 /placebo
Grade 4 (> 10.0 x ULN)	Discontinue LEE011 /placebo
<p>Confounding factors and/or alternative causes for increase of total bilirubin should be excluded before dose interruption/reduction. They include but are not limited to: evidence of obstruction, such as elevated ALP and GGT typical of gall bladder or bile duct disease, hyperbilirubinemia due to the indirect component only (i.e. direct bilirubin component ≤ 1 x ULN) due to hemolysis or Gilbert Syndrome, pharmacologic treatment, viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs.</p> <p>For patients with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only. Bilirubin will be fractionated if elevated.</p>	

HEPATOTOXICITY (BILIRUBIN, SGPT/ALT, SGOT/AST)	
AST or ALT	
AST or ALT without bilirubin elevation > 2 x ULN	
Same grade as baseline or increase from baseline grade 0 to grade 1 (confirmed 48 – 72 h later by repeat testing)	No dose adjustment required with LFTs monitored per protocol if same grade as baseline or bi-weekly in case of increase from baseline grade 0 to 1
Increase from baseline grade 0 or 1 to grade 2 (> 3.0 – 5.0 x ULN)	<p>Dose interruption of LEE011/placebo</p> <ul style="list-style-type: none"> • If resolved to ≤ baseline grade in ≤ 21 days, then maintain dose level • If resolved to ≤ baseline grade in > 21 days or toxicity recurs, then reduce 1 dose level • Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption • If toxicity recurs after two dose reductions or recovery to ≤ baseline grade is > 28 days, discontinue LEE011/placebo
Increase from baseline grade 0 or 1 to grade 3 (> 5.0 – 20.0 x ULN)	<p>Dose interruption of LEE011 until resolved to ≤ baseline grade, then lower 1 dose level of LEE011</p> <ul style="list-style-type: none"> • Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption • If recovery to ≤ baseline grade is > 28 days, discontinue LEE011 • If toxicity recurs, discontinue LEE011/placebo
Increase from baseline grade 2 to grade 3 (> 5.0 – 20.0 x ULN)	<p>Dose interruption of LEE011/placebo until resolved to ≤ baseline grade, then lower 1 dose level of LEE011/placebo</p> <ul style="list-style-type: none"> • Repeat liver enzyme and bilirubin tests twice weekly for 2 weeks after dose resumption • If toxicity recurs after two dose reductions or recovery to ≤ baseline grade is > 28 days, discontinue LEE011/placebo.
Grade 4 (> 20.0 x ULN)	Discontinue LEE011 /placebo
AST or ALT and concurrent Bilirubin	
<p>For patients with normal ALT AND AST AND total bilirubin at baseline: AST or ALT >3.0 x ULN ≥ combined with total bilirubin > 2 x ULN without evidence of cholestasis</p> <p>Or</p> <p>For patient with elevated AST or ALT or total bilirubin at baseline; baseline: [AST or ALT >2 x baseline AND >3.0 x ULN] OR [AST or ALT 8.0 x ULN]- whichever is lower- combined with [total bilirubin > 2x baseline AND >2.0 x ULN]</p>	Discontinue LEE011/placebo
<p>Confounding factors and/or alternative causes for increased transaminases should be excluded before dose interruption/reduction. They include but are not limited to: concomitant medications, herbal preparations or dietary supplements, infection, hepato-biliary disorder or obstruction, new or progressive liver metastasis, and alcohol intake.</p>	





6.3.1.6 Additional follow-up for QTc prolongation

Table 6-5 LEE011/placebo dose adjustment and management recommendations for QTcF prolongation

Grade	Dose Modification
For All Grades	<ul style="list-style-type: none"> • Check the quality of the ECG and the QT value and repeat if needed • Perform analysis of serum electrolytes (K+, Ca++, Phos, Mg++). If outside the normal range, interrupt LEE011/placebo administration, correct with supplements or appropriate therapy as soon as possible, and repeat electrolytes until documented as normal. • Review concomitant medication usage for the potential to inhibit CYP3A4 and/or to prolong the QT interval. • Check compliance with correct dose and administration of LEE011/placebo. • [REDACTED]
Grade 1* QTc 450-480 ms	No dose adjustment required.
Grade 2* QTc 481-500 ms	<p>Interrupt LEE011/placebo.</p> <p>Perform a repeat ECG within one hour of the first QTcF of ≥ 481 ms.</p> <ul style="list-style-type: none"> • If QTcF < 481 ms, restart LEE011/placebo at the same dose. No dose adjustment required for first occurrence. • If QTcF remains ≥ 481 ms, repeat ECG as clinically indicated until the QTcF returns to < 481 ms. Restart LEE011/placebo at the same dose. • If QTcF ≥ 481 ms recurs, LEE011/placebo should be reduced by 1 dose level. Refer to Table 6-2 for dosing schedule. • Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 481 ms

Grade	Dose Modification
Grade 3 QTc ≥ 501 ms on at least two separate ECGs	<p>Interrupt LEE011/placebo.</p> <ul style="list-style-type: none"> Transmit ECG immediately and confirm prolongation/abnormalities with central assessment. <p>Perform a repeat ECG within one hour of the first QTcF of ≥501 ms.</p> <ul style="list-style-type: none"> If QTcF remains ≥ 501 ms, consult with a cardiologist (or qualified specialist) and repeat cardiac monitoring as clinically indicated until the QTcF returns to < 481 ms. If QTcF returns to < 481 ms, LEE011/placebo will be reduced by 1 dose level. Refer to Table 6-2 for dosing schedule. Repeat ECGs 7 days and 14 days after dose resumption (then as clinically indicated) for any patients who had therapy interrupted due to QTcF ≥ 501 ms If QTcF of ≥ 501 ms recurs, discontinue LEE011/placebo.
Grade 4* [QT/QTc ≥ 501 or > 60 ms change from baseline] and [Torsades de pointes or polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia]	<p>Discontinue LEE011/placebo.</p> <ul style="list-style-type: none"> Obtain local cardiologist (or qualified specialist) consultation and repeat cardiac monitoring as indicated until the QTcF returns to <481 ms
*All values refer to the average of triplicate measurements	

6.3.1.7 Guidance for all other adverse reactions

Consider performing an analysis of serum potassium, calcium, phosphorus, and magnesium for all adverse reactions, if indicated. If electrolyte values are outside of the normal range, interrupt LEE011/placebo administration, correct electrolytes with supplements or appropriate therapy as soon as possible, and repeat electrolyte testing until documented normalization of the electrolytes.

Table 6-6 LEE011/placebo dose adjustment and management recommendation for all other adverse reactions

Grade	Dose Adjustment and Management Recommendations
1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
2	<p>Dose interruption until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Re-initiate LEE011/placebo at the same dose.</p> <ul style="list-style-type: none"> If the same toxicity recurs at grade 2, interrupt LEE011/placebo until recovery to grade ≤1. Re-initiate LEE011/placebo at the next lower dose level.
3	<p>Dose interruption until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Re-initiate LEE011/placebo at the next lower dose level.</p> <ul style="list-style-type: none"> If toxicity recurs at grade 2: temporary dose interruption until recovery to grade ≤1 and reduce LEE011/placebo dose the next lower dose level. If toxicity recurs at grade 3, discontinue LEE011/placebo.
4	Discontinue LEE011/placebo and treat with appropriate medical therapy.

6.3.1.7.1 Adjustment of starting dose in special populations

Renal impairment

Insufficient data are available to provide a dosage recommendation for LEE011 in patients with renal impairment. Based on rat ADME data, LEE011 was predominantly excreted in the bile as metabolites, with limited excretion of unchanged drug in urine. A human ADME is ongoing to confirm the metabolic and excretion pathways of LEE011 in humans.

Increases in tamoxifen serum concentrations did not occur in a 51 year-old woman with renal impairment who received tamoxifen for metastatic breast cancer, however further studies are lacking ([Sutherland 1984](#)).

Studies with goserelin in female patients with renal impairment do not indicate a need for dose adjustment with the use of the depot formulation ([Zoladex® Prescribing Information AstraZeneca](#)).

Renal impairment does not affect letrozole or anastrozole PK in humans ([Femara® Prescribing Information Novartis](#), [Arimidex® Prescribing Information AstraZeneca](#)).

Patients with baseline renal impairment or with AST/ALT or bilirubin values beyond certain thresholds as specified in the eligibility criteria are excluded from the study. Patients who experience renal impairment of grade 2 or higher during the treatment period should discontinue treatment and should be followed for safety assessments.

6.3.2 Follow-up for toxicities

Patients who complete treatment or whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event. All patients will be followed up for safety up to 30 days following the last dose of study treatment (tamoxifen or a NSAI + goserelin + LEE011/placebo).

6.3.3 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria, as well as specific dose modification and stopping rules are included in this protocol. Refer to [Section 6.3.1](#) for details.

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheal are allowed.

The patient must be told to notify the investigational site about any new medications she takes after the start of the study treatment. All medications (other than study drugs) and significant non-drug therapies (including vitamins, physical therapy and blood transfusions) administered within 30 days of study entry and during the study must be listed on the Concomitant medications/Significant non-drug therapies eCRF.

6.4.1.1 Bisphosphonates and denosumab

Bisphosphonates and denosumab are generally allowed with the following comments:

- Chronic concomitant bisphosphonate/denosumab therapy for the prevention of bone metastasis is not permitted.
- Bisphosphonate/denosumab therapy for the treatment of osteoporosis is permitted.
- Bisphosphonate/denosumab therapy for the prevention of skeletal related events for patients with bone metastases is permitted.
- If bisphosphonate/denosumab therapy is to be started after the first dose of study drug, prior consultation and approval by Novartis is required and the reason for its use must be clearly documented.

Patients taking concomitant medication chronically should be maintained at the same dose and dose schedule throughout the study period, as medically feasible. The days of full PK blood sampling should be representative of the other study days with regard to the use of the chronically administered concomitant medications. [REDACTED]

6.4.1.2 Corticosteroids

Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to lead to induction of CYP3A enzymes, thereby potentially increasing the risk of reducing LEE011 drug exposure to sub-therapeutic levels. Systemic corticosteroid treatment should not be given during the study, except for:

- Topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops or local injections (e.g., intra-articular);
- A short duration (< 5 days) of systemic corticosteroids \leq to the anti-inflammatory potency of 4 mg dexamethasone (e.g. for chronic obstructive pulmonary disease, or as an antiemetic)

6.4.1.3 Hematopoietic growth factors

Hematopoietic growth factors may be used according to ASCO guidelines.

6.4.1.4 Palliative radiotherapy

Palliative radiation is permitted. It should not be delivered to a target lesion and it should not encompass more than 25% of the irradiated bone marrow (See [Appendix 4](#)). If palliative radiotherapy is initiated after start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be ruled out.

No dose modification of study treatment is mandated during palliative radiotherapy.

Refer to the [LEE011 Investigator's Brochure], tamoxifen package insert, goserelin package insert, letrozole and anastrozole package inserts, and [Appendix 1](#) for information on possible interactions with other drugs.

6.4.2 Concomitant therapy requiring caution

Medications to be used with caution during combined LEE011, tamoxifen/NSAI, and goserelin treatment in this study (see [Table 14-2](#) in [Appendix 1](#)) are listed below. These medications should be excluded if possible. If they must be given based on the investigator's judgment, then use with caution and consider a LEE011/placebo interruption if the concomitant medication is only needed for a short time:

- Moderate inhibitors or inducers of CYP3A4/5
- Sensitive substrates of CYP3A4/5 that do not have narrow therapeutic index
- Strong inhibitors of BSEP
- Sensitive substrates of the renal transporters, MATE1 and OCT2
- Sensitive substrates of BCRP
- Medications that carry a possible risk for QT prolongation
- Substrates metabolized predominantly by CYP2C9 or CYP2D6 with a narrow therapeutic index (that could be affected by tamoxifen)
- Substrates metabolized predominantly by CYP2C19 or CYP2A6 with a narrow therapeutic index (that could be affected by letrozole)

6.4.3 Prohibited concomitant therapy

The following medications are prohibited during combined LEE011, tamoxifen/NSAI, and goserelin treatment in this study ([Table 14-1](#) in [Appendix 1](#)):

- Strong inhibitors or inducers of CYP3A4/5
- Substrates of CYP3A4/5 with a narrow therapeutic index
- Medications with a known risk for QT prolongation
- Additionally, for patients receiving tamoxifen: strong inhibitors or inducers of CYP2D6 (that could affect tamoxifen exposure)
- Warfarin and coumarin derivatives
- Other investigational and antineoplastic therapies
- Herbal medications/preparations and dietary supplements (except for vitamins) including but not limited to: St. John's wort, Kava, ephedra (ma huang), ginkgo biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh and ginseng. Patients should stop using all herbal medications and dietary supplements at least 7 days prior to first dose of study treatment.

6.4.4 Drugs with QT prolongation

As far as possible, avoid co-administration of QT prolonging drugs or any other drugs with the potential to increase the risk of drug-related QT prolongation (e.g., via a potential DDI that increases the exposure of LEE011 or the exposure of the QT prolonging drug). A definitive list of drugs with a known risk, possible risk, or conditional risk of QT prolongation and/or Torsades de Pointes (TdP) is available online at [//qtdrug.org](http://qtdrug.org).

Medications with a known risk for QT prolongation are prohibited during study treatment.

6.4.5 Concomitant medications associated with menopausal status

It is important to consider potential drug-drug interactions when using concomitant medications associated with hot flushes and other anticipated symptoms associated with this indication/use of endocrine therapy. Please refer to [Table 14-1](#) in [Appendix 1](#) for further information on prohibited concomitant medications.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.) that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface at that location.

The investigator or designated staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to be randomized or start treatment for any reason, the reason will be entered into the Screening Disposition page.

IRT must be notified within 2 days that the patient was not randomized.

6.5.2 Treatment assignment or randomization

Patients will be randomized to one of the **two** treatment arms ([Section 4.1](#) and [Section 6.1](#)) in a ratio of 1:1.

Randomization will be stratified by the following factors:

1. Lung or liver metastases: (yes versus no)
2. Prior chemotherapy for advanced disease: (yes versus no)
3. Endocrine combination partner (tamoxifen and goserelin versus NSAI (letrozole or anastrozole) and goserelin)

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study treatments.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will call or log on to the

IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

6.5.3 Treatment blinding

This is a double blind study. In particular, patients, investigators, study team, or anyone involved in the study conduct will remain blinded to the identity of the treatment from the time of randomization until database lock. The local (or Novartis-designated) radiologists will remain blinded to the identity of the treatment from the time of randomization until final database lock.

Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible to anyone involved in the conduct of the study. The identity of the treatments will be concealed by the use of investigational drugs (LEE011 or LEE011 matching placebo) that are identical in packaging, labeling, schedule of administration and in appearance. Confidentiality of randomization data is required to limit the occurrence of potential bias arising from the influence that the knowledge of treatment may have on the recruitment and allocation of patients.

Unblinding of study drug assignment will only occur for safety reasons in the case of patient emergencies ([Section 8.3](#)), for regulatory reporting purposes and at the conclusion of the study.

In rare cases when unblinding occurs because of safety reasons for emergency patient management, the actual treatment arm will not be communicated to any of the Novartis employees involved in running the trial in order to remain blinded.

An independent statistical group (external to Novartis), not involved in the trial conduct, will prepare data reports for the DMC. [REDACTED]

[REDACTED] Details will be presented in the DMC charter.

6.6 Study drug preparation and dispensation

Patients will be provided with an adequate supply of study drug for self-administration at home, including instructions for administration, until at least their next scheduled study visit. Patients will receive LEE011/placebo on an outpatient basis. The investigator shall provide the patient with instructions for LEE011/placebo administration according to the protocol.

Tamoxifen, letrozole, anastrozole, and goserelin should be dispensed according to local prescribing information and practice.

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

6.6.1 Study drug packaging and labeling

The study medication packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the treatment arms and a [specific visit or dose/dose level]. Responsible site personnel will identify the study treatment package(s) to dispense to the patient by using the IRT and obtaining the medication number(s). Site personnel will add the patient number on the label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient’s unique patient number.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug and the medication number but no information about the patient.

Table 6-7 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
LEE011/placebo	Capsules in bottles	Study treatment packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the two treatment arms.
Tamoxifen	Refer to local product information	Refer to local product information
Anastrozole	Refer to local product information	Refer to local product information
Letrozole	Refer to local product information	Refer to local product information
Goserelin	Refer to local product information	Refer to local product information

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the **study treatment** should be stored according to the instructions specified on the drug labels and in the [Investigator’s Brochure].

Table 6-8 Supply and storage of study treatments

Study treatments	Supply	Storage
LEE011/ placebo	Centrally supplied by Novartis	Refer to study treatment label
Tamoxifen	Locally	Refer to local product information
Letrozole	Locally	Refer to local product information
Anastrozole	Locally	Refer to local product information
Goserelin	Locally	Refer to local product information

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

Compliance will be assured by administrations of the study treatment under the supervision of investigator or his/her designee, and will be verified by determinations of LEE011, tamoxifen, NSAIs and goserelin in plasma.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.6.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. Study drug destruction at the investigational site will only be permitted if authorized by Novartis in a prior agreement and if permitted by local regulations.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an “X”, the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation. The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) (“Category” column). Allowed visit windows are specified as follows:

- There will be no visit window for Cycle 1 Day 1.
- A general +/-3 day window is permitted on assessments to take into account scheduling over public holidays, if not explicitly specified otherwise. Restrict the use of windows before Cycle 3 Day 16 when feasible.
- [REDACTED]
- Radiological assessments must be performed as outlined in Table 7-1. A visit window of +/- 7 days is allowed (The whole body bone scan should be performed within 42 days or 6 weeks prior to randomization).
- Vital signs, physical exam, ECOG performance status, hematology, biochemistry, INR, lipid panel, and urinalysis should be performed within 14 days of randomization.

Note: If the physical examination, ECOG performance status, and/or laboratory screening assessments were performed ≤ 7 days prior to the first dose of LEE011/placebo, then they do not need to be repeated on Cycle 1 Day 1.

- [REDACTED]
- A +/- 7 day window is permitted on the ECHO/MUGA scans.
- [REDACTED]
- Collection of FSH and/or estradiol (if necessary for determining pre-menopausal status for eligibility) and serum pregnancy test (β -hCG) (unless the patient has had a hysterectomy) must occur within 28 days before starting study treatment.

All other screening assessments must be completed within 28 days before randomization. Every effort should be made to follow the schedule outlined in [Table 7-1](#).

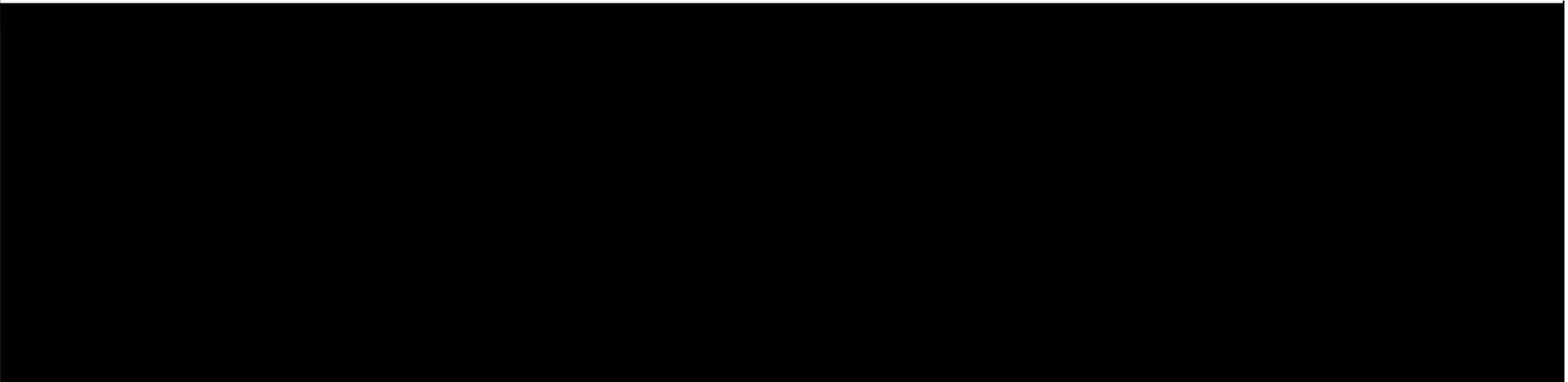
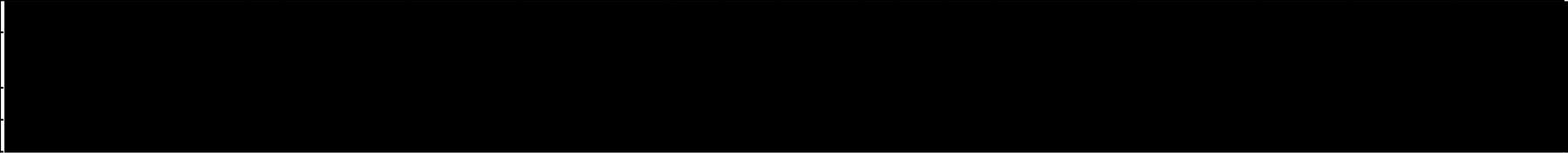
Visit name	Category	Reference to Protocol Section	Screening Phase		Treatment Phase								Post-treatment Phase		
			Screening		Cycle 1	Cycle 2	Cycle 3	Subsequent cycles	End of study treatment (EOT) within 15 days from the last dose	Safety follow up EOT + 30 days	Efficacy Follow up	Survival Follow up (Every 12 weeks)			
Treatment days			-28 to -1	-14 to -1	1	15	1	1	15	16	1				N/A
Prior antineoplastic therapy	D	7.1.2.3	x												
Prior / concomitant medication	D	7.1.2.3	Continuous – up to 30 days after last dose												
Randomization															
Eligibility checklist (within IRT)	S	7.1.2.1			x										
IRT – randomization	D	7.1.2			x										
Physical Examination															
Physical examination	S	7.2.2.1	x	(x)	x	x	x				x	x			
Performance status (ECOG)	D	7.2.2.4	x	(x)	x	x	x	x			x	x			
Height	D	7.2.2.3	x												
Weight	D	7.2.2.3	x			x	x				As clinically indicated	x			
Vital signs	D	7.2.2.2	x		x	x	x	x	x		x	x			
Laboratory assessments															
Hematology	D	7.2.2.5.1	x	(x)	x	x	x	x	x		x	x			
Biochemistry (including fasting glucose)	D	7.2.2.5.2	x	(x)	x	x	x	x	x		x	x			

Visit name	Category	Reference to Protocol Section	Screening Phase		Treatment Phase								Post-treatment Phase		
			-28 to -1	-14 to -1	Cycle 1	Cycle 2	Cycle 3	Subsequent cycles	End of study treatment (EOT) within 15 days from the last dose	Safety follow up EOT + 30 days	Efficacy Follow up	Survival Follow up (Every 12 weeks)			
Treatment days			-28 to -1	-14 to -1	1	15	1	1	15	16	1				N/A
Fasting Lipid panel	D	7.2.2.5.2		x							Every fourth cycle	x			
FSH (Local at screening for eligibility)	S	5.2	x												
FSH	D	7.2.2.5.5			x						Every fourth cycle				
Plasma estradiol (Local at screening for eligibility)	S	5.2	x												
Coagulation	D	7.2.2.5.3		x			x		x		x	x			
Urinalysis	D	7.2.2.5.4		x			x	x			x	x			
Tumor Assessment															

Visit name	Category	Reference to Protocol Section	Screening Phase		Treatment Phase							Post-treatment Phase		
			Cycle 1	Cycle 2	Cycle 3	Subsequent cycles	End of study treatment (EOT) within 15 days from the last dose	Safety follow up EOT + 30 days	Efficacy Follow up	Survival Follow up (Every 12 weeks)				
Treatment days			-28 to -1	-14 to -1	1	15	1	1	15	16	1			N/A
Tumor Assessment	D	7.2.1.1	x		Every 8 weeks during the first 18 months and every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, subject/guardian decision, and at EOT (If PR/CR is reported, confirmation of response is required; confirmatory assessment should be performed ≥ 4 weeks after response is first documented.)							x		
Fluid/Tissue collection results (if available)	D	7.2.1	As clinically indicated until disease progression											
Whole body bone scan	D	7.2.1	x (within 42 days prior to randomization)	As clinically indicated										
Safety														
Triplicate ECG (standard 12-lead)	D	7.2.2.7.1	x	x	x	x	x	x			x For all cycles up to Cycle 6	x		
ECHO or MUGA with EF	D	7.2.2.7.2	x	As clinically indicated							x			
Serum Pregnancy Test (Central or Local)	D	7.2.2.5.5	x											
Urine Pregnancy test	D	7.2.2.5.5		x		x	x				x	x		
Concomitant medications/procedures	D	6.4	x	Continuous							x	x		

Visit name	Category	Reference to Protocol Section	Screening Phase		Treatment Phase							Post-treatment Phase			
			-28 to -1	-14 to -1	Cycle 1	Cycle 2	Cycle 3	Subsequent cycles	End of study treatment (EOT) within 15 days from the last dose	Safety follow up EOT + 30 days	Efficacy Follow up	Survival Follow up (Every 12 weeks)			
Treatment days			-28 to -1	-14 to -1	1	15	1	1	15	16	1				N/A
Adverse events	D	8	x		Continuous							x	x		
End of Phase Disposition	D	7										x		x	

Visit name	Category	Reference to Protocol Section	Screening Phase		Treatment Phase							Post-treatment Phase		
			Screening	Screening	Cycle 1	Cycle 2	Cycle 3	Subsequent cycles	End of study treatment (EOT) within 15 days from the last dose	Safety follow up EOT + 30 days	Efficacy Follow up	Survival Follow up (Every 12 weeks)		
Treatment days			-28 to -1	-14 to -1	1	15	1	1	15	16	1			N/A



Visit name	Category	Reference to Protocol Section	Screening Phase		Treatment Phase							Post-treatment Phase		
			Screening	Screening	Cycle 1	Cycle 2	Cycle 3	Subsequent cycles	End of study treatment (EOT) within 15 days from the last dose	Safety follow up EOT + 30 days	Efficacy Follow up	Survival Follow up (Every 12 weeks)		
Treatment days			-28 to -1	-14 to -1	1	15	1	1	15	16	1			N/A
Patient Reported Outcome														
EORTC QLQ-C30	D	7.2.6	x		Every 8 weeks during the first 18 months and every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, subject/guardian decision and at EOT and safety follow-up							x		
EORTC QLQ-BR23	D	7.2.6	x		Every 8 weeks during the first 18 months and every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, subject/guardian decision and at EOT and safety follow-up							x		
EQ-5D-5L	D	7.2.6	x		Every 8 weeks during the first 18 months and every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, subject/guardian decision and at EOT and safety follow-up							x		

7.1.1 Molecular pre-screening

Not applicable.

7.1.2 Screening

After signing the study ICF, the screening assessments will be done within 1 to 28 days prior to randomization or within 1 to 14 days prior to randomization for selected assessments (see [Table 7-1](#) for list of assessments to be performed).

Note: Any screening assessment that is done outside the screening window (Day -28 to Day -1 or Day -14 to Day -1 as applicable) must be repeated prior to randomization.

Re-screening of patients is only allowed once per patient if the patient was not registered as entering the treatment phase before (i.e. IRT randomization). In this case the Subject No assigned to the patient initially will be used and the patient will be identified with this number throughout her entire participation to the study.

For laboratory evaluations used to determine eligibility, a repeated evaluation within the screening window is permitted for screening results out of the defined range before screen failing the patient. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. If the repeated laboratory result does not meet the criteria, the patient will be considered a screening failure. In case rescreening occurs, all evaluations re-assessed should meet the eligibility criteria. A new informed consent form must be signed only if there is an interruption in the patient's eligibility evaluation and the investigator chooses to re-screen the patient following screen failure; the 28 day screen period does not apply to the informed consent process. If a new informed consent form is signed, adverse events and medical history will be assessed relative to the new informed consent date.

Assessments of patient reported outcomes should be collected prior to any clinical assessments, drug dosing or diagnostic testing.

Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to randomization, including before signing the main study ICF can be considered as the baseline images for this study.

7.1.2.1 Eligibility screening

Following registering in the IRT for screening, patient eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

7.1.2.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Phase Disposition Page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient

experienced a Serious Adverse Event during the Screening Phase (see [Section 8](#) for SAE reporting details).

7.1.2.3 Patient demographics and other baseline characteristics

The data that will be collected on patient characteristics at screening includes:

- Demography (Date of birth and initials (where permitted), sex, race, ethnicity, source of patient referral)
- Diagnosis and extent of cancer (including staging at study entry and histology/cytology)
- Medical history (e.g., important medical, surgical, and allergic conditions from the patient's medical history which could have an impact on the patient's evaluation) / current medical conditions (e.g., all relevant current medical conditions which are present at the time of signing informed consent). Ongoing medical conditions, symptoms and disease which are recorded on the Medical History eCRF should include the toxicity grade.
- ER, PgR and HER2 status
- All prior antineoplastic therapies including surgical interventions and chemo-, biologic-, immunologic- and radiation-therapies provided as treatment for cancer prior to the administration of study drug.
- All medications and significant non-drug therapies taken within 30 days before the first dose is administered. They must be recorded on the Prior and Concomitant medication or Surgical and medical procedures eCRF page and updated on a continual basis if there are any new changes to the medications.
- Patient-reported outcome questionnaires (EORTC QLQ-C30, EORTC QLQ-BR23, EQ-5D-5L, [REDACTED] (See [Section 7.2.6](#)).

Furthermore the following assessments will be performed:

- Vital signs
- Height, weight
- Physical examination
- Performance status (ECOG)
- Laboratory evaluations (hematology, , INR, chemistry, lipid panel, urinalysis)
- ECG
- ECHO/MUGA
- Radiological assessments (e.g. CT Scan)

7.1.3 Run-in period

Not applicable.

7.1.4 Treatment period

Patients will be treated with tamoxifen or a NSAID + goserelin + LEE011 **or** tamoxifen or a NSAID + goserelin + placebo until disease progression, unacceptable toxicity, withdrawal of consent by the patient, patient is lost to follow up, death, discontinuation from the study

treatment due to any other reason or the sponsor terminates the study. For details of assessments, refer to [Table 7-1](#).

7.1.5 End of treatment visit including study completion and study treatment discontinuation

Patients who completely discontinue study treatment should be scheduled for an End of Treatment (EOT) visit within 15 days following the date study treatment is permanently discontinued, at which time all of the assessments listed for the EOT visit will be performed. For details of assessments, refer to [Table 7-1](#). If the decision to discontinue the patient occurs at a regularly scheduled visit, that visit may become the EOT visit rather than having the patient return for an additional visit.

An End of phase disposition eCRF page should be completed, giving the date and reason for stopping the study treatment. If a withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the EOT eCRF page. The EOT visit is not considered the end of the study.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study treatment.

If a patient discontinues study treatment, but continues study assessments, the patient remains on study until such time as she completes protocol criteria for ending study assessments. At that time, the reason for study completion should be recorded on the End of Post Treatment Phase Disposition CRF page.

The Investigator must contact the IRT to register the subject's discontinuation.

7.1.5.1 Discontinuation of study treatment

Patients **may** voluntarily discontinue from the study treatment for any reason at any time.

If a patient decides to discontinue from the study treatment, the investigator must make reasonable effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Patients may be withdrawn from the study treatment if any of the following occur:

- Adverse Event (including, but not limited to QTcF \geq 501 msec, confirmed at repeated ECG measurements and recurrent after dose adjustment was performed; documented episode of ventricular tachycardia, or ventricular fibrillation)
- Lost to follow-up
- Physician decision
- Progressive Disease

- Protocol deviation
- Study terminated by sponsor
- Technical problems

Patients must be withdrawn from the study treatment if any of the following occur:

- Pregnancy
- Death
- Subject/Guardian decision

In addition to the general withdrawal criteria, the following study specific criteria will also require study treatment discontinuation:

- Adjustments to study treatment that result in discontinuation. Please refer to [Section 6.3](#).
- Use of prohibited medication. Please refer to [Section 6.4.3](#).

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in [Section 7.1](#). If they fail to return for these assessments for unknown reasons, reasonable effort (e.g. telephone, email, letter) should be made to contact them as specified in [Section 7.1.5](#).

Patients who discontinue study treatment should undergo an End of Treatment (EOT) visit followed by a 30 day safety follow-up.

7.1.5.2 Replacement policy

Not applicable.

7.1.6 Follow-up period

7.1.6.1 Safety follow-up

All patients will be followed up for safety up to 30 days after last dose of study treatment (tamoxifen/NSAI + goserelin + LEE011/placebo). Patients whose treatment is interrupted or permanently discontinued due to an AE, including abnormal laboratory value, must be followed until resolution or stabilization of the event, whichever comes first. This could include all study assessments appropriate to monitor the event.

7.1.6.2 Efficacy follow-up

For patients who discontinue treatment for reasons other than disease progression, death, lost to follow-up, or withdrawal of consent, tumor assessments (see [Section 7.2.1](#)) and selected patient reported outcomes (see [Section 7.2.6](#)) must continue to be performed every 8 weeks during the first 18 months and every 12 weeks thereafter until disease progression, death, lost to follow-up, or withdrawal of consent. At that time, the reason for study completion should be recorded on the End of Post treatment phase Disposition eCRF page. If a patient starts a new anti-cancer therapy prior to progression, tumor evaluations should continue with the same above schedule ([Table 7-1](#)) until disease progression is documented. In addition, all new anticancer therapies given after the last dose of the study drug, until disease progression, death, lost to follow-up, or withdrawal of consent will be recorded in the eCRFs.

7.1.6.3 Survival follow-up

All patients will be followed for survival status every 12 weeks (see [Section 4.1.5](#)) including documentation of the start of new antineoplastic therapy, until death, lost to follow-up, or withdrawal of consent. Additional survival assessments may be performed outside the 12 weeks follow up schedules if a survival update is required for an interim assessment to meet safety or regulatory needs.

Survival information can be obtained via phone, and information will be documented in the source documents and relevant eCRFs.

During the survival follow up, subsequent anti-neoplastic therapies initiated after study treatment discontinuation will be collected along with the start/end date and date of disease progression on subsequent therapies.

7.1.6.4 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow-up should be recorded as such on the appropriate Disposition CRF.

7.1.7 End of post-treatment follow-up visit

Prior to collecting survival follow-up information, the end of post treatment phase disposition eCRF page will be completed once a patient has discontinued study treatment, completed safety follow-up, and can no longer perform efficacy assessment.

End of post-treatment follow-up may occur for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Progressive disease
- Protocol deviation
- Study terminated by the sponsor
- Technical problems
- Subject/guardian decision
- Death

7.1.8 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow up.

7.2 Assessment types

7.2.1 Efficacy assessments

7.2.1.1 Imaging tumor assessments

Tumor response will be assessed locally and centrally according to the Novartis guideline version 3.2 ([Appendix 3](#)) based on RECIST Version 1.1 ([Eisenhauer et al 2009](#)). Further details regarding blinded independent review committee (BIRC) assessment will be provided in the BIRC charter. The central review of the scans will be carried out in a blinded fashion for a randomly selected subgroup of patients (see [Section 9.3.6](#)). The decision regarding patient management will remain with the local investigator.

Patients should have at least one documented measurable lesion (per RECIST v1.1) or in the absence of measurable disease, have at least one predominantly lytic bone lesion at study entry.

Imaging assessments will be performed at screening within 28 days prior to randomization and subsequently every 8 weeks following randomization during the first 18 months and every 12 weeks thereafter. See [Table 7-2](#) for details of assessments. The 8-week (or 12 week) interval should be respected regardless of whether study treatment is temporarily withheld.

After baseline, all assessments should be performed within ± 7 days of the scheduled day of assessment. The same method of assessment and the same technique should be used to characterize each individual and reported lesion at baseline and during follow up.

If a patient discontinues treatment for reasons other than radiological documentation of progression of disease, an efficacy assessment should be performed at the time of End of Treatment unless a CT/MRI for tumor measurement was performed within 21 days. Efficacy assessments should continue as per the scheduled visit per [Table 7-1](#) and [Table 7-2](#).

To the extent possible, each lesion should be assessed using the same imaging method throughout the study.

All patients will undergo CT or MRI of the chest, abdomen and pelvis at baseline and subsequent scheduled visits per [Table 7-1](#) and [Table 7-2](#). The preferred imaging methodology is CT with intravenous (i.v.) contrast. However, if at baseline, a patient is known to have a contraindication to CT i.v. contrast media or develops a contraindication during the trial, a non-contrast CT of chest (MRI is not recommended due to respiratory artifacts) plus contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.

A whole body bone scan according to institutional guidelines (e.g. Tc-99 bone scan, whole body bone MRI, FDG-PET or sodium fluoride positron emission tomography (NaF PET)) should be acquired at baseline for all subjects if not collected previously within 42 days (6 weeks) prior to randomization. Skeletal lesions identified on the whole body bone scan at baseline, which are not visible on the chest, abdomen and pelvis CT (or MRI) scan should be imaged at baseline and followed at scheduled visits using localized CT, MRI or x-ray. Whole body bone scans need not be repeated after baseline unless clinically indicated.

Color photography, including a metric ruler to estimate the size of the lesion, must be acquired for all **skin lesions** present at baseline per instructions provided in the manual from the designated vendor. These should be followed throughout the study according to the schedule outlined in [Table 7-2](#).

Other metastatic disease sites will be followed by CT or MRI, as clinically indicated.

Chest x-ray or ultrasound should not be used to assess tumor lesions. Partial Response (PR) and Complete Response (CR) must be confirmed by repeat assessments performed not less than 4 weeks and after the criteria for objective response are first met. In case tumor assessment is performed <8 weeks from the first assessment of an objective response to confirm PR/CR, subsequent tumor assessments should revert back to the protocol schedule outlined in [Table 7-1](#). Positron Emission Tomography (PET)/CT may be used only if the CT component is of similar diagnostic quality as a CT performed without PET, including the utilization of oral and i.v. contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document progressive disease per RECIST 1.1 ([Appendix 3](#)). If possible, a single radiologist should perform all tumor response evaluations for an individual patient. Any lesions in previously irradiated areas should not be considered measurable unless they have experienced progression since the radiotherapy. Any pre-existing radiographic findings which may mimic metastatic disease and any prior radiotherapy should be recorded in the eCRF.

Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to randomization (and 42 days for the whole body bone scan), including before signing the main study ICF can be considered as the baseline images for this study.

Results from tissue or body fluid collection should be recorded in the eCRF to complement radiographic findings.

All study imaging performed, including any intercurrent or off-schedule imaging studies acquired (e.g., to fulfill a progression or response criterion), should be submitted to the designated imaging CRO for quality control promptly after acquisition. If an off-schedule imaging assessment is performed to confirm response or if progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Physical exam tumor assessments, photography, pathology/histology and cytology results, as well as information regarding prior interventions, pre-existing radiographic findings that mimic metastatic disease at baseline/screening and on-study interventions should be captured in the appropriate eCRFs and may be transmitted to the imaging CRO for additional review if appropriate.

Table 7-2 Imaging collection plan

Procedure	Screening: day -28 to day -1	Treatment phase*	End of treatment*	Post-Treatment Phase
CT or MRI (Chest, Abdomen, Pelvis)	Mandated	Every 8 weeks during the first 18 months and every 12 weeks thereafter (+/- 7 days)	Mandated	Every 8 weeks during the first 18 months and every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, or subject/guardian decision (+/- 7 days)
Brain CT or MRI	Only if suspected brain metastases	Only if suspected brain metastases		
Whole body bone scan**	Mandated, within 42 days (6 weeks) prior to randomization.	As clinically indicated	As clinically indicated	As clinically indicated
Bone X-ray, CT or MRI	Only if skeletal abnormalities identified by whole body bone scan (or skeletal survey) at screening, which are not visible in the chest, abdomen, pelvis CT/MRI.	If bone lesion at screening, every 8 weeks during the first 18 months and every 12 weeks thereafter (+/- 7 days)	Mandated only if bone lesion at screening	If bone lesion at screening, every 8 weeks during the first 18 months and every 12 weeks thereafter (+/- 7 days)
Skin color Photography	Only if skin lesions at screening	If skin lesions at screening, every 8 weeks during the first 18 months and every 12 weeks thereafter (+/- 7 days)	Mandated if skin lesions at screening	If skin lesions at screening, every 8 weeks during the first 18 months and every 12 weeks thereafter (+/- 7 days)

Procedure	Screening: day -28 to day -1	Treatment phase*	End of treatment*	Post-Treatment Phase
CT or MRI of any disease outside of chest, abdomen and pelvis (e.g., neck)	Only if suspected lesion at screening	If lesion identified at screening, every 8 weeks during the first 18 months and every 12 weeks thereafter (+/- 7 days)	Mandated if lesion at screening	If lesion identified at screening, every 8 weeks during the first 18 months and every 12 weeks thereafter (+/- 7 days)
<p>*Tumor evaluation at EOT is required for patients who discontinue study treatment before the first scheduled post-baseline tumor assessment (week 8) and for patients whose previous tumor assessment did not demonstrate PD and was done more than 21 days prior to end of treatment visit.</p> <p>** Whole body bone scan according to institutional guidelines (e.g. Tc-99 bone scan, whole body bone MRI, sodium fluoride positron emission tomography (NaF PET) or fluorodeoxyglucose (FDG) PET.</p> <p>Note: All scans will be read locally and centrally.</p>				

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examinations, ECOG performance status, height and weight, vital signs, ECG, patient reported outcomes, laboratory assessments including hematology, chemistry, lipid panel, [REDACTED] and INR as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to [Section 8.3](#).

7.2.2.1 Physical examination

The physical examination comprises a total body examination that should include: general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph-nodes, extremities, vascular and neurological review. If indicated, rectal, external genitalia, breast and pelvis exams will be performed. Information about the physical examination must be present in the source documentation at the study site. Physical examination is to be performed according to the visit schedule as outlined in [Table 7-1](#).

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

7.2.2.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure) will be monitored as per the visit schedule (see [Table 7-1](#)). Blood pressure (systolic and diastolic) and pulse should be measured after the patient has been sitting for approximately five minutes.

7.2.2.3 Height and weight

Height and body weight will be measured as outlined in the visit schedule (see [Table 7-1](#)).

7.2.2.4 Performance status

The performance status will be assessed according to the ECOG performance status scale ([Table 7-3](#)) ([Oken 1982](#)) following the schedule given in [Table 7-1](#).

Table 7-3 ECOG performance status

Grade	ECOG status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work
2	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	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

7.2.2.5 Laboratory evaluations

Clinical laboratory analyses (Hematology, Chemistry, Coagulation, Urinalysis, Lipid Panel) are performed by the central laboratory. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. Visit windows of +/- 3 days are allowed for all visits except at Cycle 1 Day 1.

Novartis must be provided with a copy of the laboratory's certification (if applicable), and a tabulation of the normal ranges and units of each parameter collected in the eCRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the new effective date. Additionally, if at any time a patient has laboratory parameters obtained from a different (outside) laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well. The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

For assessment of patients' eligibility to the study, only laboratory results from the central laboratory will be used.

Unscheduled local laboratory assessments may be performed if medically indicated to document a (potential) adverse event or when the treating physician cannot wait for central laboratory results for decision making (e.g. dose modifications). In this particular situation, if possible, the blood sample obtained at the same time point should be submitted to the central laboratory for analysis in parallel with local analysis.

The results of the local laboratory will be recorded in the eCRF if any the following criteria are met:

- A treatment decision was made based on the local results, or
- There are no concomitant central results available, or
- Local lab results document an adverse event not reported by the central lab, or
- Local lab results document an adverse event where the severity is worse than the one reported by the central lab

At any time during the study, abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE eCRF page. Laboratory data will be summarized using the Common Terminology Criteria for Adverse events (CTCAE) version 4.0.3. Additional analyses are left to the discretion of the investigator.

Table 7-4 Central clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Complete blood count (CBC) including total white blood cell count (WBC) with differential (neutrophil count including lymphocyte, monocyte, eosinophil, and basophil counts) RBC, hemoglobin (Hgb), hematocrit (Hct), and platelet count.
Biochemistry (with fasting glucose)	Total proteins, albumin, total bilirubin, direct bilirubin, indirect bilirubin, AST, ALT, GGT, bicarbonate, calcium, corrected calcium, chloride, creatinine kinase, alkaline phosphatase, amylase, lipase, magnesium, sodium, potassium, urea or BUN, uric acid, serum creatinine, phosphorous, and fasting glucose
Fasting Lipid Panel	Total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides (fasting)
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) If there are any significant findings on the dipstick then a microscopic evaluation should be measured: Microscopic Panel (WBC and RBC sediments, Casts, Crystals, Bacteria, Epithelial cells)
Coagulation	INR
Other Test	FSH, [REDACTED]

7.2.2.5.1 Hematology

Hematology tests are to be performed according to the Visit Schedules outlined in [Table 7-1](#). For details of the Hematology panel refer to [Table 7-4](#). Note: If the laboratory screening assessments were performed ≤ 7 days prior to the first dose of LEE011/placebo, then they do not need to be repeated on Cycle 1 Day 1.

Hematology should be assessed on the scheduled day, even if study drug is being withheld.

7.2.2.5.2 Biochemistry

Biochemistry tests are to be performed according to the Visit Schedules outlined in [Table 7-1](#) and [Table 7-4](#). Note: If the laboratory screening assessments were performed ≤ 7 days prior to the first dose of LEE011/placebo, then they do not need to be repeated on Cycle 1 Day 1.

Biochemistry should be assessed on the scheduled day, even if study drug is being withheld.

7.2.2.5.3 Coagulation

INR is to be performed according to the Visit Schedules outlined in [Table 7-1](#). If the coagulation blood sample collected at screening is clotted when received by central laboratory for testing or the central laboratory results of only the coagulation are delayed, the patient is still eligible to enter the study with a local INR test ≤ 1.5 .

7.2.2.5.4 Urinalysis

Urinalysis is to be performed according to the Visit Schedules outlined in [Table 7-1](#) and [Table 7-4](#).

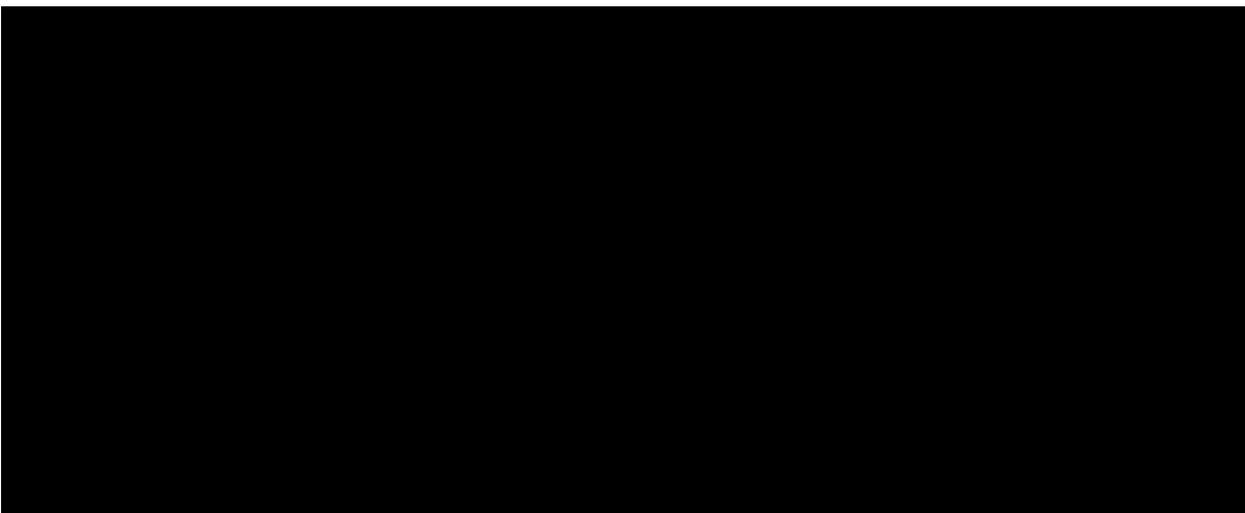
7.2.2.5.5 Additional laboratory tests

FSH, [REDACTED] and serum or urine pregnancy tests (patients who have undergone a hysterectomy do not need pregnancy tests performed) are to be performed according to the Visit Schedules outlined in [Table 7-1](#) and [Table 7-4](#). At screening, a serum pregnancy test should be performed regardless of the age of the patients, while at baseline, during the study, and at the end of trial, urinary pregnancy tests are sufficient.

FSH [REDACTED] will be collected locally at screening for eligibility, while during the study, FSH will then be collected by the central laboratory.

[REDACTED]

[REDACTED]

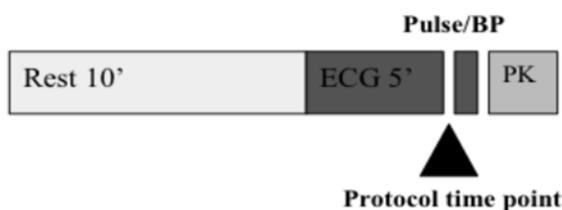


7.2.2.7 Cardiac assessments

7.2.2.7.1 Electrocardiogram (ECG)

Standard triplicate 12 lead ECG assessments will be performed after the patient has been resting for 5-10 minutes prior to each time point indicated in [Table 7-5](#) below. Triplicate ECGs should be taken approximately 2 minutes apart. The combined QTcF values from these triplicate ECGs will be averaged to provide a single value for each time point. Eligibility will be based on the average of the triplicate ECGs conducted at screening.

Timing of study procedures:



*ECG assessments are to be done prior [redacted]

Table 7-5 Central ECG collection plan

Cycle	Patients	Day	Time	ECG Type
Screening	All	-14 to -1	Anytime	Triplicate 12 Lead
1	All	Day 1	Pre-dose ¹	Triplicate 12 Lead
	All	Day 15 ²	Pre-dose ¹	Triplicate 12 Lead
	All		2 h post-dose (± 15 min)	Triplicate 12 Lead
	All		4 h post-dose (± 15 min)	Triplicate 12 Lead
2	All	Day 1	Pre-dose ¹	Triplicate 12 Lead
3	All	Day 1	Pre-dose ¹	Triplicate 12 Lead

Cycle	Patients	Day	Time	ECG Type
3	All	Day 15 ²	Pre-dose ¹	Triplicate 12 Lead
	All		2 h post-dose (± 15 min)	Triplicate 12 Lead
4	All	Day 1	Pre-dose ¹	Triplicate 12 Lead
5	All	Day 1	Pre-dose ¹	Triplicate 12 Lead
6	All	Day 1	Pre-dose ¹	Triplicate 12 Lead
			2h post-dose (± 15 min)	Triplicate 12 Lead
All other cycles ³	Patients with QTcF ≥ 481 ms at any time prior to cycle 7	Day 1	Pre-dose ¹	Triplicate 12 Lead
9 and every 3rd cycle ³	For patients with QTcF ≥ 481 ms at any time prior to cycle 7	Day 1	Pre-dose ¹	Triplicate 12 Lead
			2h post-dose (± 15 min)	Triplicate 12 Lead
EOT			Anytime	Triplicate 12 Lead
Unscheduled ECG			Anytime	Triplicate 12 Lead
¹ The exact date and time of dosing must be recorded on the appropriate eCRF. ² ECG assessments are to be done prior [REDACTED] (if applicable) ³ Pre-dose ECG on the first day of every cycle. Additionally, 2 h post-dose in every 3rd cycle (i.e. Cycle 9, 12, 15, 18, etc.)				

In order for an accurate evaluation of baseline QTcF, a total of three 12-lead ECGs will be performed pre-dose on Cycle 1 Day 1.

Note: In order to ensure ECG evaluation is received from the central laboratory for eligibility assessment, it is advisable to perform the ECG at least 24 hours prior the scheduled randomization date.

If any of the triplicate readings include an abnormal ECG or an average QTcF value of ≥ 481 is obtained at any time after randomization, study treatment must be interrupted, repeat ECG (triplicate) and follow management guidelines detailed in [Table 6-5](#).

An unscheduled ECG may be repeated at the discretion of the investigator at any time during the study and as clinically indicated. Unscheduled ECGs with clinically significant findings should be collected in triplicate. Local cardiologist ECG assessment may be performed at any time during the study at the discretion of the investigator.

All ECGs including unscheduled triplicate ECGs with clinically relevant findings, collected during the study should be transmitted to the central laboratory and will be centrally reviewed by an independent reviewer. The results of the centrally assessed ECGs are electronically transferred into the clinical database. Any original ECG not transmitted to a central laboratory should be forwarded for central review. Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant ECG abnormalities present at screening when the patient signed informed consent should be reported on the Medical History

CRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page.

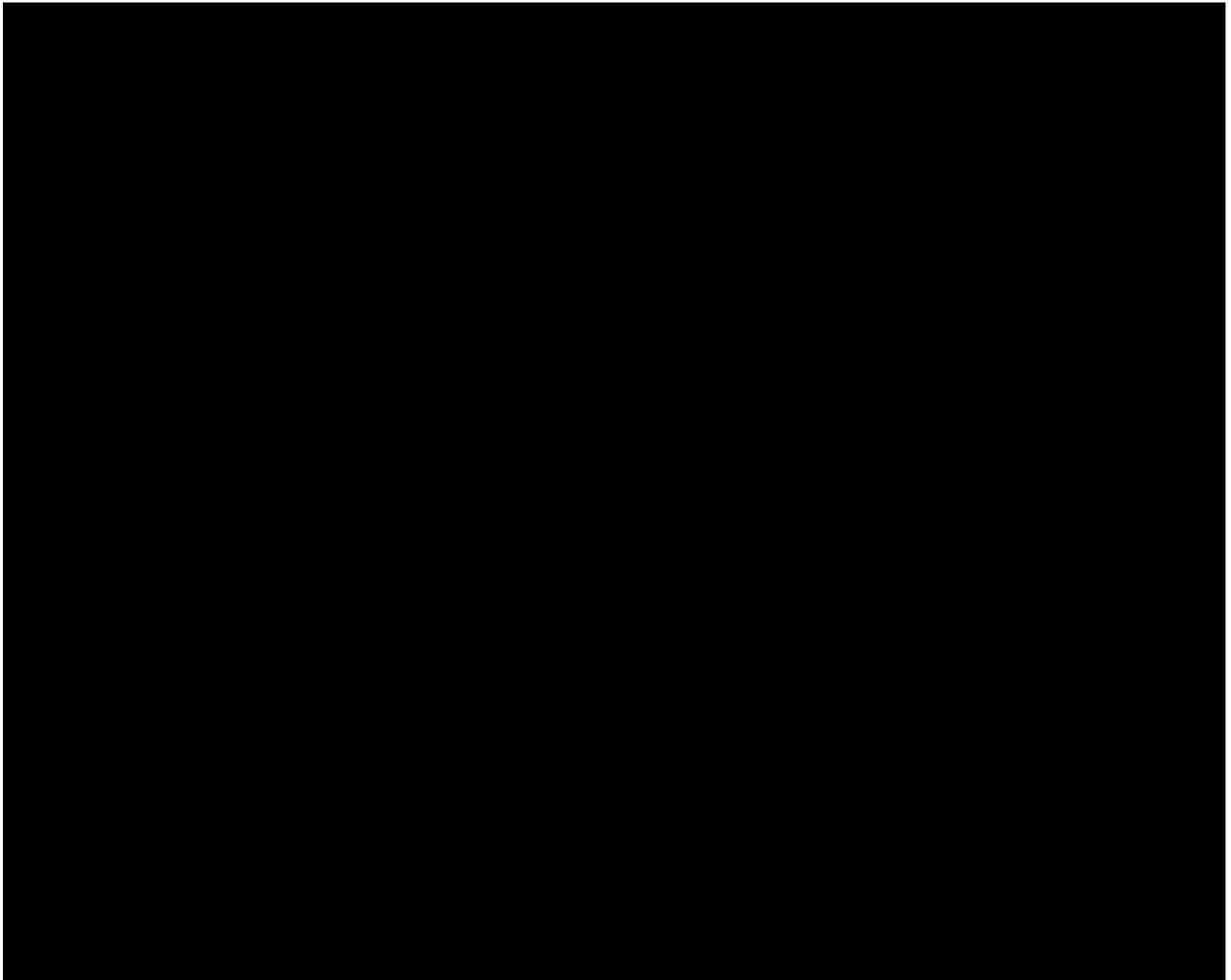
In the event that a QTcF value of > 500 ms is observed or if an unscheduled ECG is performed for safety reasons, [REDACTED] record the time and date of the last study drug intake to determine the drug exposure.

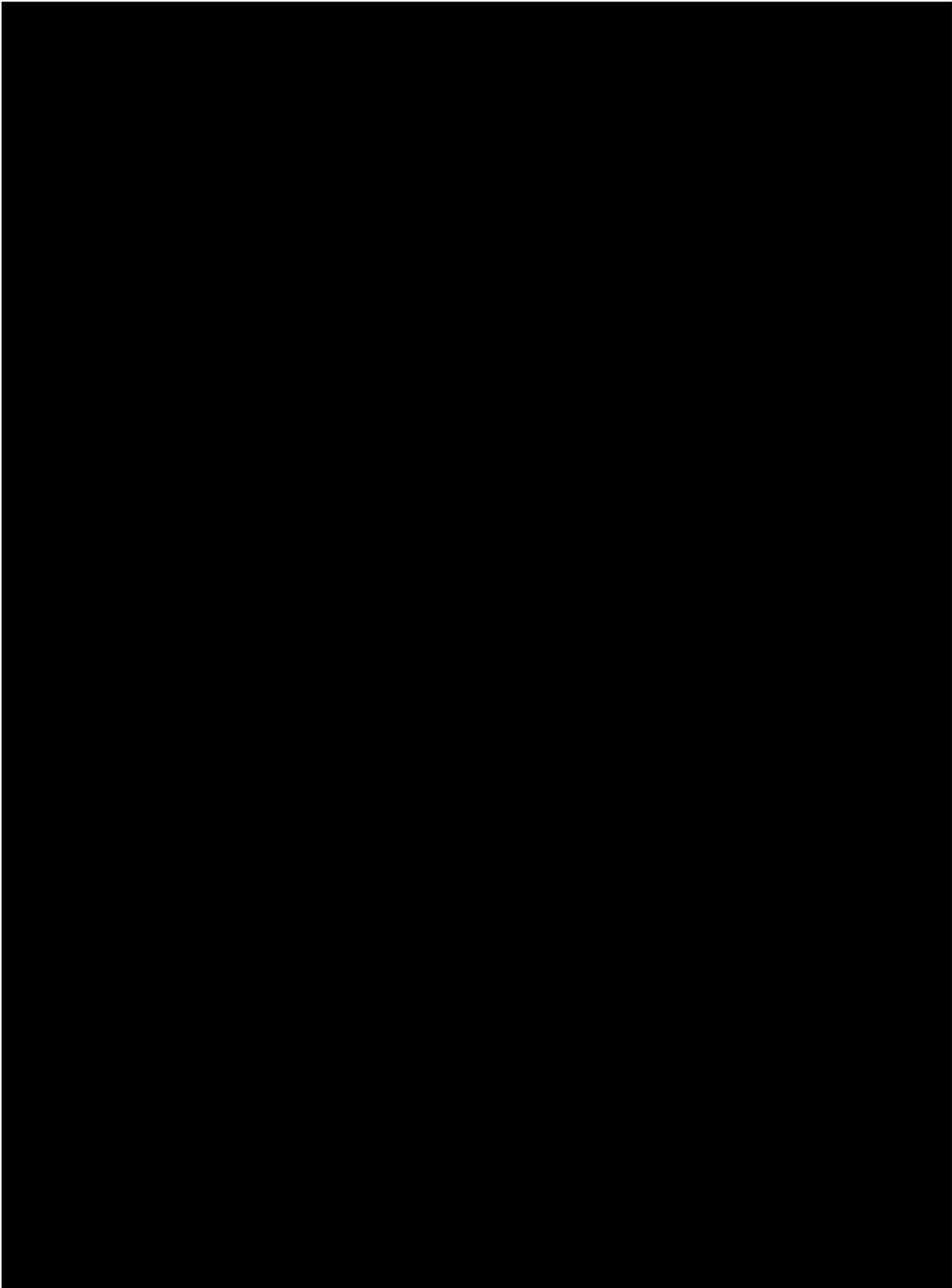
7.2.2.7.2 Cardiac imaging - MUGA (multiple gated acquisition) scan or echocardiogram

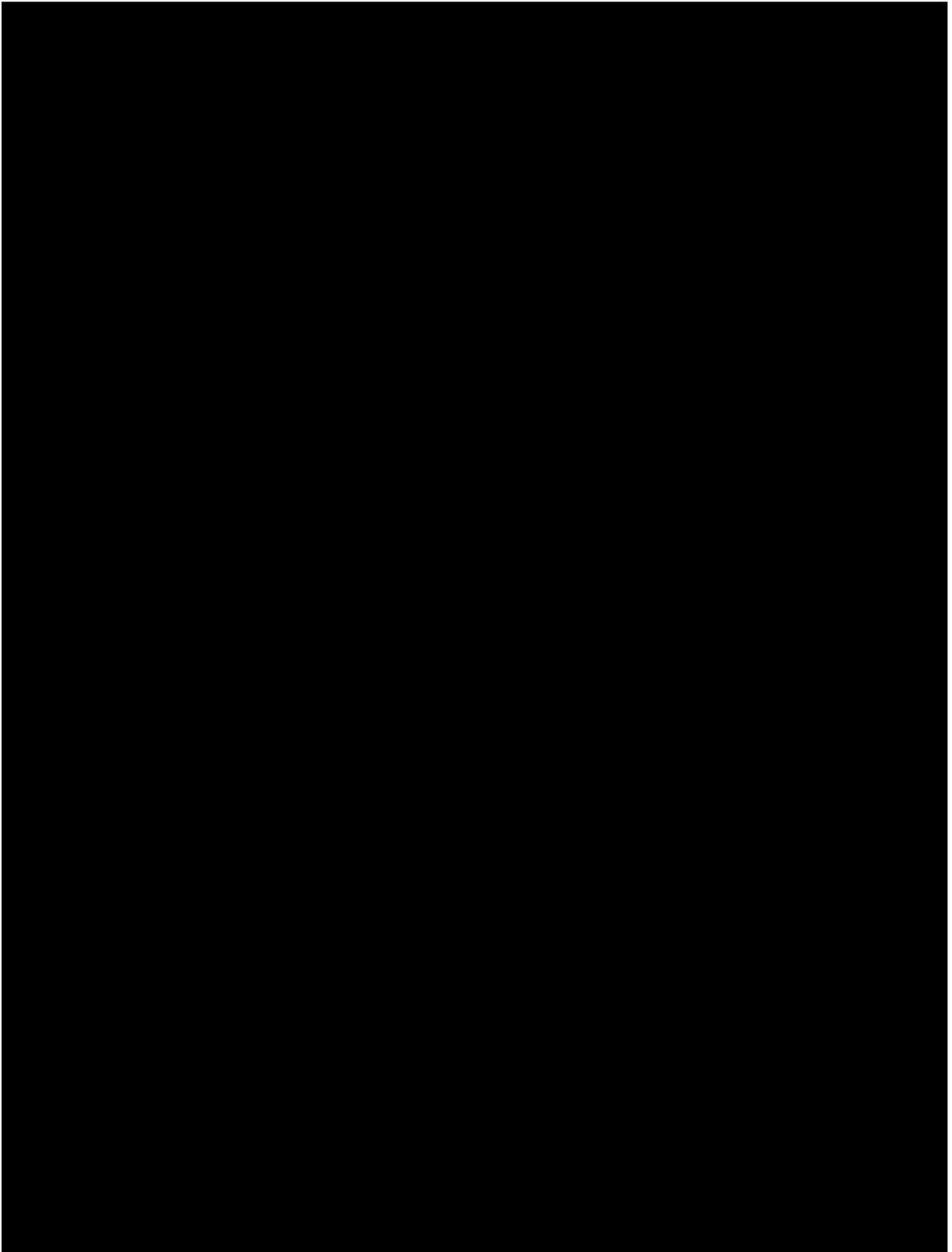
Cardiac imaging will be performed by Multiple Gated acquisition (MUGA) scan or Echocardiogram (ECHO) in order to assess the left ventricular ejection fraction (LVEF). This assessment will be performed according to the schedule given in [Table 7-1](#).

The same technique (MUGA or ECHO) must be used during the course of the trial, and the method used will be recorded in the eCRF. Only clinically significant abnormalities should be reported in the Adverse Events eCRF.

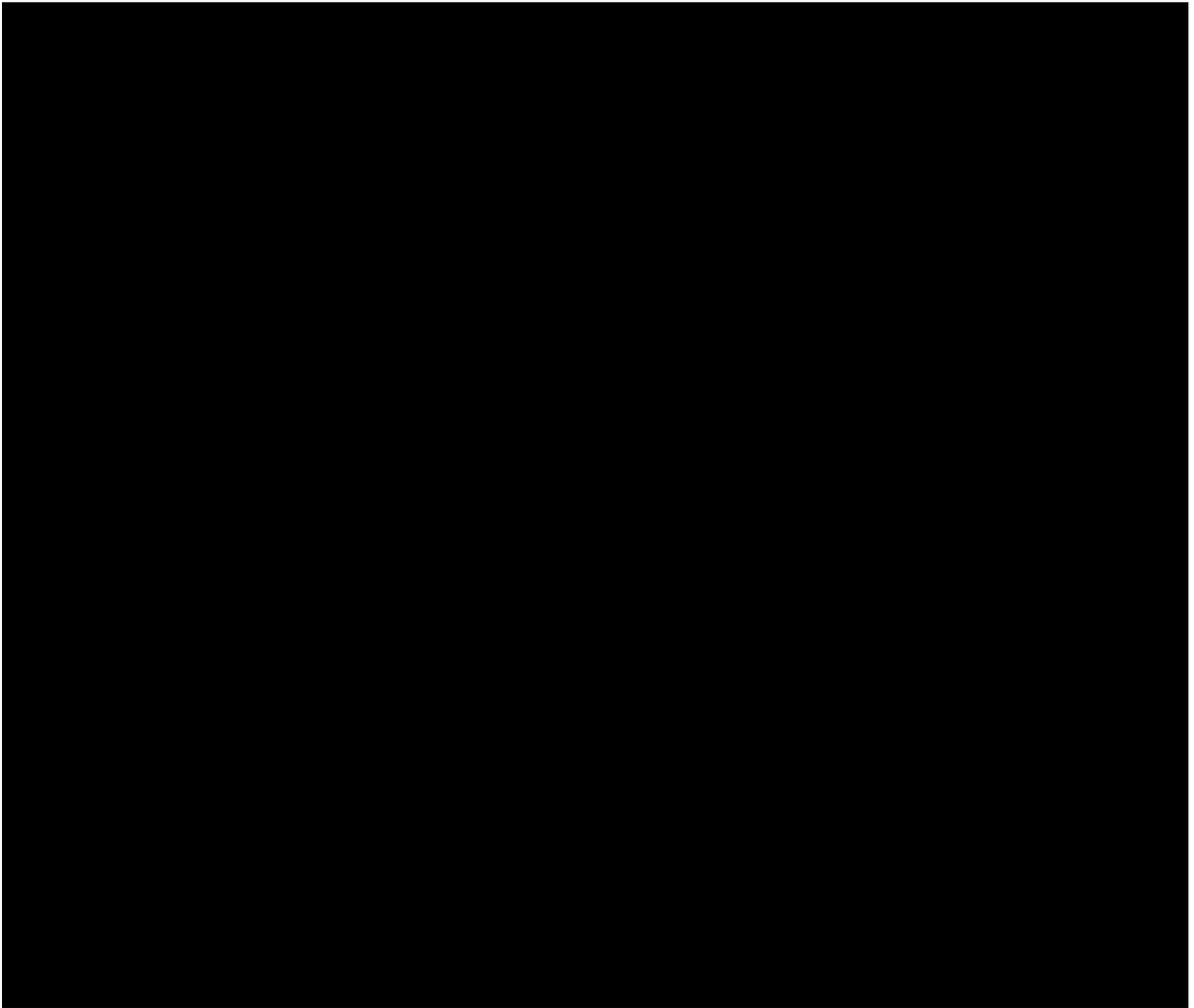
In case a patient develops left ventricular systolic dysfunction while on study treatment dose adjustment guidelines described in [Table 6-6](#) must be followed.

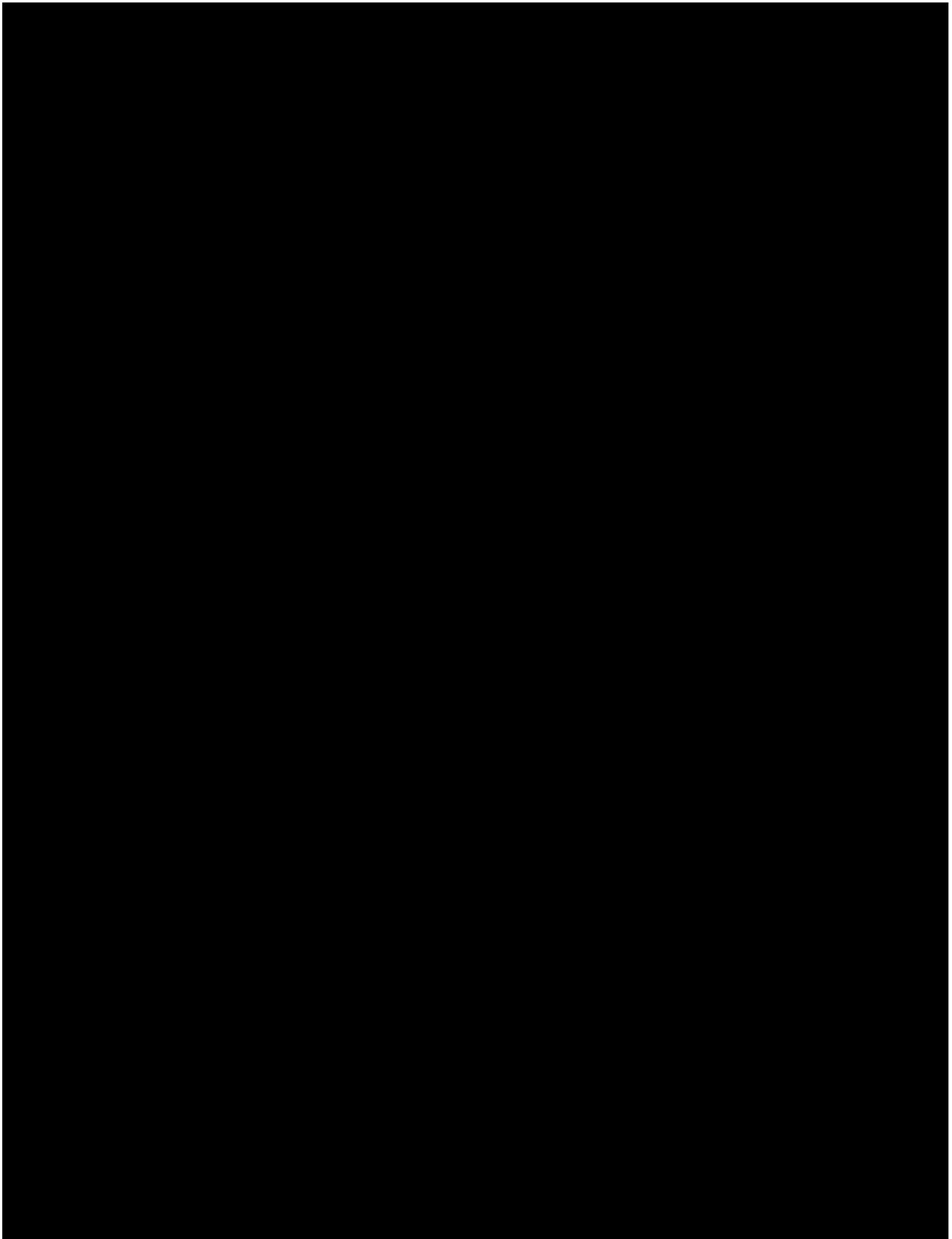


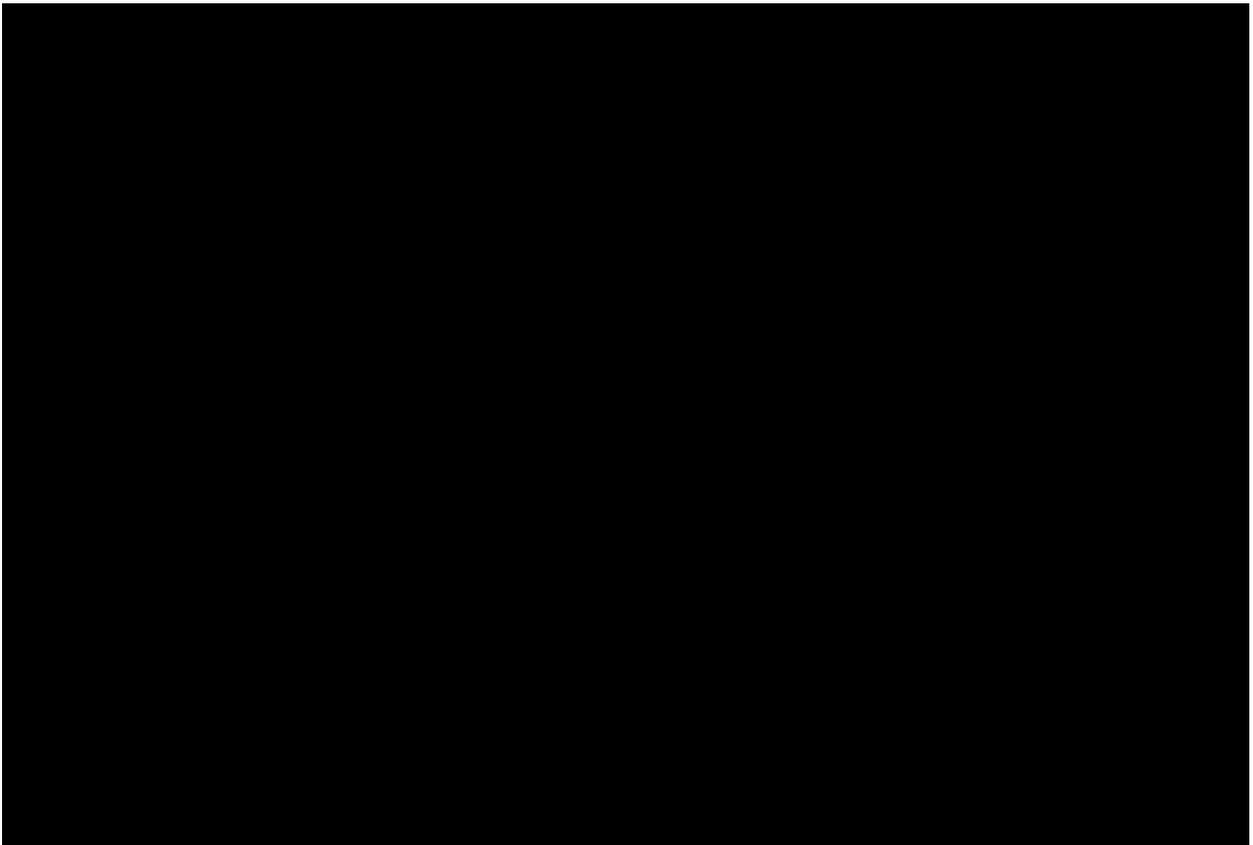








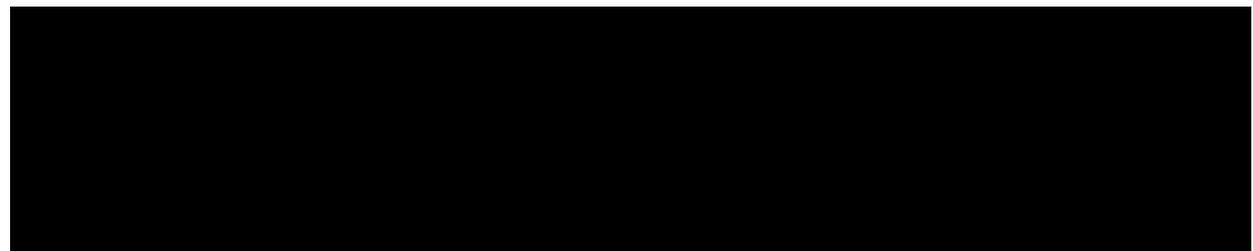


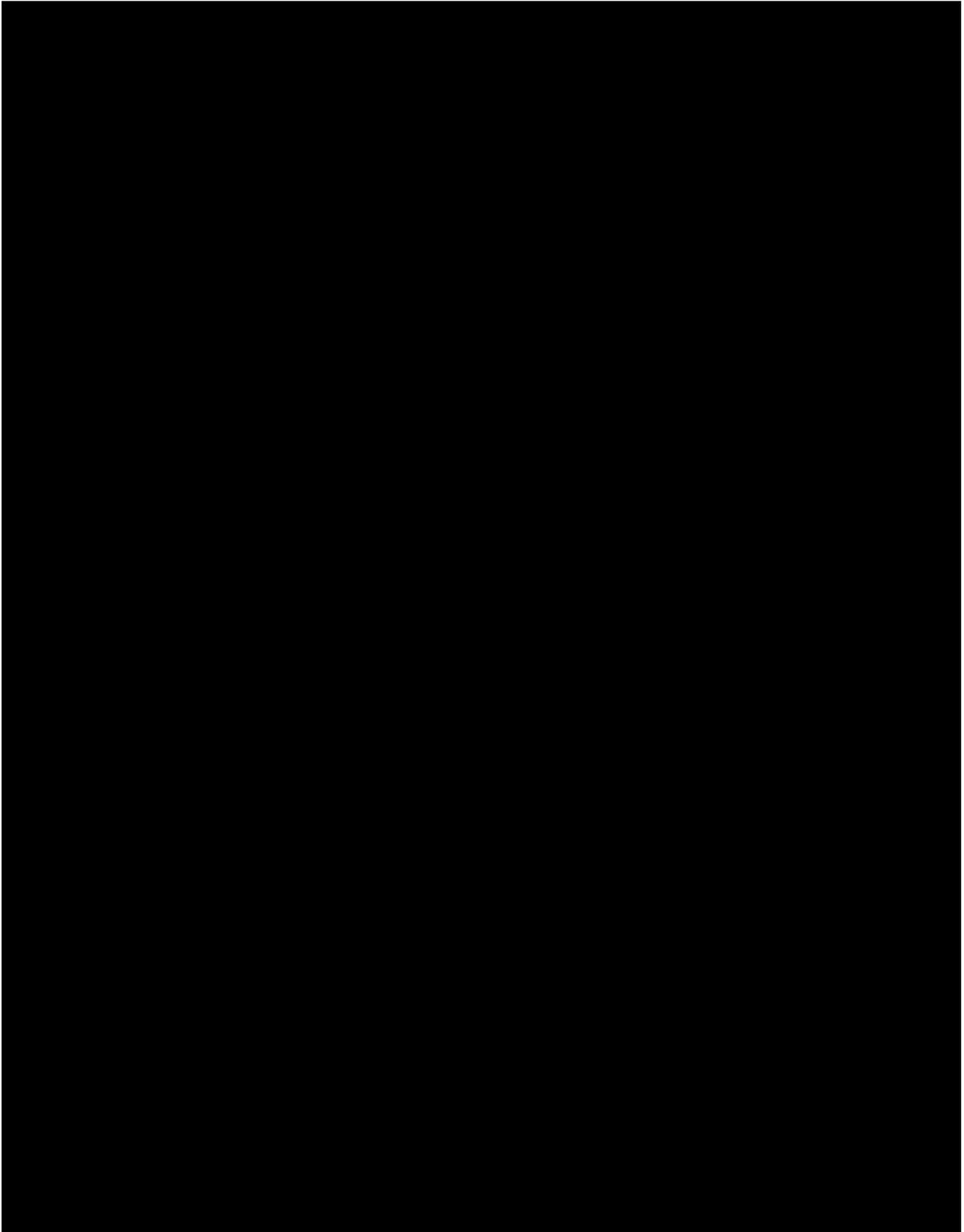


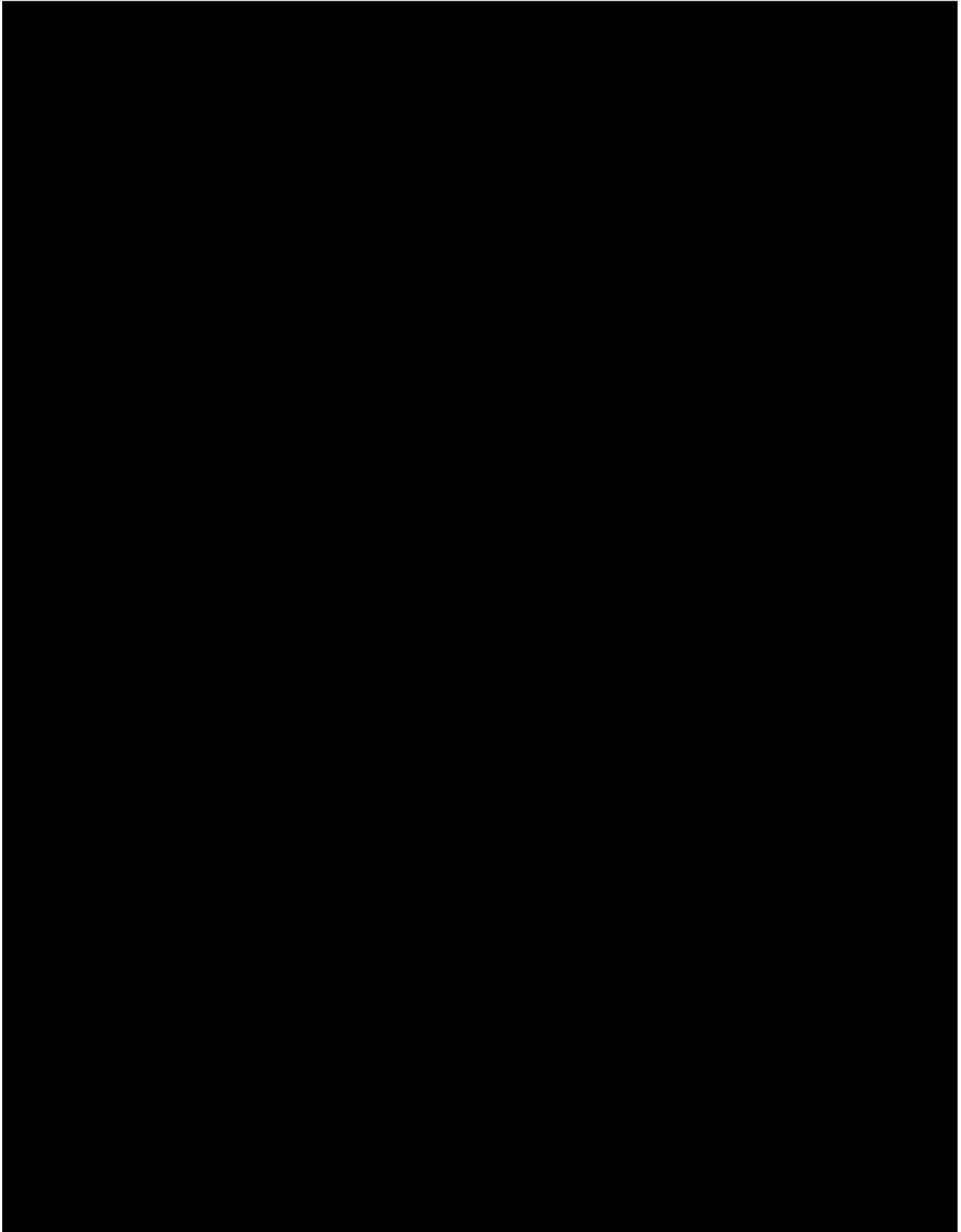
7.2.3.1 Analytical method

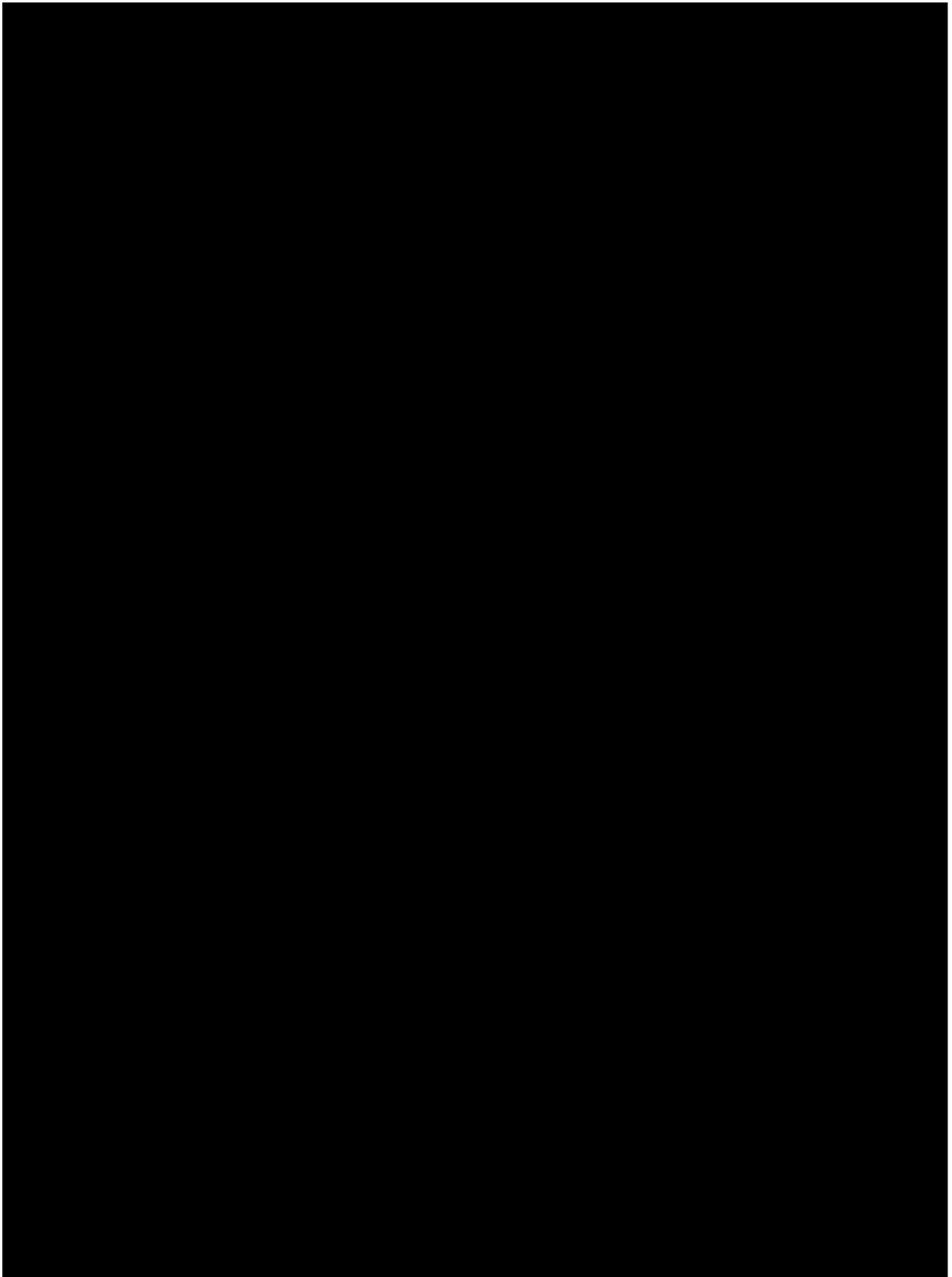
Sample analysis will be performed by Novartis or a Novartis designated laboratory using validated methods. Plasma concentrations of LEE011 (and any relevant metabolites such as LEQ803), tamoxifen (and any relevant metabolites such as N-desmethyltamoxifen, 4-hydroxytamoxifen, and endoxifen), letrozole and anastrozole will be measured using a liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods with a lower limit of quantification (LLOQ) of approximately 1.00 ng/mL, 10 ng/mL, 2 ng/mL, and 10 ng/mL for LEE011, tamoxifen, letrozole, and anastrozole, respectively. Any results below the LLOQ and any missing samples will be recorded accordingly.

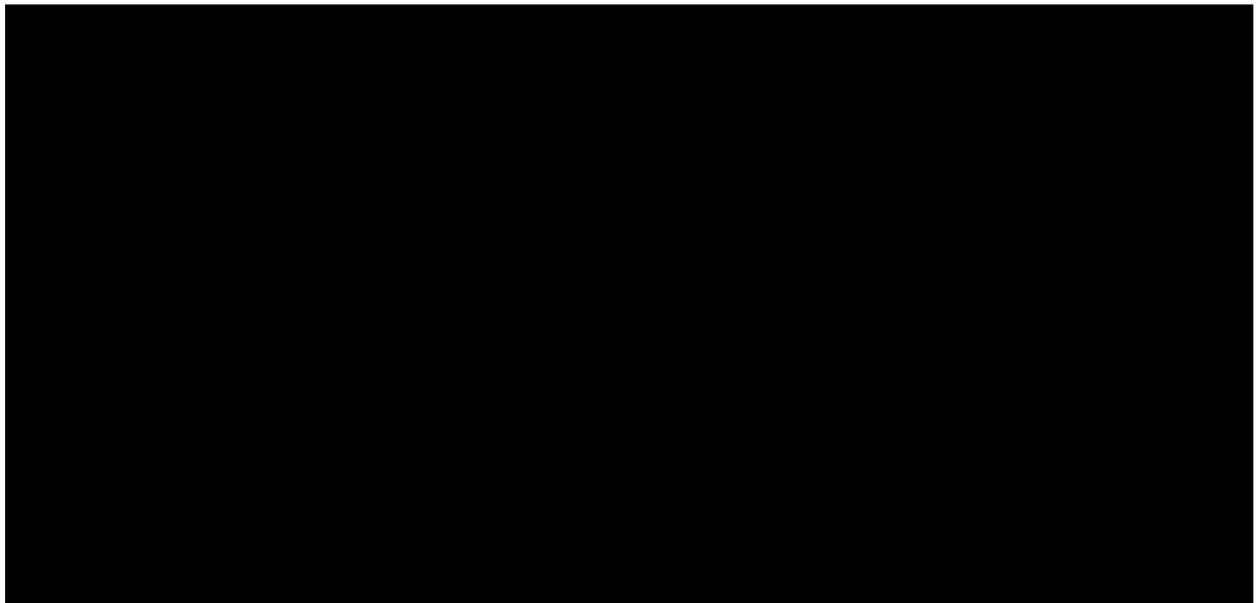
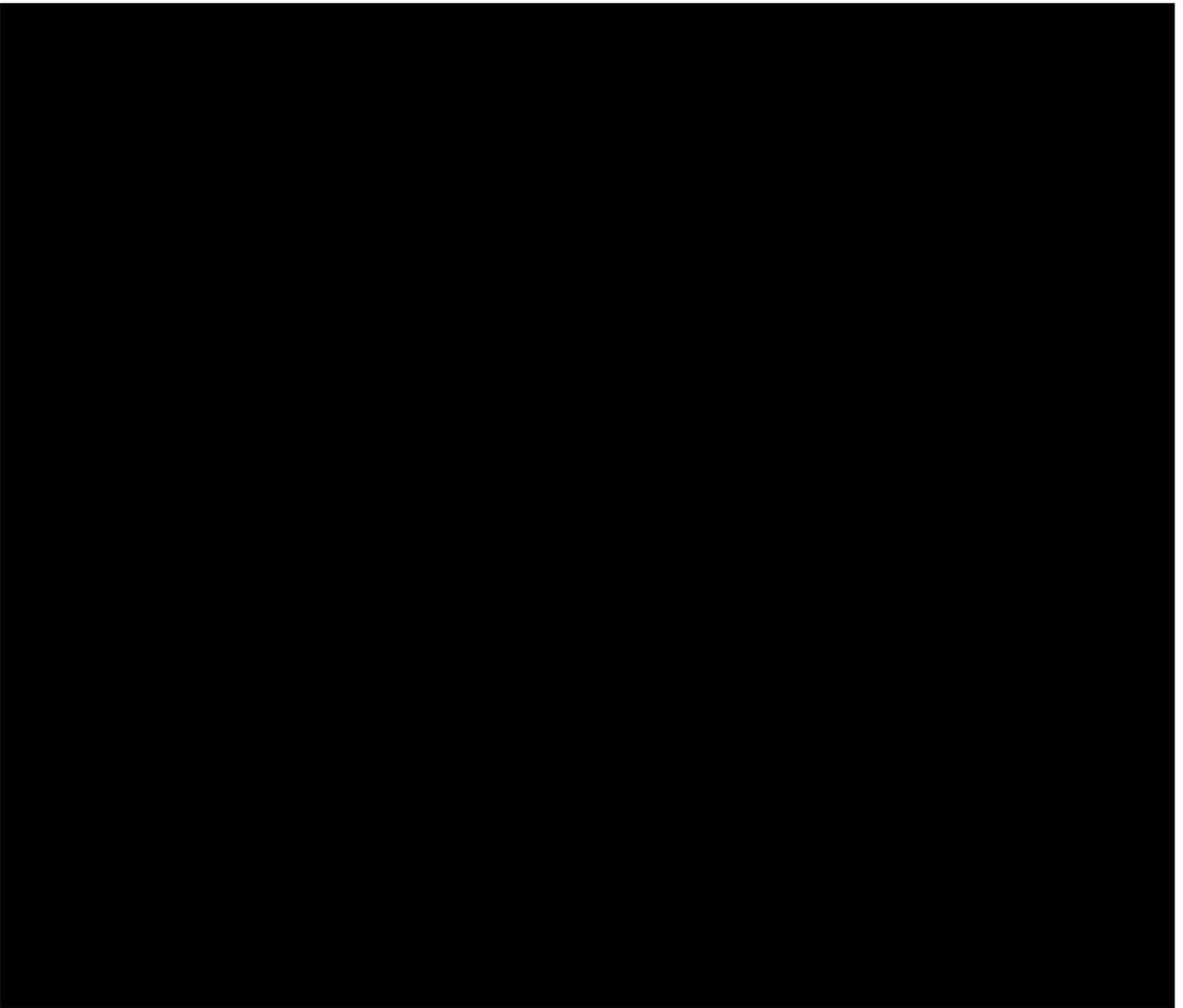
Leftover plasma from analysis may be used for exploratory metabolite assessments or other bioanalytical purposes (e.g., cross check between different sites, stability assessment). Given the exploratory nature of the work, the analytical method used for those assessments will not be validated.











7.2.6 Patient reported outcomes

The European Organization for Research and Treatment of Cancer's core quality of life questionnaire (EORTC-QLQ-C30, version 3.0) and breast cancer specific questionnaire (EORTC QLQ-BR23, version 1.0) and the EuroQoL 5-level instrument (EQ-5D-5L, Version 4.0) will be used to evaluate patient-reported outcome measures of health-related quality-of-life, functioning, disease symptoms and treatment-related side effects. The EORTC QLQ-C30, EORTC QLQ-BR23 and the EQ-5D-5L are recognized reliable and valid measures ([Aronson 1993](#), [Sprangers 1996](#), [Rabin 2001](#)) frequently used in clinical trials of patients with advanced or metastatic breast cancer.

In addition to the all health-related quality of life questionnaires, EORTC QLQ-C30, EORTC QLQ-BR23, and the generic health utility measure EQ-5D-5L will be administered before any study drug administrations at the visits indicated in [Table 7-1](#), [Table 7-14](#) and [Table 7-15](#). Collection of all PRO measures (e.g., EORTC QLQ-C30, EORTC QLQ-BR23, EQ-5D-5L,) have a ± 3 day window unless otherwise indicated.

All questionnaires should be administered in the patient's local language at the beginning of the study visit prior to any interaction with the study investigator including any tests, treatments or receipt of results from any tests to avoid biasing the patient's perspective. This is to avoid potentially biasing patients or their responses to study questionnaires. Patients should be given sufficient space and time to complete all study questionnaires and all administered questionnaires should be reviewed for completeness. If missing responses are noted, patients should be encouraged to complete any missing responses. Attempts should be made to collect responses to all questionnaires for all patients, including from those who discontinue prior to the study evaluation completion visit, however, if patients refuse to complete questionnaires, this should be documented in study source records. Patient's refusal to complete study questionnaires are not protocol deviations.

Completed questionnaires, including both responses to the questions and any unsolicited comments written by the patient, must be reviewed and assessed by the investigator before the clinical examination for responses which may indicate potential AEs or SAEs. This review should be documented in study source records.

If an AE or SAE is confirmed then the physician should record the event as instructed in [Section 8](#) of this protocol. Investigators should not encourage the patients to change responses reported in questionnaires.

7.2.6.1 EORTC QLQ-C30 and EORTC QLQ-BR23

The EORTC QLQ-C30 contains 30 items and is composed of both multi-item scales and single-item measures. These include five functional scales (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue, nausea/vomiting, and pain), six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact) and a global health status/QoL scale ([Aaronson et al 1993](#)). The EORTC QLQ-BR23 is used in conjunction with the EORTC QLQ-C30 and provides information on an additional 23 items specifically related to breast cancer. It incorporates five multi-item scales to assess systemic therapy side effects, arm symptoms, breast symptoms, body image and sexual functioning. In addition, single items assess sexual enjoyment, hair loss and future perspective.

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high / healthy level of functioning; a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems. All scoring will follow the scoring procedures defined by the EORTC Scoring Manual ([Fayers et al 2001](#)).

7.2.6.2 EQ-5D-5L

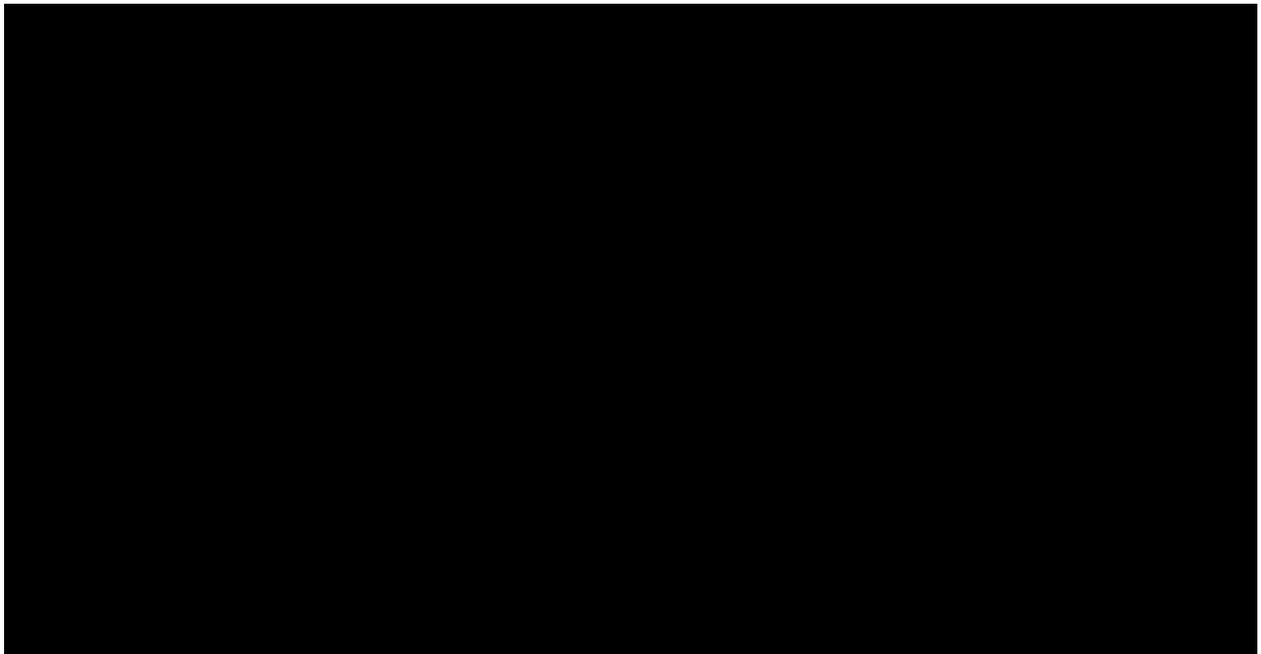
The EQ-5D-5L (Version 4.0) is a standardized measure of health utility that provides a single index value for one’s health status. The EQ-5D-5L is frequently used for economic evaluations of health care and has been shown to be a valid and reliable instrument ([The EuroQol Group 1990](#), [Rabin 2001](#)). The EQ-5D-5L contains one item for each of five dimensions of HRQOL (i.e., mobility, self-care, usual activities, pain or discomfort, and anxiety or depression). Response options for each item vary from having no problems (e.g., “...no problems walking about”), moderate problems (e.g., “...some problems walking about”), or extreme problems (e.g., “...unable to walk about”). Patient responses to the five dimensions of HRQOL reflect a specific health state that corresponds to a population preference weight for that state on a continuous scale of 0 (death) to 1 (perfect health). A visual analog scale (ranging from 0 to 100) is also included to capture patient’s rating of their overall health status. Higher scores of the EQ-5D-5L represent better health states. All scoring and handling of data will follow the User’s Guide defined by the EuroQoL Group ([Rabin 2011](#)).

The EORTC QLQ-C30, EORTC QLQ-BR23 and EQ-5D-5L should be administered as per [Table 7-1](#) and [Table 7-14](#).

Table 7-14 Patient reported outcomes collection plan

Patient Questionnaire	Cycle	Day	Time
	Screening	-28 to Day -1	

Patient Questionnaire	Cycle	Day	Time
EORTC QLQ-C30 EORTC QLQ-BR23 EQ-5D-5L	Subsequent cycles	Every 8 weeks after randomization during the first 18 months and every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, subject/guardian decision	Prior to any clinical assessments, drug dosing or diagnostic testing.
	End of treatment	Day of EOT visit	
	Safety follow-up	Day of Safety follow-up visit	
	Efficacy follow-up	Continue collection every 8 weeks after randomization during the first 18 months and every 12 weeks thereafter until disease progression, death, withdrawal of consent, loss to follow-up, subject/guardian decision	



8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study but is collected as seriousness criteria; rather, information about deaths will be collected through a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in [Section 8.2.1](#), and which seriousness criteria have been met
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

If the event worsened, the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For Grade 3 and 4 adverse events only, if improvement to a lower grade is determined, a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already

reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
 - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
 - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent.
 - Social reasons and respite care in the absence of any deterioration in the patient's general condition.
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event.

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Emergency unblinding should only be undertaken when it is essential for effective treatment of the patient. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency code breaks are performed using the IRT. When the investigator contacts the IRT to unblind a patient, he/she must provide the requested patient identifying information and confirm the necessity to unblind the patient. The investigator will then receive details of the drug treatment for the specified patient and a fax confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Lead that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable. The protocol number, study treatment name if available, patient number and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) will be provided to the patient in case emergency unblinding is required at a time when the investigator and backup are unavailable. However, if a mechanism is already in place to ensure that the investigator and/or back-up can always be reached in case of emergency then the procedure above is not required.

Study treatment must be discontinued once emergency unblinding has occurred.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data monitoring committee

An independent data monitoring committee (IDMC) will be established to assess the safety and available PK results of LEE011 in combination with tamoxifen + goserelin or a NSAI + goserelin in an unblinded manner. The IDMC will be responsible for reviewing the safety results and overseeing the safety data accruing in the trial at regular intervals, approximately every six months. Also, if requested by the IDMC Chair, additional safety reviews may be performed.

The IDMC will consist of at least two oncologists and one biostatistician and will be formed prior to the randomization of the first patient. Detailed recruitment status and interim safety reports will be provided to the IDMC on a regular basis. Recruitment will not be interrupted. Details will be provided in the IDMC charter.

A subset of the PK data reported to the IDMC for patients receiving anastrozole may also be used to support ongoing health authority interactions related to the initial filing of ribociclib. To ensure trial integrity and blinding are maintained, processes will be established and documented in the appropriate study documents (e.g. Data Handling Plan, DMC Charter) and an independent team within Novartis will be formed to receive and submit these data. The analysis will be limited to PK summary tables; no patient-level data will be included.

8.7 Steering committee

The SC will be established comprising investigators participating in the trial, and Novartis representatives from the Clinical Trial Team.

The SC will be an advisory board for the study according to the protocol through recommending modifications as circumstances require. The SC will be consulted for protocol amendments as

appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results. The details of the role of the SC will be defined in a SC charter. The SC will not have access to unblinded trial data.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or

assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

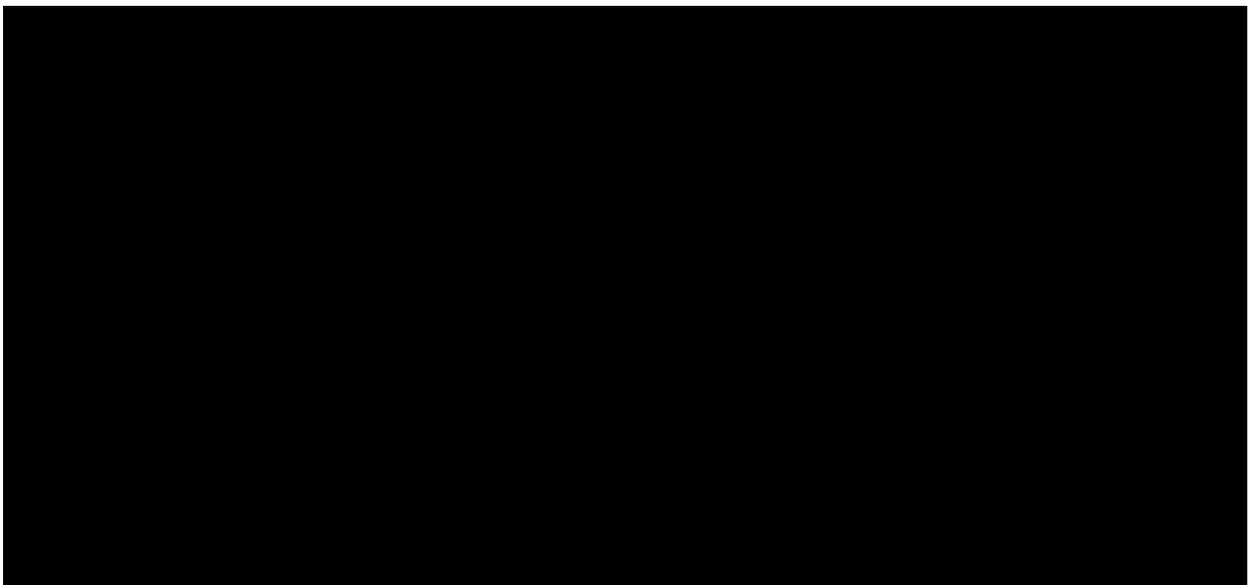
9.3 Data collection

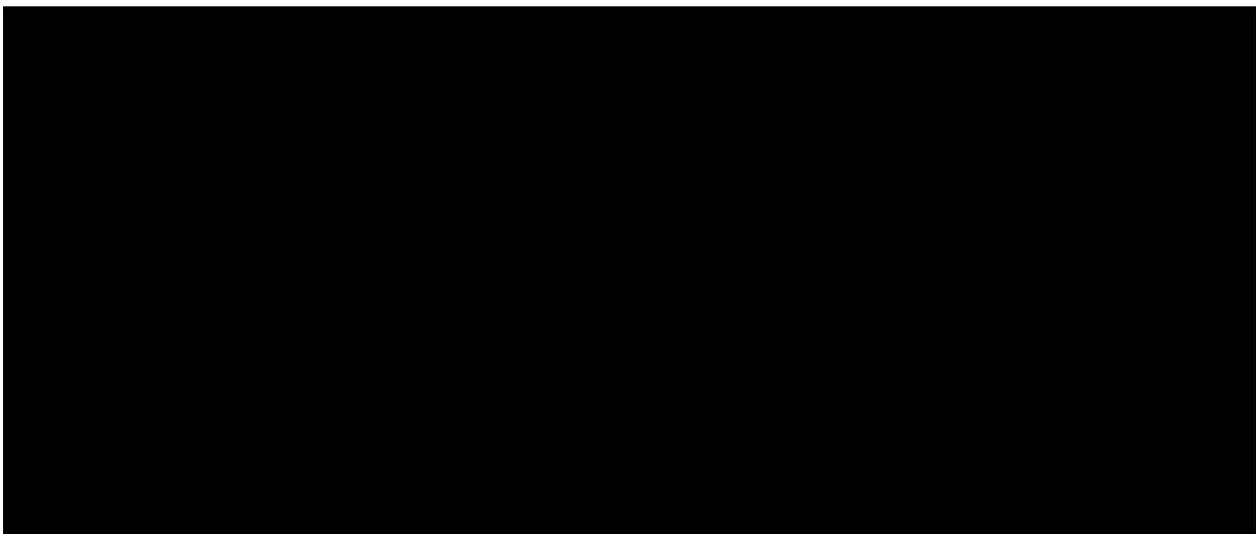
For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

9.3.1 ECG data collection

ECG data will be collected via 12-lead digital ECG machines. The data will be transmitted to a designated CRO for centralized cardiac safety analysis, as well as further processing and data reconciliation.





9.3.4 IRT data collection

Patient eligibility and enrollment will be tracked using an Interactive Response Technology. The system will be supplied by a vendor, who will also manage the database for that system.

9.3.5 Central laboratory

Laboratory samples will be analyzed centrally and the results will be sent electronically to Novartis or the designated data management CRO. Local lab results are entered on the eCRF only if they document an adverse event not reported by the central lab, the severity Grade differs from what is reported by the central lab or, in the absence of central lab results, support the decision for study treatment continuation. Lab normal ranges and certification are then required.

9.3.6 Central radiology

Radiological imaging and photography data will be acquired by the sites and interpreted locally. Additionally, radiological and photography data will be transmitted by the sites to the CRO designated by Novartis to undergo quality checks and central review by a blinded independent review committee (BIRC). The BIRC will perform an assessment of PFS data for a randomly selected subgroup of patients. An independent random sampling process will select all scans (and relevant information) from approximately 40% of randomized patients (see [Section 10.8](#)), whose BIRC randomization identity will be unknown to the investigators. If consistency of treatment effect is not established, the BIRC may perform an assessment of PFS data for all patients.

Tissue and fluid collections results and pre-existing radiographic findings will be recorded in the eCRF and may be transmitted to the imaging CRO for review if appropriate. Further details regarding BIRC assessment will be provided in the BIRC charter. The central review of the scans will be carried out in a blinded fashion. The decision regarding patient management will remain with the local investigator.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis.

Randomization codes and data about all study treatments dispensed to the patient and all IRT assigned dosage changes will be tracked using an Interactive Response Technology. The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel.

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis personnel (or designated CRO). The occurrence of any protocol violations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and the treatment codes will be unblinded and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

It is planned that the data from all centers participating in the trial will be combined, so that an adequate number of patients are available for analysis. Novartis and/or a designated CRO will perform all analyses. Any data analyses performed independently by any investigator should be submitted to Novartis before publication or presentation.

10.1 Analysis sets

10.1.1 Full analysis set

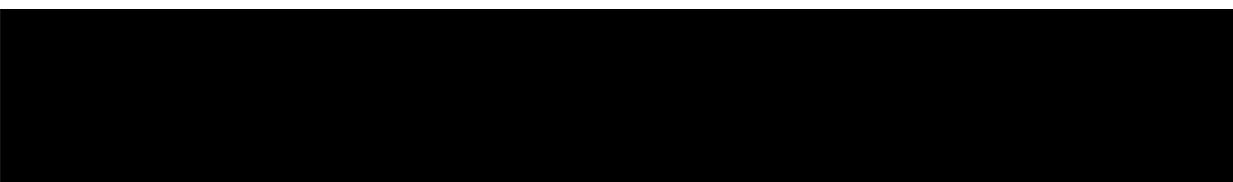
The full analysis set (FAS) comprises all randomized patients. Following the ITT principle, patients will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure. The FAS will be the primary population for all the efficacy analyses.

10.1.2 Safety set

The Safety Set includes all patients who received at least one dose of study medication defined as tamoxifen/NSAI, goserelin, LEE011 or placebo. Patients will be analyzed according to the study treatment they actually received. Actual treatment refers to the treatment that the patient was randomized to, unless the alternative treatment was received throughout the trial.

10.1.3 Per-protocol set

The per-protocol set (PPS) will include the subset of the patients in the FAS without major protocol deviations. All protocol deviations or conditions leading to exclusion from the PPS will be detailed in the data handling plan and analysis plan. Sensitivity analyses of the primary endpoint of PFS may be performed using data from the PPS if the FAS and PPS differ and if the primary analysis is significant.



10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristic/prognostic data will be summarized descriptively by treatment group using data from the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The safety set will be used for the analyses below.

The actual dose and duration of tamoxifen/NSAI, goserelin, LEE011 and placebo treatment, as well as dose intensity (computed as the ratio of actual dose received to actual duration) and the relative dose intensity (computed as the ratio of the dose intensity to planned dose received/planned duration), will be listed and summarized using descriptive statistics. The total daily doses of tamoxifen/NSAI, goserelin, LEE011 and placebo for each patient will be summarized using descriptive statistics (e.g. mean, median, and mode).

Concomitant medications and significant non-drug therapies will be listed by patient and summarized by ATC (Anatomical therapeutic chemical classification system) term for each treatment group. These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment. Any prior concomitant medications or significant non-drug therapies starting and ending prior to the start of study treatment will be listed.

Compliance to the study drug will be assessed by the number of dose reductions and dose interruptions.

10.4 Primary objective

The primary objective in the study is to determine whether treatment with tamoxifen or a NSAI + goserelin + LEE011 prolongs PFS compared to treatment with tamoxifen or a NSAI + goserelin + placebo in premenopausal women with HR+, HER2- advanced breast cancer who received no prior hormonal therapy for advanced breast cancer.

10.4.1 Variable

The primary efficacy endpoint of the study is PFS, defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. If a patient has not had an event, PFS will be censored at the date of the last adequate tumor assessment (see RECIST 1.1 in [Appendix 3](#) for further details). Clinical deterioration without objective radiological evidence will not be considered as documented disease progression. PFS will be assessed via a local radiology assessment according to RECIST 1.1. PFS as assessed through blinded independent central review will be used for supportive evidence of the primary efficacy endpoint.

10.4.2 Statistical hypothesis, model, and method of analysis

The primary efficacy analysis will be the comparison of PFS between the two treatment groups using a stratified log-rank test at one-sided 2.5% level of significance.

Assuming proportional hazards model for PFS, the following statistical hypotheses will be tested to address the primary efficacy objective:

$$H_{01}: \theta_1 \geq 0 \text{ vs. } H_{a1}: \theta_1 < 0$$

where θ_1 is the log-hazard ratio (Tamoxifen or a NSAI+goserelin+LEE011 arm vs. tamoxifen or a NSAI+goserelin + placebo arm) of PFS.

The primary efficacy endpoint PFS will be analyzed based on the FAS according to the treatment group patients were randomized and the strata they were assigned at randomization (strata formed using the randomization factor as obtained via IRT). PFS will be estimated using the Kaplan-Meier method. The median PFS along with 95% confidence intervals will be presented by treatment group. A stratified Cox regression model will be used to estimate the hazard ratio of PFS, along with 95% confidence interval. The primary analysis for PFS will be performed after approximately 329 PFS events have been documented per local assessment.

In addition to the primary analysis in all patients, the treatment effect in terms of PFS for

1. tamoxifen + goserelin + LEE011 vs. tamoxifen + goserelin + placebo, and
2. NSAI + goserelin + LEE011 vs. NSAI + goserelin + placebo

will be estimated using separate Cox regression models. Estimated hazard ratios with corresponding 95% CIs will be presented for each subgroup. PFS will be estimated using Kaplan-Meier methodology within each subgroup.

10.4.3 Handling of missing values/censoring/discontinuations

PFS will be censored if no PFS event is observed before the cut-off date. The censoring date will be the date of last adequate tumor assessment before this date. If a PFS event is observed after two or more missing or non-adequate tumor assessments, then PFS will be censored at the last adequate tumor assessment. If a PFS event is observed after a single missing or non-adequate tumor assessment, the actual date of event will be used (see RECIST 1.1 [Appendix 3](#)).

10.4.4 Supportive analyses

PFS as assessed by BIRC will be used for supportive evidence of the primary efficacy endpoint. A sample-based BIRC audit approach ([Section 9.3.6](#)) will be used to assess PFS by BIRC. Two methods will be used to summarize the data from the sample-based BIRC assessment of PFS. The NCI (National Cancer Institute) method ([Dodd et al. 2011](#)), uses an auxiliary variable estimator of the log-hazard ratio that combines information from patient-level investigator assessment from all patients and the BIRC assessment of patients randomly selected (see [Section 9.3.6](#)) for central review. This estimate and its one-sided 95% CI will be provided. Details of the sample size calculation for the BIRC assessment are provided in [Section 10.8](#). The NCI method will be used for audit sample size determination and summary of treatment effect (HR, 95% CI) based on the supportive BIRC assessment.

The data from the BIRC assessment generated following the sampling scheme as above will also be summarized using the method proposed by [Amit et al. 2011](#), referred to as the PhRMA (Pharmaceutical Research and Manufacturers of America) method. With this approach, the differential discordance of early discrepancy rate (EDR) and late discrepancy rate (LDR) between the two arms will be estimated as the rate on the tamoxifen or a NSAI+goserelin+LEE011 arm minus the rate on the tamoxifen or a NSAI+goserelin+placebo arm. The EDR and LDR results will also be summarized by treatment arm. Further definitions and details will be provided in the analysis plan.

As a sensitivity analysis, the distribution of PFS will be compared between the treatment groups using an unstratified log-rank test and the hazard ratio along with the associated 95% confidence interval resulting from an unstratified Cox model will be presented.

The primary analysis for PFS may be repeated with data based on the PPS if the primary analysis is statistically significant. A sensitivity analysis will be performed in which PFS is censored at date of the last adequate tumor assessment before any new antineoplastic therapy is started. Other sensitivity analyses may be performed such as (1) including PFS events even if the events are recorded after two or more missed assessments, (2) backdating events occurring after missing tumor assessments.

In addition to the subgroup analyses for patients receiving tamoxifen and those receiving NSAI ([Section 10.4.2](#)), subgroup analyses will be performed on each level of stratification factors if the primary analysis is significant. The analysis will include Kaplan-Meier summaries and estimation of hazard ratios from un-stratified Cox regression models. Additional subgroup analyses to assess the homogeneity of treatment effect based on demographic and baseline disease characteristics may be performed; details about the subgroups to be included will be provided in the study analysis plan.

Patterns of censored data will be examined by the treatment groups using descriptive statistics (the numbers of censored patients and reasons for censoring).

10.5 Secondary objectives

The secondary objectives in this study are to compare the two treatment groups with respect to OS, and evaluate ORR, CBR, time to response, duration of response, time to definitive deterioration in the quality of life and ECOG PS, and safety. OS is identified as the key secondary endpoint. A hierarchical testing strategy will be taken to control overall type-I error rate; therefore OS will be statistically evaluated and interpreted only if the primary efficacy endpoint PFS is significantly different between the 2 treatment groups.

10.5.1 Key secondary objective(s)

The key secondary objective of the study is to determine whether treatment with tamoxifen or a NSAI + goserelin + LEE011 prolongs OS compared to treatment with tamoxifen or a NSAI + goserelin + placebo.

OS is defined as the time from date of randomization to date of death due to any cause. If a patient is not known to have died, then OS will be censored at the date of last known date patient alive.

Assuming proportional hazards model for OS, the following statistical hypothesis for OS will be tested using a stratified log-rank test (stratified according to randomization stratification factors) at the one-sided 2.5% level of significance:

$$H_{02}: \theta_2 \geq 0 \text{ vs. } H_{a2}: \theta_2 < 0$$

where θ_2 is the log-hazard ratio (tamoxifen or a NSAI+goserelin+LEE011 arm vs. tamoxifen or a NSAI+goserelin+placebo arm) of OS.

The analyses for OS will be based on the FAS. The distribution of OS will be compared between the two treatment groups using a stratified log-rank test at one-sided 2.5% level of significance.

The final OS analysis will not be performed at the time point of the primary PFS analysis, but after additional follow-up. Therefore, a three-look design is considered for OS.

OS will be hierarchically tested in the following way:

1. The first potential time point for OS analysis will be at the time of the primary PFS analysis, when 123 deaths are expected. If PFS is statistically significant at this stage, OS will also be tested.
2. If OS is not statistically significant at this stage, the 2nd OS analysis will be planned after approximately 189 deaths.
3. If OS is not statistically significant at this stage, a final analysis is planned after approximately 252 deaths have been recorded.
4. If PFS is not statistically significant at the primary analysis, then OS will not be tested.

The type I error probability for OS tests will be controlled by using a Lan-DeMets (O'Brien-Fleming) alpha spending function at the one-sided type I error of $\alpha=0.025$. This guarantees the protection of the overall level $\alpha = 2.5\%$ across the two hypotheses and the repeated testing of the OS hypotheses in the interim and the final analyses (Glimm 2010).

The distribution function of OS will be estimated using the Kaplan-Meier method. The median OS along with 95% confidence intervals will be presented by treatment group. The stratified Cox regression will be used to estimate the hazard ratio (HR) of OS, along with 95% confidence interval.

10.5.2 Other secondary efficacy objectives

10.5.2.1 Overall response rate

Overall response rate is defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR) according to RECIST 1.1.

ORR will be calculated based on the FAS according to the ITT principle; however patients with only non-measurable disease at baseline will be included in the numerator if they achieve a complete response. ORR will be presented by treatment group along with approximate 95% confidence intervals. The Cochran-Mantel Haenszel chi-square test (stratified by baseline stratification factors) will be used to compare the two treatment groups with respect to the ORR at one-sided 2.5% level of significance. As a supportive analysis, ORR as assessed by the blinded independent central review will be calculated by treatment group and presented along with the approximate 95% confidence intervals. As a sensitivity analysis, ORR for patients with measurable disease at baseline will be calculated and presented by treatment group together with approximate 95% confidence intervals.

10.5.2.2 Clinical benefit rate

Clinical Benefit is defined as CR or PR, or SD for 24 weeks or longer. CR, PR and SD are defined according to RECIST 1.1. CBR will be calculated based on the FAS; however patients with only non-measurable disease at baseline will be included in the numerator if they achieve a complete response. CBR will be summarized for the two treatment groups using descriptive statistics. The Cochran-Mantel Haenszel chi-square test (stratified by baseline stratification factor) at 2.5% one-sided level of significance, will be used to compare the two treatment groups with respect to the CBR. As a supportive analysis, CBR as assessed by the blinded independent central review will be summarized for the two treatment groups using descriptive statistics.

10.5.2.3 Time to response

Time to response is the time from the date of randomization to the first documented response (CR or PR, which must be confirmed subsequently) according to RECIST 1.1. All patients will be included in time to response calculations. Patients who do not achieve a confirmed response will be censored at the maximum follow-up time (i.e. first patient first visit to last patient last visit used for the analysis) for patients who had a PFS event (i.e. either progressed or died due to any cause) or at the date of last adequate tumor assessment otherwise. Time to response data will be listed and summarized by treatment group. Distribution of time to response will be estimated using Kaplan-Meier method if sufficient number of responses are recorded.

10.5.2.4 Duration of response

Duration of Overall Response (DoR) applies only to patients whose best overall response is CR or PR according to RECIST 1.1. The start date is the date of first documented response (CR or

PR) and the end date is the date defined as first documented progression or death due to underlying cancer. In other words, the start date should be determined using the time that the response was first determined and not using the time the response was confirmed. If a patient had not had an event, duration will be censored at the date of last adequate tumor assessment. DoR will be listed and summarized by treatment arm.

10.5.2.5 ECOG performance status

ECOG PS scale as described in [Table 7-3](#) will be used to assess physical health of patients. An analysis of time to definitive deterioration of the ECOG PS by one category of the score from baseline will be performed. Deterioration is considered definitive if no improvement in ECOG PS is observed at a subsequent time of measurement during the treatment period following the time point where the deterioration is observed.

Patients that have not worsened at the data cut-off point will be censored at the date of last assessment prior to data cut-off. Kaplan-Meier method will be used to estimate the distribution of time to definitive worsening and median time to definitive worsening will be presented along with a 95% confidence interval. A stratified log-rank test at one-sided 2.5% level of significance will be used to compare the distribution of time to definitive worsening between the 2 treatment arms.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group. Subgroup analyses by endocrine therapy (tamoxifen vs. NSAI) may also be performed.

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. On-treatment period: from day of first dose of study medication to **30** days after last dose of study medication
3. Post-treatment period: starting at day 31 after last dose of study medication.

10.5.3.2 Adverse events

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment by treatment group.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and treatment group.

Specific safety event categories (SEC) will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s). SEC will be defined at project level and may be regularly updated. The grouping of AEs in SEC according to project standards will be specified in the project level master statistical analysis and/or the study statistical analysis plan.

For each specified SEC, number and percentage of patients with at least one event part of the SEC will be reported by treatment group.

10.5.3.3 Laboratory abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, the study's biostatistics and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

In some cases (e.g., white blood cell differentials), the lower limits of normal ranges used in CTCAE definition have to be replaced by a clinical meaningful limit expressed in absolute counts.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following by-treatment summaries will be generated separately for hematology, biochemistry and urinary laboratory tests:

- Frequency table for newly occurring on-treatment grades 3 or 4
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high)
- Classification to compare baseline to the worst on-treatment value.
- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the analysis plan.

10.5.3.4 Other safety data

10.5.3.4.1 ECG

- Shift table from baseline to worst on-treatment result for overall assessments
- Listing of ECG evaluations for all patients with at least one abnormality.

10.5.3.4.2 Vital signs

- Shift table from baseline to worst on-treatment result
- Table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

10.5.3.5 Supportive analyses for secondary objectives

Not applicable.

10.5.3.6 Tolerability

Tolerability will be studied in terms of dose reductions and drug interruptions due to AE. Reasons for dose reductions and interruptions will be listed and summarized by treatment.

10.5.4 Patient-reported outcomes

Health-related quality of life questionnaires

The EORTC QLQ-C30 questionnaire along with the disease-specific breast cancer module (EORTC QLQ-BR23) and the EQ-5D-5L will be used to assess patient's QoL data. The global health status/QoL scale score of the EORTC QLQ-C30 is identified as the primary patient-reported outcome variable of interest. Physical functioning, emotional functioning and social functioning scale scores of the EORTC QLQ-C30, the breast cancer symptoms scale score of the EORTC QLQ-BR23 and the visual analog scale of the EQ-5D-5L are identified as secondary patient-reported outcome variables of interest.

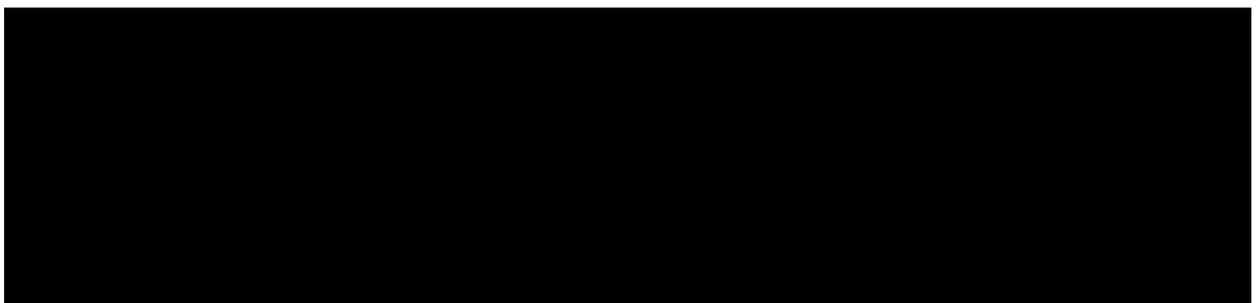
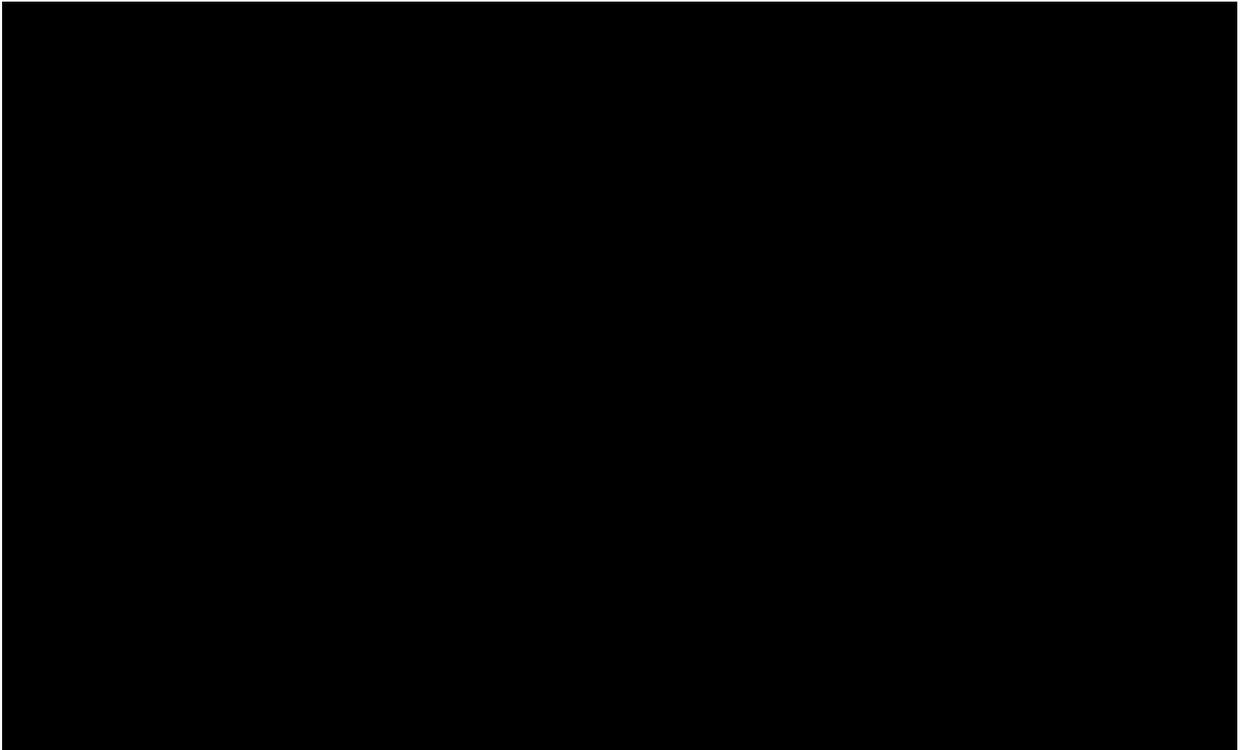
Scoring of raw QoL data and methods for handling of missing items or missing assessments will be handled according to scoring manuals for each respective patient questionnaire ([Fayers et al 2001](#), [Rabin 2011](#)). The number of patients completing each patient questionnaire and the number of missing or incomplete assessments will be summarized by each treatment group for each scheduled assessment time point for the EORTC QLQ-C30, EORTC QLQ-BR23 questionnaires, and EQ-5D-5L. No formal statistical tests will be performed on PRO data and hence no multiplicity adjustment will be applied. The FAS will be used for analyzing PRO data.

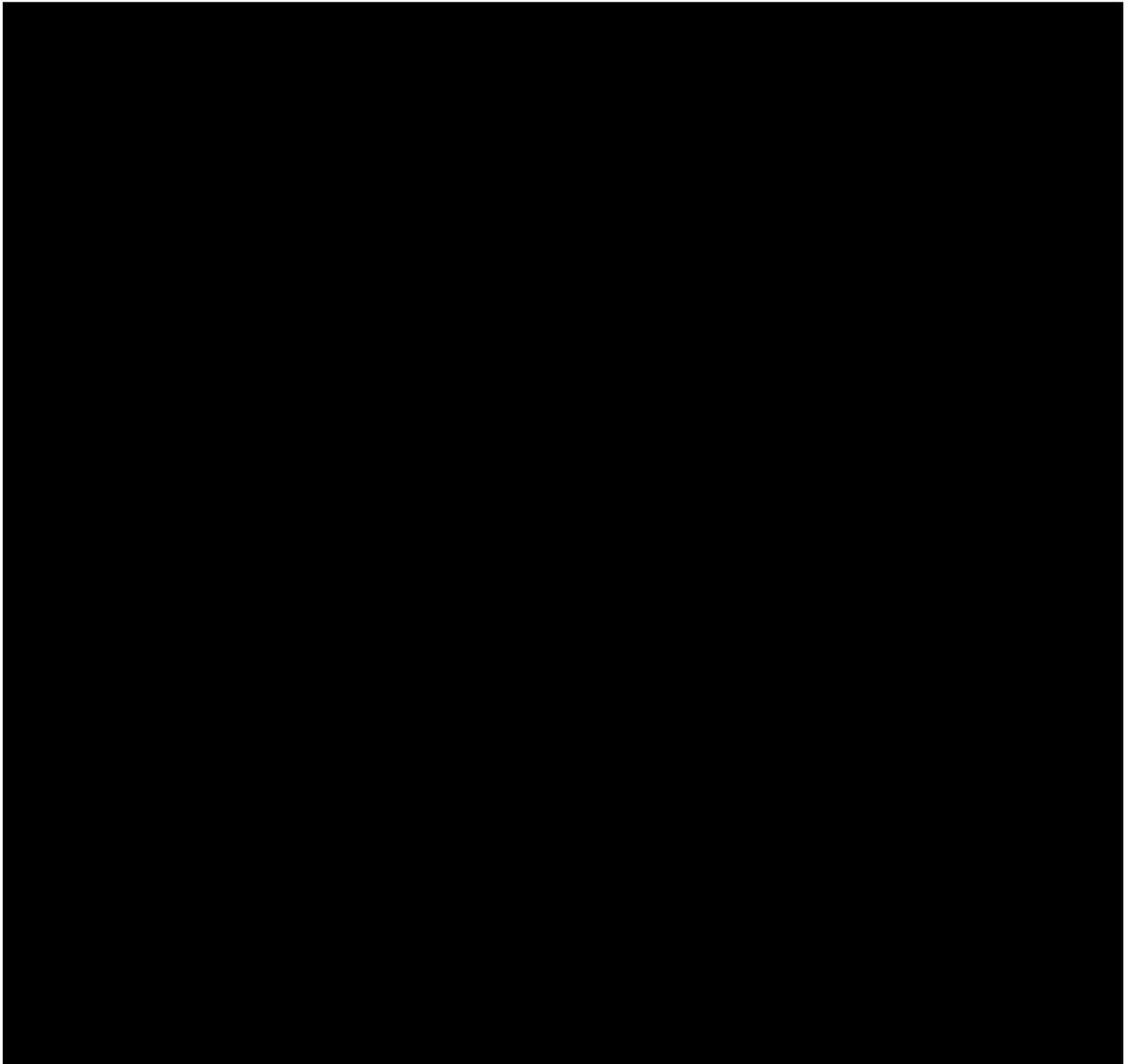
Descriptive statistics will be used to summarize the scored scales for the EORTC questionnaires and the EQ-5D-5L at each scheduled assessment time point. Additionally, change from baseline in the domain scores at the time of each assessment will be summarized. Patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses.

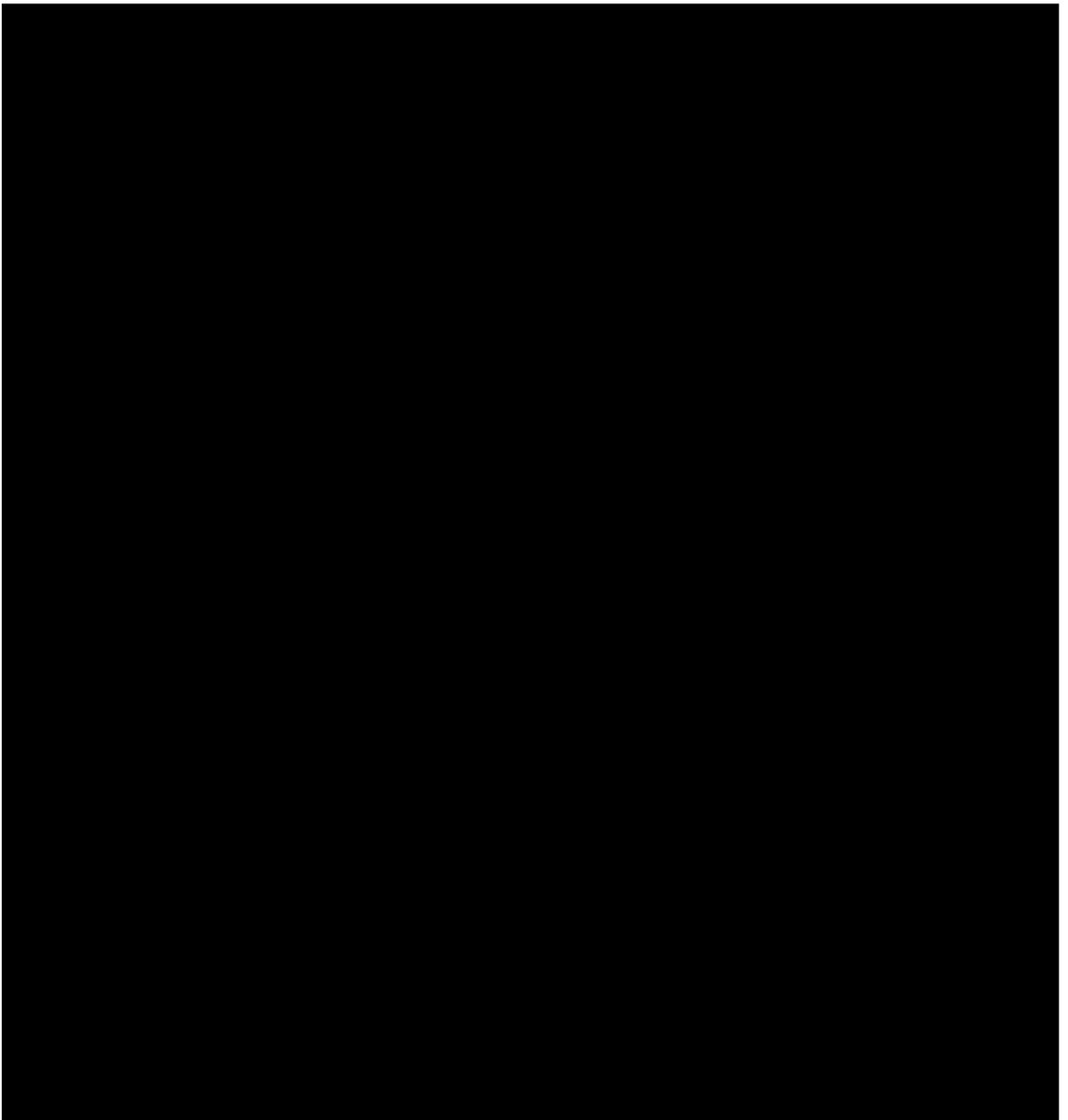
The distribution of time to definitive 10% deterioration in the global health status/QoL from EORTC questionnaires will be assessed in the two treatment arms. The time to definitive 10% deterioration is defined as the time from the date of randomization to the date of event, which

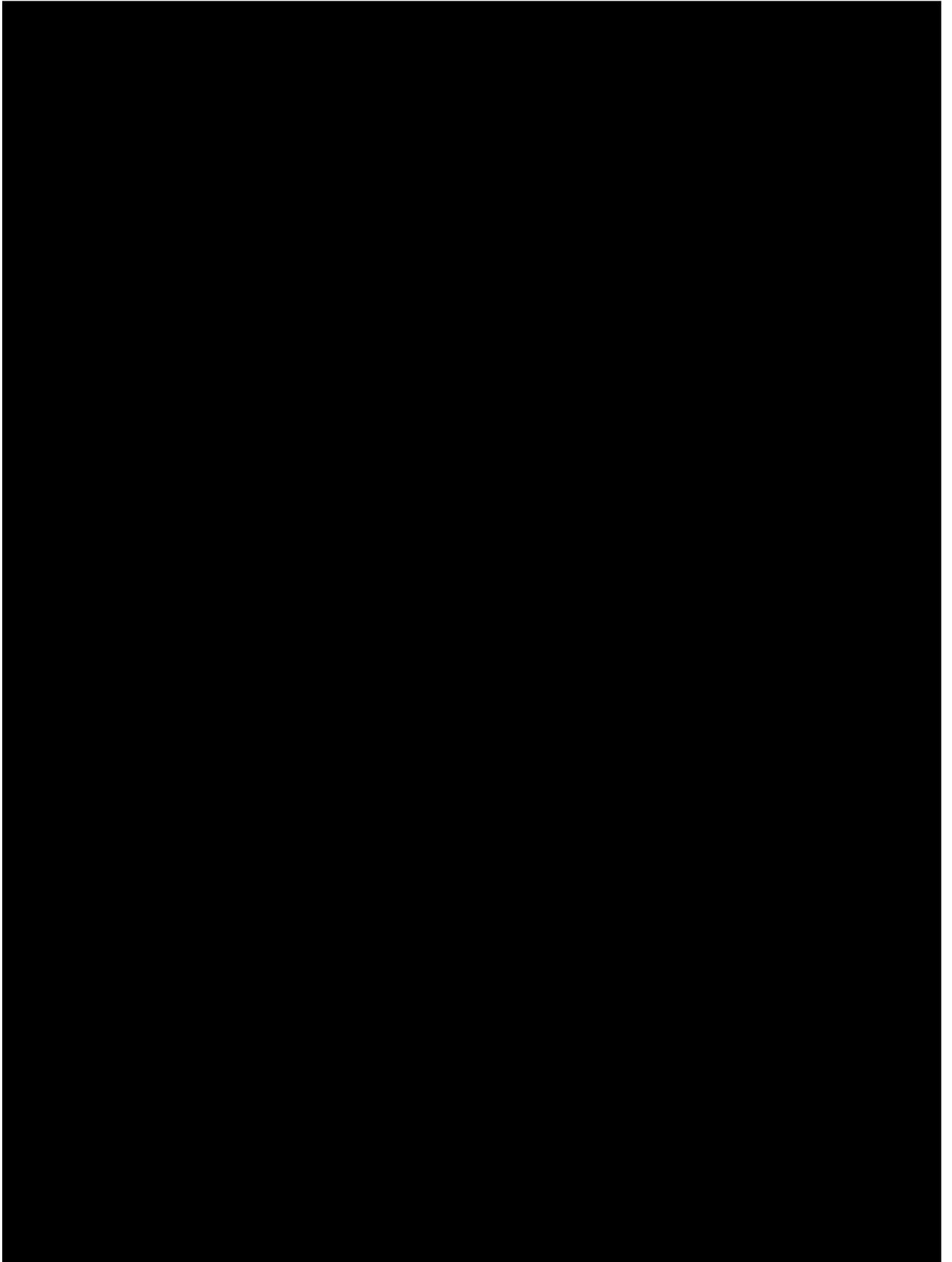
is defined as at least 10% relative to baseline worsening of the corresponding scale score (without further improvement above the threshold) or death due to any cause. If a patient has not had an event, time to deterioration will be censored at the date of the last adequate PRO evaluation. If a patient did not have any baseline PRO assessment, time to deterioration will be censored at the date of randomization. The distribution will be presented descriptively using Kaplan-Meier curves. Summary statistics from Kaplan-Meier distributions will be determined, including the median time to definitive 10% deterioration along with two-sided 95% CI. Additionally, time to definitive deterioration with different cutoff definitions (e.g. 5%, 15%) may be specified in the analysis plan as deemed appropriate. A stratified Cox regression will be used to estimate the hazard ratio, along with two-sided 95% CI. In addition, a longitudinal analysis will be performed to evaluate the two treatment groups with respect to changes in the global health status/QoL over time.

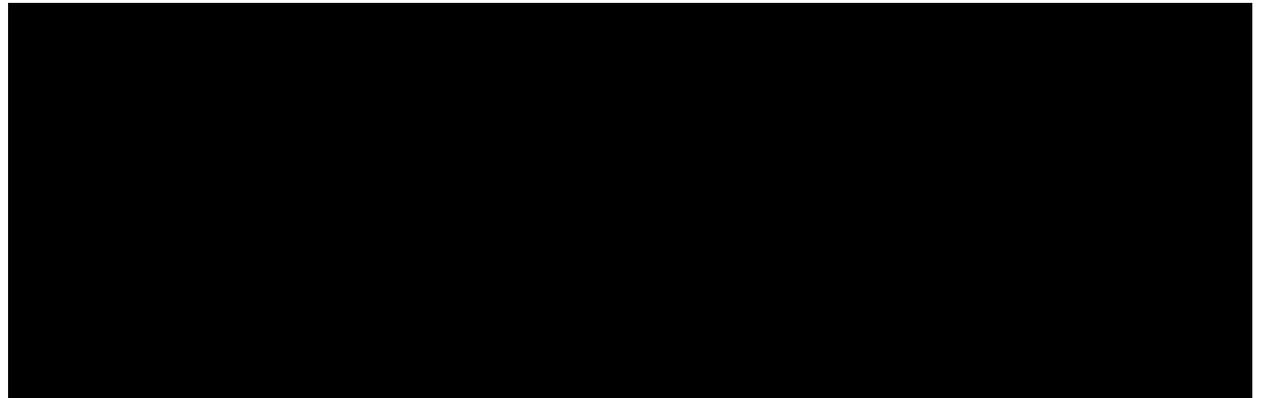
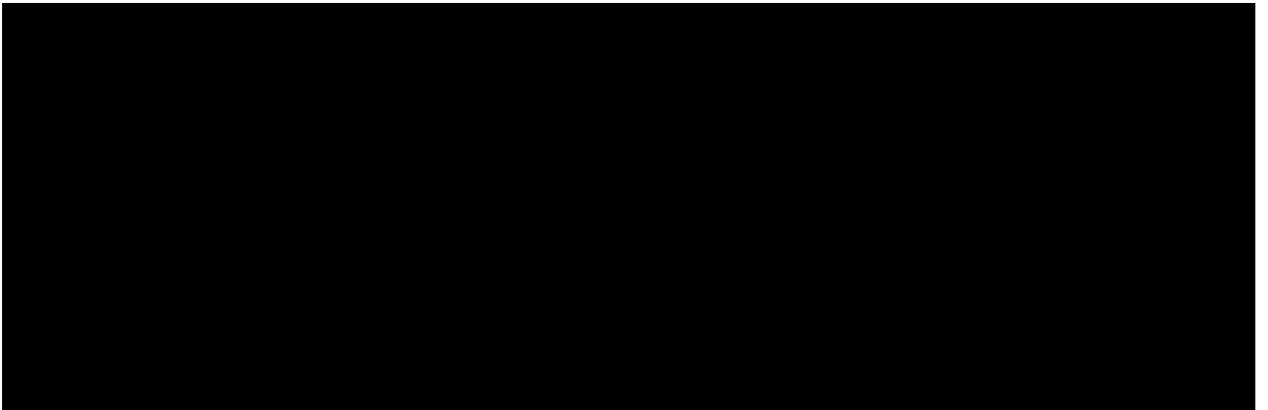
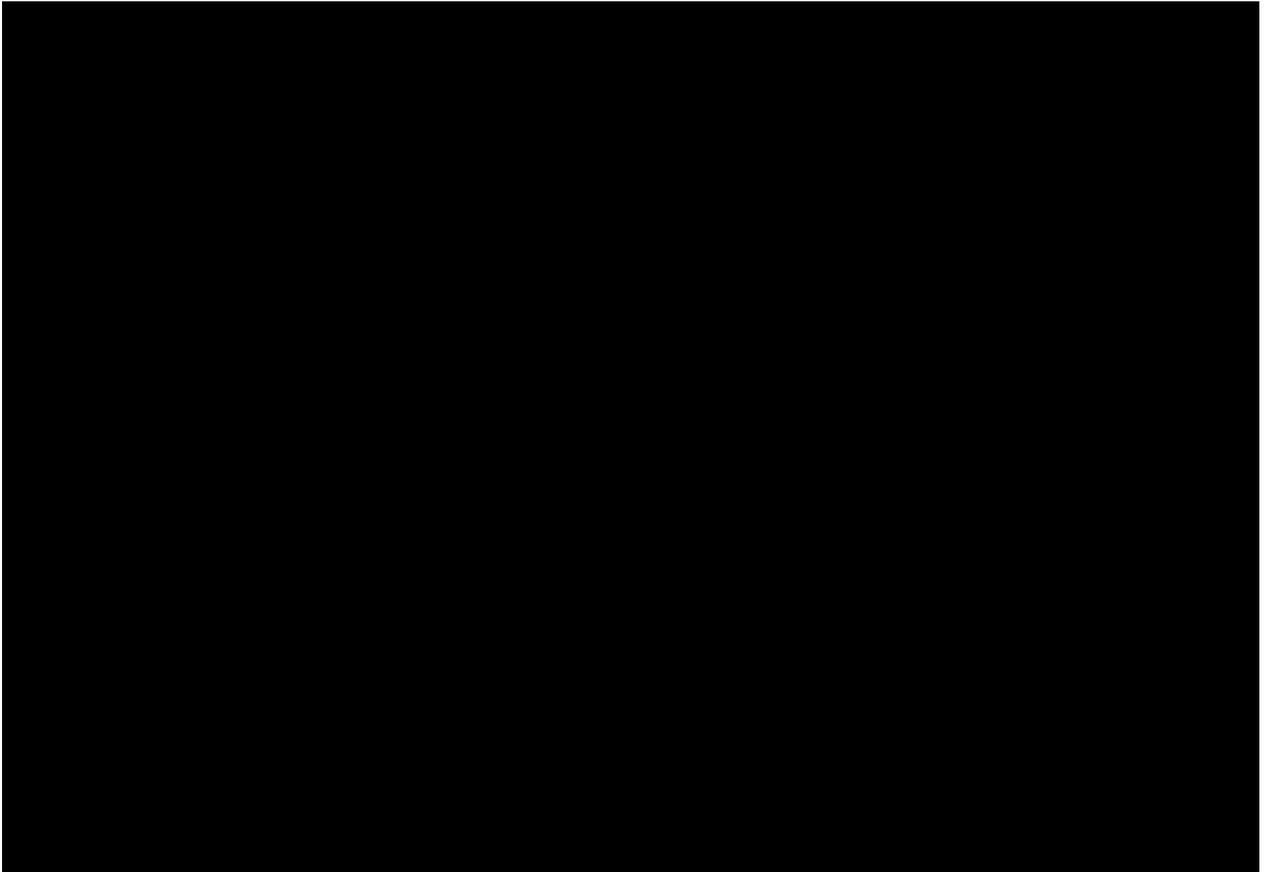
Similar survival and longitudinal analyses will be performed to evaluate the two treatment groups for physical functioning, emotional functioning and social functioning scale scores of the EORTC QLQ-C30 and the breast cancer symptoms scale score of the EORTC QLQ-BR23 as additional PRO analyses to facilitate the interpretation of these data.











10.7 Interim analysis

10.7.1 Progression free survival

No PFS interim analysis is planned in this study. The primary PFS analysis will be performed after approximately 329 PFS events have been documented per investigator assessment.

10.7.2 Key secondary endpoint: overall survival

Overall survival will be compared between the two treatment groups, provided the primary endpoint PFS is statistically significant favoring the test treatment arm (tamoxifen or a NSAI + goserelin + LEE011). A hierarchical testing procedure will be adopted in this study and the OS analyses will be performed only if the primary efficacy endpoint PFS is statistically significant. A maximum of three analyses are planned for OS: at the time of the primary analysis for PFS (provided PFS is significant), at which point a total of 123 deaths are expected, after approximately 189 events have been documented, and a final analysis for OS when 252 deaths are expected (expected 40 months from date of first patient to be randomized).

An α -spending function according to Lan-DeMets (O'Brien-Fleming), (as implemented in East 6.3) along with the testing strategy outlined below will be used to maintain the overall type I error probability (Lan and DeMets 1983). This guarantees the protection of the 2.5% overall level of significance across the two hypotheses and the repeated testing of the OS hypotheses in the interim and the final analysis (Glimm 2010). The trial allows for the stopping of the study for a superior OS result, provided the primary endpoint PFS has already been shown to be statistically significant favoring the test treatment arm (tamoxifen or a NSAI + goserelin +

LEE011). Further, the exact nominal p-values that will need to be observed to declare statistical significance at the time of these analyses for OS will depend on the number of OS events that have been observed at the time of these analyses and the α for OS already spent at the time of earlier analyses.

The projected timing of interim analysis is summarized in [Table 10-1](#).

Table 10-1 Estimated timelines for interim and final analyses

Months after randomization of the first patient	PFS events	Cumulative Power (%) against a hazard ratio of 0.67	OS events	Cumulative Conditional Power (%) against hazard ratio of 0.7
22	329 (100%)	95	123 (49%)	15
30	--	--	189 (75%)	54
40	--	--	252(100%)	80
Statistical significance of OS will only be declared if significance for primary PFS analysis has been declared				

At the time of primary PFS analyses, both PFS and interim OS analysis will be performed by the Sponsor's clinical team. Investigators and patients will remain blinded to study treatment and all patients will continue to be followed for OS until the final OS analysis (or earlier if OS reaches statistical significance at any of the interim analyses).

10.8 Sample size calculation

The assumption of median PFS of 9 months in the control arm (tamoxifen/NSAI + goserelin) for sample size calculation is based on the meta analysis of 4 trials in premenopausal advanced breast cancer treated with combination of tamoxifen and luteinizing hormone-releasing hormone agonist ([Klijn 2001](#)) and the results of the letrozole study in breast cancer patients ([Mouridsen 2003](#)). It is expected that the addition of LEE011 will result in 33% reduction in the hazard rate (corresponding to an increase in median PFS to 13.4 months assuming PFS has an exponential model assumption).

If the true hazard ratio is 0.67 (under alternative hypothesis), a total of 329 PFS events provide 95% power at a one-sided overall 2.5% level of significance to reject the null hypothesis (hazard ratio=1). Considering a recruitment period of approximately 18 months at a uniform rate of 33 patients/month, 600 patients will need to be randomized to the two treatment arms in a 1:1 ratio. Assuming about 10% patients will be lost to follow-up for PFS, a total of 660 patients will need to be randomized. Given the above assumptions, it is estimated that the 329th PFS event will be observed at approximately 22 months from the date of first patient randomized in the study. The sample size calculation was conducted with software package East 6.3.

It is expected that both the endocrine treatment types (tamoxifen and NSAI) will have an adequate number of patients randomized for the respective subgroup analyses (Section 10.4.2). However, this will be monitored closely in a blinded fashion and the protocol may be amended for further randomization in a given group if enrollment is found to be slow.

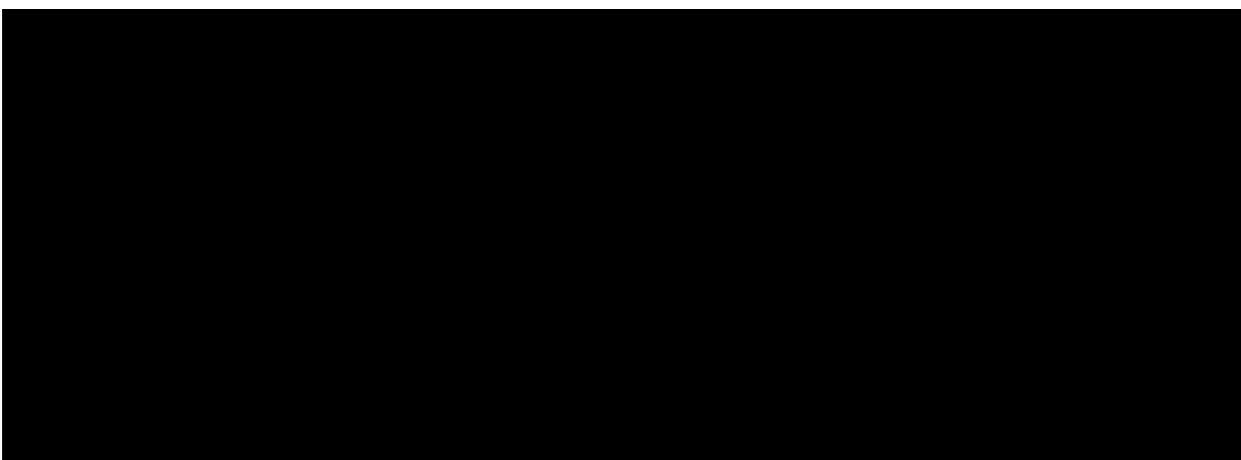
Audit size calculation for BIRC assessment of PFS

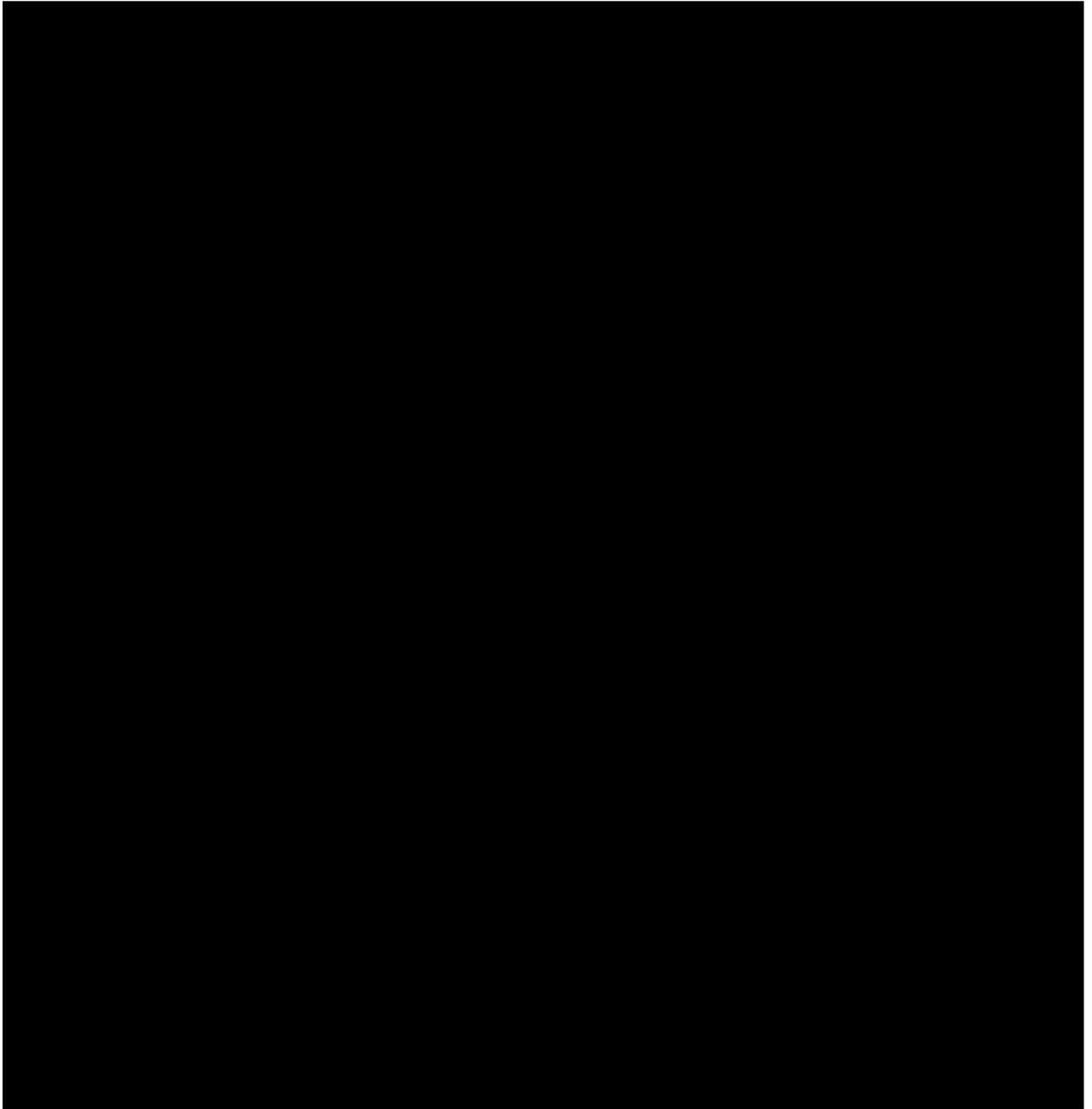
The audit size of the sample-based BIRC assessment will be 40% of all randomized patients. Based on the audit size calculation approach proposed by [Dodd et al \(2011\)](#), assuming investigator and BIRC assessments are similar and the estimated log of investigator-based HR is -0.40 (i.e. HR=0.67), the audit size of 40% will ensure that the upper bound of a one-sided 95% CI for BIRC-based log-hazard ratio has 86% probability of being below zero (i.e. HR < 1) if the correlation between investigator assessment and BIRC assessment is 0.7 (the estimated correlation based on data from the BELLE-2 [\[CBKM120F2302\]](#) study in metastatic breast cancer).

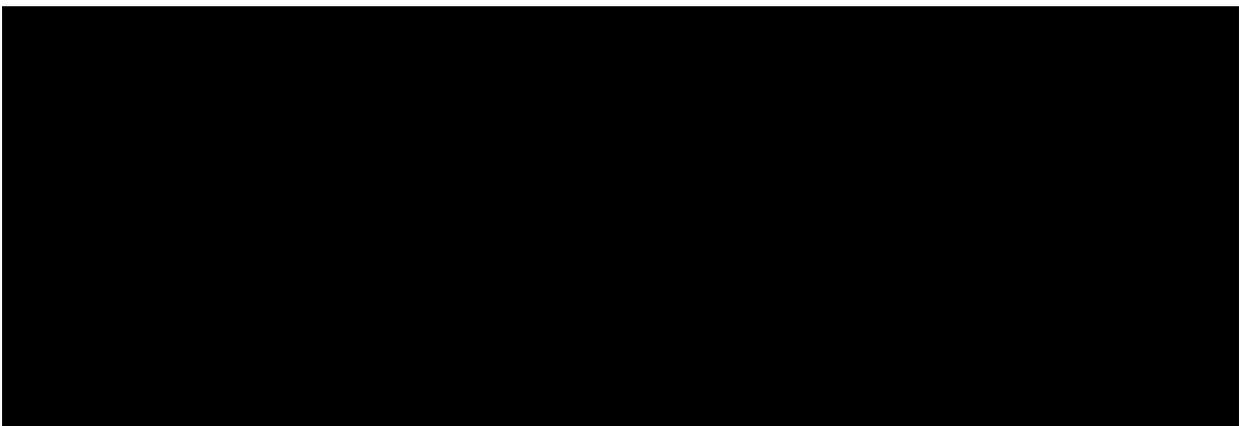
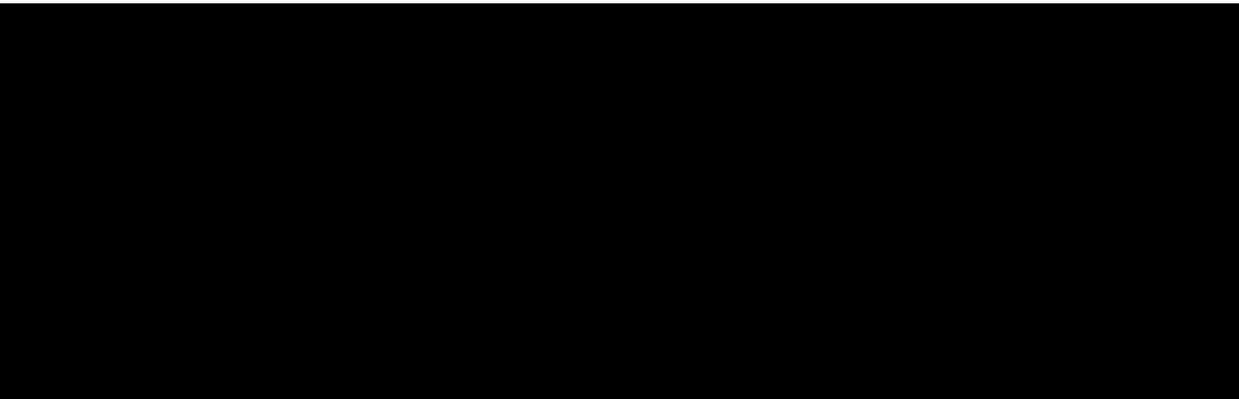
10.9 Power for analysis of key secondary variables

10.9.1 Power for analysis of overall survival

OS will be compared between the two treatment arms, provided that the primary endpoint, PFS, is statistically significant. Based on available data ([Klijn 2001](#), [Jonat 1995](#)) the median OS in control arm is expected to be around 33 months. It is hypothesized that test treatment arm (LEE011 + tamoxifen or a NSAI + goserelin) will result in a 30% reduction in the hazard rate for OS (corresponding to an increase in median survival to 47 months under the exponential model assumption). If the true hazard ratio is 0.7 (under alternative hypothesis), a total of 252 deaths need to be observed to have 80% power at a one-sided overall 2.5% level of significance to reject the null hypotheses (hazard ratio = 1) using a log-rank test and a 3-look group sequential design. Based on the same number of patients that are planned to be enrolled in this study to detect the primary endpoint, it is estimated that these 252 deaths will be observed at approximately 40 months from the date of first patient to be randomized. Therefore the estimated time for the final OS evaluation will be 18 months after the primary analysis of the PFS endpoint has been conducted. The power calculation was conducted with software package East 6.3.







11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent or, if incapable of

doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given her understanding. If the patient is capable of doing so, she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in [Section 4.4](#).

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. www.clinicaltrials.gov before study start. In addition, results of interventional clinical trials in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e., LPLV), those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. For electronic CRFs an audit trail will be maintained by the system.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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14 Appendices

14.1 Appendix 1 - Concomitant medications

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited below. Combination administration of study drugs could result in drug-drug interactions (DDI) that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or LEE011 and/or tamoxifen.

The following lists are not comprehensive and are only meant to be used as a guide. The lists are based on the Oncology Clinical Pharmacology guidance, Drug-Drug Interaction and Co-Medication Considerations (v05, release date: 2015), which was compiled from the Indiana University School of Medicine's P450 Drug Interaction Table (<http://medicine.iupui.edu/clinpharm/ddis/main-table/>) and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012) (<http://fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf>), and the University of Washington's Drug Interaction Database (<http://druginteractioninfo.org/>). For current lists of medications that may cause QT prolongation and/or torsades de pointes (TdP), refer to the CredibleMeds® website (<https://qtdrugs.org/>). Please contact the medical monitor with any questions.

Table 14-1 List of prohibited medications during study drug treatment

Category	Drug Name
Strong CYP3A4/5 inhibitors	Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, eltegravir/ritonavir, grapefruit juice, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole
Strong CYP3A4/5 inducers	Avasimibe ^{2,3} , carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin) ³ , St. John's wort (<i>hypericum perforatum</i>) ³
Strong CYP2D6 inhibitors or inducers (for patients receiving tamoxifen)	Bupropion, dacomitinib, fluoxetine, paroxetine, quinidine
CYP3A4/5 substrates with NTI ¹	Alfentanil, apixaban (doses >2.5 mg only), aprepitant, astemizole, cisapride, cyclosporine, diergotamine, dihydroergotamine, ergotamine, fentanyl, lovastatin, nicardipine, nisoldipine, pimozide, quinidine, rivaroxaban, simvastatin, sirolimus, tacrolimus, terfenadine, thioridazine
Medications with a known risk for QT prolongation ⁴	Amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl, mesoridazine, methadone, moxifloxacin, ondansetron (i.v. only), pentamidine, pimozide, probucol, procainamide, propofol, quinidine, sevoflurane, sotalol, sparfloxacin, sulpiride, terfenadine, thioridazine, vandetanib, venlafaxine
Herbal preparations/medications and dietary supplements	Herbal preparations/medications are prohibited throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), ginkgo biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh, and ginseng. Patients should stop using these medications 7 days prior to first dose of study drug.
Other investigational and antineoplastic therapies	Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued study drug.
¹ NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes). ² Herbal product ³ P-gp inducer ⁴ Source: //qtldrugs.org (as of Apr 7, 2015)	

Table 14-2 List of medications to be used with caution during study drug treatment

Category	Drug Name
Moderate CYP3A4/5 inhibitors	Amprenavir, atazanavir, casopitant, cimetidine, darunavir, diltiazem, fosamprenavir, lomitapide, netupitant, tofisopam, verapamil
Moderate CYP3A4/5 inducers	Bosentan, efavirenz, etravirine, genistein, lersivirine, modafinil, nafcillin, talviraline
Sensitive CYP3A4/5 substrates ¹	Alpha-dihydroergocryptine, almorexant, alpaviroc, apixaban (doses < 2.5 mg only), atazanavir, atorvastatin, avanafil, bosutinib, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, darifenacin, darunavir, ebastine, eletriptan, eplerenone, felodipine, fluticasone, ivacaftor, lomitapide, lumefantrine, lurasidone, maraviroc, midazolam, perospirone, quetiapine, ridaforolimus, sildenafil, ticagrelor, tilidine, tolvaptan, triazolam, vardenafil, vicriviroc, voclosporin
Strong BSEP inhibitors	Bosentan, fusidate, glibenclamide, , sulindac, troglitazone (TGZ-sulfate)
MATE1 and OCT2 substrates ²	Acyclovir, amantadine, amiloride, cephalixin, cephradine, cimetidine, famotidine, fexofenadine, memantine, metformin (also a substrate for OCT1, MATE1, and MATE2K), pindolol, procainamide, ranitidine, varencicline
BCRP substrates	Rosuvastatin and sulfasalazine
Medications that carry a possible risk for QT prolongation ³	Alfuzosin, apomorphine, aripiprazole, atazanavir, atomoxetine, bedaquiline, clozapine, dexmedetomidine, dolasetron, eribulin, famotidine, felbamate, fingolimod, foscarnet, gatifloxacin, gemifloxacin, granisetron, iloperidone, isradipine, lithium, mirabegron, mirtazapine, moexipril, norfloxacin, ofloxacin, olanzapine, ondansetron (p.o. only at 4 mg or 8 mg), oxytocin, paliperidone, pasireotide, pipamperone, promethazine, quetiapine, ranolazine, rilpivirine, risperidone, roxithromycin, sertindole, telavancin, tetrabenazine, tizanidine, tolterodine, vardenafil, ziprasidone
CYP2C19 or CYP2A6 substrates with NTI (for patients receiving letrozole)	S-mephenytoin
CYP2C9 or CYP2D6 with NTI (for patients receiving tamoxifen)	Phenytoin, warfarin
¹ Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor. ² FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and implications for Dosing and Labeling (February 2012) and Yonezawa and Inui (2011) Importance of the multidrug and toxin extrusion MATE/SLC47A family to pharmacokinetics, pharmacodynamics/toxicodynamics and pharmacogenomics. Br J Pharmacology 164:1817-25 ³ Source: //qtodrugs.org (as of Apr 7, 2015)	

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> 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

Note: The questionnaire provided here is a sample for information purposes only. Paper questionnaires for patient completion in the study will be provided by Novartis to be used as source documents.

Figure 14-2 EORTC QLQ-BR23



ENGLISH

EORTC QLQ - BR23

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

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

ENGLISH

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

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Note: The questionnaire provided here is a sample for information purposes only. Paper questionnaires for patient completion in the study will be provided by Novartis to be used as source documents.

Figure 14-3 EQ-5D-5L

Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

- I have no problems walking
- I have slight problems walking
- I have moderate problems walking
- I have severe problems walking
- I am unable to walk

SELF-CARE

- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

PAIN / DISCOMFORT

- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

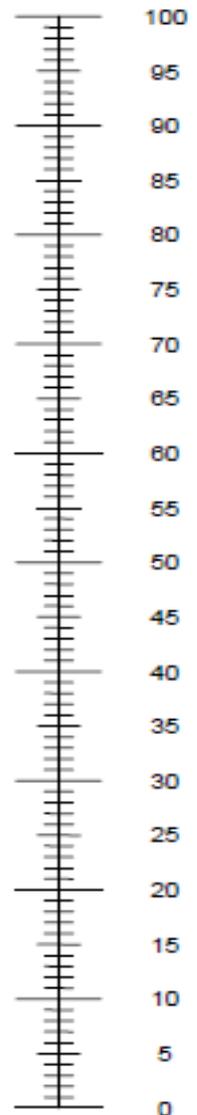
ANXIETY / DEPRESSION

- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

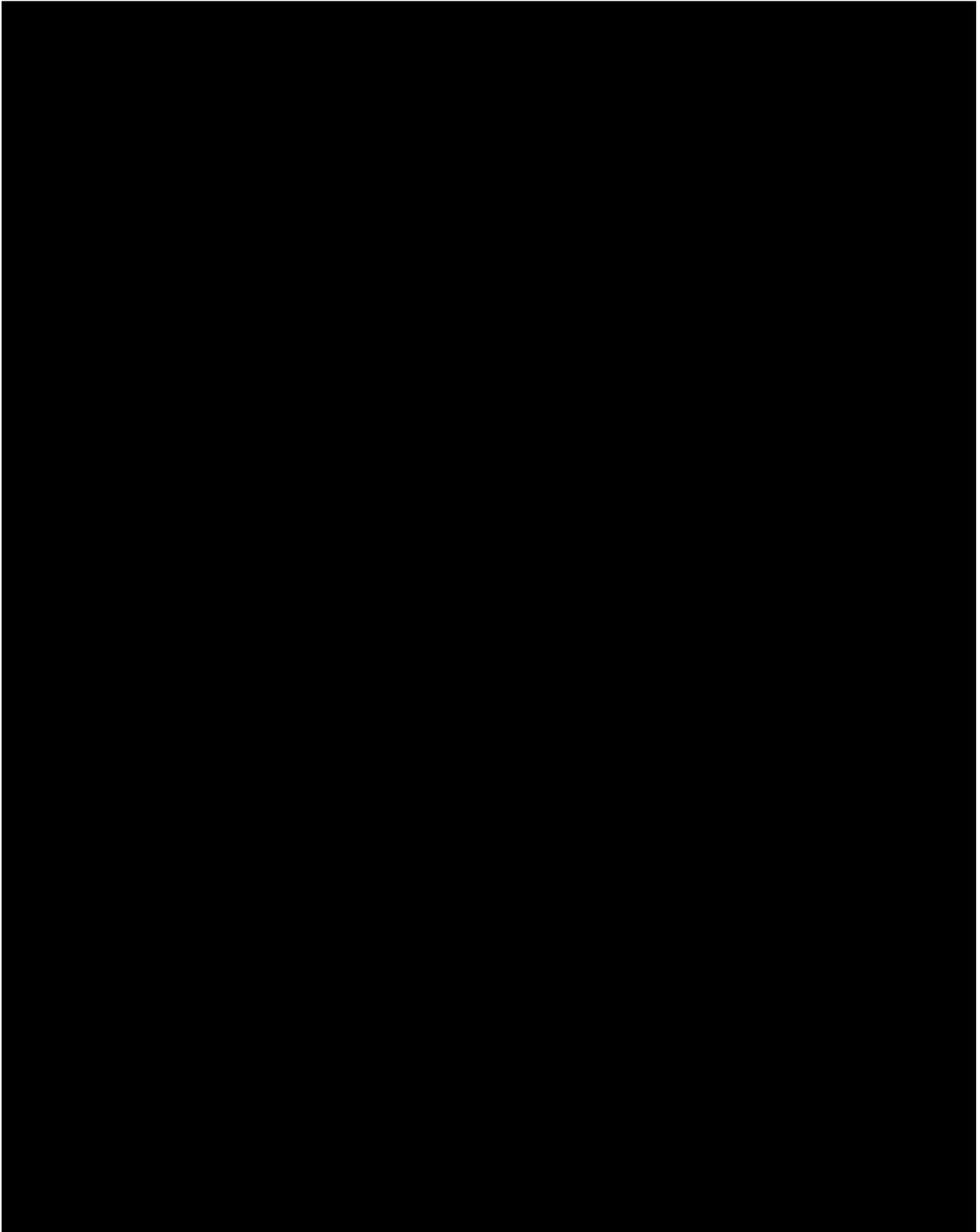
YOUR HEALTH TODAY =

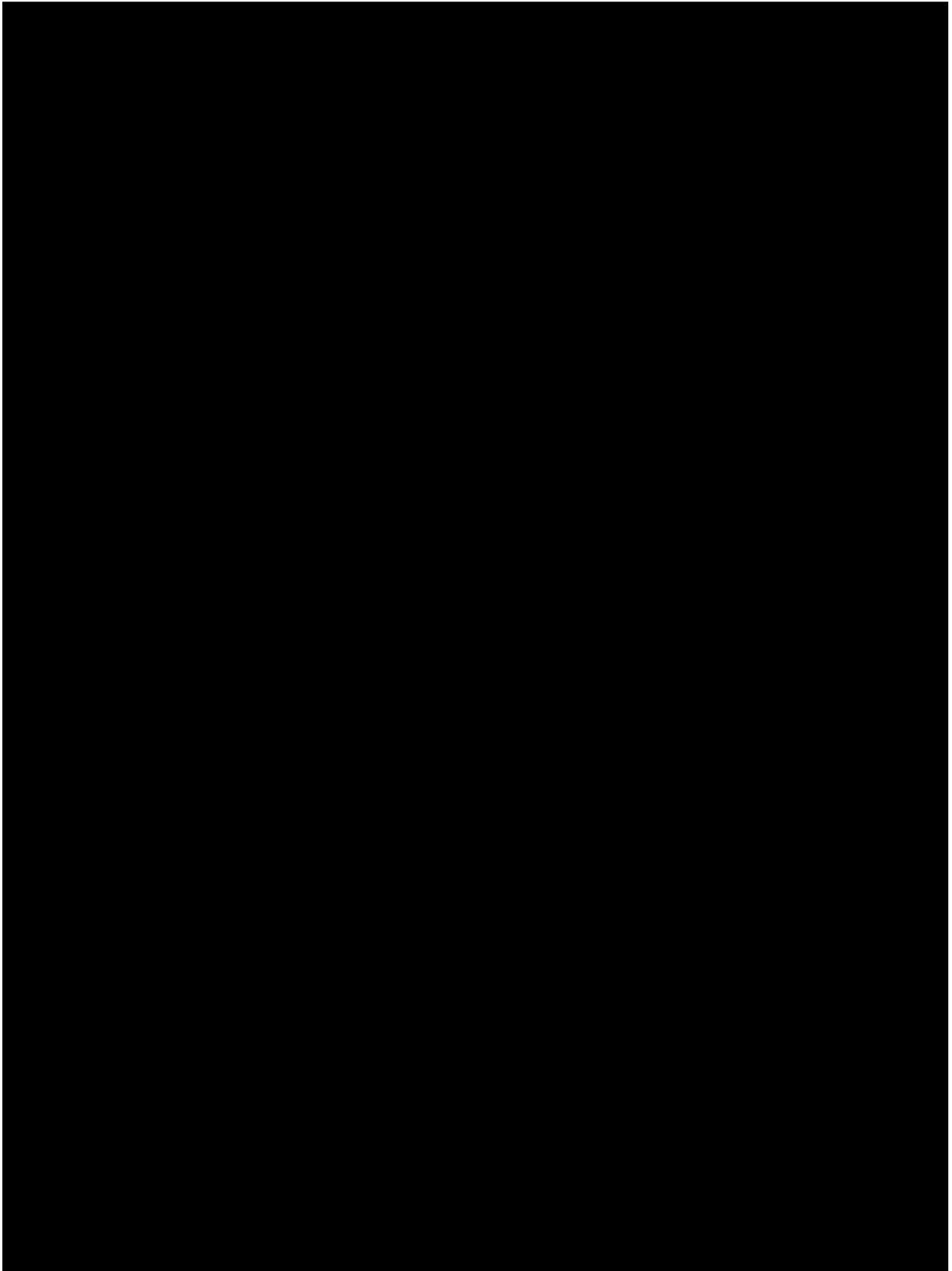
The best health
you can imagine



The worst health
you can imagine

Note: The questionnaire provided here is a sample for information purposes only.
Paper questionnaires for patient completion in the study will be provided by Novartis to be used as source documents.





14.3 Appendix 3 - Guidelines for response, duration of overall response, TTF, TTP, progression-free survival and overall survival (based on RECIST 1.1)

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Glossary

CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FPFV	First patient first visit
GBM	Glioblastoma multiforme
LPLV	Last patient last visit
MRI	Magnetic resonance imaging
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression
UNK	Unknown

1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses ([Therasse et al 2000](#)) and the revised RECIST 1.1 guidelines ([Eisenhauer et al 2009](#)).

The efficacy assessments described in [Section 2](#) and the definition of best response in [Section 3.1](#) are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. [Section 3.2](#) is summarizing the “time to event” variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. [Section 4](#) of this guideline describes data handling and programming rules. This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.

2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria ([Therasse et al 2000](#)), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) ([Eisenhauer et al 2009](#)) European Journal of Cancer; 45:228-247.

Indicate the assessment schedule for tumor assessments in the protocol. Frequency of tumor re-evaluation while on treatment should be adapted to the type and schedule of treatment, and the type of tumor treated. It should also be clearly stated how patients are followed for progression after discontinuation of study treatment.

It is assumed that all information which is considered for assessment of the tumor is captured in the RECIST eCRF, i.e. not merged from several sources.

2.1 Definitions

2.1.1 Disease measurability

In order to evaluate tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability, a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

- **Measurable disease** - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see [Section 3.2.9](#).

Measurable lesions (both nodal and non-nodal)

- **Measurable non-nodal** - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.

- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥ 15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥ 10 mm and < 15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.
- **Cystic lesions:**
 - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
 - ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- **Non-measurable lesions** - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter < 10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

If any lesion should be handled differently, this must be clearly stated and justified in the protocol, e.g. tumor lesions that are situated in a previously irradiated area might or might not be considered measurable, and the conditions under which such lesions should be considered must be defined in the protocol when appropriate.

2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in [Section 3.2.9](#).

2.2 Methods of tumor measurement - general guidelines

In this document, the term “contrast” refers to intravenous (i.v) contrast.

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

If different window for baseline assessments is allowed in the protocol this must be justified in the protocol.

- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.
- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a major change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT or vice versa will not constitute a major “change in method” for the purposes of response assessment. A change in methodology will result by default in a UNK overall lesion response assessment as per Novartis calculated response. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.

If head and neck tumors and those of extremities are evaluated in the study, please specify the methods in detail in the protocol.

- **FDG-PET:** can complement CT scans in assessing progression (particularly possible for ‘new’ disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
 - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
 - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If new disease is indicated by a positive PET scan but is not confirmed by CT (or some other conventional technique such as MRI) at the same assessment, then follow-up assessments by CT will be needed to determine if there is truly progression occurring at that site. In all cases, PD will be the date of confirmation of new disease by CT (or some other conventional technique such as MRI) rather than the date of the positive PET scan. If there is a positive PET scan without any confirmed progression at that site by CT, then a PD cannot be assigned.

- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- **Chest x-ray:** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Physical exams:** Evaluation of lesions by physical examination is accepted when lesions are superficial, with at least 10mm size and can be assessed using calipers.
- **Ultrasound:** When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions, unless pre-specified by the protocol. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy:** The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- **Tumor markers:** Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

Less validated exploratory soluble biomarkers are not considered in this document but can be included on study by study basis.

If tumor markers are used in the study for the response assessment, the criteria must be clearly stated in the protocol and the presence of abnormality in tumor markers must be entered in the eCRF page for RECIST evaluations (see also [Section 2.4](#)).

- **Cytology and histology:** Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).

When pathological response is being used, the protocol must clearly state details on how pathological responses are documented.

- **Clinical examination:** Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

If the protocol is considering specific symptoms as objective signs of clinical progression, e.g. bone pain or GI bleeding, then the criteria for clear worsening of these non-measurable ‘lesions’ indicative of PD should be clearly specified in the protocol. In that case, the protocol should clearly specify that additional criteria are used to complement RECIST criteria.

2.3 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- **Target lesions:** All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target:** Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See [Section 2.1.1](#).
- **Nodal target:** See [Section 2.1.1](#).

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- **Non-target lesions:** All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

If the protocol is considering specific symptoms for assessment of the tumor, e.g. bone pain or GI bleeding, then these symptoms are to be entered as non-target lesions with either presence or absence or as a new lesion (based on protocol specified criteria). In that case, the protocol should clearly specify that additional criteria are used to complement RECIST criteria.

For cancers which are known to metastasize to bone, the protocol should specify if and how bone lesions should be handled, e.g., if they should be followed throughout the study by CT, MRI or x-ray.

2.4 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 2-1) and non-target lesions (Table 2-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 2-3) as well as the presence or absence of new lesions.

If tumor markers are used as non-target lesions to evaluate response, please specify criteria for CR, SD and PD in the protocol, e.g. CR='Normalization of tumor marker level', PD='Elevation of tumor markers to certain level', SD='Not qualifying for CR or PD'. These criteria are indication and study specific. In that case, the protocol should clearly specify that additional criteria are used to complement RECIST criteria.

2.4.1 Follow-up and recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number.

2.4.1.1 Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are subject to substantial "partial volume" effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

2.4.1.2 Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a “non-zero size” will always persist.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

2.4.2 Determination of target lesion response

Table 2-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm ¹
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm ² .
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline. ³

¹. SOD for CR may not be zero when nodal lesions are part of target lesions

². Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR

³. In exceptional circumstances an UNK response due to change in method could be over-ruled by the investigator or central reviewer using expert judgment based on the available information (see Notes on target lesion response and methodology change in [Section 2.2](#)).

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the “0 mm” recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in [Table 2-1](#) above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- **Missing measurements:** In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.
- **Nodal lesion decrease to normal size:** When nodal disease is included in the sum of target lesions and the nodes decrease to “normal” size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- **Lesions split:** In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- **Lesions coalesced:** Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the “merged lesion” should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the “merged lesion” should be recorded for the size of one of the original lesions while a size of “0”mm should be entered for the remaining lesion numbers which have coalesced.

- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
 - Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
 - Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
 - Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion “reappears” or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.
 - A change in method for the evaluation of one or more lesions will usually lead to an UNK target lesion response unless there is progression indicated by the remaining lesions which have been evaluated by the same method. In exceptional circumstances an investigator or central reviewer might over-rule this assignment to put a non-UNK response using expert judgment based on the available information. E.g. a change to a more sensitive method might indicate some tumor shrinkage of target lesions and definitely rule out progression in which case the investigator might assign an SD target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria.

2.4.3 Determination of non-target lesion response

Table 2-2 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions. ¹
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline ²

¹. The assignment of PD solely based on change in non-target lesions in light of target lesion response of CR, PR or SD should be exceptional. In such circumstances, the opinion of the investigator or central reviewer does prevail.

². It is recommended that the investigator and/or central reviewer should use expert judgement to assign a Non-UNK response wherever possible (see notes section for more details)

Notes on non-target lesion response

- The investigator and/or central reviewer can use expert judgment to assign a non-UNK response wherever possible, even where lesions have not been fully assessed or a different method has been used. In many of these situations it may still be possible to identify equivocal progression (PD) or definitively rule this out (non-CR/Non-PD) based on the available information. In the specific case where a more sensitive method has been used indicating the absence of any non-target lesions, a CR response can also be assigned.

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK).
- **Unequivocal progression:** To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in [Section 2.4.2](#) for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

2.4.4 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion CRF page.

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see [Section 2.5](#)).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See [Section 2.2](#).

2.5 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in [Table 2-3](#).

Table 2-3 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR ¹
CR	Non-CR/Non-PD ³	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR ¹
SD	Non-PD and not UNK	No	SD ^{1,2}
UNK	Non-PD or UNK	No	UNK ¹
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

¹. This overall lesion response also applies when there are no non-target lesions identified at baseline.

². Once confirmed PR was achieved, all these assessments are considered PR.

³. As defined in [Section 2.4](#)

If there are no baseline scans available at all, then the overall lesion response at each assessment should be considered Unknown (UNK).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. [Section 3.2.9](#) outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

3.1 Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

Where a study requires confirmation of response (PR or CR), changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- -For non-randomized trials where response is the primary endpoint, confirmation is needed.
- -For trials intended to support accelerated approval, confirmation is needed
- For all other trials, confirmation of response may be considered optional.

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).

The protocol should state if randomization or start of treatment is used as start date (baseline). This is then used in all definitions.

If a different minimum follow-up period is required to classify for best overall response= 'stable disease', this must be specified in the protocol.

- PD = progression \leq 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).

If PD in a different follow-up period is considered to classify for best overall response='progressive disease', this must be specified in the protocol.

The protocol should state if discontinuation due to 'Disease progression' or death due to study indication is considered PD even if this was not accompanied by documentation of PD based on tumor measurements. This depends on Phase of the study and the primary endpoint (e.g. Phase III studies in which progression-free survival is primary endpoint should consider only documented PD, whereas Phase I and II studies may consider all clinical deteriorations PD). The following sentence therefore is only applicable if this is specified in the protocol:

Patients with symptoms of rapidly progressing disease without radiologic evidence will be classified as progression only when clear evidence of clinical deterioration is documented and/or patient discontinued due to 'Disease progression' or death due to study indication.

- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

The time durations specified in the SD/PD/UNK definitions above are defaults based on a 6 week tumor assessment frequency. However these may be modified for specific indications which are more or less aggressive. In addition, it is envisaged that the time duration may also take into account assessment windows. E.g. if the assessment occurs every 6 weeks with a time window of +/- 7 days, a BOR of SD would require a SD or better response longer than 5 weeks after randomization/start of treatment.

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR ($\geq 30\%$ reduction of tumor burden compared to baseline) at one assessment, followed by a $< 30\%$ reduction from baseline at the next assessment (but not $\geq 20\%$ increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

If the patient progressed but continues study treatment, further assessments are not considered for the determination of best overall response.

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- Novartis calculated overall lesion response (based on measurements from either Investigator or Central Review)

The primary analysis of the best overall response will be based on the sequence of investigator/central blinded review/calculated (investigator)/calculated (central) overall lesion responses.

Specify which determination of best overall response will be considered primary (and delete the other terms in the text). If a central blinded review is used (e.g. in an open-label study in which response is the primary endpoint), the best overall response evaluated by the central blinded review will always be considered the primary response.

Based on the patients' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD. The objective of this endpoint is to summarize patients with signs of "activity" defined as either shrinkage of tumor (regardless of duration) or slowing down of tumor growth.

Clinical benefit rate (CBR) is the proportion of patients with a best overall response of CR or PR, or an overall lesion response of SD or Non-CR/Non-PD which lasts for a minimum time duration (with a default of at least 24 weeks in breast cancer studies). This endpoint measures signs of activity taking into account duration of disease stabilization.

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of patients with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of [Dent and Zee \(2001\)](#) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks \pm window) do not have an overall lesion response of SD, PR or CR. Patients with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

3.2 Time to event variables

The protocol should state which of the following variables is used in that study.

3.2.1 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a

patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

PFS rate at x weeks is an additional measure used to quantify PFS endpoint. It is recommended that a Kaplan Meier estimate is used to assess this endpoint.

3.2.2 Overall survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death (“Study indication” or “Other”).

Overall survival (OS) is defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.

3.2.3 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable “Time to progression” might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

3.2.5 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure

may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than ‘Protocol violation’ or ‘Administrative problems’. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

3.2.6 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by [Morgan \(1988\)](#).

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a “responders only” descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates... If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to “responders” only) using appropriate statistical methods such as the techniques described in [Ellis et al \(2008\)](#). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on “responders” only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall complete response (CR): For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

3.2.7 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the “responders” subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in [Section 3.2.6](#). It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a “responders only” descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

Indicate in the protocol whether a subgroup analysis of responders only will be performed in addition to the full population analysis (which should be included as default).

3.2.8 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

In the calculation of the assessment date for time to event variables, any unscheduled assessment should be treated similarly to other evaluations.

Start dates

State in the protocol if date of randomization or date of start of treatment is to be used for all definitions. For randomized studies specify exactly where the randomization date comes from, e.g. from IVRS, or if start of treatment is used as randomization date. For non-randomized studies please specify which treatment start date is taken if more than one treatment is to be given.

For all “time to event” variables, other than duration of response, the randomization/ date of treatment start will be used as the start date.

For the calculation of duration of response the following start date should be used:

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates

The end dates which are used to calculate ‘time to event’ variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.

If applicable, if patients who discontinued due to ‘Disease progression’ are considered to be PD solely based on clinical deterioration, then add the following text in the protocol:

When there is no documentation of radiologic evidence of progression, and the patient discontinued for ‘Disease progression’ due to documented clinical deterioration of disease, the date of discontinuation is used as date of progression.

- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see [Section 3.2.10](#)).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is

used. If no survival follow-up is available, the date of discontinuation is used as last contact date.

In comparative studies with long follow-up period and therefore extended visit schedule, it may be useful to collect the survival status at a pre-specified cut-off within a limited timeframe for all patients with no documented death. In this case, this requires a contact to be made with the patient or with any reliable source of information on the patient's status, but not requiring a specific visit to be scheduled

- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

If this is applicable for the study, it should be specified in the protocol if new cancer therapy is considered an event or endpoints are censored.

3.2.9 Handling of patients with non-measurable disease only at baseline

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

The protocol should state clearly whether patients with non-measurable disease only at baseline will be allowed into the study. If patients with non-measurable disease only are allowed to be enrolled then the statistical section should describe clearly how data from these patients will be incorporated into the primary analysis and main analyses of the key secondary endpoints. In studies where presence of measurable disease is expected to have a relatively large impact on the primary endpoint, this factor can even be considered as a stratification factor in the randomization process.

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

For studies which specifically exclude patients with non-measurable disease only at baseline the pre-specified analysis plan should describe how to handle data from these types of patients if they are enrolled by error or if central readers do not identify measurable disease despite investigators having declared the contrary, or conversely perhaps they do identify measurable disease when it has not been identified at the local site. It is recommended for these types of studies that patients with non-measurable disease identified through the local site evaluation be included in the list of protocol violations. However, decisions on exclusion from a per protocol analysis should relate to whether the patient has measurable disease according to the primary data source. For example, if the primary data source is from a central independent review then patients with non-measurable disease only according to this central review should be excluded from the relevant per protocol analyses.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with non-measurable disease is derived slightly differently according to Table 3-1.

Table 3-1 Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD ¹	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

¹ As defined in [Section 2.4](#)

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as “responders” with respect to ORR and all other patients as “non-responders”.

Study teams may also want to perform sensitivity analyses excluding patients from the analysis of ORR (e.g. possibly as part of a per-protocol type analysis). Similar considerations should be given to other endpoints which rely on a clear distinction being made between a PR and a SD response.

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients with only non-measurable disease.

3.2.10 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in [Section 3.2.8](#), and using the draft FDA guideline on endpoints ([Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005](#)) as a reference, the following analyses can be considered:

Table 3-2 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring) ¹ (1) = default unless specified differently in the protocol or RAP	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment ³	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment ²	Progressed Progressed
C1	Progression or death after exactly one missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment ²	Progressed Progressed
C2	Progression or death after two or more missing assessments	(1) Date of last adequate assessment ² (2) Date of next scheduled assessment ² (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) Ignore clinical progression and follow situations above (2) Date of discontinuation (visit date at which clinical progression was determined)	As per above situations Progressed
F	New anticancer therapy given	(1) Ignore the new anticancer therapy and follow situations above (ITT approach) (2) Date of last adequate assessment prior to new anticancer therapy (3) Date of secondary anti-cancer therapy (4) Date of secondary anti-cancer therapy	As per above situations Censored Censored Event
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

¹.=Definitions can be found in [Section 3.2.8](#)
².=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in [Section 3.2.8](#).
³.=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may

be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), (ITT) is the recommended approach; events documented after the initiation of new cancer therapy will be considered for the primary analysis i.e. progressions and deaths documented after the initiation of new cancer therapy would be included as events. This will require continued follow-up for progression after the start of the new cancer therapy. In such cases, it is recommended that an additional sensitivity analysis be performed by censoring at last adequate assessment prior to initiation of new cancer therapy.

Option (2), i.e. censoring at last adequate assessment may be used as a sensitivity analysis. If a high censoring rate due to start of new cancer therapy is expected, a window of approximately 8 weeks performed after the start of new cancer therapy can be used to calculate the date of the event or censoring. This should be clearly specified in the analysis plan.

In some specific settings, local treatments (e.g. radiation/surgery) may not be considered as cancer therapies for assessment of event/censoring in PFS/TTP/DoR analysis. For example, palliative radiotherapy given in the trial for analgesic purposes or for lytic lesions at risk of fracture will not be considered as cancer therapy for the assessment of BOR and PFS analyses. The protocol should clearly state the local treatments which are not considered as antineoplastic therapies in the PFS/TTP/DoR analysis.

The protocol should state that tumor assessments will be performed every x weeks until radiological progression irrespective of initiation of new antineoplastic therapy. It is strongly recommended that a tumor assessment is performed before the patient is switched to a new cancer therapy.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in [Table 3-2](#) the “Date of last adequate assessment” by the “Date of previous scheduled assessment (from baseline)”, with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

4 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

4.1 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

4.2 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

Patients may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor

- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

Death is a reason which “*must*” lead to discontinuation of the patient from the trial.

4.3 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor

4.4 Medical validation of programmed overall lesion response

In order to be as objective as possible, the RECIST programmed calculated response assessment is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD). This contrasts with the slightly more flexible guidance given to local investigators (and to the central reviewers) to use expert judgement in determining response in these types of situations, and therefore as a consequence, discrepancies between the different sources of response assessment often arise. To ensure the quality of response assessments from the local site and/or the central reviewer, the responses may be re-evaluated by clinicians (based on local investigator data recorded in the eCRF or based on central reviewer data entered in the database) at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators’ or central reader’s opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader’s response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the

RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

4.5 Programming rules

The following should be used for programming of efficacy results:

4.5.1 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

4.5.2 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in [Section 3.2.8](#)). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

4.5.3 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

4.5.4 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

4.5.5 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

4.5.6 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see [Table 3-2](#))
- Death due to reason other than underlying cancer (*only used for TTP and duration of response*)
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in [Section 3.2.8](#). This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

5 References (available upon request)

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Eisenhauer E, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). *European Journal of Cancer*, Vol.45: 228-47

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14.4 Appendix 4 - Bone Marrow Reserve in Adults

Adapted from R.E. ELLIS: The Distribution of Active Bone Marrow in the Adult, Phy. Med. Biol. 5, 255-258, 1961

MARROW DISTRIBUTION OF THE ADULT

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
CRANIUM AND MANDIBLE	Head:			136.6	13.1	13.1
	Cranium	165.8	0.75	124.3		
	Mandible	16.4	0.75	12.3		
HUMERI, SCAPULAE, CLAVICLES	Upper Limb Girdle :	26.5	0.75	86.7	8.3	8.3
	2 Humerus, head & neck			20.0		
	2 Scapulae	67.4	0.75	50.5		
	2 Clavicles	21.6	0.75	16.2		
STERNUM AND RIBS	Sternum	39.0	0.6	23.4	2.3	10.2
	Ribs:			82.6	7.9	
	1 pair	10.2	All 0.4	4.1		
	2	12.6		5.0		
	3	16.0		6.4		
	4	18.6		7.4		
	5	23.8		9.5		
	6	23.6		9.4		
	7	25.0		10.0		
	8	24.0		9.6		
	9	21.2		8.5		
	10	16.0		6.4		
	11	11.2		4.5		
12	4.6		1.8			
PELVIC BONES	Sacrum	194.0	0.75	145.6	13.9	36.2
	2 os coxae	310.6	0.75	233.0	22.3	
FEMUR	2 Femoral head and neck	53.0	0.75	40.0		3.8