Official Title: A Randomized, Multicenter, Open Label Phase III Study to Evaluate the Efficacy and Safety of Trastuzumab Emtansine Versus Trastuzumab as Adjuvant Therapy for Patients with HER2-POSITIVE Primary Breast Cancer who have Residual Tumor Present Pathologically in the Breast or Axillary Lymph Nodes Following Preoperative Therapy

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STATISTICAL ANALYSIS PLAN

STUDY TITLE:	**A RANDOMIZED, MULTICENTER, OPEN LABEL PHASE III STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TRASTUZUMAB EMTANSINE VERSUS TRASTUZUMAB AS ADJUVANT THERAPY FOR PATIENTS WITH HER2-POSITIVE PRIMARY BREAST CANCER WHO HAVE RESIDUAL TUMOR PRESENT PATHOLOGICALLY IN THE BREAST OR AXILLARY LYMPH NODES FOLLOWING PREOPERATIVE THERAPY**
STUDY NUMBER:	BO27938
STUDY NAME:	KATHERINE
VERSION NUMBER:	3
ROCHE COMPOUND(S):	Trastuzumab Emtansine (RO5304020)
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PLAN PREPARED BY:	[redacted], PhD

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

SPONSOR:	F. Hoffmann-La Roche Ltd
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STATISTICAL ANALYSIS PLAN VERSION HISTORY

SAP Version	Approval Date	Based on Protocol (Version, Approval Date)
3	See electronic date stamp on the final page of this document.	Version 7, 18 June 2021
2	1 November 2012	Version 1, 19 October 2012
1	28 June 2012	—

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

Statistical Analysis Plan (SAP) BO27938 has been amended to align with the protocol amendment version 7.

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

Sections	Description of Change	Rationale for Change
2.2; 2.3; 4.10.1	The study completion has been extended from 10 years post-first patient in (FPI) to 12 years post-FPI. extension of the study. The details of the planned interim and final analyses of OS have been updated accordingly. Notably, based on the revised projection for OS events, the third interim analysis of OS has been removed	Determination of sample size and interim analyses have been updated to reflect the extension of the study and to align with the revised projection for OS events as detailed in Protocol BO27938 version 7.

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Description
AE	adverse event
ATA	anti-therapeutic antibody
CHR	congestive heart failure
CI	confidence interval
CIS	carcinoma in situ
CTCAE	Common Terminology Criteria for Adverse Events
DCIS	ductal carcinoma in situ
DFS	disease-free survival
DRFI	distant recurrence-free interval
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
ePRO	electronic patient-reported outcome
EORTC	European Organisation for Research and Treatment of Cancer
ER	estrogen receptor
FDA	Food and Drug Administration
FPI	first patient enrolls in the study
HR	hazard ratio
HRQOL	health-related quality of life
ICH	International Conference on Harmonisation
iDCC	independent Data Coordinator Center
IDFS	invasive disease-free survival
iDMC	independent Data Monitoring Committee
IVRS/IWRS	interactive voice response system/interactive web response system
LCIS	lobular carcinoma in situ
LFT	liver function laboratory test
LVEF	left ventricular ejection fraction
MUGA	multiple-gated acquisition
NCI	National Cancer Institute
NSABP	National Surgical Adjuvant Breast and Bowel Project

1. BACKGROUND

The use of adjuvant trastuzumab in HER2-positive early-stage breast cancer improves patient outcomes as demonstrated in several large, randomized trials.

Preoperative chemotherapy in combination with trastuzumab is a standard of care for patients with HER2-positive locally advanced (Stage IIB to IIIC) breast cancer or in cases where patients wish to minimize the extent of breast cancer surgery. Compared with patients who attain a pathologic complete response (pCR) after preoperative therapy, patients with residual disease have a greater risk of recurrence and death. It is not known whether the application of additional non–cross-resistant agents in the adjuvant setting may benefit these patients, and there are no approved therapies for this specific clinical setting.

Trastuzumab emtansine has shown positive benefit – risk in patients who have previously progressed after chemotherapy and HER2-directed therapy. Study BO27938 is designed to evaluate the efficacy and safety of trastuzumab emtansine in patients with HER2-positive breast cancer who have not had pCR to commonly recommended preoperative therapy regimens.

This document describes the Statistical Analysis Plan (SAP) for the Phase III randomized Study BO27938.

The analyses described in this SAP will supersede those specified in Protocol BO27938 for the purposes of a regulatory filing.

2. STUDY DESIGN

Study BO27938 is a prospective, two-arm, randomized, multicenter, multinational, open label Phase III study evaluating the efficacy and safety of trastuzumab emtansine in patients with HER2-positive primary breast cancer who have received preoperative chemotherapy and HER2-directed therapy, followed by surgery, with a finding of residual invasive disease in the breast or axillary lymph nodes.

The trial will recruit approximately 1484 patients from approximately 400 sites worldwide. Only patients with centrally confirmed HER2-positive disease will be enrolled into this study. Patients will be randomized in a 1:1 ratio to either trastuzumab emtansine 3.6 mg/kg every 3 weeks (q3w) or trastuzumab 6 mg/kg q3w (an 8 mg/kg loading dose should be given if it has been more than 6 weeks since the last dose of trastuzumab). Study treatment will continue for 14 cycles, unless any of the following occurs: disease relapse, unacceptable toxicity, initiation of another anti-cancer therapy, or patient decision to discontinue study treatment. Patients who discontinue trastuzumab emtansine due to toxicity before 14 cycles may complete the duration of their study therapy with trastuzumab if appropriate based on toxicity considerations. Following discontinuation of study treatment, patients will be followed for invasive disease-free

survival (IDFS) events and survival. Patients in either treatment arm will be allowed to receive standard radiotherapy and/or hormonal therapy (for patients with hormonal positive disease) during the study as clinically indicated.

The primary efficacy endpoint of this Phase III study is IDFS, defined as the time between randomization and date of first occurrence of an IDFS event. Secondary endpoints include IDFS including second primary non-breast cancer, disease-free survival (DFS), overall survival (OS), and distant recurrence-free interval (DRFI). In addition, cardiac safety, liver safety, overall safety and patient-reported outcomes (PROs) of trastuzumab emtansine compared with control arm will also be evaluated.

2.1 PROTOCOL SYNOPSIS

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

2.2 DETERMINATION OF SAMPLE SIZE

The sample size of the study is primarily driven by the analysis of IDFS. To detect a hazard ratio (HR) of 0.75 in IDFS (a 6.5% improvement in 3-year IDFS from 70% in the control arm to 76.5% in the trastuzumab emtansine arm), approximately 384 IDFS events will be required to achieve 80% power at a two-sided significance level of 5%. Approximately 1484 patients will be enrolled in the study.

With the study sample size of 1484 patients and approximately *12 years* of follow-up from the date of randomization of the first patient, this study has approximately *43%* power to detect a HR of 0.8 in OS (a 2.8% improvement in 3-year OS from 85% in the control arm to 87.8% in the trastuzumab emtansine arm) at a two-sided significance level of 5%.

The sample size estimation was performed using East→Version 5.2 software (Cytel, Inc., Cambridge, MA).

2.3 ANALYSIS TIMING

The study is expected to be fully enrolled around 35 months after the first patient enrolls in the study (FPI).

The interim efficacy analysis of IDFS is planned after 67% of the targeted IDFS events have occurred, which is estimated to be approximately 48 months after the first patient is enrolled in the study. If the accrual rate or event rate are different from expected, the timing of the interim analysis may be delayed such that the interim analysis will only take place after all patients have enrolled and have completed treatment. The final IDFS analysis will be performed after approximately 384 events have occurred, which is projected to be approximately *107 months* from FPI. Additional details are provided in Section 4.10.1.

Two formal interim OS analyses and one final OS analysis are planned: the first OS interim analysis will be performed at the time of the interim IDFS analysis (approximately 48 months from FPI) if the interim IDFS analysis crosses the boundary; *the second interim OS analysis will be performed at the time of the final IDFS analysis when 384 IDFS events have occurred (approximately 107 months from FPI) in the case where the interim IDFS analysis crosses the boundary*. The final OS analysis will be performed at the end of *12 years* of follow-up from the date of randomization of the first patient. Additional details are provided in Section 4.10.1.

One safety interim analysis regarding death and hepatic events is planned after 600 patients have been randomized and followed for 3 months (approximately 21 months from FPI). Additional details are provided in Section 4.10.2.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Eligible patients will be randomized in a 1:1 ratio by a permuted block randomization scheme to one of the two treatment arms (trastuzumab or trastuzumab emtansine) through use of the interactive voice response system/interactive web response system (IVRS/IWRS).

Randomization will be stratified by the stratification factors:

- Clinical stage at presentation: inoperable (Stage T4NxM0 or TxN2–3M0) versus operable (Stages T1-3N0–1M0)
- Hormone receptor status: estrogen receptor (ER) or progesterone receptor (PR) positive versus ER and PR negative/unknown
- Preoperative HER2-directed therapy: trastuzumab versus trastuzumab plus additional HER2-directed agent(s)
- Pathologic nodal status evaluated after preoperative therapy: node positive versus node negative/not done

3.2 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (iDMC) will monitor accumulating safety data every 6 months. In addition, the iDMC will review data on deaths and serious adverse events (SAEs) every 3 months. The iDMC will also assess safety and efficacy as part of the interim efficacy and safety analyses. At each iDMC review, relevant safety information from ongoing trastuzumab emtansine studies will be provided to the iDMC. An independent Data Coordinator Center (iDCC) will perform unblinded analyses to support the periodic iDMC review of safety data. Additional details will be provided in the iDMC Charter.

3.3 CLINICAL EVENTS COMMITTEE

An independent safety advisory board will adjudicate prespecified safety events of interest (cardiac and hepatic dysfunction events). Additional details will be provided in the Clinical Events Committee Charter. An independent safety advisory board will adjudicate prespecified safety events of interest (cardiac and hepatic dysfunction events). Additional details will be provided in the Clinical Events Committee Charter.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

Two analysis populations will be used for the analysis of data from this study: the randomized patient population and the safety-evaluable population. All patients who are randomized to the study will be included in the randomized patient population, regardless of whether they receive any study treatment; and the safety-evaluable population will include all randomized patients who receive any amount of study treatment.

Analyses of demographics and other baseline information will be based on the randomized patient population, and per treatment assigned by the IVRS/IWRS.

The randomized patient population will form the basis for all efficacy analyses. In all efficacy analyses, following the intent-to-treat principle, patients will be included in the treatment group to which they were randomized by the IVRS/IWRS.

The safety-evaluable population will form the basis for all safety analyses. Safety analyses will be based on actual treatment received. Specifically, a patient will be included in the trastuzumab emtansine arm in safety analyses if the patient receives any trastuzumab emtansine, regardless of the initial treatment assignment by IVRS/IWRS.

4.2 ANALYSIS OF STUDY CONDUCT

Patient enrollment will be tabulated by study site for each treatment arm. Patient disposition and reasons for discontinuations will be summarized by treatment arm for all randomized patients. Compliance with protocol-specified schedule of disease status clinical assessments will also be summarized by treatment arm. In addition, protocol deviations and eligibility violations will be summarized by treatment arm.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

The evaluation of treatment group comparability between the two treatment arms will include summaries of demographics and baseline characteristics, including age, sex, race, breast cancer characteristics, medical history, and prior cancer treatment. Descriptive statistics (mean, median, standard deviation, 25th percentile, 75th percentile, and range) will be presented for continuous variables, and proportions will be presented for categorical variables.

4.4 EFFICACY ANALYSIS

4.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is IDFS, defined as the time between randomization and date of first occurrence of any one of the following events:

- Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion)
- Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall and/or skin of the ipsilateral breast)
- Distant recurrence (i.e., evidence of breast cancer in any anatomic site—other than the two above mentioned sites—that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer)
- Contralateral invasive breast cancer
- Death attributable to any cause including breast cancer, non-breast cancer or unknown cause (but cause of death should be specified if at all possible)

Patients who have not had an event will be censored at the date they are last known to be alive and event free on or prior to the clinical data cutoff date.

The log-rank test, stratified by the protocol-defined stratification factors (clinical stage at presentation [inoperable vs. operable]; hormone receptor status [ER or PR positive vs. ER and PR negative/unknown]; preoperative HER2-directed therapy: [trastuzumab vs. trastuzumab plus additional HER2-directed agent(s)]; and pathologic nodal status evaluated after preoperative therapy [node positive vs. node negative/not done]), will be used to compare IDFS between the two treatment arms. The unstratified log-rank test results will also be provided as a sensitivity analysis. If, at the time of analysis, it is deemed that the smallest stratum is <5 patients in either arm and so robust stratified analyses cannot be conducted, the unstratified analysis will be used as the primary analysis. Cox proportional hazards model, stratified by the protocol-defined stratification factors, will be used to estimate the HR between the two treatment arms and its 95% confidence interval (CI). The Kaplan−Meier approach will be used to estimate 3-year IDFS rates and corresponding 95% CIs for each treatment arm.

4.4.2 Secondary Efficacy Endpoints

Secondary efficacy outcome measures include the following:

- IDFS: including second primary non-breast cancer: defined the same way as IDFS for the primary endpoint but including second primary non breast invasive cancer as an event (with the exception of non-melanoma skin cancers and carcinoma in situ [CIS] of any site)
- DFS: defined as the time between randomization and the date of the first occurrence of an invasive disease-free survival event including second primary non-breast cancer event or contralateral or ipsilateral ductal carcinoma in situ (DCIS)

- OS: defined as the time from randomization to death due to any cause
- DRFI: defined as the time between randomization and the date of distant breast cancer recurrence

Patients who have not had an event will be censored at the date that they are last known to be event free on or prior to the clinical data cutoff date.

Secondary endpoints will be analyzed in a similar manner as the primary endpoint to estimate 3-year event rates (and 5-year survival rate for OS) for each treatment arm and the HR between the two treatment arms with 95% CI.

A testing hierarchy will be used to control the overall type I error rate at 5%. If the primary endpoint IDFS reaches statistical significance, the formal hypothesis testing of OS will be performed. More details of OS interim analyses are specified in Section 4.10.1.

4.4.3 Exploratory Efficacy Endpoints

Exploratory analyses will be performed to explore the correlation between biomarker, anti-therapeutic antibody (ATA) and clinical outcomes as appropriate.

4.4.4 Sensitivity Analyses

Alternative definitions of IDFS include: IDFS including second primary non-breast cancer; and DFS (including second primary non-breast cancer event or contralateral or ipsilateral ductal CIS). Both of these two definitions are secondary endpoints of the study, and they serve as sensitivity analyses for the primary analysis of IDFS.

Additional sensitivity analyses to assess the robustness of the primary endpoint IDFS include the following:

- Censoring patients at the time they begin a new anti-cancer therapy before experiencing an IDFS event. This includes patients who continue on trastuzumab after discontinuation of trastuzumab emtansine before 14 cycles without experiencing an IDFS event. For these patients, data will be censored at the time of initiation of trastuzumab treatment.
- Censoring patients at the time they discontinue study treatment due to any reason before experiencing an IDFS event. This includes for patients who continue on trastuzumab after discontinuation of trastuzumab emtansine before 14 cycles without experiencing an IDFS event. For these patients, data will be censored at the time of last trastuzumab emtansine treatment.

4.4.5 Subgroup Analyses

Subgroup analyses of IDFS and OS will be performed based on age, race, stratification factors, and other potential baseline prognostic factors as appropriate.

4.5 PATIENT-REPORTED OUTCOME ANALYSIS

The patient-reported outcomes of health-related quality of life (HRQOL) and breast cancer specific and treatment-related symptoms will be assessed using the Quality of Life Questionnaire–Core 30 (QLQ–C30), and its corresponding module for breast cancer, Quality of Life Questionnaire–Breast Cancer 13 (QLQ–BR23) developed by the European Organization for the Research and Treatment of Cancer (EORTC). The EORTC QLQ-C30 and the QLQ-BR23 are both validated and reliable self-report measures (Aaronson et al. 1993; Fayers et al. 1999). The EORTC QLQ-C30 consists of 30 questions which assess five functional domains (physical, role, cognitive, emotional, and social), a global health status/quality of life scale, three symptom scales (fatigue, pain, nausea, and vomiting), five single items (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea), and a perceived financial impact of the disease item. The QLQ-BR23 includes questions assessing breast cancer-associated symptoms, side effects of treatment, arm symptoms, and upset by hair loss, and functions of body image, sexual functioning, sexual enjoyment, and future perspective. In total there are 5 functional and 10 symptoms subscales for the QLQ-C30 and 3 symptom and 3 functioning subscales for QLQ-BR23. The EuroQol EQ-5D is a five-item questionnaire assessing self-care, usual activities, pain and anxiety/depression with three response categories (no problem, moderate problem, and severe problems). The visual analog scale (VAS) scale associated with the EuroQol EQ-5D will not be used in this study.

Summary of the compliance rate will be provided at each assessment time point as specified in the protocol by treatment arm. Compliance rate is defined as the ratio of number of patients with completed assessments (i.e., at least 1 item has been answered) and the total number of eligible patients at that time point according to protocol specified assessment schedule.

For the QLQ-C30 and QLQ-BR23 questionnaires, if more than 50% of the constituent items are completed, a pro-rated score will be computed consistent with the scoring manuals and validation papers (Fayers et al. 1999). For subscales with less than 50% of the items completed, the subscale will be considered to be missing.

Summary statistics (mean, standard deviation, median, 25th and 75th percentiles, and range) of absolute scores and change from baseline scores of the QLQ-C30 and QLQ-BR23 subscales will be summarized at each assessment time point for the two treatment arms. Only patients with a baseline assessment and at least one post-baseline assessment will be included in this analysis.

Repeated measures mixed-effects models will be performed on each subscale to explore the impact of treatment on patients over time. Each model will have an intercept term, a linear time trend term, a term for treatment group, and a term for treatment-by-time interaction. Covariates will be added as appropriate. Only patients with a baseline assessment and at least 1 post-baseline assessment will be included in this analysis.

The EQ-5D data analysis will be performed to support reimbursement dossiers and will not be included in the clinical study report.

4.6 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Blood and serum samples for measurement of trastuzumab emtansine, total trastuzumab, and DM1 will be obtained from patients randomized to the trastuzumab emtansine arm. Individual and mean trastuzumab emtansine and total trastuzumab serum levels and DM1 plasma concentrations versus time data will be plotted, tabulated, and summarized (e.g., mean, standard deviation, coefficient of variation, median, minimum, maximum, and range). Inter-patient variability and drug accumulation after multiple dosing will be evaluated. Compartmental, noncompartmental, and/or population approaches will be considered as appropriate. Additional pharmacokinetic and pharmacodynamic analyses and exposure-efficacy and toxicity (alanine aminotransferase [ALT]/serum aspartate aminotransferase [AST], platelets, etc.) analyses will be conducted in conjunction with data from other studies, as appropriate. Any remaining plasma samples may be used for measurement of trastuzumab emtansine metabolites as an exploratory assessment and will be plotted, tabulated, and summarized.

Blood and serum samples for measurement of trastuzumab will be obtained from patients randomized to the trastuzumab arm. Individual and mean trastuzumab serum concentrations versus time data will be plotted, tabulated, and summarized (e.g., mean, standard deviation, coefficient of variation, median, minimum, maximum, and range).

4.7 SAFETY ANALYSES

Safety analyses will be performed on the treated population, which is defined as patients who receive any amount of study treatment and will be based on the treatment they actually receive. Specifically, a patient will be included in the trastuzumab emtansine arm in safety analyses if the patient receives any trastuzumab emtansine, regardless of the initial treatment assignment by IVRS/IWRS.

4.7.1 Study Treatment Exposure

Study treatment exposure, such as treatment duration, number of cycles, dose intensity, and dose modification (including dose delay, dose reduction etc.) will be summarized for each treatment arm with descriptive statistics. Reasons for treatment discontinuation will also be summarized.

4.7.2 Adverse Events

Verbatim descriptions of adverse events (AEs) will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0. All AEs, SAEs, AEs leading to death, and AEs leading to study treatment discontinuation, occurring on or after the first dose of study treatment (i.e., treatment-

emergent AE), will be summarized by NCI CTCAE grade. For repeated events of varying severity in an individual patient, the highest grade will be used in the summaries. Deaths and causes of death will be summarized.

Subgroup analyses of AEs based on age, and race will also be provided.

4.7.3 Laboratory Data

Laboratory toxicities will be summarized by NCI CTCAE grade for each treatment arm with shift tables.

4.7.4 Cardiac Safety

Incidence of cardiac events, defined as death from cardiac cause or severe congestive heart failure (New York Heart Association [NYHA] Class III or IV) with a decrease in left ventricular ejection fraction (LVEF) of 10 percentage points or more from baseline to an LVEF of < 50%, will be summarized by treatment arm. Other cardiac-related events (e.g., any symptomatic congestive heart failure [CHF] associated with a 10% drop in LVEF to $<50\%$; asymptomatic declines in LVEF requiring dose delay) will also be summarized. Change in LVEF over time will be summarized by treatment arm.

4.7.5 Liver Safety

Incidence of hepatotoxicity events will be summarized by treatment arm. Analyses of liver function laboratory test (LFT) results will include the following:

- Shift in NCI CTCAE grade from baseline to worst post-baseline level in ALT, AST, total bilirubin (TBILI), and alkaline phosphatase (ALK)
- Summary of number/percentage of patients with AST, ALT, TBILI, and ALK elevation by NCI CTCAE grade and by treatment cycle
- Scatterplots of worst LFT value (AST vs. ALT, ALT vs. TBILI, AST vs. TBILI) relative to upper limit normal (ULN)
- Kaplan–Meier plots of time to first $ALT > 3 \times ULN$, first $ALT > 5 \times ULN$, and first $ALT > 8 \times ULN$ events
- Patient LFT profiles (including ALT, AST, TBILI, and ALK) over time points for patients satisfying one of the following two conditions:
  - TBILI elevation $> 2 \times ULN$ within 21 days after AST/ALT elevation $> 3 \times ULN$
  - ALT elevation $> 8 \times ULN$

4.8 EXPLORATORY SAFETY ANALYSES

For patients who continue on trastuzumab after discontinuation of trastuzumab emtansine due to toxicity before 14 cycles, exploratory safety analyses will be performed. Summary of trastuzumab exposure, SAEs, cardiac-specific AEs, and NCI CTCAE Grade 3 or above AEs will be provided. Other exploratory safety analyses differentiating two treatment phases for these patients will be performed as appropriate.

4.9 MISSING DATA

For the analyses of IDFS, IDFS including second primary non-breast cancer, DFS and DRFI, data for patients who do not experience an event will be censored at the date they are last known to be alive and event free. Data for patients who are randomized without any post-baseline assessments will be censored at the date of randomization plus one day. For the analysis of OS, data for patients who are alive at the time of the data cutoff will be censored at the last date they were known to be alive. Data for patients who are randomized without any post-baseline information will be censored at the date of randomization plus one day.

For the QLQ-C30 and QLQ-BR23 questionnaires, if less than 50% of the constituent items of a subscale are completed, data for the subscale will be considered to be missing. No imputation will be performed.

4.10 INTERIM ANALYSES

4.10.1 Interim Efficacy Analyses

One interim analysis of IDFS and *two* interim analyses of OS are planned.

The interim efficacy analysis of IDFS is planned after 67% of the targeted IDFS events have occurred, which is estimated to be approximately 48 months after the first patient is enrolled in the study. If the accrual rate or event rate are different from expected, the timing of the interim analysis may be delayed such that the interim analysis will only take place after all patients have enrolled and have completed treatment.

At this interim analysis, IDFS will be tested at the significance level determined using the Lan–DeMets alpha spending function with an O'Brien–Fleming boundary so that the overall two-sided type I error rate will be maintained at the 5% level for the IDFS primary endpoint.

Table 1 presents a summary of the planned IDFS analyses, the efficacy stopping boundary, and the estimated timing of these analyses.

Table 1 Summary of Planned Analyses of Invasive Disease-Free Survival

Analysis of IDFS	No. of events	Efficacy Stopping Boundary [a]	Estimated Timing [b]
Interim	257	$p < 0.0124$ or observed HR < 0.732	48 months
Final	384	$p < 0.0462$ or observed HR < 0.816	*107 months*

HR = hazard ratio; IDFS = invasive disease-free survival.

[a] p-value will be based on two-sided stratified log-rank test.

[b] Time from the enrollment of first patient to data cutoff.

The interim analysis will be performed by the iDCC statistician and the results will be presented to the iDMC by the iDCC statistician.

The purpose of the interim analysis is to evaluate whether there is an overwhelming difference in the efficacy observed in the trastuzumab emtansine arm compared with the trastuzumab arm in terms of IDFS. If the test is not significant, the study will continue as planned. If the test is significant, the iDMC may recommend releasing the primary endpoint results before the targeted number of 384 events is reported. In this latter situation, the Sponsor will be unblinded to the study results and a full data package would be prepared for discussion with regulatory authorities. The study will continue until *12 years* of follow-up from the date of randomization of the first patient and IDFS analysis will be updated when 384 IDFS events have occurred.

Two formal interim OS analyses and one final OS analysis are planned: the first OS interim analysis will be performed at the time of the interim IDFS analysis (approximately 48 months from FPI) if the interim IDFS analysis crosses the boundary; *the second interim OS analysis will be performed at the time of the final IDFS analysis when 384 IDFS events have occurred (approximately 107 months from FPI) in the case where the interim IDFS analysis crosses the boundary*. The final OS analysis will be performed at the end of *12 years* of follow-up from the date of randomization of the first patient. The Sponsor will perform these analyses. A survival data sweep will be conducted prior to each analysis.

The overall type I error will be controlled at 0.05 for the formal OS interim analyses and final OS analysis using the Lan–DeMets alpha spending function with an O'Brien–Fleming boundary. The boundaries used at each interim and final OS analysis will depend on the timing of the analyses and the number of death events actually included in the analyses.

Table 2 presents a summary of the planned OS analyses, the efficacy stopping boundary, and the estimated timing of these analyses.

Table 2 Summary of Planned Analyses of Overall Survival

Analysis of OS	No. of Events	Efficacy Stopping Boundary [a]	Estimated Timing [b]
Interim 1 (at interim IDFS)	150	*p <0.0005 or observed HR <0.494*	48 months
Interim 2 (at final IDFS) [c]	206	*p <0.0143 or observed HR <0.696*	*107 months*
Final	367	*p <0.0456 or observed HR <0.781*	*144 months*

HR = hazard ratio; IDFS = invasive disease-free survival; OS = overall survival.

[a] p-value will be based on two-sided stratified log-rank test

[b] Time from the enrollment of first patient to data cutoff.

[c] *Estimated number of events. Efficacy boundaries will be calculated based on the actual number of events at the time of analysis.*

4.10.2 Interim Safety Analyses

An iDMC will monitor accumulating patient safety data at least once every 6 months until the last patient has completed study treatment. In addition, data on serious AEs and deaths will be monitored by the iDMC at least once every 3 months during this period.

At each iDMC review, relevant safety information from ongoing trastuzumab emtansine studies will be provided to the iDMC.

After the first 600 patients have been randomized and followed for 3 months (approximately 21 months after FPI), the iDMC will perform an interim safety analysis regarding death and hepatic events. The Clinical Events Committee will communicate their findings regarding hepatic events to the iDMC to aid iDMC review.

If an absolute increase of > 3% in the percentage of death (from any cause) is observed in trastuzumab emtansine arm compared with the trastuzumab arm, the iDMC will consider recommending holding enrollment for further data review, stopping or modifying the trial.

If the true difference in the percentage of death is > 3% (e.g., 2% vs. 6%) then there is approximately 70% chance of observing an absolute difference of > 3% at the interim with 600 patients. Table 3 presents the probability of observing more than 3% increase in the percentage of death in trastuzumab emtansine arm compared with the trastuzumab arm with different assumption on the percentage of death in 2 arms.

Table 3 Probability of Observing >3% Increase of Death

Percentage of death		
Trastuzumab (N=300)	Trastuzumab emtansine (N=300)	Probability of observing >3% increase
2%	2%	0.00
2%	3%	0.05
2%	4%	0.20
2%	5%	0.45
2%	6%	0.70

If an absolute increase of > 3% in the percentage of Hy's law cases (confirmed by the independent clinical events committee) is observed in trastuzumab emtansine arm compared with the control arm, the iDMC will consider recommending holding enrollment for further data review, stopping or modifying the trial.

If the true difference in the percentage of confirmed Hy's law cases is > 3% (e.g., 0.33% vs. 3.67%) then there is approximately 54% chance of observing an absolute difference of > 3% at the interim with 600 patients. Table 4 presents the probability of observing more than 3% increase in the percentage of Hy's law cases in trastuzumab emtansine arm compared with the trastuzumab arm with different assumption on the number of Hy's law cases in two arms.

Table 4 Probability of Observing >3% Increase of Confirmed Hy's Law Cases

Number of confirmed Hy's law cases (%)		
Trastuzumab (N=300)	Trastuzumab emtansine (N=300)	Probability of observing >3% increase
1 (0.33%)	4 (1.33%)	<0.01
1 (0.33%)	6 (2%)	0.05
1 (0.33%)	8 (2.67%)	0.19
1 (0.33%)	10 (3.33%)	0.43
1 (0.33%)	11 (3.67%)	0.54
1 (0.33%)	12 (4%)	0.66

The iDMC will work according to the guidelines defined in the iDMC Charter. The iDMC Charter will contain details regarding frequency of meetings, guidelines for decision making and process for requesting further information. The iDMC members will review and sign off the charter before the first review.

5. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–6.

Fayers PM, Aaronson NK, Bjordal K, Curran D, Groenvold M on behalf of the EORTC Quality of Life Study Group. The EORTC QLQ-C30 Scoring Manual (2nd Edition). Published by: European Organization for Research and Treatment of Cancer, Brussels 1999.

Appendix 1
Study BO27938 Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL PHASE III STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TRASTUZUMAB EMTANSINE VERSUS TRASTUZUMAB AS ADJUVANT THERAPY FOR PATIENTS WITH HER2-POSITIVE PRIMARY BREAST CANCER WHO HAVE RESIDUAL TUMOR PRESENT PATHOLOGICALLY IN THE BREAST OR AXILLARY LYMPH NODES FOLLOWING PREOPERATIVE THERAPY**
PROTOCOL NUMBER:	BO27938
VERSION NUMBER:	7
EUDRACT NUMBER:	2012-002018-37
IND NUMBER:	71,072
NCT NUMBER:	NCT01772472
NSABP/GBG PROTOCOL NUMBERS:	NSABP B-50-I/GBG 77
TEST PRODUCT:	Trastuzumab Emtansine (RO5304020)
PHASE:	III
INDICATION:	HER2-positive primary breast cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES

PRIMARY EFFICACY OBJECTIVE

The primary efficacy objective for this study is as follows:

- To compare invasive disease-free survival (IDFS) in patients with residual invasive breast cancer after treatment with preoperative chemotherapy and HER2-directed therapy including trastuzumab followed by surgery between the 2 treatment arms

The secondary efficacy objective for this study is as follows:

- To compare IDFS including second non-breast cancers, disease-free survival (DFS), overall survival (OS), and distant recurrence-free interval (DRFI) between the 2 treatment arms

SAFETY OBJECTIVES

The safety objective for this study is as follows:

- To compare cardiac safety and overall safety between the 2 treatment arms according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0

PATIENT REPORTED OUTCOME OBJECTIVES

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

- To compare PROs between the 2 treatment arms using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Core 30 (QLQ-C30) questionnaire and Quality of Life Questionnaire – Breast Cancer (QLQ-BR23) module

PHARMACOKINETICS OBJECTIVES

The pharmacokinetics (PK) objectives for this study are as follows:

- To characterize the PK of trastuzumab emtansine (including total trastuzumab and DM1) in trastuzumab emtansine treated patients
- To characterize the PK of trastuzumab in trastuzumab-treated patients and permit an intra-study comparison of trastuzumab exposure in the 2 treatment arms
- To investigate exposure–effect (efficacy and safety) relationships in this patient population

EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To assess correlations between biomarker status and efficacy and/or safety
- To assess the incidence of anti-therapeutic antibodies (ATAs) and the effect of ATAs on PK, safety, and efficacy

STUDY DESIGN

DESCRIPTION OF STUDY

This is a Phase III, 2-arm, randomized, multicenter, multinational, open-label study in patients with HER2-positive primary breast cancer who have received preoperative chemotherapy and HER2-directed therapy including trastuzumab followed by surgery, with a finding of residual invasive disease in the breast or axillary lymph nodes.

Patients who provide consent will commence a screening period, which will last up to 30 days. Informed consent forms may be obtained at any time (including prior to the 30-day screening period) but must be obtained prior to the performance of any screening assessments. Patients who have pathologically documented residual invasive disease in either the breast or axillary lymph nodes following completion of preoperative therapy (including, but not limited to, at least 9 weeks of HER2-directed therapy, including trastuzumab, and at least 9 weeks of taxane-based chemotherapy (or, if receiving dose-dense chemotherapy regimens, at least 6-8 weeks of taxane-based therapy and at least 8 weeks of trastuzumab) and at least 16 weeks of total systemic treatment in the preoperative setting) will be eligible to participate in the study.

At the end of the screening period, eligible patients will be randomized in a 1:1 ratio to receive open-label study treatment (trastuzumab emtansine 3.6 mg/kg every 3 weeks [q3w] for 14 cycles or trastuzumab 6 mg/kg q3w for 14 cycles). Randomization will be stratified by clinical stage at presentation (inoperable [Stage T4NxM0 or TxN2–3M0], operable [stages T1-3N0-1M0]), hormone receptor status (estrogen receptor [ER] or progesterone receptor [PgR] positive, ER and PgR negative), preoperative HER2-directed therapy (trastuzumab, trastuzumab plus additional HER2-directed agent[s]), and pathological nodal status evaluated after preoperative therapy (node positive, node negative or not done). Patients will be administered radiotherapy and/or hormonal therapy (for patients with hormone receptor-positive tumors) in addition to receiving study treatment for 14 cycles if indicated based on the following guidelines:

- Hormonal therapy (aromatase inhibitor, tamoxifen, etc.) should be initiated in patients with hormone receptor-positive disease at presentation.
- For patients undergoing breast-conserving surgery, whole breast irradiation is required. Primary tumor bed boost may be administered according to local policy. Regional node irradiation is required if the patient presented at initial diagnosis with clinical T3 (except for T3N0) or T4 disease and/or with clinical N2 or N3 disease; it is recommended for T3N0 or if there is residual disease in lymph nodes.

- For post-mastectomy patients, chest wall and regional node irradiation is required if the patient presented at initial diagnosis with clinical T3 (except for T3N0) or T4 disease and/or with clinical N2 or N3 disease; it is recommended for T3N0 or if there is residual disease in lymph nodes. For post-mastectomy patients who do not meet these criteria, radiotherapy is at the discretion of the investigator based on institutional standards.

The first dose of study treatment will be administered on Day 1 of a 3-week cycle (i.e., dosing will be repeated once q3w to complete a maximum of 14 cycles of treatment). Treatment will be discontinued prior to 14 cycles in the event of disease recurrence, unacceptable toxicity, or study termination by the Sponsor. Patients who discontinue trastuzumab emtansine may complete the duration of their study therapy with trastuzumab, if appropriate based on toxicity considerations. Efficacy, safety, laboratory, and PRO measures will be assessed throughout the study, as detailed in the schedule of assessments (see Appendix 1). PK measures will be assessed as specified in the schedule of PK assessments (see Appendix 2). The primary efficacy endpoint is the IDFS and will be measured from the time of randomization until its first occurrence. Following discontinuation or completion of study treatment, all patients will continue to be followed for efficacy and safety objectives until the end of the study.

NUMBER OF PATIENTS

A planned total of 1484 patients will be enrolled in the study.

TARGET POPULATION

Patients must meet the following criteria for study entry:

1. HER2-positive breast cancer

   HER2-positive status will be based on pretreatment biopsy material and defined as an immunohistochemistry (IHC) (Appendix 6) score of 3+ and/or positive by in situ hybridization (ISH) (Appendix 7) prospectively confirmed by a central laboratory prior to study enrollment. ISH positivity is defined as a ratio of $\geq$2.0 for the number of HER2 gene copies to the number of signals for chromosome 17 copies. Formalin-fixed paraffin-embedded tumor tissue block or a partial block must be available for central evaluation of HER2 expression. If sites are unable to send a tissue block due to local regulations, at least 8 unstained slides should be sent for HER2 testing, and in addition up to 5 slides for exploratory biomarker research. A central laboratory will perform both IHC and ISH assays; however, only one positive result is required for eligibility. In the event that sufficient material from the pretreatment biopsy is not available for submission, central HER2 determination for eligibility may be performed on residual tumor tissue from the time of definitive surgery.

   Patients with synchronous bilateral invasive disease are eligible provided both lesions are HER2-positive.
2. Histologically confirmed invasive breast carcinoma
3. Clinical stage at presentation: T1–4, N0–3, M0 (Note: Patients with T1a/bN0 tumors will not be eligible)
4. Completion of preoperative systemic chemotherapy and HER-2 directed treatment. Systemic therapy must consist of at least 6 cycles of chemotherapy with a total duration at least 16 weeks, including at least 9 weeks of trastuzumab and at least 9 weeks of taxane-based chemotherapy. Patients may have received an anthracycline as part of preoperative therapy in addition to taxane chemotherapy

   Patients receiving dose-dense chemotherapy regimens are eligible, provided at least 8 weeks of taxane-based therapy and at least 8 weeks of trastuzumab have been given. A dose-escalated (225 mg/m2 q2w) dose-dense regimen of paclitaxel over 6 weeks is allowed.

   Patients may have received more than one HER2-directed therapy. Note: HER-2 directed therapy alone periods will not satisfy the requirements for cycles of preoperative systemic chemotherapy.

   All systemic chemotherapy should be completed preoperatively.
5. Adequate excision: surgical removal of all clinically evident disease in the breast and lymph nodes as follows:

Breast surgery: total mastectomy with no gross residual disease at the margin of resection, or breast-conserving surgery with histologically negative margins of excision

For patients who undergo breast-conserving surgery, the margins of the resected specimen must be histologically free of invasive tumor and ductal carcinoma in situ (DCIS) as determined by the local pathologist. If pathologic examination demonstrates tumor at the line of resection, additional operative procedures may be performed to obtain clear margins. If tumor is still present at the resected margin after re-excision(s), the patient must undergo total mastectomy to be eligible. Patients with margins positive for lobular carcinoma in situ (LCIS) are eligible without additional resection.

Lymph node surgery:

In case of positive results from a fine-needle aspiration, core biopsy, or sentinel node biopsy performed prior to preoperative therapy, additional surgical evaluation of the axilla following preoperative therapy is required.

If only micrometastases are present in sentinel nodes preoperatively (i.e., if the greatest diameter of the nodal metastasis in a sentinel node is 0.2 mm or less), no additional surgical evaluation of the axilla is required.

If sentinel node biopsy performed before preoperative therapy was negative, no additional surgery evaluation of the axilla is required after preoperative therapy.

If the only sentinel node identified by isotope scan is in the internal mammary chain, surgical evaluation of the axilla is recommended.

If sentinel node biopsy performed after preoperative therapy is positive, additional surgical evaluation of the axilla is recommended.

If sentinel node evaluation after preoperative therapy is negative, no further additional surgical evaluation of the axilla is required.

Axillary dissection without sentinel node evaluation is permitted after preoperative therapy.

6. Pathologic evidence of residual invasive carcinoma in the breast or axillary lymph nodes following completion of preoperative therapy. If invasive disease is present in both breasts, residual invasive carcinoma must be present in at least 1 breast or axillary lymph nodes postoperatively.
7. An interval of no more than 12 weeks between the date of primary surgery and the date of randomization
8. Known hormone receptor status

   Hormone receptor–positive status can be determined by either known positive ER or known positive PgR status; hormone receptor–negative status must be determined by both known negative ER and known negative PgR.
9. Signed written informed consent approved by the study site's Institutional Review Board (IRB)/Ethical Committee (EC)
10. Age $\geq$ 18 years
11. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
12. Life expectancy $\geq$ 6 months
13. Adequate organ function during screening, defined as:
    a. Absolute neutrophil count $\geq$ 1200 cells/mm^3
    b. Platelet count $\geq$ 100000 cells/mm^3
    c. Hemoglobin $\geq$ 9.0 g/dL; patients may receive red blood cell transfusions to obtain this level
    d. Serum creatinine $< 1.5 \times$ upper limit of normal (ULN)
    e. International normalized ratio (INR) and activated partial thromboplastin time (aPTT) $\leq 1.5 \times$ ULN
    f. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 1.5 \times$ ULN

g. Serum total bilirubin (TBILI) $\leq 1.0 \times$ ULN (within normal limits), except for patients with Gilbert's syndrome, for whom direct bilirubin should be within the normal range

h. Serum alkaline phosphatase (ALK) $\leq 1.5 \times$ ULN

i. Screening left ventricular ejection fraction (LVEF) $\geq 50\%$ on echocardiogram (ECHO) or multiple-gated acquisition (MUGA) after receiving neoadjuvant chemotherapy and no decrease in LVEF by more than 15% absolute points from the pre-chemotherapy LVEF. Or, if pre-chemotherapy LVEF was not assessed, the screening LVEF must be $\geq 55\%$ after completion of neoadjuvant chemotherapy.

i. LVEF assessment may be repeated once up to 3 weeks following the initial screening assessment to assess eligibility

14. For women who are not postmenopausal ($\geq$ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 7 months after the last dose of study drug.

a. Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. Examples of contraceptive methods with a failure rate of $< 1\%$ per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a spermicide.

b. Male patients whose partners are pregnant must use condoms or truly refrain from sexual activity for the duration of the pregnancy.

15. Negative serum pregnancy test for premenopausal women including women who have had a tubal ligation and for women less than 12 months after the onset of menopause

16. Documentation of hepatitis B virus (HBV) and hepatitis C virus (HCV) serologies is required: this includes HB surface antigen (HBsAg) and/or total HB core antibody (anti-HBc) in addition to HCV antibody testing. The most recent serologic testing must have occurred within 3 months prior to initiation of neoadjuvant therapy. If such testing has not been done, it must be performed during screening.

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

1. Stage IV (metastatic) breast cancer
2. History of any prior (ipsi- or contralateral) breast cancer except LCIS
3. Evidence of clinically evident gross residual or recurrent disease following preoperative therapy and surgery
4. An overall response of progressive disease (PD) according to the investigator at the conclusion of preoperative systemic therapy
5. Treatment with any anti-cancer investigational drug within 28 days prior to commencing study treatment
6. History of other malignancy within the last 5 years except for appropriately treated carcinoma in situ (CIS) of the cervix, non-melanoma skin carcinoma, Stage I uterine cancer, or other non-breast malignancies with an outcome similar to those mentioned above
7. Patients for whom radiotherapy would be recommended for breast cancer treatment but for whom it is contraindicated because of medical reasons (e.g., connective tissue disorder or prior ipsilateral breast radiation)
8. Current NCI CTCAE (Version 4.0) Grade ≥ 2 peripheral neuropathy
9. History of exposure to the following cumulative doses of anthracyclines:

   Doxorubicin > 240 mg/m^2

   Epirubicin or Liposomal Doxorubicin-Hydrochloride (Myocet®) > 480 mg/m^2

   For other anthracyclines, exposure equivalent to doxorubicin > 240 mg/m^2

10. Cardiopulmonary dysfunction as defined by any of the following:

    History of NCI CTCAE (Version 4.0) Grade $\geq$ 3 symptomatic congestive heart failure (CHF) or New York Heart Association (NYHA) criteria Class $\geq$ II Angina pectoris requiring anti-anginal medication, serious cardiac arrhythmia not controlled by adequate medication, severe conduction abnormality, or clinically significant valvular disease

    - High-risk uncontrolled arrhythmias: i.e., atrial tachycardia with a heart rate $>$ 100/min at rest, significant ventricular arrhythmia (ventricular tachycardia) or higher-grade AV-block (second degree AV-block Type 2 [Mobitz 2] or third degree AV-block)

    Significant symptoms (Grade $\geq$ 2) relating to left ventricular dysfunction, cardiac arrhythmia, or cardiac ischemia while or since receiving preoperative therapy.

    History of a decrease in LVEF to $<$ 40% with prior trastuzumab treatment (e.g., during preoperative therapy)

    Uncontrolled hypertension (systolic blood pressure $>$ 180 mmHg and/or diastolic blood pressure $>$ 100 mmHg)

    Evidence of transmural infarction on ECG

    Requirement for continuous oxygen therapy

11. Prior treatment with trastuzumab emtansine
12. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound healing disorders; ulcers)
13. For female patients, current pregnancy and/or lactation
14. Major surgical procedure unrelated to breast cancer or significant traumatic injury within approximately 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment
15. Any known active liver disease, for example, due to HBV, HCV, autoimmune hepatic disorders, or sclerosing cholangitis. Patients who have positive HBV or HCV serologies without known active disease must meet the eligibility criteria for ALT, AST, TBILI, INR, aPTT, and alkaline phosphatase (ALK) on at least two consecutive occasions, separated by at least 1 week, within the 30 day screening period.
16. Concurrent, serious, uncontrolled infections or known infection with HIV
17. History of intolerance, including Grade 3 to 4 infusion reaction or hypersensitivity to trastuzumab or murine proteins or any components of the product
18. Active, unresolved infections at screening requiring treatment
19. Assessment by the investigator as being unable or unwilling to comply with the requirements of the protocol

LENGTH OF STUDY

The total length of this study will be approximately *12* years from randomization of the first patient to completion of the last follow-up assessment of the last patient.

END OF STUDY

The study will end after the last patient randomized into the study has undergone the last follow-up assessment. To enable long-term follow-up for survival and safety information, the last follow-up assessment is scheduled to occur *12* years after the first patient is randomized.

PRIMARY EFFICACY OUTCOME MEASURE

The primary efficacy outcome measure is IDFS, defined as the time from randomization until the date of the first occurrence of any one of the following events:

- Ipsilateral invasive breast tumor recurrence (i.e., an invasive breast cancer involving the same breast parenchyma as the original primary lesion)
- Ipsilateral local-regional invasive breast cancer recurrence (i.e., an invasive breast cancer in the axilla, regional lymph nodes, chest wall and/or skin of the ipsilateral breast)
- Distant recurrence (i.e., evidence of breast cancer in any anatomic site—other than the 2 above-mentioned sites—that has either been histologically confirmed or clinically diagnosed as recurrent invasive breast cancer)
- Contralateral invasive breast cancer
- Death attributable to any cause including breast cancer, non-breast cancer or unknown cause (but cause of death should be specified if at all possible)

SECONDARY EFFICACY OUTCOME MEASURES

Secondary efficacy outcome measures include the following:

- IDFS including second primary non-breast cancer: defined the same way as IDFS for the primary endpoint but including second primary non-breast invasive cancer as an event (with the exception of non-melanoma skin cancers and CIS of any site)
- DFS: defined as the time between randomization and the date of the first occurrence of an IDFS event including second primary non-breast cancer event or contralateral or ipsilateral DCIS
- OS: defined as the time from randomization to death due to any cause
- DRFI: defined as the time between randomization and the date of distant breast cancer recurrence

SAFETY OUTCOME MEASURES

The safety outcome measures are the following protocol-specific adverse events (AEs):

- Incidence, type and severity of all AEs based on NCI CTCAE Version 4.0
- Incidence, type, and severity of serious adverse events (SAEs)
- Incidence and type of AEs leading to dose discontinuation, modification, or delay
- Cause of death on study
- Abnormal laboratory values
- LVEF decreases
- Cardiac events, defined as death from cardiac cause or severe CHF (NYHA Class III or IV) with a decrease in LVEF of ≥ 10 percentage points from baseline to an LVEF of $< 50\%$.

PATIENT-REPORTED OUTCOME MEASURES

The PRO outcome measures for this study are as follows:

- Incidence of treatment-related symptoms and assessment of health-related quality of life (HRQOL) as measured using the EORTC QLQ-C30 questionnaire and QLQ-BR23 module
- Assessment of health status as measured using the EuroQol EQ-5D™ questionnaire for health economic modeling

PHARMACOKINETIC OUTCOME MEASURES

The PK outcome measures to be assessed in patients receiving trastuzumab emtansine are the following:

- Observed serum concentrations and relevant PK parameters of trastuzumab emtansine (trastuzumab emtansine conjugated) and total trastuzumab (sum of conjugated and unconjugated trastuzumab)
- Observed plasma concentrations of DM1
- Explore relationship between trastuzumab emtansine exposure and efficacy/safety
- Characterize ATA and assess impact of ATA on PK, safety and efficacy.

EXPLORATORY OUTCOME MEASURES

The exploratory outcome measure for this study is as follows:

- The relationship between molecular markers and efficacy outcomes

Efficacy outcomes considered for this analysis will include IDFS and OS, as appropriate.

INVESTIGATIONAL MEDICINAL PRODUCTS

Trastuzumab emtansine is provided as a single-use lyophilized formulation. The lyophilized product should be reconstituted using sterile water for injection (SWFI). Patients will receive trastuzumab emtansine infusions q3w. Vials should be refrigerated at 2°C to 8°C (36°F to 46°F) until use. The vial and the solution of trastuzumab emtansine should not be shaken or frozen. Information on the formulation, packaging, handling, and administration of trastuzumab emtansine is provided in the trastuzumab emtansine Investigator's Brochure (IB) and local prescribing information.

Information on the formulation, packaging, handling, and administration of trastuzumab is provided in the local prescribing information as appropriate.

Accurate records of all investigational medicinal products (IMPs), including trastuzumab emtansine and trastuzumab, that are received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

STATISTICAL METHODS

PRIMARY ANALYSIS

The primary efficacy variable is IDFS, defined as the time between randomization and date of first occurrence of an IDFS event. Patients who have not had an event will be censored at the date they are last known to be alive and event free on or prior to the clinical data cutoff date.

The log-rank test, stratified by the protocol-defined stratification factors (clinical stage at presentation [inoperable vs. operable]; hormone receptor status [ER or PgR positive vs. ER and PgR negative/unknown]; preoperative HER2-directed therapy [trastuzumab vs. trastuzumab plus additional HER2-directed agent(s)]; and pathologic nodal status evaluated after preoperative therapy [node positive vs. node negative/not done]), will be used to compare IDFS between the 2 treatment arms. The unstratified log-rank test results will also be provided as a sensitivity analysis. If at the time of analysis it is deemed that the smallest strata per arm is <5 patients to conduct robust stratified analyses, unstratified analyses will be used as the primary analysis.

Cox proportional hazards model, stratified by the protocol-defined stratification factors, will be used to estimate the HR between the 2 treatment arms and its 95% confidence interval (CI). The Kaplan-Meier approach will be used to estimate 3-year IDFS rates and corresponding 95% CIs for each treatment arm.

DETERMINATION OF SAMPLE SIZE

The sample size of the study is primarily driven by the analysis of IDFS. To detect a hazard ratio (HR) of 0.75 in IDFS (a 6.5% improvement in 3-year IDFS from 70% in the control arm to 76.5% in the trastuzumab emtansine arm), approximately 384 IDFS events will be required to achieve 80% power at a 2-sided significance level of 5%. Approximately 1484 patients will be enrolled in the study.

The study is expected to be fully enrolled around 35 months after the first patient enrolls in the study (FPI). The final IDFS analysis will be performed after approximately 384 events have occurred, which is projected to be approximately 107 months from FPI.

With the study sample size of 1484 patients and approximately 12 years of follow-up, this study has about 43% power to detect a HR of 0.8 (a 2.8% improvement in 3-year OS from 85% in the control arm to 87.8% in the trastuzumab emtansine arm) at a 2-sided significance level of 5%.

INTERIM ANALYSES

One interim analysis of IDFS and 2 interim analyses of OS are planned.

The interim efficacy analysis of IDFS is planned after 67% of the targeted IDFS events have occurred, which is estimated to be approximately 48 months after the first patient is enrolled in the study. At this interim analysis, IDFS will be tested at the significance level determined using the Lan–DeMets alpha spending function with an O'Brien–Fleming boundary so that the overall 2-sided type I error rate will be maintained at the 5% level for the IDFS primary endpoint. A summary of the planed IDFS analyses is shown in the table below:

Analysis of IDFS	No. of events	Efficacy Stopping Boundary [a]	Estimated Timing [b]
Interim	257	$p < 0.0124$ or observed HR < 0.732	48 months
Final	384	$p < 0.0462$ or observed HR < 0.816	107 *months*

HR = hazard ratio; IDFS = invasive disease-free survival.

[a] p-value will be based on 2-sided stratified log-rank test.

[b] Time from the enrollment of first patient to data cutoff.

The purpose of the interim analysis is to evaluate whether there is an overwhelming difference in the efficacy observed in the trastuzumab emtansine arm compared with the trastuzumab arm in terms of IDFS. If the test is not significant, the study will continue as planned. If the test is significant, the independent Data Monitoring Committee (iDMC) may recommend releasing the primary endpoint results before the targeted number of 384 events is reported. In this latter situation, the Sponsor will be unblinded to the study results and a full data package would be prepared for discussion with regulatory authorities. The study will continue until 12 years of follow-up and IDFS analysis will be updated when 384 IDFS events have occurred.

Two formal interim OS analyses and one final OS analysis are planned, as detailed in the table below. The final OS analysis will be performed at the end of 12 years of follow-up. A survival data sweep will be conducted prior to each analysis.

The overall type I error will be controlled at 0.05 for the formal OS interim analyses and final OS analysis using the Lan–DeMets alpha spending function with an O'Brien–Fleming boundary. The boundaries used at each interim and final OS analysis will depend on the timing of the analyses and the number of death events actually included in the analyses.

Analysis Of OS	No. of Events	Efficacy Stopping Boundary [a]	Estimated Timing [b]
Interim 1 (at interim IDFS)	*98*	*$p < 0.0005$ or observed HR < 0.494*	48 months
Interim 2 (at final IDFS)[c]	*183*	*$p < 0.0143$ or observed HR < 0.696*	*107 months*
Final[c]	*263*	*$p < 0.0456$ or observed HR < 0.781*	*144 months*

HR = hazard ratio; IDFS = invasive disease-free survival; OS = overall survival.

[a] p-value will be based on 2-sided stratified log-rank test.

[b] Time from the enrollment of first patient to data cutoff.

[c] *Estimated number of events. Efficacy boundaries will be calculated based on the actual number of events at the time of analysis.*

An iDMC will monitor accumulating patient safety data at least once approximately every 6 months until the last patient has completed study treatment. In addition, data on SAEs and deaths will be monitored by the iDMC at least once approximately every 3 months during this period. At each iDMC review, relevant safety information from ongoing trastuzumab emtansine studies will be provided to the iDMC.

After the first 600 patients have been randomized and followed up for 3 months (approximately 21 months after FPI), the iDMC will perform an interim safety analysis regarding death and hepatic events. The Clinical Events Committee will communicate their findings regarding cardiac and hepatic events to the iDMC to aid iDMC review.

If an absolute increase of > 3% in the percentage of death (from any cause) or in the percentage of Hy's law cases (confirmed by the independent clinical events committee) is observed in the trastuzumab emtansine arm compared with the trastuzumab arm, the iDMC will consider recommending holding enrollment for further data review, stopping, or modifying the trial.

If an absolute increase of > 3% in the percentage of Hy's law cases (confirmed by the independent clinical events committee) is observed in the trastuzumab emtansine arm compared with the control arm, the iDMC will consider recommending holding enrollment for further data review, stopping, or modifying the trial.

The iDMC will work according to the guidelines defined in the iDMC Charter. The iDMC Charter will contain details regarding the frequency of meetings, guidelines for decision making, and process for requesting further information. The iDMC members will review and sign off on the charter before the first review.

Appendix 2 Schedule of Activities

	Screening [a]	Cycles 1 and 2		Cycles 3–14		Study Drug Completion Visit [b]	Survival Follow-Up [c]
Day	–30 to –1	1	14–21	1	14–21		
Informed consent [a]	x						
Assignment of patient numbers through IVRS/IWRS	x						
Tumor tissue submission for HER2 determination and exploratory biomarkers (mandatory)	x [d]						x [d]
Blood sample for plasma/serum biomarker analyses (optional)		x [e]		x [e]		x [e]	x [e]
Whole blood sample for genetic analyses (optional)		x [e]					
Medical history and demographics	x						
Disease status assessments [f]		x					x [f]
Complete physical examination	x						x [f]
Limited physical examination [g]		x		x		x	
Height [h]	x						
Vital signs [i]	x	x		x		x	
ECOG performance status	x					x	
Concomitant/follow-up medication reporting	x [j]	x		x		x	x [f, z]
AE reporting [k]	x [l]	x		x		x	x
12-lead ECG	x						
ECHO/MUGA [m]	x		x [m]		x [m]	x [m]	x [m]
HBV and HVC serology[n]	x						

Appendix 2: Schedule of Activities (cont.)

	Screening [a]	Cycles 1 and 2		Cycles 3–14		Study Drug Completion Visit [b]	Survival Follow-Up [c]
Day	–30 to –1	1	14–21	1	14–21		
Hematology [o]	x [p]	x [q]		x [q]		x	x [r]
Biochemistry [s]	x [p]	x [q]		x [q]		x[t]	x[r]
PK samples (serum and plasma)		See Appendix 2 for details					
ATA assessment [u]		x [u]		x [u]		x [u]	x [u]
INR/aPTT	x [p]	As clinically indicated					
Pregnancy test [v]	x			x [v]		x	x
Bilateral mammogram	x (within 1 year)						x [w]
Patient-reported outcome assessment [x]	x			x [x]		x	x
Arm B: trastuzumab administration [y]		x		x			
Arm A: trastuzumab emtansine administration [y]		x		x			

AE = adverse event; ALK = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; ATA = anti-therapeutic antibody; *CT = computed tomography;* ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; *eCRF = electronic Case Report Form;* HBV = hepatitis B virus; HCV = hepatitis C virus; INR = international normalized ratio; IVRS/IWRS = interactive voice response system/interactive web response system; *MRI = magnetic resonance imaging;* MUGA = multiple-gated acquisition; PK = pharmacokinetics; TBILI = total bilirubin.

NOTE: Unscheduled visits may be conducted at any time for studies that may include hematology, biochemistry, INR/aPTT, ECG, ECHO/MUGA, or disease assessment.

[a] Informed consent may be obtained at any time (including prior to the 30-day screening period) but must be obtained prior to the performance of any screening assessments. Results of screening tests or examinations performed as standard of care prior to obtaining informed consent and within 30 days prior to randomization may be used rather than repeating required tests.

[b] Performed within approximately 30 days after the last dose of study treatment.

[c] The follow-up period begins from the date of the study drug completion/early termination visit with a duration of up to *12* years from the date of randomization of the first patient. Visit windows are ± 28 days for quarterly and semiannual assessments and ± 42 days for annual assessments.

[d] Tumor tissue samples (formalin-fixed paraffin-embedded [FFPE] material) obtained for HER2 testing from the primary site before preoperative therapy, or if not possible, from the surgical specimen along with the pathology reports. Paraffin-embedded tumor tissue blocks or partial blocks from pretreatment material must be obtained from the preoperative biopsy in addition to the surgical specimen. If sites are unable to send tissue blocks due to local regulations, at least 8 unstained slides should be sent, and in addition, up to 5 slides for exploratory biomarker research from the preoperative biopsy and 25 slides must be submitted for exploratory biomarker analysis from the surgical specimen. Alternatively, 15 slides could be sent along with a biopsy core from the surgical specimen. If a biopsy is collected as part of routine medical practice at relapse/recurrence, a tissue block or up to five unstained slides should be sent for biomarker analysis in order to gain better understanding of resistance mechanisms.

[e] If optional consent was given, serum and plasma samples will be collected for exploratory biomarker analyses and/or for long-term storage in the study's central biomarker repository for future biomarker analyses. Serum and plasma samples should be drawn at C1D1 baseline, C1D8, C4, C8, and C12, as well as at the study drug completion/early termination visit and at time of relapse/recurrence. The whole blood sample for genetic analyses should be drawn at C1D1 but can be drawn during study execution if forgotten at baseline.

[f] Disease status based on all available clinical assessments should be documented from the date of randomization at the following timepoints: every 3 months during study treatment and up to 2 years, every 6 months from 3 to 5 years, and annually *thereafter through to 03 April 2023*. Whenever possible, disease recurrence should be confirmed pathologically. In cases of disease recurrence diagnosed at any time during the study, patients will be followed once a year (starting 1 year after first relapse) until *03 April 2023* for anti-cancer medications and new relapse events. *All patients still in the study will be followed with at least annual contact (virtual, telephone, or in-person) for survival until 03 April 2025, a 2-year extension. Disease status assessment in the extension period (April 2023 – April 2025) is not mandatory but can be recorded on unscheduled survival follow-up visit CRFs if performed as part of standard of care.*

[g] Limited symptom-directed physical exam focusing on organ systems related to a potential AE based on patient's interim medical history and/or existing AE profiles of the study drugs. Disease status based on all available clinical assessments should be documented every 3 months during study treatment.

[h] Height to be obtained at screening or at Cycle 1 Day 1 only.

[i] Vital signs should be obtained and reviewed but, aside from weight, are not required to be entered into the eCRF. Abnormal vital signs at any time during the course of study treatment should be recorded as AEs or SAEs if clinically significant.

[j] Record all prior anti-cancer therapies and concomitant medications.

[k] Patients will be followed for new or worsening AEs for 30 days following the last infusion of study drug or until the early termination visit, until treatment related AEs resolve or stabilize, or until the initiation of another anti-cancer therapy, whichever occurs first. After 30 days following last study treatment administration, the investigator should continue to follow all unresolved study-related AEs and SAEs until their resolution or stabilization, the patient is lost to follow-up, or it is determined that the study treatment or participation is not the cause of the AE/SAE. The investigator should notify the Sponsor of any death, SAE, or other AE of concern occurring at any time after a patient has discontinued study treatment or study participation if the event is believed to be related to prior study drug treatment or study procedures.

[l] During screening, only SAEs considered related to protocol-mandated procedures will be collected.

[m] Cardiac monitoring (ECHO/MUGA) will be performed in all patients enrolled in the study. ECHO is the preferred method. The same method used for a given patient at screening should be used throughout the study. ECHO/MUGA should be obtained during the last week (Days 14–21) of C2, and every 4 cycles thereafter (C6, C10, C14). ECHO/MUGA should be obtained at the study drug completion/early termination visit if not performed within the previous 6 weeks and at 3, 6, 12, 18, 24, 36, 48, and 60 months. Cardiac monitoring should continue to be performed in all patients according to the schedule above. For patients who have not had a recurrence, record the assessment(s) on a Survival Follow-Up eCRF. For patients who have had a recurrence, even if receiving treatment for the recurrence, the assessment should be performed annually and recorded on a Post-Recurrence Survival Follow-Up eCRF.

[n] Documentation of HBV and HCV serologies is required: this includes HB surface antigen (HBsAg) and/or total HB core antibody (anti-HBc) in addition to HCV antibody testing. The most recent serologic testing must have occurred within 3 months prior to initiation of neoadjuvant therapy. If such testing has not been done, it must be performed during screening.

[o] Hematologic assessments include hemoglobin (Hb), hematocrit, platelet count, and WBC, including determination of absolute neutrophil count (ANC).

[p] Screening: to be performed within 7 days prior to randomization. Screening laboratory assessments may be done on the day of randomization and their results may be used for randomization visit purposes.

[q] Cycle 1 Day 1 hematology and biochemistry assessments are not mandatory if the screening assessment was conducted within 7 days prior to randomization. Scheduled for Day 1 of Cycle 2 and beyond: to be performed within 72 hours preceding administration of study treatment; results must be reviewed and documented prior to administration of study treatment.

[r] CBC and platelet counts, TBILI, ALT, AST, and ALK will be measured every 3 months during the follow-up period for 1 year after the study drug completion/early termination visit. If platelet counts are decreased or if TBILI, ALT, AST, or ALK are elevated, testing should continue per Footnote t.

[s] Biochemistry assessments at baseline include sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN) or urea, creatinine, total and direct bilirubin, total protein, albumin, ALT, AST, and ALK. Patients who have positive HBV or HCV serology without known active disease must meet the eligibility criteria for ALT, AST, TBILI, INR, aPTT, and ALK on at least two consecutive occasions, separated by at least 1 week, within the 30 day screening period. Further assessment of disease activity may be done per standard local practice, e.g., PCR. Assessments at each treatment and at study discontinuation include potassium, TBILI (and direct bilirubin when TBILI > ULN), ALT, AST, and ALK; other assessments may be obtained as clinically indicated.

[t] The investigator should follow each elevated liver test finding at least monthly until the event has resolved to baseline, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent.

[u] To be assessed in approximately 50% of patients from each treatment arm at the following timepoints: pre-dose Cycle 1, Day 1 and Cycle 4, Day 1, study treatment termination, and at 3-4 months after the last study treatment. (See Appendix 2 for additional details.)

Appendix 2: Schedule of Activities (cont.)

[v] Serum β-HCG test must be performed during screening. Urine β-HCG test may be performed at subsequent time points for women of childbearing potential (including pre-menopausal women who have had a tubal ligation) and for women not meeting the definition of postmenopausal. For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential. Urine pregnancy tests in women of childbearing potential in all treatment arms every 3 cycles and at 3 and 6 months after the study drug completion visit. All positive urine pregnancy tests must be confirmed by a serum β-HCG test.

[w] Mammograms of any remaining breast tissue should be performed at least annually. Mammograms and/or other relevant imaging, such as CT or MRI scans of the breast as determined by clinical practice, should continue to be performed in all patients at least annually. Each recurrence should be documented, including type of recurrence and method of diagnosis (including imaging), either on a Survival Follow-Up eCRF if the patient has not yet had a recurrence or on a Post-Recurrence Survival Follow-Up eCRF if a recurrence has already been recorded.

[x] Patient-reported outcome (PRO) questionnaires should be completed before or upon arrival at the study site before any study-specific procedures are performed, and before the patient sees the physician, during screening, at Cycles 5 and 11, at the study drug completion visit, and every 6 months in follow-up for 12 months after the study drug completion visit.

[y] If the timing coincides with a holiday that precludes administration, administration should be performed within 5 business days following randomization for Cycle 1 and within 5 business days of the scheduled date for subsequent cycles. Patients who discontinue trastuzumab emtansine may complete the duration of their study therapy with trastuzumab, if appropriate, based on toxicity considerations. If so, they should perform the scheduled assessments as indicated for the study treatment period.

[z] Medications related to the treatment of SAEs are to be reported during the follow-up period, as well as ongoing or new breast cancer treatments (e.g., hormone therapy), anticancer treatments for recurrence, and bisphosphonate or denosumab therapy.

Appendix 3 Schedule of Pharmacokinetic and Pharmacodynamic Assessments

PK and ATA Assessments for Trastuzumab Emtansine- and Trastuzumab-Treated Patients [a]		
Study Visit	**Time**	**Sample Acquisition**
Cycle 1, Day 1 and Cycle 4, Day 1	Pre-trastuzumab emtansine infusion	• Serum sample for trastuzumab emtansine and total trastuzumab • Plasma sample for DM1 [b] • Serum sample for anti-trastuzumab emtansine antibody (ATA)
Cycle 1, Day 1 and Cycle 4, Day 1	15-30 min post-trastuzumab emtansine infusion	• Serum sample for trastuzumab emtansine and total trastuzumab • Plasma sample for DM1 [b]
Cycle 1, Day 1 and Cycle 4, Day 1	2 hours (± 15 min) post-trastuzumab emtansine infusion	• Serum sample for trastuzumab emtansine • Plasma sample for DM1 [b]
Cycle 2, Day 1 and Cycle 5, Day 1	Pre-trastuzumab emtansine infusion	• Serum sample for trastuzumab emtansine
Study Treatment Termination	Any point during study visit	• Serum sample for trastuzumab emtansine • Serum sample for anti-trastuzumab emtansine antibody (ATA)
3-4 months after last dose of trastuzumab emtansine	Any point during study visit	• Serum sample for anti-trastuzumab emtansine antibody (ATA)
Cycle 1, Day 1 and Cycle 4, Day 1	Pre-trastuzumab infusion	• Serum sample for trastuzumab • Serum sample for anti-trastuzumab antibody (ATA)
Cycle 1, Day 1 and Cycle 4, Day 1	15-30 min post-trastuzumab infusion	• Serum sample for trastuzumab
Study Drug Termination	Any point during study visit	• Serum sample for trastuzumab • Serum sample for anti-trastuzumab antibody (ATA)
3-4 months after last dose of trastuzumab	Any point during study visit	• Serum sample for anti-trastuzumab antibody (ATA)

Note: Samples for PK analyses should be obtained from the arm not used for the infusion of study drug. If taking PK samples from the opposite arm is not possible (e.g., due to surgery), PK samples should be taken from an alternative site on the arm used for the infusion of study drug. The PK samples should not be taken from the same site as the infusion of study drug.

[a] Samples collected in approximately 50% of trastuzumab emtansine-treated patients and 50% of trastuzumab-treated patients.

[b] Any remaining plasma samples after DM1 analysis may be used for measurement of trastuzumab emtansine metabolites (e.g., MCC-DM1, Lys-MCC-DM1) as an exploratory assessment (if stability acceptable and at discretion of sponsor).

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