Official Title: **A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE III TRIAL COMPARING TRASTUZUMAB PLUS PERTUZUMAB PLUS A TAXANE FOLLOWING ANTHRACYCLINES VERSUS TRASTUZUMAB EMTANSINE PLUS PERTUZUMAB FOLLOWING ANTHRACYCLINES AS ADJUVANT THERAPY IN PATIENTS WITH OPERABLE HER2-POSITIVE PRIMARY BREAST CANCER**

NCT Number: NCT01966471

Document Date: Protocol Version 3: 30-July-2015

PROTOCOL

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PROTOCOL NUMBER:	BO28407
VERSION NUMBER:	3
EUDRACT NUMBER:	2012-004902-82
IND NUMBER:	71072
TEST PRODUCTS:	Trastuzumab Emtansine (RO5304020) and Pertuzumab (RO4368451)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 7 October 2013
DATE AMENDED:	Version 2: 16 June 2014 Version 3: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	30-Jul-2015 17:56:09

PROTOCOL AMENDMENT, VERSION 3:
RATIONALE

Protocol BO28407 has been amended in light of new data from the Phase III study TDM4788g/BO22589 (MARIANNE) in metastatic breast cancer, in which efficacy (PFS) of trastuzumab emtansine with and without pertuzumab was shown to be non-inferior to trastuzumab+taxane, with improvements in tolerability and quality of life (QoL); however neither of the trastuzumab emtansine-containing regimens showed PFS superiority over taxane plus trastuzumab. Further, in the early breast cancer (EBC) study (WGS-ADAPT), a planned interim analysis of pathological complete response (pCR) (ypT0/is, ypN0) rates after neoadjuvant trastuzumab emtansine with or without endocrine therapy as treatment of ER+, HER2 breast cancer was highly promising. These preliminary pCR rates observed are substantially higher than those seen with previous studies evaluating trastuzumab+endocrine therapy or chemotherapy + trastuzumab ± pertuzumab as treatment of ER+, HER2+ EBC. These data, together with those from Study TDM4997g/BO25734 (TH3RESA), TDM4370g/BO21977 (EMILIA), TDM4450g, and TDM4874g/BO22857 support continuation of the BO28407 study with the following key protocol modifications:

- Sample size reduction: In light of the MARIANNE study results, it is assumed that the likelihood of this study meeting its primary efficacy endpoint for superiority has decreased. To address this updated assessment of potential study outcome sample size was reduced while maintaining statistical validity of the study in addressing its primary endpoint. Section 3.3.2.3 (Rationale for Sample Size Reduction) was added to detail the reasons for this study design modification.
    - Since the study enrollment is stopped earlier than planned, the capping of enrollment that was prespecified in Protocol Versions 1 and 2 will not be implemented, and thus Section 3.3.2.1 (Rationale for Capping Subgroup Enrollment) has been updated. Relevant protocol sections have also been updated to reflect this change accordingly (Sections 3.1, 4.1, 4.1.1, 6.1)
- The study rationale, background information and benefit-risk assessment sections have been updated considering new data for trastuzumab emtansine (Sections 1.2.1, 1.3.1 and 1.3.2). In addition, the Rationale for Adjuvant Regimens and Duration of Therapy (Section 3.3.4) was updated to reflect the impact of new data on the rationale for adjuvant regimens.

Additional changes to the protocol, by topic, are as follows:

1. Provision of updated clinical data

In order to provide a better overview of benefit-risk, in light if all new data, the following sections were updated:

- Background section 1.2.1.1.1 (Single-agent studies) have been updated to provide latest data for Study TDM4997g/BO25734

- Background section 1.2.1.1.2 (Combination studies) have been updated to provide latest data for Study TDM4788g/BO22589 (MARIANNE)
- Background section 1.2.1.2 (Trastuzumab emtansine clinical experience in EBC) have been updated to include Study BO28408 and to provide latest data for Studies TDM4874g/BO22857, BP22572, and BO27938.
- Background section 1.2.1.3 (Pooled safety analysis of single-agent trastuzumab emtansine) and Table 1 have been updated to provide changes with the latest data cut as of 31 July 2012.
- Background section 1.2.2.1 (Pertuzumab clinical experience in MBC) has been updated to provide latest data for WO20698/TOC4129g (CLEOPATRA)
- Background section 1.2.2.2 (Pertuzumab clinical experience in EBC) has been updated to provide latest data for WO20697 (NEOSPHERE), and BO25126 (APHINITY).
- Pooled safety analysis of trastuzumab emtansine in combination with pertuzumab (Section 1.2.3) and Table 4 have been updated to provide changes with the latest data cut as of 30 September 2013.

2. Patient Reorted Outcomes

- Patient-Reported Outcomes has been updated to include additional analyses to assess the patient experience with therapy (Section 6.6)

3. Safety Reporting Updates

- The following changes were made, to align with most recent data or guidance
- The section on persistent or recurrent adverse events (Section 5.3.5.3) was updated per new template to include information regarding Adverse Event Intensity or Grade Changes eCRF.
- Emergency medical contacts (Section 5.4.1) have been updated to reflect personnel changes.
- Reporting requirements for pregnancies have been updated to align with the Herceptin, Perjeta, and Kadcyla Global Enhancement Pharmacovigilance Pregnancy Program (Section 5.4.3.2).

4. Futility Analysis

- Section 6.8.1 (interim analysis) has been updated to indicate the potential for a futility analysis to evaluate lack of superiority for the treatment arm of trastuzumab emtansine + pertuzumab following anthracyclines that will be further detailed in the Statistical Analysis Plan.

5. Effective contracption

- Intrauterine device (IUD) was recognized as highly effective contraception. Highly effective contraception is defined as a method of birth control that results in a very low failure rate (i.e., less than 1% per year) when used consistently and correctly

(theoretical effectiveness). Per the new World Health Organization data, IUD should be categorized as a highly effective method as it has a failure rate of less than 1% per year with either theoretical use or typical use (Appendix 10).

Additional minor changes have been made to improve clarity and consistency and to reflect current recommendations. Substantive new information appears in italics.

PROTOCOL AMENDMENT, VERSION 3:
SUMMARY OF CHANGES

GLOBAL CHANGES

~~A total of 2500~~*Approximately 1850* patients ~~will~~ *are anticipated to* be enrolled at approximately 350 sites worldwide.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.2.1.1.1: Single-Agent Studies

Study TDM4997g/BO25734 (TH3RESA) is a Phase III study to evaluate efficacy of trastuzumab emtansine versus Treatment of Physician's Choice (TPC) in patients who received at least two prior regimens of HER2-directed therapies, including trastuzumab and lapatinib, in the metastatic or unresectable locally advanced/recurrent setting. Co-primary efficacy endpoints were PFS per investigator assessment and OS. There were 404 patients who received trastuzumab emtansine as their planned treatment, and 198 patients who received TPC. Patients receiving trastuzumab emtansine had a 47.2% reduction in the risk of disease progression or death. Median PFS was 3.3 months in the TPC arm and 6.2 months in the trastuzumab emtansine arm (HR =0.528; 95% CI: 0.422, 0.661; p <0.0001). There was a strong positive trend in OS in favor of trastuzumab emtansine at the first interim analysis. Patients receiving trastuzumab emtansine had a 44.8% reduction in the risk of death (HR =0.552; 95% CI: 0.369, 0.826; p =0.0034) compared with patients receiving TPC; however, this result did not cross the pre-specified O'Brien-Fleming stopping boundary of HR <0.363 (p <0.0000013). Patients receiving trastuzumab emtansine also showed a consistent treatment benefit compared with the subgroup of TPC patients receiving a trastuzumab-containing regimen (74.7% of the intent-to-treat [ITT] population).

Numerically fewer patients receiving trastuzumab emtansine than those receiving TPC had Grade ≥3 AEs (39.0% vs. 46.2%) or AEs leading to dose reduction (12.4% vs. 20.7%). The incidence of SAEs (24.1% vs. 22.3%) and of AEs leading to treatment discontinuation of any component of therapy (11.7% vs. 10.9%) are similar between treatment arms. Across the majority of the most commonly affected body systems, patients receiving trastuzumab emtansine reported more AEs compared with those receiving TPC. However, the higher frequency of events seen for trastuzumab emtansine was driven by Grade 1–2 AEs.

The patient-reported outcome (PRO) measures including "time to pain symptom progression" were utilized to evaluate QoL. The time to pain symptom progression was similar different between the two treatment arms (HR =1.115; 95% CI: 0.819, 1.517).

SECTION 1.2.1.1.2: Combination Studies

A total of 1095 patients *were enrolled in this study.*

Efficacy and safety data were recently described (Ellis et al. 2015). For the primary endpoint of PFS based on independent review facility (IRF) assessment, both trastuzumab emtansine +placebo and trastuzumab emtansine + pertuzumab were non-inferior to trastuzumab +taxane: the upper bounds of the 97.5% CIs for the stratified HRs were below the pre-specified non-inferiority margin of HR 1.1765: 1.13 for trastuzumab emtansine +placebo (HR =0.91; 97.5% CI: 0.73, 1.13) and 1.08 for trastuzumab emtansine +pertuzumab (HR =0.87; 97.5% CI: 0.69, 1.08), each versus trastuzumab +taxane. The addition of pertuzumab to trastuzumab emtansine did not result in a statistically significant increase in PFS in the ITT population. Median PFS was 13.7 months for trastuzumab +taxane, 14.1 months for trastuzumab emtansine +placebo and 15.2 months for trastuzumab emtansine +pertuzumab.

The safety profile of trastuzumab emtansine as a single agent or in combination with pertuzumab was consistent with prior experience, with no new safety signals identified compared with those already known for these study drugs. Trastuzumab emtansine as a single agent or in combination with pertuzumab was more tolerable than trastuzumab +taxane, with respect to a numerical lower incidence and/or severity of certain clinically important and/or symptomatic toxicities, fewer Grade ≥3 AEs and fewer AEs leading to treatment discontinuation (Ellis et al. 2015).

~~As of July 2013, unblinded safety and efficacy data were not available to the Sponsor, but the independent Data Monitoring Committee (iDMC), which reviews data from the trial on a quarterly basis, had thus far recommended that the study continue as planned.~~

SECTION 1.2.1.2: Trastuzumab Emtansine Clinical Experience in Early Breast Cancer

~~As of 22 April 2013, a total of 148 patients had received trastuzumab emtansine. N~~*The final analysis (clinical cut–off 12 June 2013) indicated that there were n*o prespecified cardiac events occurred ~~(95% CI: 0.00%, 2.45%),~~ and there were no reports of symptomatic left ventricular systolic dysfunction (LVSD) or heart failure. ~~One patient discontinued trastuzumab emtansine due to asymptomatic left ventricular ejection fraction (LVEF) decline.~~ Overall, 123 (83.1%) patients completed the planned course of trastuzumab emtansine treatment, 119 (80.4%) of whom had no dose reduction. Twenty patients (13.5%) had adverse events leading to trastuzumab emtansine discontinuation: in 11 of these patients, the adverse events were laboratory abnormalities requiring discontinuation (none were Grade 4), and in 9 patients, discontinuation was because of symptomatic adverse events (2 were Grade 3 [fatigue, joint crepitation]; none were Grade 4). Of the 148 patients, 32.4% had Grade 3 trastuzumab emtansine–related adverse events and 2.7% had Grade 4 trastuzumab emtansine–related adverse events (1 patient each: febrile neutropenia and pancytopenia, atrial fibrillation, decreased platelet count, and hypokalemia); no deaths occurred. The adverse events observed to date are consistent with the known safety profile of trastuzumab emtansine. There were no cases of portal hypertension/nodular regenerative hyperplasia (NRH) reported. *For*

additional safety details for this study, please refer to the trastuzumab emtansine Investigator's Brochure.

In the MBC population (n =25), the ORR was 80.0% (95% CI: 59.3, 93.2). In the overall LABC population (n =73), the pCR rate was 60.3% (95% CI: 48.1, 71.5). In LABC patients receiving trastuzumab emtansine +docetaxel (n =40), the pCR rate was 60.0%, and in those receiving trastuzumab emtansine +docetaxel +pertuzumab (n =33), it was 60.6%.

Study WSG-ADAPT is a Phase II study evaluating trastuzumab emtansine with or without endocrine therapy in comparison to trastuzumab + endocrine therapy as neoadjuvant treatment in HER2+/HR+ EBC patients. After 4 cycles of either neoadjuvant trastuzumab + endocrine therapy or neoadjuvant trastuzumab emtansine with or without endocrine therapy, patients underwent definitive breast surgery with total pCR serving as the primary endpoint. Notable therapeutic activity was observed at the planned interim analysis (January 2015) among 130 patients. Total pCR (ypT0/is, ypN0) rates after 4 cycles of neoadjuvant trastuzumab + endocrine therapy, trastuzumab emtansine + endocrine therapy, or trastuzumab emtansine alone were 6.7%, 45.8%, and 40.5%, respectively (Harbeck et al. 2015).

Study BO27938 (KATHERINE) is a randomized, multinational, multicenter, open-label Phase III study, evaluating adjuvant treatment with trastuzumab emtansine compared with trastuzumab in patients with EBC who have not achieved a pCR following neoadjuvant treatment with chemotherapy and trastuzumab. The primary objective of this trial, which started in April 2013, is to compare invasive disease–free survival (IDFS) between treatment arms. *As of 11 May 2015, unblinded safety and efficacy data were not available to the Sponsor, but the independent Data Monitoring Committee (iDMC), which reviews data from the trial, had thus far recommended that the study continue as planned.*

Study BO28408/TRIO021 (KRISTINE) is a randomized, multicenter, open-label Phase III study, evaluating neoadjuvant treatment with trastuzumab emtansine +pertuzumab compared with chemotherapy +trastuzumab and pertuzumab in patients with EBC. The primary objective of this trial, which started in June 2014, is to compare the pCR rate (ypT0/is, ypN0) using local evaluation between treatment arms.

SECTION 1.2.1.3: Pooled Safety Analysis of Single-Agent Trastuzumab Emtansine

Pooled safety data are available for 884 patients with MBC treated with single-agent trastuzumab emtansine at a dose of 3.6 mg/kg q3w. The most common adverse events associated with single-agent trastuzumab emtansine (in ≥25% of patients) were fatigue (~~46.3~~*46.4*%), nausea (~~42.9~~*43.0*%), thrombocytopenia (~~32.1~~*29.6*%), headache (~~29.2~~*29.4*%), and constipation (26.4*5*%). Most of these events were Grade 1 or 2 in intensity. The most common Grade ≥3 adverse events (occurring in >2% of patients)

were thrombocytopenia (~~11~~*10*.7%), increased AST (4.3%), fatigue (3.2%), increased ALT (3.1%), hypokalemia (2.9%), and anemia (2.~~7~~*9*%). ~~Fifty eight~~*Sixty-two* patients (~~6.6~~*7.0*%) experienced adverse events that resulted in their trastuzumab emtansine treatment being discontinued: The most common adverse events leading to discontinuation were blood and lymphatic system disorders (primarily thrombocytopenia [1.5%]) and investigations system organ classes (SOCs) (increased AST [0.8%] and increased ALT [0.5%]).

Selected a~~A~~dverse events ~~of special interest~~ for all patients include hepatotoxicity, peripheral neuropathy, thrombocytopenia, infusion-related reactions (IRR)/hypersensitivity, cardiac dysfunction, and pneumonitis.

SECTION 1.2.2.1: Pertuzumab Clinical Experience in MBC

The primary endpoint of this randomized trial was PFS as assessed by an IRF. The randomized trial demonstrated a statistically significant improvement in IRF-assessed PFS in the pertuzumab-treated group compared with the placebo-treated group (HR = 0.62 [95% CI: 0.51, 0.75]; p < 0.0001) and an increase in median PFS of 6.1 months (median PFS of 18.5 months in the pertuzumab-treated group vs. 12.4 months in the placebo-treated group) (Baselga et al. 2012c). *The final analysis of OS took place when 389 deaths had occurred, after a median follow-up of 50 months. Despite crossover, OS benefit in favor of the pertuzumab-treated group was maintained (HR =0.68; 95% CI: 0.56, 0.84; p =0.0002). The median OS was longer by 15.7 months in the pertuzumab-treated group (median 56.5 months) compared to the placebo-treated group (median 40.7 months)* (Swain et al*. 2015*).

SECTION 1.2.2.2: Pertuzumab Clinical Experience in Early Breast Cancer

Results from the post-treatment follow-up period (up to the third clinical cutoff of 12 July 2013) showed that there were no clinically relevant, long-term toxicities.

Five-year pre-planned analyses of pertuzumab in combination with trastuzumab and docetaxel compared with trastuzumab and docetaxel showed 81% and 82% PFS (similar to event-free survival) and 88% and 84% DFS rate, respectively. These analyses showed that these results are consistent with breast pCR results and shows long-term benefits of adding pertuzumab to trastuzumab and docetaxel as neoadjuvant therapy (Gianni et al. 2015).

SECTION 1.2.3: Pooled Safety Analysis of Trastuzumab Emtansine in Combination with Pertuzumab

Pooled safety data are available for 87 patients treated with trastuzumab emtansine and pertuzumab (Studies TDM4373g*/BO22495* [n = 67] and TDM4688g [n = 20]; including follow-up data for any patients continuing to receive treatment in the extension study [TDM4529g/BO25430]). The most common adverse events of any grade (in ≥ 20% of patients) were fatigue (52.9%), nausea (42.5%), diarrhea (3*5*~~4~~.*6*~~5~~%), cough (33.3%), decreased appetite (31%), thrombocytopenia (27.6%), constipation (26.4%), vomiting

(~~26~~*27*.~~4~~*6*%), pyrexia (26.4%), increased AST (26.4%), chills (25.3%), epistaxis (~~24~~*25*.~~1~~*3*%), increased ALT (23%), headache (23%), dyspnea (23%), dysgeusia (20.7%), and rash (2*1*~~0~~.~~7~~*8*%), with most of these events being Grade 1 or 2. The most common Grade ≥3 adverse events (occurring in >2 patients [2.5%]) were *fatigue (11.5%),* thrombocytopenia (10.3%), ~~fatigue (10.3%),~~ increased AST (9.2%), dyspnea (~~8.0~~*9.2*%), increased ALT (6.9%), anemia (5.7%), cellulitis (4.6%), peripheral sensory neuropathy (4.6%), pleural effusion (3.4%)~~, hypokalemia (3.4%)~~, and pneumonia (3.4%).

~~Adverse~~ *Selected adverse* events *of relevance to trastuzumab emtansine* ~~of special interest~~ for all patients include hepatotoxicity, peripheral neuropathy, thrombocytopenia, infusion reactions, cardiac dysfunction, and pneumonitis. Table 4 provides an overview of these adverse events.

SECTION 1.3.1: Study Rationale

The highly potent chemotherapeutic agent DM1 should complement the HER2 signaling pathway inhibition caused by the combination of trastuzumab and pertuzumab. Furthermore, DM1 may provide higher dose intensity and longer duration when delivered as a HER2-targeted chemotherapy with potentially less systemic toxicity compared with conventional chemotherapy. Therefore, trastuzumab emtansine ~~should substantially~~ *may* reduce the risk of recurrence and increase the likelihood of DFS in HER2-positive EBC, with an acceptable safety profile compared with the current or anticipated future SoC.

The Phase III EMILIA study demonstrated improved efficacy (PFS and OS), with a favorable safety profile and QoL, with trastuzumab emtansine as a single agent compared with lapatinib plus capecitabine in patients with recurrent/metastatic HER2-positive breast cancer who have previously received taxanes and trastuzumab. *Furthermore, this benefit was seen both in patients treated as first-line therapy for MBC who had progressed early as well as those who received therapy in second line and later* (Section 1.2.1.1.1*;* Blackwell et al. 2012*;* Verma et al. 2012).

The Phase III TH3RESA study also showed improved efficacy in PFS and a trend for OS benefit at the first interim analysis, with a favorable safety profile for single-agent trastuzumab emtansine compared with TPC in patients who received at least two prior regimens of HER2-directed therapies, including trastuzumab and lapatinib, in the metastatic or unresectable locally advanced/recurrent setting (Section 1.2.1.1.1; Krop et al. 2014).

A randomized Phase II study, TDM4450g*/BO21976* (Section 1.2.1.1.1), demonstrated improvements in PFS, safety, and QoL with trastuzumab emtansine compared with trastuzumab combined with docetaxel in the first-line recurrent/metastatic setting (Hurvitz et al. 2013).

The Phase III MARIANNE study demonstrated that trastuzumab emtansine as single agent or in combination with pertuzumab were non-inferior to taxane +trastuzumab with respect to PFS as assessed by independent review, with numerical improvements in tolerability and QoL; however, neither of the trastuzumab emtansine-containing arms showed superiority over taxane plus trastuzumab (Section 1.2.1.1.2; Ellis et al. 2015).

These results*, taken in context with the totality of data from all the MBC studies described above,* demonstrated the therapeutic potential of trastuzumab emtansine, as an ADC, to improve *or at least provide similar* benefit and decrease safety risk compared with trastuzumab *or lapatinib* plus a concurrent systemic *chemotherapy/*taxane *in the MBC setting*.

In Study TDM4874g*/BO22857*, trastuzumab emtansine following anthracycline-based chemotherapy showed acceptable safety as neoadjuvant and/or adjuvant treatment in HER2-positive early-stage breast cancer. Furthermore, clinical activity in the neoadjuvant setting *(pCR [ypT0/is, ypN0] rate of 56%)* was also demonstrated (Section 1.2.1.2).

In the WSG-ADAPT Study MO23078 (Section 1.2.1.2), a planned interim analysis demonstrated clinically meaningful pCR (ypT0/is, ypN0) rates (>40%) in HER2+/HR+ EBC patients treated with 4 cycles of neoadjuvant trastuzumab emtansine alone or with endocrine therapy, versus a pCR rate of 6.7% treated with trastuzumab +endocrine therapy. These interim pCR results observed in the WGS-ADAPT trial are among the highest reported for ER+, HER2+ EBC and are an improvement over the previously reported 22% total pCR rate observed with 4 cycles of docetaxel, trastuzumab, and pertuzumab in subset of patients with ER+ breast cancer treated in the WO20697 (NEOSPHERE) study (Gianni et al. 2012). With the acknowledged caveats regarding cross trial comparisons, these promising pCR data from the TDM4874g/BO22857 and WSG-ADAPT studies indicate that trastuzumab emtansine is an active agent in HER2-positive EBC, regardless of hormonal receptor status, and further supported developing trastuzumab emtansine +pertuzumab as a treatment option for the EBC population.

Synergy has been demonstrated in the nonclinical setting between trastuzumab emtansine and pertuzumab. Studies with three HER2-positive mouse xenograft models in vivo consistently showed enhanced anti-tumor activity when trastuzumab emtansine was administered in combination with pertuzumab compared with trastuzumab emtansine administered as a single agent. Furthermore, the combination of trastuzumab emtansine and pertuzumab has shown clinical activity and acceptable tolerability in patients with recurrent LABC/MBC in the Phase Ib/II Studies TDM4373g/BO22495 and TDM4688g (see details in Section 1.2.1.1.2 and Section 1.2.3).

In MARIANNE, no clinically or statistically significant synergy between trastuzumab emtansine and pertuzumab was observed in the ITT population. Uncertainties exist regarding the translation of results of MBC trials where equivalent or inferior outcomes are observed into results of adjuvant studies due to differences in tumor biology (e.g., less intratumor heterogeneity in EBC due to temporal variaions in cancer evolution, bulky disease in MBC vs. microscopic disease in the adjuvant setting, and the hypothesized potential pre-existing suppression of anti-cancer immunoresponse in the metastatic tumor microenvironment), study endpoints (imaging based PFS vs. IDFS), as well as the mechanism of action of trastuzumab emtansine and pertuzumab (e.g., potential MOA as immunotherapy) (Liakou et al. 2007; Stagg et al. 2011; Loi et al 2013; Apolo et al. 2014; Bianchini et al. 2014; Perez et al. 2015). As an example, the Phase III study comparing docetaxel, doxorubicin, and cyclophosphamide (TAC) to 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) as the first-line chemotherapy for MBC patients demonstrated similar time to tumor progression (HR =1.0380; p =0.51) (Mackey et al. 2002). However, it was reported in the BCIRG001 study that adjuvant TAC showed improved DFS rates compared to FAC (HR =0.72, p =0.0020) (Mackey et al. 2013). Therefore, the lack of clinically meaningful synergy between trastuzumab emtansine and pertuzumab in the MBC setting may not be of full predictive value on whether there would be a potential synergy between trastuzumab emtansine and pertuzumab in the adjuvant setting.

In the adjuvant setting, it may be of particular clinical importance to e~~E~~valuat~~ing~~*e* trastuzumab emtansine without concurrent taxane*, which may* ~~can~~ utilize the full potential of this ADC in efficacy and safety improvement *or demonstrating numerically equivalent efficacy with better tolerability or different safety profile in EBC* and avoid compromised safety and dose intensity observed in Studies TDM4652g and BP22572 (Section 1.2.1). The combination of trastuzumab emtansine and pertuzumab without a taxane will therefore be compared with trastuzumab and pertuzumab plus taxane in this study. The goal is to assess whether trastuzumab emtansine–based adjuvant regimens will ~~significantly~~ improve the benefit-risk outcome of high-risk patients with HER2-positive EBC*. This study question remains clinically and scientifically important since MARIANNE results in the MBC setting may not fully predict the outcome of the combination of trastuzumab emtansine and pertuzumab in the adjuvant setting.*

Further rationales for the study design *and study design changes* can be found in Section 3.3.

SECTION 1.3.2: Benefit-Risk Assessment

Trastuzumab emtansine has shown a favorable benefit-risk profile in patients whose disease has progressed after prior HER2-directed therapies for MBC (*Krop et al. 2014),* Blackwell et al. 2012, Verma et al. 2012). Trastuzumab emtansine also appears to have a*n acceptable or* favorable benefit-risk profile in patients who have not received prior chemotherapy for metastatic disease, including patients who have previously received trastuzumab in the adjuvant setting (Hurvitz et al. 2013*; Ellis et al. 2015*). Trastuzumab

emtansine monotherapy has demonstrated a favorable or tolerable toxicity profile across studies conducted to date in patients with breast cancer, including a Phase II cardiac safety study of trastuzumab emtansine in patients with EBC (Study TDM4874g/BO22857, see Section 1.2.1.2) *and the WSG-ADAPT Study, see Section 1.2.1.2). Furthermore, Studies TDM4874g and WSG-ADAPT indicate that trastuzumab emtansine is an active agent in HER2-positive EBC, regardless of hormonal receptor status.*

Although ~~initial~~ safety data to date involving trastuzumab emtansine in previously untreated patients in both the adjuvant (Dang et al. 2012) and the metastatic setting (Hurvitz et al. 2013; *Ellis et al. 2015*) appear acceptable, the long-term safety of trastuzumab emtansine in the EBC setting is not fully known. A safety plan for this study, including appropriate eligibility criteria, dose modification guidelines, interim safety analyses for overall deaths and hepatic events defined as confirmed Hy's law cases, and regular monitoring of accumulating patient safety data by an iDMC, has been put into place to minimize any potential risk in the trial patient population. Furthermore, iDMC recommendations and~~/or~~ available safety *and efficacy* data from Study MARIANNE (TDM4788g/BO22589; see Section 1.2.1.1.2) *have been provided to the iDMC; and iDMC recommendations and available safety and efficacy data from* ~~and~~ Study BO25126 (APHINITY; see Section 1.2.2.2) will be ~~available~~ *provided as applicable* to the iDMC for consideration during the conduct of Study BO28407.

The combination of trastuzumab emtansine and pertuzumab following systemic anthracyclines has the potential to further ~~significantly~~ improve the efficacy outcome in high-risk patients with HER2-positive EBC. *The totality of data regarding trastuzumab emtansine and pertuzumab (see Sections 1.2.1, 1.2.2, and 1.3.1), support that the experimental arm (trastuzumab emtansine and pertuzumab following anthracyclines) in this study is highly likely to demonstrate a risk/benefit profile at least equivalent to the current anthracycline-trastuzumab based adjuvant SoC for patients with HER2-positive EBC. Specifically, the efficacy in MARIANNE is at least equivalent to taxane and trastuzumabin the MBC setting with AE profile that may be more tolerable than taxane and trastuzumab which is the current EBC adjuvant SoC. In addition the interim data from WGS-ADAPT demonstrated clinically meaningful pCR rates (> 40%) with single agent trastuzumab emtansine, which is better than or comparable to pCR rates achieved with trastuzumab containing regimens with concurrent systemic chemotherapy in the EBC setting. (Harback et al, 2015).*

Toxicities observed in studies with combination of trastuzumab emtansine and pertuzumab appear to be manageable, on the basis of final Phase II study results (TDM4373g/BO22495 and TDM4688g) and ~~iDMC recommendations to continue the~~ Phase III MARIANNE Study TDM4788g/BO22589. On the basis of available data, the safety of trastuzumab emtansine when combined with pertuzumab appears consistent with the known toxicity profiles of each drug as a single agent (see Section 1.2.3). *MARIANNE data suggested that the combination of trastuzumab emtansine and*

pertuzumab may be more tolerable than trastuzumab +taxane, which may be of particular importance to the EBC population(see Sections 1.2.1, 1.2.2, and 1.3.1).

Overall, c~~C~~onsidering the known *tolerable* safety profiles of these *study* drugs, *the totality of efficacy data in the MBC and EBC settings, a potential better efficacy outcome of the combination of trastuzumab emtansine and pertuzumab in the adjuvant setting compared to the MBC setting due to the long treatment duration of additional HER2 targeted DM1 and biology differeneces between EBC and MBC (see Section 1.3.1 for more details), and the known benefit-risk for the current anthracycline-trastuzumab–based adjuvant SOC,* it is anticipated that the combination regimen*s in this study* will have a manageable safety profile and has an acceptable benefit-risk assessment for the conduct of the study. *It is important and justified to evaluate the benefit-risk of trastuzumab emtansine plus pertuzumab following anthracyclines, compared with the anticipated new SOC (taxane +trastuzumab +pertuzumab following anthracyclines), in the adjuvant clinical trial setting.*

SECTION 3.3.1: Rationale for Test Product Dosage

The dose of 3.6 mg/kg of trastuzumab emtansine has been combined with pertuzumab (loading dose of 840 mg with a subsequent dose of 420 mg) q3w in the Phase I/II Studies TDM4373g/BO22495 and TDM4688g and in the Phase III Study TDM4788g/BO22589 (MARIANNE). Toxicities in these studies appear to be manageable*/tolerable*, on the basis of final study results (Studies TDM4373g/BO22495*,* ~~and~~ TDM4688g*, and*~~)~~ ~~and available study data and iDMC recommendations to continue Study~~ TDM4788g/BO22589*)* (see details in Section 1.2.1.1).

SECTION 3.3.2.1: Rationale for Capping Subgroup Enrollment

The capping as of Protocol Version 2 will not be implemented since the study enrollment is stopped earlier than planned. Therefore, the planned proportion of node-positive patients with one to three nodes and/or node-negative patients may not be achieved as described above.

SECTION 3.3.2.3: *Rationale for Sample Size Reduction*

The MARIANNE study results (see Section 1.2.1.1.1) have further informed the assumptions that drove the original study design (i.e., trastuzumab emtansine improves both PFS and safety and a synergy between trastuzumab emtansine and pertuzumab will be demonstrated clinically in the first-line MBC setting). Therefore, the likelihood of this study meeting its primary efficacy endpoint for superiority has decreased. A sample size reduction is warranted to mitigate the risk of this study not meeting its primary efficacy endpoint. However, due to the uncertainty of translating MBC results to the adjuvant setting (see details in Section 1.3.1), the study question of whether the regimen of trastuzumab emtansine in combination with pertuzumab following anthracyclines may be superior to the regimen of trastuzumab in combination with a taxane and pertuzumab following anthracyclines in the adjuvant setting remains

unanswered and is of clinical/scientific importance. With a sample size reduction from 2500 to approximately 1850 patients, the study objectives can still be adequately addressed with the original statistical power and validity with the prolonged analyses timing (see Table 19 in Section 6.1).

SECTION 3.3.4: Rationale for Adjuvant Regimens and Duration of Therapy

Proof of concept has been established in the randomized *MBC* Studies TDM4450g*/BO21976*, ~~and~~ TDM4370g*/BO21977* (EMILIA)*, and TDM4997g/BO25734 (TH3RESA)* that trastuzumab emtansine as a single agent can improve efficacy and safety compared with a combination of a HER2-directed agent and traditional chemotherapy. *The TDM4788g/BO22589 (MARIANNE) study supports trastuzumab emtansine+pertuzumab as a non-inferior regimen to trastuzumab +taxane, with a more tolerable safety profile in the first-line MBC setting.* In addition, the pCR rates observed in the single-arm Study TDM4874g*/BO22857 and WGS-ADAPT Study MO23078* suggest robust clinical activity of trastuzumab emtansine in EBC. Furthermore, a meta-analysis (EBCTCG 2013) of long-term outcome among 100,000 patients with EBC in 123 randomized trials has shown that in trials adding four cycles of taxane to a fixed anthracycline-based control regimen, extending treatment duration, mortality due to breast cancer was reduced (RR = 0.86, SE = 0.04, two-sided significance p = 0.0005). However, in trials with four such extra cycles of taxane, counterbalanced in controls by extra cycles of other cytotoxic drugs, roughly doubling non-taxane dosage, there was no significant difference (RR = 0.94, SE = 0.06, two-sided significance p = 0.33). On the basis of this analysis, *the totality of data for trastuzumab emtansine and/or pertuzumab in the MBC and EBC setting, and the uncertainties regarding the translation of results of trastuzumab emtansine plus pertuzumab in the MARIANNE study into results of this combination in this adjuvant study,* it is anticipated that 1 year of *trastuzumab emtansine +pertuzumab, with* the HER2-targeted chemotherapeutic agent DM1 (i.e., with higher dose intensity and longer duration than four cycles of concurrent taxane) will provide risk reduction that is the same as or better than that provided by the four cycles of concurrent taxane *and 14 cycles of trastuzumab +pertuzumab* in the control arm. Therefore, this study will evaluate whether trastuzumab emtansine without concurrent taxane as a replacement for trastuzumab plus taxane, in combination with pertuzumab following anthracyclines, can provide an improved benefit-risk ratio in high-risk patients with HER2-positive EBC. Systemic anthracyclines will mitigate potential efficacy risk due to *intra*tumor heterogeneity. The cardiac safety of both pertuzumab and trastuzumab emtansine following anthracycline-based regimens appears acceptable to date on the basis of data from Study BO22280 (TRYPHAENA; see Section 1.2.2.2) and Study TDM4874g/BO22857 *EBC safety study;* (~~MARIANNE;~~ see Section*1.2.1.1.1* ~~1.2.1.1.2~~).

SECTION 3.4.3: Patient-Reported Outcome Measures

- Time from first HER2-targeted treatment, ± a taxane, to *clinically meaningful deterioration in the* ~~worsening of~~ global health status/QoL *and functional (physical, role, and cognitive)* ~~(~~subscale*s* of the QLQ-C30~~)~~. The event of worsening of global health status/QoL for a given patient is defined as a decrease in *baseline* mean score by 10 points or more at two consecutive timepoints~~ after initiation of HER2-directed therapy, plus a taxane~~. A 10-point or greater change in mean score is defined as being a "moderate" to "very much" *and* perceived *an* important change from the patient's perspective (Osoba et al. 1998). *Deterioration in function will be assessed using the published corresponding MIDs by Cocks et al. (2011).*

SECTION 4.1.1: <u>Inclusion Criteria</u>

- Pathological tumor-node-metastasis staging (Union for International Cancer Control/American Joint Committee on Cancer [UICC/AJCC], 7th edition): Patients must have had sentinel lymph node biopsy (SLNB) and/or axillary lymph node dissection for evaluation of pathologic nodal status (minimum requirements for patients undergoing SLNB are provided in Section 4.4.1). Pathological classification of regional lymph node micrometastases (tumor deposits >0.2 mm and ≤ 2 mm) is considered to be pN1, and isolated tumor cells are considered to be pN0.

  Eligible patients must have one of the following:

  Node-positive disease (pN ≥ 1), any tumor size except T0, and any hormonal receptor status

  Enrollment of patients with 1–3 nodes ~~will~~ *was planned to* be limited to no more than 50% of the total number of randomized patients. *However, no formal capping of enrollment will be implemented (see Section 3.3.2.1 for details).*

  There is no prespecified limit for the enrollment of patients with ≥ 4 nodes.

  Node-negative disease (pN0) with pathologic tumor size >2.0 cm by standard local assessment AND negative for ER and PR as determined by a central pathology laboratory

  Enrollment of patients with node-negative disease *was planned to* ~~will~~ be limited to no more than 10% of the total number of randomized patients. *However, no formal capping of enrollment will not be implemented (see Section 3.3.2.1 for details).*

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

  Patients who have positive HBV or HCV serologies without known active disease must meet the eligibility criteria for ALT, AST, total bilirubin (TBILI), INR, activated partial thromboplastine time (aPTT), and alkaline phosphatase (ALP) on at least two consecutive occasions, separated by at least 1 week, within the

30-day screening period. The second of these evaluations must be performed within 3 days prior to the first administration of study drug. *Note: positive serology markers that indicate immunity will not be considered as clinically meaningful positive serology to trigger these tests.*

SECTION 4.3.2.2.1: Trastuzumab plus Pertuzumab plus Taxane Treatment (Arm 1)

Trastuzumab will be given at a loading dose of 8 mg/kg and pertuzumab at 840 mg. For subsequent cycles, trastuzumab will be given as a maintenance dose of 6 mg/kg and pertuzumab at 420 mg q3w. The dose of trastuzumab does not need to be recalculated unless the body weight has changed by ±10% or greater from baseline. Dose must be readjusted for ± 10% or greater weight change based on the previous weight used for dose recalculation. *The Investigator may choose to re-calculate dose at every cycle using actual weight at that time according to their local practice.* If the patient misses a dose of trastuzumab for any cycle (i.e., the two sequential administration times are 6 weeks or more apart), a re-loading dose of 8 mg/kg of trastuzumab should be given. If the patient misses a dose of pertuzumab for any cycle and the time between doses is 6 weeks or more, a re-loading dose of pertuzumab (840 mg) should be given. *Re-loading of doses for trastuzumab per local prescribing information may be followed.* Patients who experience trastuzumab or pertuzumab infusion–related symptoms may be pre-medicated with paracetamol and anti-histamines for subsequent infusions.

SECTION 4.3.2.2.2: Trastuzumab Emtansine plus Pertuzumab Treatment (Arm 2)

Trastuzumab emtansine will be given at a dose of 3.6 mg/kg by IV infusion in combination with pertuzumab at an initial loading dose of 840 mg IV followed by a maintenance dose of 420 mg IV q3w. The dose of trastuzumab emtansine does not need to be recalculated unless the body weight has changed by ± 10% or greater from baseline. Dose must be readjusted for ± 10% or greater weight change based on the previous weight used for dose recalculation. *The Investigator may choose to re-calculate dose at every cycle using actual weight at that time according to local practice.* If the patient misses a dose of pertuzumab for any cycle and the time between doses is 6 weeks or more, a re-loading dose of pertuzumab (840 mg) should be given. Patients who experience pertuzumab infusion–related symptoms may be pre-medicated with paracetamol and anti-histamines for subsequent infusions.

SECTION 4.7.1.2: Physical Examinations

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations focusing on organ systems related to adverse events or disease should be performed. Weight is to be measured on Day 1 of the specified cycles and compared with baseline. If ± 10% or greater variation occurs, then study treatment doses will be recalculated. Dose must be readjusted for ± 10% or greater weight change based on the previous weight used for dose recalculation. *The investigator may choose to re-calculate dose at every cycle using actual weight at that time according to local*

practice. For anthracyclines and taxanes, local standards for dose calculations will be followed.

SECTION 4.7.1.8: Patient-Reported Outcomes

The EORTC QLQ-BR23 breast cancer module was first validated for use in 1995, uses a recall period of ”the past week,“ and is intended for use across multiple treatment modalities (i.e., surgery, chemotherapy, radiotherapy, and hormonal treatment*; Sprangers et al. 1998*). As peripheral neuropathy (1 item), joint/muscle pain (1 item), and skin problems (2 items) are key symptoms of therapy not assessed by currently available tools, validated items from the EORTC Item Bank will be added to assess the presence and bothersomeness of these treatment-related side effects. Data analysis will be performed on the final modified BR23 data set *outside of the protocol* in parallel with the final data analysis to confirm the psychometric properties of the modified instrument ~~and will be reported along with the clinical trial results~~. Scale scores can be obtained for each of the multi-item and single-item scales by using a linear transformation for standardization of the calculated raw score.

SECTION 5.2.3: ~~Non Serious~~ Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

~~Non serious~~ AEs of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). AEs of special interest for this study include the following:

SECTION 5.3.5.3: Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. ~~The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.~~*The initial severity (intensity or grade) of the event should be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, then the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any increases in severity should be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, then it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from “non-serious” to “serious,” providing the date that the event became serious, and completing all data fields related to SAEs.*

SECTION 5.4: IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

- ~~Non serious~~ AEs of special interest

SECTION 5.4.1: Emergency Medical Contacts

Alternate Medical Monitor Contact Information for All Sites:

Medical Monitor: [redacted], M.D., *M.S.*

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

SECTION 5.4.3.2: Pregnancies in Female Partners of Male Patients

Additional information on any trastuzumab, pertuzumab, or and trastuzumab emtansine–exposed pregnancy and infant will be requested by Roche Drug Safety at specific timepoints (i.e., after having received the initial report, at the end of the second trimester, 2 weeks after the expected date of delievery, and at 3, 6, and 12 months of the infant's life.)

SECTION 6: STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The statistical considerations and analysis plan are summarized below. Further details of the analyses will be described in the Statistical Analysis Plan (SAP) as part of the Data Analysis Plan (DAP). The SAP overrides the analyses as described in the study protocol, as applicable.

SECTION 6.1: DETERMINATION OF SAMPLE SIZE

The IDFS analysis is powered ~~at 82.25%~~ at 80% for the node-positive subpopulation. Additionally, the IDFS analysis with the assumptions stated below is powered at ~~83~~*82.5*% for the overall protocol-defined population. It is assumed that the overall protocol-defined population has approximately 10% more patients and 6% more IDFS events than the node-positive subpopulation. These percentages were observed in the BCIRG 006 (Slamon et al. 2006, 2009, 2011) trial after subsetting for the respective populations in this study.

To detect a target HR of 0.64 in IDFS in the overall protocol-defined population and the node-positive subpopulation, approximately 171 and 160 IDFS events will be required to achieve ~~83~~*82.5*% and 80% power, respectively, in the two populations, at a two-sided significance level of 5% using a log-rank test. Approximately *1850 and 1665* ~~2500 and 2250~~ patients will be enrolled in the overall protocol-defined population and node-positive subpopulation, respectively, including a dropout/ineligibility rate of 8% for both arms as estimated from previous trials in this setting. The assumed 3-year IDFS rate for the control arms for both the populations were based on the IDFS rate from the BCIRG 006 data for the proposed populations and the assumed target HR from Study BO25126. The six piecewise Kaplan-Meier estimates of the IDFS function in the control group for the overall protocol-defined population and the node-positive subpopulation were 99.6% and 99.5% during the first 6 months, 98.2% and 98.0% during the second 6 months, 93.7% and 93.1% during Year 2, 89.5% and 89.1% during Year 3, 87.7% and 87.1% during Year 4, and 86.2% and 85.5% during Year 5. With the assumed target HR of 0.64, the estimated 3-year IDFS rate for the experimental arms in each of the two populations is shown in Table 19.

~~After a 1 year ramp up period, it is estimated that the monthly accrual of patients per site will build to a peak rate of 0.41.~~ *A total of approximately 1850 patients are anticipated to be enrolled*. The study is expected to be fully enrolled approximately ~~24~~ *17* months after FPI. The final IDFS analysis will be performed after at least ~~172~~ *160* events have occurred in the node-positive subpopulation and approximately ~~183~~ *171* events have occurred in the overall protocol-defined population, which is projected to be approximately ~~47~~ *57* months after FPI.

The sample size calculations are performed using EAST v*6*~~5.4~~ software (Cytel Inc.).

SECTION 6.6: PATIENT-REPORTED OUTCOME ANALYSES

Summary statistics (mean, SD, median, 25th and 75th percentiles, and range) of linear transformed scores will be reported for all the subscales (including peripheral neuropathy, joint/muscle pain, and skin problems) of the EORTC QLQ-C30 questionnaire and the modified BR23 *for each assessment time-point* according to the EORTC scoring manual guidelines for each assessment timepoint. The mean change of the linear transformed scores from baseline (and 95% CI*s* using the normal approximation) will also be assessed. Line charts depicting the mean changes (and standard errors) of ~~items and~~ subscales over time will be provided for each treatment arm from the baseline assessment.

Completion and compliance rates will be summarized at each timepoint for each measure by treatment arm with reasons for missing data. Only patients with a baseline assessment and at least one post-treatment assessment will be included in the analyses.

The number and proportion of patients *reporting clinically meaningful differences in treatment-related symptoms based on the threshold reported by Cocks et al. (2011) at each time-point will be the primary analysis. In addition, the proportion of patients reporting "a little" or "quite a bit" for each of the neuropathy, joint/muscle pain and skin single items will be reported by treatment arm*~~who improved, worsened, or remained stable for all of the symptom and functional domains, global QoL, and single items of the EORTC QLQ-C30 and modified BR23 will be summarized at each timepoint~~.

The proportion of patients with clinically meaningful deterioration in global health status/HRQoL and function (physical, role, and cognitive) scales will also be assessed. The deterioration will be based on the respective thresholds reported by Osaba et al (1998) and Cocks et al. (2011).

Analysis will be performed to compare the two treatment arms at the "Cycle 1 Day 1 (C1D1) of anthracycline treatment period" timepoint and the "C1D1 of HER2-targeted treatment period" timepoint to descriptively assess treatment group comparability between the two treatment arms. The "'C1D1 of HER2-targeted treatment" timepoint will be utilized as the reference for time-to-event Kaplan-Meier analysis, provided that the treatment groups are comparable at this timepoint.

The time to clinically meaningful deterioration in the global health status/HRQoL subscale (question 29 and 30 ~~Time-to-event Kaplan-Meier analysis of global health status/QoL (subscale~~ of the QLQ-C30) will be used to *assess*~~demonstrate~~ the time from first HER2-targeted treatment to worsening in HRQoL. An event for a given patient is a decrease in mean score by 10 points or more, at two consecutive time points, with a 10-point or greater change in mean score defined as a "moderate" to "very much" perceived important change from the patient's perspective (Osoba et al. 1998). *Time-to-event analyses to investigate the time to clinically meaningful deterioration in function (physical, role, and cognitive function scales) will also be assessed using the published thresholds by Cocks et al. (2011).* A stratified log-rank test will be used to test the differences between treatment arms.

Additionally, in order to elucidate if the taxane-sparing arm reduces patient treatment burden, ~~an~~ analys*e*~~i~~s of covariance (*repeated* mixed *effects* model) will be used to compare change from baseline in *the global health status/HRQoL and functional scales of the EORTC QLQ-C30.* ~~each symptom score of special interest resulting in three individual models. The symptom subscale scores to be assessed are joint/muscle pain, peripheral neuropathy, and skin problems.~~ In each mixed model, change from baseline ~~of the symptom of special interest~~ will be the response variable; treatment, visit, and treatment by visit interaction terms will be the fixed *factors*~~effects~~; ~~baseline of the symptom subscale score (joint/muscle pain, peripheral neuropathy, and skin problem) will be the covariate;~~ and *the* patient will be *denoted as a repeated factor. If substantial interaction effect is present, pair-wise comparison will be conducted*~~the random effect~~.

SECTION 6.8.1: Interim Efficacy Analyses

A futility analysis may be incorporated to evaluate lack of superiority for the treatment arm of trastuzumab emtansine +pertuzumab following anthracyclines. The timing and details of this futility analysis will be described in the SAP and aligned with the availability of information from other relevant studies (e.g., KRISTINE and/or APHINITY).

Interim IDFS Analyses

~~The~~ *An* interim efficacy analysis of IDFS will be performed after approximately 75% of the targeted IDFS events are observed in the overall protocol-defined population (i.e. 128 of the 171 target events) and node-positive population (i.e. 120 of 160 target events) and is projected to occur approximately ~~40~~ *43* months from FPI (see Table 20). A hierarchical testing procedure will be used for the primary endpoint IDFS for the node-positive subpopulation and the overall protocol-defined population as defined in Section 6.4.3. The type I error will be controlled at the 5% level at the interim and final analyses within the node-positive subpopulation and the overall protocol-defined population using a Lan-DeMets α-spending function with an O'Brien-Fleming boundary.

Interim OS Analyses

For the OS interim analyses and final OS analysis, the Lan-DeMets α-spending function with an O'Brien-Fleming boundary will be used such that the overall type I error will be controlled at the 5% level for the OS endpoint. With the study sample size and approximately 10 years of follow-up from FPI, this study has *38%* ~~47%~~ power in the overall protocol-defined population and *35%* ~~44%~~ power in the node-positive subpopulation to detect an HR of 0.8. This in the overall protocol-defined population corresponds to a 0.8% improvement in 3-year OS, from 96.1% in the control arm to 96.9% in the experimental arm and in the node-positive subpopulation to a 0.9% improvement in 3-year OS, from 95.7% in the control arm to 96.6% in the experimental arm, at a two-sided significance level of 5%.

All OS interim and final analyses will be performed by the Sponsor subsequent to the primary IDFS analysis and after the Sponsor is unblinded. If the interim IDFS analyses in both the node-positive subpopulation and the overall protocol-defined population cross the statistical efficacy boundaries, the first OS interim analysis will be performed in both populations hierarchically at that time (approximately at *43*~~40~~ months from FPI). If the final IDFS analysis crosses the statistical boundaries, then the second interim OS analysis will be performed hierarchically at the time of the final IDFS analysis (approximately *57*~~47~~ months from FPI), followed by the third and the final OS analyses performed hierarchically in both populations (planned to occur at 84 months [7 years] and 120 months [10 years], respectively, from FPI). If, at any OS interim analysis, the O'Brien-Fleming efficacy boundary is crossed, that analysis of OS will be considered as confirmatory and all subsequent analyses of OS will be considered as descriptive.

SECTION 9.5: PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of

additional endpoints and exploratory data that are clinically meaningful and statistically sound..,

The investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

~~The Sponsor will comply with the requirements for publication of study results.~~ In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

TABLE 1: Overview of *Selected* Adverse Events ~~of Special Interest~~ with Trastuzumab Emtansine *Alone* (n=884)

Table 1 was updated to reflect the available safety data.

TABLE 4: Overview of *Selected* Adverse Events ~~of Special Interest~~ with Trastuzumab Emtansine in Combination with Pertuzumab (n=87)

Table 1 was updated to reflect the available safety data.

TABLE 5: *Overview of Adverse Events (Safety Population)*

Table 5 was added. Subsequent tables have been renumbered accordingly.

TABLE 19: Summary of Sample Size Assumptions for IDFS

Table 19 was updated to reflect the new sample size calculations.

TABLE 20: Summary of Planned Analyses of IDFS in Overall Protocol-Defined Population and Node-Positive Subpopulation

Table 20 was updated to reflect the new estimated timing.

TABLE 22: Summary of Planned Analyses of IDFS in Overall Protocol-Defined Population and Node-Positive Subpopulation

Table 22 was updated to reflect the new timing and number of events for analyses.

APPENDIX 1: Schedule of Assessments

The schedule of assessments has been revised to reflect the changes to the protocol.

APPENDIX 10: Acceptable Contraception Methods

Appendix 10 has been revised to note the effective nonhormonal contraception and altenatives thereto.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE III TRIAL COMPARING TRASTUZUMAB PLUS PERTUZUMAB PLUS A TAXANE FOLLOWING ANTHRACYCLINES VERSUS TRASTUZUMAB EMTANSINE PLUS PERTUZUMAB FOLLOWING ANTHRACYCLINES AS ADJUVANT THERAPY IN PATIENTS WITH OPERABLE HER2-POSITIVE PRIMARY BREAST CANCER**
PROTOCOL NUMBER:	BO28407
VERSION NUMBER:	3
EUDRACT NUMBER:	2012-004902-82
IND NUMBER:	71072
TEST PRODUCTS:	Trastuzumab Emtansine (RO5304020) and Pertuzumab (RO4368451)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return the signed original of this form to your local study monitor. Please retain a copy for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, MULTICENTER, OPEN-LABEL, PHASE III TRIAL COMPARING TRASTUZUMAB PLUS PERTUZUMAB PLUS A TAXANE FOLLOWING ANTHRACYCLINES VERSUS TRASTUZUMAB EMTANSINE PLUS PERTUZUMAB FOLLOWING ANTHRACYCLINES AS ADJUVANT THERAPY IN PATIENTS WITH OPERABLE HER2-POSITIVE PRIMARY BREAST CANCER**
PROTOCOL NUMBER:	BO28407
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EUDRACT NUMBER:	2012-004902-82
IND NUMBER:	71072
TEST PRODUCTS:	Trastuzumab Emtansine (RO5304020) and Pertuzumab (RO4368451)
PHASE:	III
INDICATION:	HER2-positive operable primary breast cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Efficacy Objectives

The co-primary efficacy objective for this study is as follows:

- To compare invasive disease–free survival (IDFS) (1) in the node-positive subpopulation and (2) in the overall protocol-defined population of patients with human epidermal growth (HER) factor 2–positive breast cancer randomized to receive either a taxane and 1 year of trastuzumab plus pertuzumab following anthracycline-based chemotherapy or 1 year of trastuzumab emtansine plus pertuzumab following anthracycline-based chemotherapy

The secondary efficacy objectives for this study are as follows:

- To compare IDFS plus second non-breast primary cancers, disease-free survival (DFS), and distant recurrence–free interval (DRFI) (1) in the node-positive subpopulation and (2) in the overall protocol-defined population between the two treatment arms
- To compare overall survival (OS) (1) in the node-positive subpopulation and (2) in the overall protocol-defined population between the two treatment arms

Safety Objective

The safety objective for this study is as follows:

- To compare overall safety, cardiac safety, hepatic, and pulmonary safety in the overall protocol-defined population between the two treatment arms

Patient-Reported Outcome Objectives

Patient-reported outcome (PRO) objectives in the overall protocol-defined population for this study are as follows:

- To compare PROs of treatment-related symptoms, patient functioning, and health-related quality of life (HRQoL) to better understand treatment impact and tolerability, as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) and the modified EORTC Breast Cancer module (Quality of Life Questionnaire–Breast Cancer 23 [QLQ-BR23]), between 'Trastuzumab + Pertuzumab + Taxane following Anthracyclines' and 'Trastuzumab Emtansine + Pertuzumab following Anthracyclines' treatment arms.

Exploratory Objectives

The exploratory biomarker objectives for this study are as follows:

- To evaluate the impact of HER2 mRNA level on treatment benefit using the efficacy endpoints
- To evaluate the impact of the PIK3CA mutation status on prognosis and treatment benefit using the efficacy endpoints
- To assess correlations between candidate biomarkers or biomarker panels and efficacy and/or safety in the overall protocol-defined population
- To identify whether changes in expression levels of biomarker or biomarker panels during treatment correlate with treatment efficacy in the overall protocol-defined population

Efficacy endpoints considered for these objectives will include IDFS and OS, as appropriate.

The exploratory anti-therapeutic antibodies (ATAs) objective in the trastuzumab emtansine–treated patient population for this study is as follows:

- To assess the incidence of ATAs to trastuzumab emtansine and the effect of ATAs on safety and efficacy

The health economic exploratory objective is as follows:

- To assess health status as measured using the EuroQol 5-Dimension Questionnaire (EQ-5D) questionnaire for health economic modeling

Study Design

Description of Study

This is a prospective, two-arm, Phase III, randomized, multicenter, multinational, open-label study in patients with newly diagnosed HER2-positive primary invasive breast cancer who have had curative-intent surgery of their primary tumor and are candidates for adjuvant systemic chemotherapy following surgery. HER2-positive status of the primary tumor will be confirmed by the central pathology laboratory prior to enrollment of the patient in the study. Approximately *1850* patients *are anticipated to* be randomized to one of the two treatment arms listed below in a 1:1 ratio.

- Arm 1: Anthracycline chemotherapy of choice followed by trastuzumab at 6 mg/kg every 3 weeks (q3w; 8-mg/kg loading dose) in combination with pertuzumab 420 mg q3w (840-mg loading dose) and paclitaxel (80 mg/m^2) weekly (qw) or docetaxel q3w (see protocol for details of dose and duration). After the taxane-concurrent phase, HER2-targeted therapy (i.e., trastuzumab at 6 mg/kg q3w in combination with pertuzumab 420 mg q3w) will continue for up to 1 year.
- Arm 2: Anthracycline chemotherapy of choice followed by trastuzumab emtansine 3.6 mg/kg q3w in combination with pertuzumab 420 mg q3w (840-mg loading dose). HER2-targeted therapy (i.e., trastuzumab emtansine at 3.6 mg/kg q3w in combination with pertuzumab 420 mg q3w) will continue for up to 1 year.

Randomization will be stratified by world region (United States/Canada, Western Europe/Australia/New Zealand, Asia, or rest of the world); nodal status (0, 1–3, or ≥4 positive

nodes); centrally assessed hormonal receptor status (estrogen receptor [ER] and/or progesterone receptor [PR] positive or both ER and PR negative); and type of anthracycline (doxorubicin or epirubicin).

In Arm 1, HER2-targeted study therapy with trastuzumab plus pertuzumab must start concurrently with the taxane component of chemotherapy following anthracycline therapy. In both arms, after anthracycline treatment, a minimum interval of 3 weeks from the last dose of anthracycline to initiation of HER2-targeted therapy is required. Prior to commencing the HER2-targeted therapy, patients must have a left ventricular ejection fraction (LVEF) ≥ 50% and must not have experienced any clinical symptoms suggesting heart failure or asymptomatic LVEF declines of 15 percentage points or more from baseline *and below the lower limit of normal*.

Patients will receive up to 1 year of HER2-targeted therapy. Study treatment will be discontinued in the event of invasive disease recurrence, unacceptable toxicity, withdrawal of consent, or study termination by the Sponsor.

Adjuvant radiotherapy is to be given as clinically indicated at the end of chemotherapy (end of taxane in Arm 1; after four cycles of trastuzumab emtansine plus pertuzumab in Arm 2, to be consistent with Arm 1 in terms of timing of initiation) while receiving HER2-targeted therapy. For patients with ER-positive and/or PR-positive tumors, hormonal agents should be administered at the end of chemotherapy (end of taxane in Arm 1; after four cycles of trastuzumab emtansine plus pertuzumab in Arm 2, to be consistent with Arm 1 in timing of initiation).

Number of Patients

Approximately 1850 patients *are anticipated to* be enrolled at approximately 350 sites worldwide.

Target Population

The target population for this study will be patients with newly diagnosed primary invasive breast cancer that is HER2 positive (as determined by the central pathology laboratory) and who will be treated with adjuvant systemic chemotherapy following definitive surgery.

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Age ≥ 18 years
- Eastern Cooperative Oncology Group Performance Status ≤ 1
- Non-metastatic histologically confirmed primary invasive breast carcinoma that was operable
- HER2-positive breast cancer prospectively determined on the primary tumor by a central pathology laboratory and defined as follows:

  Immunohistochemistry (IHC) score of 3+ and/or positive by in situ hybridization (ISH), as defined by ISH ratio of ≥ 2.0 for the number of *HER2* gene copies to the number of chromosome 17 copies. Both IHC and ISH assays will be performed; however, only one positive result is required for eligibility.

  Availability of formalin-fixed paraffin-embedded (FFPE) tissue block or partial block (for minimum dimensions, see laboratory manual) with a representative invasive part of the tumor for central pathology laboratory confirmation of HER2 eligibility, hormonal receptor status, and additional biomarker analysis is required.
- Known hormone receptor status of the primary tumor determined by a central pathology laboratory

  Hormone receptor-positive status can be determined by either known positive ER or known positive PR status. Hormone receptor–negative status must be determined by both known negative ER and known negative PR.
- Adequately excised: Patients must have undergone either breast-conserving surgery or mastectomy/nipple- or skin-sparing mastectomy.

  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.

For patients who undergo mastectomy/nipple- or skin-sparing mastectomy, margins must be free of gross residual tumor. *It is recommended that p*atients should have a negative microscopic margin in accordance with local pathology protocol. Patients with a microscopic positive deep margin are eligible (see radiation therapy [RT] requirements in the protocol).

- Pathological tumor-node-metastasis staging (Union for International Cancer Control/American Joint Committee on Cancer [UICC/AJCC], 7th edition): Patients must have had sentinel lymph node biopsy and/or axillary lymph node dissection for evaluation of pathologic nodal status. Pathological classification of regional lymph node micrometastases (tumor deposits >0.2 mm and ≤ 2 mm) is considered to be pN1, and isolated tumor cells are considered to be pN0.

  Eligible patients must have one of the following:

  Node-positive disease (pN ≥ 1), any tumor size except T0, and any hormonal receptor status

  Enrollment of patients with 1–3 nodes *was planned to* be limited to no more than 50% of the total number of randomized patients. *However, no formal capping of enrollment will be implemented (see Section 3.3.2.1 for details).*

  There is no prespecified limit for the enrollment of patients with ≥ 4 nodes.

  Node-negative disease (pN0) with pathologic tumor size >2.0 cm by standard local assessment AND negative for ER and PR as determined by a central pathology laboratory

  Enrollment of patients with node-negative disease *was planned to* be limited to no more than 10% of the total number of randomized patients. *However, no formal capping of enrollment will be implemented (see Section 3.3.2.1 for details).*
- Patients with synchronous bilateral invasive disease are eligible only if both lesions are HER2 positive.
- No more than 9 weeks (63 days) may elapse between definitive breast surgery (or the last surgery if additional resection required for breast cancer) and randomization.
- Baseline LVEF $\geq 55\%$ measured by echocardiogram (preferred) or multiple-gated acquisition scans
- Documentation of hepatitis B virus (HBV) and hepatitis C virus (HCV) serologies is required. This includes hepatitis B surface antigen and/or total hepatitis B core antibody in addition to HCV antibody testing. The most recent serologic testing must have occurred within 3 months prior to randomization. If such testing has not been done, it must be performed during screening.

  Patients who have positive HBV or HCV serologies without known active disease must meet the eligibility criteria for ALT, AST, total bilirubin (TBILI), INR, activated partial thromboplastine time (aPTT), and alkaline phosphatase (ALP) on at least two consecutive occasions, separated by at least 1 week, within the 30-day screening period. The second of these evaluations must be performed within 3 days prior to the first administration of study drug. *Note: positive serology markers that indicate immunity will not be considered as clinically meaningful positive serology to trigger these tests.*
- Female patients of childbearing potential must be willing to use one highly effective form of nonhormonal contraception or two effective forms of nonhormonal contraception. For male patients with partners of childbearing potential, one highly effective form of contraception or two effective forms of contraception must be used (see protocol for descriptions of highly effective and effective contraception). Contraception must continue for the duration of study treatment and for 7 months after the last dose of study treatment.

The above contraception is not a requirement in the case of any of the following:

The patient or partner of the patient is surgically sterilized.

The female patient is >45 years of age and is postmenopausal (has not menstruated for at least 12 consecutive months).

The patient truly abstains from sexual activity and when this is the preferred option to avoid conception and contraception and/or usual lifestyle of the patient.

- Male patients whose partners are pregnant must use condoms or truly refrain from sexual activity for the duration of the pregnancy
- Willing and able to comply with the requirements of the protocol
- Signed informed consent

Exclusion Criteria

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

- History of any prior (ipsilateral and/or contralateral) invasive breast carcinoma
- History of non-breast malignancies within the 5 years prior to randomization, except for the following:

  Carcinoma in situ (CIS) of the cervix

  CIS of the colon

  Melanoma in situ

  Basal cell and squamous cell carcinomas of the skin
- Any clinical T4 tumor as defined by tumor-node-metastasis classification in UICC/AJCC, 7th edition, including inflammatory breast cancer
- For the currently diagnosed breast cancer, any previous systemic anti-cancer treatment (e.g., neoadjuvant or adjuvant), including but not limited to chemotherapy, anti-HER2 therapy (e.g., trastuzumab, trastuzumab emtansine, pertuzumab, lapatinib, neratinib, or other tyrosine kinase inhibitors), hormonal therapy, OR anti-cancer RT (intraoperative radiotherapy as a boost at the time of primary surgery is acceptable)
- Previous therapy with anthracyclines, taxanes, or HER2-targeted therapy for any malignancy
- History of DCIS and/or LCIS that was treated with any form of systemic chemotherapy, hormonal therapy, or RT to the ipsilateral breast where invasive cancer subsequently developed. Patients who had their DCIS/LCIS treated with only surgery and/or contralateral DCIS treated with radiation are allowed to enter the study.
- Patients with contraindication to RT while adjuvant RT is clinically indicated
- Concurrent anti-cancer treatment in another investigational trial
- Cardiopulmonary dysfunction as defined by any of the following prior to randomization:

  History of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 Grade ≥ 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 atrioventricular [AV]-block [second degree AV-block Type 2 [Mobitz 2] or third degree AV-block])

  Significant symptoms (Grade ≥ 2) relating to left ventricular dysfunction, cardiac arrhythmia, or cardiac ischemia

  Myocardial infarction within 12 months prior to randomization

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

Evidence of transmural infarction on ECG

Requirement for oxygen therapy

- Other concurrent serious diseases that may interfere with planned treatment, including severe pulmonary conditions/illness, uncontrolled infections, uncontrolled diabetes, or known infection with HIV
- Any known active liver disease, including but not limited to disease due to HBV, HCV, autoimmune hepatic disorders, or sclerosing cholangitis. For patients who are known carriers of HBV/HCV, active hepatitis B/C infection must be ruled out on the basis of negative serologic testing and/or determination of HBV DNA/HCV RNA viral load per local guidelines.
- Any of the following abnormal laboratory tests prior to randomization:

  Serum TBILI > 1.0 times the upper limit of normal (ULN). In cases of known Gilbert's syndrome, direct bilirubin should be within the normal range.

  ALT and/or AST $>$ ULN

  ALP $> 1.5 \times$ ULN

  Serum creatinine $> 1.5 \times$ ULN

  Total WBC $< 2500/\mu L$ ($< 2.5 \times 10^9/L$)

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

  Platelets $< 100{,}000/\mu L$ ($< 100 \times 10^9/L$)

  INR or aPTT $> 1.5 \times$ ULN
- Pregnant or lactating women or women of childbearing potential without a negative serum pregnancy test result, within 7 days prior to randomization, regardless of the method of contraception used
- Hypersensitivity to any of the study medications or any of the ingredients or excipients of these medications, including hypersensitivity to benzyl alcohol
- Chronic immunosuppressive therapies, including systemic corticosteroids

Length of Study

The total length of this study will be from randomization of the first patient to completion of the last follow-up assessment of the last patient, which is estimated to occur approximately 10 years after the first patient is randomized.

End of Study

To enable long-term follow-up for survival and safety information, the study is planned to end approximately 10 years after the first patient is randomized.

The Sponsor has the right to terminate this study*, including long-term follow-up,* at any time (e.g., if emerging safety signals indicate a potential health hazard to patients).

Outcome Measures

Efficacy Outcome Measures

The primary efficacy outcome measures for this study are listed below.

- IDFS, defined as the time from randomization until the date of the first occurrence of 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)

  Contralateral or ipsilateral second primary invasive breast cancer

  Distant recurrence (i.e., evidence of breast cancer in any anatomic site [other than the three sites mentioned above]) that has either been histologically confirmed or clinically/radiographically diagnosed as recurrent invasive breast cancer

Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause

The secondary efficacy outcome measures for this study are as follows:

- IDFS plus second primary non-breast cancer, excluding non-melanoma skin cancers and CIS of any site
- DFS, defined as the time between randomization and the date of the first occurrence of any of the IDFS events described above, second primary non-breast cancer event (excluding non-melanoma skin cancers and CIS of any non-breast site), and contralateral or ipsilateral DCIS
- DRFI, defined as the time between randomization and the first occurrence of distant breast cancer recurrence
- OS, defined as the time from randomization to death due to any cause

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence, type, and severity of all adverse events based on NCI CTCAE v4.0
- Incidence, type, and severity of serious adverse events
- Incidence, type and severity of $\geq$ Grade 3 adverse events
- Incidence and type of adverse events leading to dose discontinuation, modification, or delay
- Cause of death
- Abnormal laboratory values
- Decrease in LVEF from baseline over time
- Cardiac safety outcome measures

  Primary cardiac endpoints: cardiac events defined as death from cardiac cause or severe CHF (NYHA Class III or IV) with a decrease in LVEF of $\geq$ 10 percentage points from baseline to an LVEF of $<$ 50%

  Secondary cardiac endpoints: other cardiac-related events (e.g., any mild symptomatic CHF [NYHA Class II] associated with a $\geq$ 10% drop in LVEF to $<$ 50%; asymptomatic declines in LVEF requiring dose delay or discontinuation)
- Hepatic safety outcome measures

  Death from hepatic cause

  Severe drug-induced liver injury (Hy's law cases)

  Nodular regenerative hyperplasia
- Pulmonary safety outcome measures

  Death from pulmonary cause

  Pneumonitis and interstitial lung disease

Patient-Reported Outcome Measures

The PRO outcome measures for this study are as follows:

- HRQoL, including bothersome side effects of therapy (e.g., peripheral neuropathy, joint/muscle pain, or skin problems), and patient functioning as measured using the EORTC QLQ-C30 and the modified breast cancer module QLQ-BR23

- Time from first HER2-targeted treatment, ± a taxane, to *clinically meaningful deterioration in the* global health status/quality of life (QoL) *and functional (physical, role, and cognitive)* subscale*s* of the QLQ-C30. The event of worsening of global health status/QoL for a given patient is defined as a decrease in *baseline* mean score by 10 points or more at two consecutive timepoints. A 10-point or greater change in mean score is defined as being a "moderate" to "very much" *and* perceived *an* important change from the patient's perspective. *Deterioration in function will be assessed using the published corresponding MIDs by Cocks et al. (2011).*

Exploratory Outcome Measures

The exploratory biomarker outcome measures for this study are the relationship between molecular markers and efficacy and/or safety outcomes. Efficacy outcomes considered for this analysis will include IDFS and OS, as appropriate.

Correlations between biomarker status and efficacy and/or safety will include but not be limited to the following:

- Level of HER2 mRNA expression assessed by quantitative real-time polymerase chain reaction (qRT-PCR) with efficacy outcome
- Status of PIK3CA mutations assessed by PIK3CA allele–specific polymerase chain reaction assay with efficacy outcome
- Level of *HER2* gene amplification assessed by ISH with efficacy outcome
- Level of HER2 protein expression assessed by IHC with efficacy outcome
- Level of HER3 mRNA expression assessed by qRT-PCR with efficacy outcome
- Changes in expression levels of biomarker or biomarker panels over time with efficacy outcome

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

- Incidence of ATAs to trastuzumab emtansine
- Effect of ATAs on safety and efficacy

The EQ-5D will be used to obtain health status information for health economic modeling.

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

Investigational Medicinal Products

Study treatment is defined as non-hormonal systemic adjuvant (post-operative) treatment. Trastuzumab emtansine, pertuzumab, and trastuzumab are considered investigational medicinal products (IMPs) in this study. Paclitaxel and docetaxel are also considered IMPs in this study; however, paclitaxel and docetaxel may be considered non-IMPs on the basis of local legislation.

Doxorubicin, epirubicin, cyclophosphamide, and 5-fluorouracil are considered non-IMPs in this study. Depending on local legislation, doxorubicin, epirubicin, cyclophosphamide, and 5-fluorouracil may be considered IMPs. If considered an IMP, then appropriate information on formulation, packaging, handling, and administration will be provided.

Test Product

Trastuzumab emtansine will be given at a dose of 3.6 mg/kg by intravenous (IV) infusion q3w in combination with pertuzumab 420 mg IV q3w (840 mg loading dose) for up to a total duration of 1 year.

Comparator

Pertuzumab will be given at a dose of 420 mg IV q3w (840 mg loading dose) in combination with trastuzumab at 6 mg/kg IV q3w (8 mg/kg loading dose) and paclitaxel (80 mg/m^2) qw or

docetaxel q3w (details regarding docetaxel dose and duration are described in the protocol). After the taxane concurrent phase, administration of trastuzumab/pertuzumab will continue for up to a total duration of 1 year

Non-Investigational Medicinal Products

Standard-of-care chemotherapy backbone treatments should include three to four cycles of an anthracycline-based regimen. Either 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) or doxorubicin and cyclophosphamide (AC)/epirubicin and cyclophosphamide (EC) regimens that are protocol approved may be selected at the discretion of the investigator. Paclitaxel and docetaxel may be considered non-IMPs on the basis of local legislation. In Arm 1, three to four cycles of docetaxel or 12 weeks of paclitaxel will be administered.

For non-IMPs, refer to local prescribing information/institutional guidelines for detailed guidelines on administration, premedications, dose delays/reductions for toxicities, contraindications, requirements on contraception duration, and concomitant medications.

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 as described in the Efficacy Outcome Measures section. Data from patients who have not had an event at the time of data analysis will be censored on the date on which they are last known to be alive and event free, on or before the clinical data cutoff date of the respective analysis.

The log-rank test, stratified by the protocol-defined stratification factors (excluding region), will be used to compare IDFS between the two treatment arms. Region will be excluded because of the potential that some of the strata may have very few patients, which would result in a loss of power. The unstratified log-rank test results will also be provided for sensitivity analysis. If, at the time of analysis, it is deemed that the smallest stratum per arm necessary to conduct robust stratified analyses contains < 5 events, unstratified analyses will be used as the primary analysis. The Cox proportional hazards model, stratified by the previously noted stratification factors, excluding region, will be used to estimate the hazard ratio (HR) between the two treatment arms and the corresponding 95% 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 in both the node-positive subpopulation and the overall protocol-defined population.

To detect a target HR of 0.64 in IDFS in the overall protocol-defined population and the node-positive subpopulation, approximately 171 and 160 IDFS events will be required to achieve *82.5*% and 80% power, respectively, in the two populations, at a two-sided significance level of 5% using a log-rank test. Approximately *1850* and *1665* patients will be enrolled in the overall protocol-defined population and node-positive subpopulation, respectively, including a dropout/ineligibility rate of 8% for both arms as estimated from previous trials in this setting.

Hierarchical Testing Procedure

The hierarchical testing procedure will be employed according to the order given below on the primary and secondary endpoints to control the overall study Type I error rate at 5%:

- Primary endpoint of IDFS in the node–positive subpopulation
- Primary endpoint of IDFS in the overall protocol–defined population
- Secondary endpoint of OS in the node–positive subpopulation
- Secondary endpoint of OS in the overall protocol-defined population

Interim Analyses

One interim analysis of IDFS and three interim analyses of OS in both the node-positive subpopulation and the overall protocol-defined population are planned.

A futility analysis may be incorporated to evaluate lack of superiority for the treatment arm of trastuzumab emtansine + pertuzumab following anthracyclines. The timing and details of

this futility analysis will be described in the SAP and aligned with the availability of information from other relevant studies (e.g., KRISTINE and/or APHINITY).

Interim IDFS Analyses

An interim efficacy analysis of IDFS will be performed after approximately 75% of the targeted IDFS events are observed in the overall protocol-defined population (i.e. 128 of the 171 target events) and node-positive population (i.e. 120 of 160 target events) and is projected to occur approximately 43 months from first patient initiation (FPI).

A hierarchical testing procedure will be used for the primary endpoint IDFS for the node-positive subpopulation and the overall protocol-defined population as defined in the protocol. The type I error will be controlled at the 5% level at the interim and final analyses within the node-positive subpopulation and the overall protocol-defined population using a Lan-DeMets α-spending function with an O'Brien-Fleming boundary.

The interim analysis will be performed by the independent Data Coordination Center (iDCC) statistician, and the results will be presented to the independent Data Monitoring Committee (iDMC) by the iDCC statistician.

If the interim analyses in both populations cross the interim efficacy boundaries of the O'Brien-Fleming design, on the basis of the totality of both efficacy and safety data, the iDMC may recommend releasing the primary endpoint results before the targeted number of 160 and 171 events have occurred in the node-positive subpopulation and overall protocol-defined population, respectively. In this case, the Sponsor will be unblinded to study results, and a full data package including the first OS interim analysis results will be prepared for discussion with the regulatory authorities. The study will continue until 10 years of follow-up from FPI have occurred, and the IDFS analysis will be updated descriptively. If the IDFS interim analyses fail to cross the statistical efficacy boundaries of the O'Brien-Fleming design, then the study will continue as planned. The Sponsor will conduct the final analyses.

The protocol summarizes the planned IDFS analyses in the overall protocol-defined population and the node-positive subpopulation; the efficacy stopping boundaries based on the expected number of events; and the estimated timing of these analyses. The boundaries to be used at each interim and final IDFS analysis will depend on the number of IDFS events actually included in the analyses and so may vary from the numbers stated in the protocol.

Interim OS Analyses

Three interim OS analyses and one final OS analysis are planned in both the overall protocol-defined population and the node-positive subpopulation.

For the OS interim analyses and final OS analysis, the Lan-DeMets α-spending function with an O'Brien-Fleming boundary will be used such that the overall type I error will be controlled at the 5% level for the OS endpoint. With the study sample size and approximately 10 years of follow-up from FPI, this study has 38% power in the overall protocol-defined population and 35% power in the node-positive subpopulation to detect an HR of 0.8. This in the overall protocol-defined population corresponds to a 0.8% improvement in 3-year OS, from 96.1% in the control arm to 96.9% in the experimental arm and in the node-positive subpopulation to a 0.9% improvement in 3-year OS, from 95.7% in the control arm to 96.6% in the experimental arm, at a two-sided significance level of 5%.

All OS interim and final analyses will be performed by the Sponsor subsequent to the primary IDFS analysis and after the Sponsor is unblinded. If the interim IDFS analyses in both the node-positive subpopulation and the overall protocol-defined population cross the statistical efficacy boundaries, the first OS interim analysis will be performed in both populations hierarchically at that time (approximately at 43 months from FPI). If the final IDFS analysis crosses the statistical boundaries, then the second interim OS analysis will be performed hierarchically at the time of the final IDFS analysis (approximately 57 months from FPI), followed by the third and the final OS analyses performed hierarchically in both populations (planned to occur at 84 months [7 years] and 120 months [10 years], respectively, from FPI). If, at any OS interim analysis, the O'Brien-Fleming efficacy boundary is crossed, that analysis of OS will be considered as confirmatory and all subsequent analyses of OS will be considered as descriptive.

The protocol summarizes the planned OS analyses in the overall protocol-defined population and the node-positive subpopulation, respectively; the efficacy stopping boundaries based on

the expected number of events; and the estimated timing of these analyses. The boundaries to be used at each interim and final IDFS analysis will depend on the number of IDFS events actually included in the analyses and may vary from the numbers stated in the protocol.

Interim Safety Analyses

An iDMC will monitor accruing patient safety data at least once every 6 months during the study until the last patient has completed study treatment. In addition, safety data related to concurrent radiotherapy and/or hormonal therapy, serious adverse events, and deaths will be monitored by the iDMC at least once every 3 months during the study until the last patient has completed study treatment. At each iDMC review, relevant safety information from ongoing trastuzumab emtansine and/or pertuzumab studies will also be provided to the iDMC.

After the first 600 patients have been randomized and followed for 3 months (anticipated to occur at approximately 13 months after FPI), the iDMC will perform an interim safety analysis regarding overall numbers of deaths (all causes, including cardiac deaths) and hepatic events defined as confirmed Hy's law cases. The Clinical Events Committee (CEC) will communicate their findings to the iDMC to aid iDMC review.

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

If the true difference in the percentage of death is $>$ 3% (e.g., 2% vs. 6%), then there is approximately a 70% chance of observing an absolute difference of $>$ 3% at the interim with 600 patients. The protocol presents the probability of observing an increase of $>$ 3% in the percentage of deaths in the trastuzumab emtansine + pertuzumab arm compared with the trastuzumab + pertuzumab arm, with different assumptions for the percentage of deaths in the two treatment arms.

If an absolute increase of $>$ 3% in the percentage of Hy's law cases (confirmed by the independent CEC) is observed in the trastuzumab emtansine + pertuzumab arm compared with the trastuzumab + pertuzumab arm, the iDMC will consider a recommendation of pausing enrollment for further data review, stopping the trial, 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 a 54% chance of observing an absolute difference of $>$ 3% at the interim with 600 patients. The protocol presents the probability of observing a $>$ 3% increase in the percentage of Hy's law cases in the trastuzumab emtansine + pertuzumab arm compared with the trastuzumab + pertuzumab arm, with different assumptions for the number of Hy's law cases in the two treatment arms.

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

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AC	doxorubicin and cyclophosphamide
AC-T	doxorubicin and cyclophosphamide followed by docetaxel or paclitaxel
AC-TH	doxorubicin and cyclophosphamide followed by a taxane (docetaxel or paclitaxel) with concurrent trastuzumab
ADC	antibody-drug conjugate
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastine time
AST	aspartase transaminase
ATA	anti-therapeutic antibody
AV	atrioventricular
CEC	Clinical Events Committee
CI	confidence interval
CIS	carcinoma in situ
CHF	congestive heart failure
CSR	Clinical Study Report
CT	computed tomography
DCIS	ductal carcinoma in situ
DFS	disease-free survival
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DRFI	distant recurrence–free interval
EBC	early breast cancer
EC	epirubicin and cyclophosphamide
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQol 5-Dimension Questionnaire™
ER	estrogen receptor

Abbreviation	Definition
FAC	5-fluorouracil, doxorubicin, and cyclophosphamide
FACT-B	Functional Assessment of Cancer Therapy–Breast
FDA	U.S. Food and Drug Administration
FEC	5 fluorouracil, epirubicin, and cyclophosphamide
FEC-TH	FEC followed by a taxane plus trastuzumab
FFPE	formalin-fixed paraffin-embedded
FPI	first patient initiation
G-CSF	granulocyte colony-stimulating factor
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER	human epidermal growth
HIPAA	U.S. Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
ICH	International Conference on Harmonisation
iDCC	independent Data Coordination Center
IDFS	invasive disease–free survival
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
ILD	interstitial lung disease
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IRB/EC	Institutional Review Board/Ethics Committee
IRF	independent review facility
IRR	infusion-related reaction
ISH	in situ hybridization
ITT	intent-to-treat
IV	intravenous
IVRS/IWRS	interactive voice response system/interactive web response system
LABC	locally advanced breast cancer
LCIS	lobular carcinoma in situ
LVEF	left ventricular ejection fraction
LVSD	left ventricular systolic dysfunction

Abbreviation	Definition
MBC	metastatic breast cancer
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCCN	National Comprehensive Cancer Network
NRH	nodular regenerative hyperplasia
NYHA	New York Heart Association
OBRP	optional biomarker research program
ORR	objective response rate
OS	overall survival
pCR	pathological complete response
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PO	by mouth; orally
PR	progesterone receptor
PRO	patient-reported outcome
PTEN	phosphatase and tensin homolog
QLQ-BR23	Quality of Life Questionnaire–Breast Cancer 23
QLQ-C30	Quality of Life Questionnaire–Core 30
QoL	quality of life
q2w	every 2 weeks
q3w	every 3 weeks
qw	weekly
qRT-PCR	quantitative real-time polymerase chain reaction
RNA	ribonucleic acid
RR	relative risk
RT	radiation therapy
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Steering Committee
SLNB	sentinel lymph node biopsy
SoC	standard of care
SOC	system organ class

Abbreviation	Definition
TAC	docetaxel, doxorubicin, and cyclophosphamide
TBILI	total bilirubin
TMA	tissue microarray
TOI-B	Trial Outcome Index–Breast
TPC	Treatment of Physician's Choice
ULN	upper limit of normal
UICC/AJCC	Union for International Cancer Control/American Joint Committee on Cancer
WBC	white blood cell

1. BACKGROUND

1.1 BACKGROUND ON HER2-POSITIVE EARLY BREAST CANCER AND ADJUVANT TREATMENT

Breast cancer remains a highly significant cause of morbidity and mortality worldwide. There are over 1.3 million cases of breast cancer diagnosed globally each year (Jemal et al. 2011). In 2011, in the United States alone, it is estimated that over 230,000 new cases of breast cancer were diagnosed and close to 40,000 women died from this disease (Siegel et al. 2012). Approximately 15%–20% of human breast cancers overexpress the human epidermal growth (HER) factor–2, a transmembrane receptor tyrosine kinase, because of an amplification event in the gene encoding HER2 on chromosome 17. Without treatment, HER2 overexpression is associated with aggressive tumor growth and poor clinical outcomes (Slamon et al. 1987, 1989; Wolff et al. 2007; Chia et al. 2008; Ross et al. 2009).

Trastuzumab (Herceptin®), an anti-HER2 humanized monoclonal antibody, is approved in multiple countries for the adjuvant treatment of patients with HER2-overexpressing early breast cancer (EBC). Several randomized studies (Section 1.2.1) have demonstrated that adjuvant trastuzumab improves outcomes for patients with early-stage HER2-positive breast cancer when administered in combination with chemotherapy concurrently (Romond et al. 2005, 2012; Slamon et al. 2011). Trastuzumab has also proven to be effective when given sequentially after completion of chemotherapy (Piccart-Gebhart et al. 2005, Smith et al. 2007, Gianni et al. 2011, Goldhirsch et al. 2013).

A variety of trastuzumab-based chemotherapy regimens are considered effective for the treatment of non-metastatic HER2-positive breast cancer (Benson et al. 2009, Wong and Toppmeyer 2010, Slamon et al. 2011), including the following:

- Anthracycline-based regimens, including doxorubicin and cyclophosphamide followed by a taxane (docetaxel or paclitaxel) with concurrent trastuzumab (AC-TH) or 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) followed by a taxane plus trastuzumab (FEC-TH)
- Non–anthracycline-based regimens, such as docetaxel, carboplatin, and trastuzumab (TCH) concurrently

A total of 1 year of HER2-directed adjuvant therapy with trastuzumab remains the standard of care (SoC) on the basis of recent results from studies comparing different adjuvant trastuzumab treatment durations (1 year vs. shorter [6 months] or longer [2 years]) (Pivot et al. 2013, Goldhirsch et al. 2013).

The 3-year disease-free survival (DFS) rate is approximately 85%–90% for the overall population of patients with HER2-positive EBC treated with adjuvant chemotherapy and trastuzumab in Herceptin® adjuvant trials. Recurrence rate at 10 years is reported to be approximately 26% (Romond et al. 2012). The majority of these patients eventually

have disease recurrence at distant sites, which is generally considered to be incurable. Thus, there is an unmet need and potential to further improve outcomes, particularly in higher-risk patient subpopulations, by incorporating newer HER2-directed agents, with manageable toxicity, into the treatment paradigm.

1.1.1 Herceptin® Adjuvant Trials

Two large trials (Study NSABP B-31 and Study NCCTG N9831) conducted in North America have investigated concurrent trastuzumab and paclitaxel following doxorubicin and cyclophosphamide (AC-TH) versus AC-T. The combined results of the two trials (Romond et al. 2005) demonstrated that the addition of trastuzumab to AC-T significantly improved DFS and overall survival (OS) in women with HER2-positive breast cancer. At the time of the first scheduled interim efficacy analysis, the hazard ratio (HR) for a first event in the AC-TH arm relative to the AC-T arm was 0.48 (95% CI: 0.39, 0.59; $p < 0.0001$), corresponding to a 52% reduction in relative risk (RR) for recurrence. The 3-year DFS rate for the AC-TH arm was 87.1%. There was also an increase in OS for patients who received trastuzumab + chemotherapy. For OS, the HR for trastuzumab + chemotherapy relative to chemotherapy alone was 0.67 (95% CI: 0.48, 0.92; $p = 0.014$). After a median follow-up of 5.5 years in the NCCTG N9831 study, DFS rates with AC→T, AC→T→H, and AC→TH→H were 72%, 80%, and 84%, respectively. A comparison between the two trastuzumab-containing arms demonstrated a 4% improvement in DFS in the AC→TH→H arm compared with the sequential arm AC→T→H, which represented a 25% risk reduction, although this was not statistically significant. The final planned analysis of these two studies demonstrated that at a median follow-up of 8.4 years, the AC-TH regimen was associated with a significant and substantial improvement in OS, with a RR reduction of 37% (HR = 0.63). For patients with high-risk HER2-positive breast cancer, treatment with this regimen reduced the risk of a DFS event at 10 years by 40% (HR = 0.60). The benefit of RR reduction for both DFS and OS was present and of similar magnitude in important subsets of the patients included in the analysis (e.g., regardless of hormonal receptor status, nodal status, or tumor size) (Romond et al. 2012).

A Phase III randomized trial, Study BCIRG 006 (Slamon et al. 2006, 2009, 2011), compared doxorubicin and cyclophosphamide followed by docetaxel (AC-T) versus doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC-TH) versus TCH for the adjuvant treatment of women with HER2-positive EBC. The results of the second interim efficacy analysis, at a median follow-up time of 36 months, demonstrated that the HR for a first event for the AC-TH arm relative to the AC-T arm was 0.61 (95% CI: 0.49, 0.77; $p < 0.0001$), corresponding to a 39% reduction in RR for recurrence. The 3-year DFS rate was 86.7% for the AC-TH arm. The 3-year OS rates were 95.5% for the AC-TH arm and 93% for the control arm. At a median follow-up of 65 months, the HR for the comparison of AC-TH with AC-T was 0.64 ($p < 0.001$). The estimated 3- and 5-year DFS rates for the AC-TH arm were 88% and 84%, respectively. The estimated 5-year OS rate was 92% for the AC-TH arm (HR compared with

AC-T = 0.63; p < 0.001). For patients receiving TCH, the estimated 3- and 5-year DFS rates were 87% and 81%, respectively (HR = 0.75; p = 0.04); the estimated 5-year OS rate was 91% (HR = 0.77; p = 0.04).

Trastuzumab can also be given sequentially after chemotherapy. In the HERA trial, patients had surgery and completed standard chemotherapy and radiotherapy prior to study enrollment. Patients were randomly allocated either to an observation-only arm or to a trastuzumab treatment arm every 3 weeks (q3w) for either 1 or 2 years. The efficacy analysis of the 1-year treatment arm versus the observation-only arm demonstrated that treatment with trastuzumab was associated with improved outcomes (Piccart-Gebhart et al. 2005). Patients treated with trastuzumab for 1 year experienced a 46% lower risk of a first event than patients in the observation-only arm (HR = 0.54; p < 0.0001), corresponding to an absolute DFS benefit of 8.4% at 2 years favoring trastuzumab. At a median follow-up of 8 years, HERA results showed sustained and statistically significant DFS and OS benefits for the 1-year trastuzumab treatment arm versus the observation-only arm despite selective crossover. Benefit for 1 year of trastuzumab treatment versus observation only was shown across both hormone receptor–positive and hormone receptor-negative cohorts. There is no evidence of a long-term benefit from 2 years compared with 1 year of trastuzumab treatment when administered as a sequential treatment following chemotherapy. Most cardiac events occurred during trastuzumab administration and were reversible (Goldhirsch et al. 2013).

1.2 BACKGROUND ON TRASTUZUMAB EMTANSINE AND PERTUZUMAB

1.2.1 Trastuzumab Emtansine

Trastuzumab emtansine (also known as T-DM1) is a novel antibody-drug conjugate (ADC). ADCs represent a new approach to conferring selectivity to highly potent cytotoxic agents. Linkage of a cytotoxic agent to highly specific monoclonal antibodies targeting unique and/or overexpressed cell surface tumor antigens focuses the delivery of such agents to tumor cells, creating a more favorable therapeutic window than could be achieved by the administration of such agents as free drugs. Trastuzumab emtansine is specifically designed for the treatment of HER2-positive breast cancer. It is composed of the cytotoxic agent DM1 (a thiol-containing maytansinoid anti-microtubule agent) conjugated to trastuzumab via lysine side chains, with an average drug to antibody ratio of approximately 3.5:1. The DM1 component of trastuzumab emtansine is an inhibitor of tubulin polymerization, binding to the β subunit of tubulin, at the same binding site as the vinca alkaloids; however, DM1 derivatives are up to 100-fold more cytotoxic than vinca alkaloids and taxanes (e.g., 25- to 500-fold more potent than paclitaxel) (Kovtun et al. 2010, Junttila et al. 2011).

Trastuzumab emtansine binds to HER2 with an affinity similar to that of trastuzumab; such binding is required for its anti-tumor activity. It is hypothesized that after binding to

HER2, trastuzumab emtansine undergoes receptor-mediated internalization, followed by intracellular release of DM1 and subsequent cytotoxicity.

Completed and ongoing Phase I, II, and III studies of trastuzumab emtansine have demonstrated clinical activity when trastuzumab emtansine is given as a single agent to patients with HER2-positive metastatic breast cancer (MBC) with tolerable/favorable safety. In addition, trastuzumab emtansine has been studied in patients with EBC in Phase Ib and II settings. Clinical trials of trastuzumab emtansine relevant to the design of the current trial are described in the following subsections. Please refer to the most recent version of the Trastuzumab Emtansine Investigator's Brochure for further information on all completed and ongoing nonclinical and clinical studies.

A summary of trastuzumab emtansine safety profile is provided in Section 5.1.1.1.

1.2.1.1 Trastuzumab Emtansine Clinical Experience in Metastatic Breast Cancer

Trastuzumab emtansine has been studied as a single agent as well as in combination with other therapies in MBC.

1.2.1.1.1 Single-Agent Studies

Study TDM4370g/BO21977 (EMILIA) is a randomized Phase III study of trastuzumab emtansine versus lapatinib plus capecitabine for patients with HER2-positive unresectable locally advanced breast cancer (LABC) or MBC previously treated with trastuzumab and a taxane (n = 991) (Verma et al. 2012). Patients received trastuzumab emtansine (3.6 mg/kg intravenous [IV] q3w) or capecitabine (1000 mg/m^2 orally [PO] twice daily, Days 1 to 14 q3w) + lapatinib (1250 mg PO daily) until progressive disease or unmanageable toxicity. Primary endpoints were progression-free survival (PFS) by an independent review, OS, and safety. There was a significant improvement in PFS favoring trastuzumab emtansine (HR = 0.650, $p < 0.0001$; median 9.6 vs. 6.4 months). OS was significantly improved in patients receiving trastuzumab emtansine, with a 31.8% reduction in the risk of death associated with trastuzumab emtansine compared with lapatinib and capecitabine (HR = 0.682 [95% CI: 0.548, 0.849]; p = 0.0006) (Verma et al. 2012). The median duration of survival was 25.1 months in patients treated with lapatinib plus capecitabine, compared with 30.9 months in patients treated with trastuzumab emtansine.

Trastuzumab emtansine was well tolerated. The incidence of Grade ≥ 3 adverse events in the trastuzumab emtansine arm was 40.8% versus 57% in the lapatinib plus capecitabine arm. The most frequently occurring Grade ≥ 3 adverse events in the trastuzumab emtansine arm were predominately related to laboratory test abnormalities. Thrombocytopenia was the most common Grade ≥ 3 adverse event; other Grade ≥ 3 adverse events occurring in at least 2% of patients were increased AST, increased ALT, anemia, fatigue, hypokalemia, and neutropenia. Fewer patients receiving

trastuzumab emtansine (15.5%) developed a serious adverse event (SAE) compared with patients receiving lapatinib plus capecitabine (18%).

Median time to symptom progression, as defined by a 5-point decrease in the score derived from the Trial Outcome Index–Breast (TOI-B) subscale of the Functional Assessment of Cancer Therapy–Breast (FACT-B) quality of life (QoL) questionnaire, was delayed in female patients receiving trastuzumab emtansine compared with those receiving lapatinib plus capecitabine (7.1 months for trastuzumab emtansine, compared with 4.6 months: HR = 0.796 [95% CI: 0.667, 0.951]; p = 0.0121).

Study TDM4450g/BO21976 was a randomized, multicenter, Phase II open-label trial of the efficacy and safety of trastuzumab emtansine (3.6 mg/kg IV q3w) versus trastuzumab plus docetaxel in patients with metastatic HER2-positive breast cancer who had not received prior chemotherapy for metastatic disease. The primary endpoints were investigator-assessed PFS and safety. Key secondary endpoints included OS, objective response rate (ORR), duration of objective response, clinical benefit rate, and QoL. A total of 137 patients were enrolled in the study.

Trastuzumab emtansine demonstrated significant improvement in PFS over trastuzumab plus docetaxel as first-line MBC therapy. The median PFS was 14.2 months in the trastuzumab emtansine arm compared with 9.2 months in the trastuzumab plus docetaxel arm (HR = 0.59 [95% CI: 0.364, 0.968]; log-rank p-value = 0.035), with a median follow-up of approximately 14 months in both arms. The ORR was 58.0% with trastuzumab plus docetaxel and 64.2% with trastuzumab emtansine. Tumor response was more durable with trastuzumab emtansine (median duration of response was not reached compared with the median duration of 9.5 months in the trastuzumab plus docetaxel arm). Preliminary OS results in this study were similar between treatment arms, with a median follow-up of approximately 23 months in both arms. Of note, OS data were not mature (< 20% of the patients in the study had died at the time of the data cutoff and the median duration of OS was not reached for either arm). Results were also potentially confounded by the crossover allowed in the. At the time of OS follow-up, there were 35 patients (50%) from the trastuzumab plus docetaxel arm who had crossed over to trastuzumab emtansine following documented disease progression.

Grade ≥ 3 adverse events were reported less frequently in the trastuzumab emtansine group compared with the trastuzumab plus docetaxel group (46.4% vs. 90.9%), as were adverse events leading to treatment discontinuations (7.2% vs. 34.8%) and SAEs (20.3% vs. 25.8%).

The worsening of QoL, reflected by the FACT-B and TOI-B scores, was delayed in the trastuzumab emtansine arm compared with the trastuzumab plus docetaxel arm (7.5 vs. 3.5 months; HR = 0.58; p = 0.022).

Study TDM4997g/BO25734 (TH3RESA) is a Phase III study to evaluate efficacy of trastuzumab emtansine versus Treatment of Physician's Choice (TPC) in patients who received at least two prior regimens of HER2-directed therapies, including trastuzumab and lapatinib, in the metastatic or unresectable locally advanced/recurrent setting. Co-primary efficacy endpoints were PFS per investigator assessment and OS. There were 404 patients who received trastuzumab emtansine as their planned treatment, and 198 patients who received TPC. Patients receiving trastuzumab emtansine had a 47.2% reduction in the risk of disease progression or death. Median PFS was 3.3 months in the TPC arm and 6.2 months in the trastuzumab emtansine arm (HR =0.528; 95% CI: 0.422, 0.661; p <0.0001). There was a strong positive trend in OS in favor of trastuzumab emtansine at the first interim analysis. Patients receiving trastuzumab emtansine had a 44.8% reduction in the risk of death (HR =0.552; 95% CI: 0.369, 0.826; p =0.0034) compared with patients receiving TPC; however, this result did not cross the pre-specified O'Brien-Fleming stopping boundary of HR <0.363 (p <0.0000013). Patients receiving trastuzumab emtansine also showed a consistent treatment benefit compared with the subgroup of TPC patients receiving a trastuzumab-containing regimen (74.7% of the intent-to-treat [ITT] population).

Numerically fewer patients receiving trastuzumab emtansine than those receiving TPC had Grade ≥3 AEs (39.0% vs. 46.2%) or AEs leading to dose reduction (12.4% vs. 20.7%). The incidence of SAEs (24.1% vs. 22.3%) and of AEs leading to treatment discontinuation of any component of therapy (11.7% vs. 10.9%) are similar between treatment arms. Across the majority of the most commonly affected body systems, patients receiving trastuzumab emtansine reported more AEs compared with those receiving TPC. However, the higher frequency of events seen for trastuzumab emtansine was driven by Grade 1–2 AEs.

The patient-reported outcome (PRO) measures including "time to pain symptom progression" were utilized to evaluate QoL. The time to pain symptom progression was similar different between the two treatment arms (HR =1.115; 95% CI: 0.819, 1.517).

1.2.1.1.2 Combination Studies

Study TDM4373g/BO22495 was a Phase Ib/II study of trastuzumab emtansine plus pertuzumab in patients with HER2-positive LABC (unresectable local or regional) or MBC. Sixty-seven patients were enrolled. Nine patients with relapsed MBC (i.e., treated in the second-line setting or beyond) were enrolled in the dose-escalation phase of the study (Phase Ib). On the basis of data from the Phase Ib portion, the recommended dose for the expansion phase of the study (Phase II) was trastuzumab emtansine 3.6 mg/kg q3w in combination with full-dose pertuzumab (840-mg loading dose, followed by 420 mg q3w). One patient experienced a dose-limiting toxicity (DLT) (Grade 4 thrombocytopenia) at the recommended dose level for trastuzumab emtansine and pertuzumab.

The Phase II portion enrolled 37 relapsed patients (i.e., relapsed or progressed on prior HER2-directed therapy) and 21 first-line patients (i.e., received no prior treatment for MBC) at the recommended dose level.

For the patients treated at the recommended Phase II dose (n = 64), the most common adverse events (occurring in ≥ 25% of patients) were as follows: fatigue (60.9%), nausea (50%), diarrhea (39.1%), cough (37.5%), decreased appetite (34.4%), constipation (32.8%), thrombocytopenia (32.8%), pyrexia (31.3%), chills (31.3%), vomiting (29.7%), increased AST (29.7%), increased ALT (28.1%), dyspnea (26.6%), dysgeusia (25%), peripheral sensory neuropathy (25%), mucosal inflammation (25%), epistaxis (25%), and headache (25%).

The rates of Grade 3 to 4 thrombocytopenia observed in this study were comparable to those in studies of single-agent trastuzumab emtansine (12.5% vs. 7.5%–12.9%) (Diéras et al. 2010, LoRusso et al. 2011, Verma et al. 2012). Similarly, the rates of Grade 3 to 4 AST or ALT elevation were within the range of previously reported studies (approximately 9.4% vs. 2.9%–13.4%). The overall incidence of diarrhea appeared to be greater than for single-agent trastuzumab emtansine (39.1% vs. 10.4%–25.9%), which is likely due to combination treatment with pertuzumab.

For the 64 patients treated with trastuzumab emtansine at the recommended Phase II dose (21 first-line and 43 relapsed), the ORR (complete response + partial response) was 40.6%, with a higher response rate among first-line patients (57.1%) than among relapsed patients (32.6%). The majority of responses observed in the 64 patients were partial responses (23 of 26 patients).

For the patients who had an objective response, the median duration of response was slightly longer for first-line patients (13.9 months) than for relapsed patients (11.8 months).

Study TDM4688g was a Phase Ib/II, single-arm study to evaluate the effect of trastuzumab emtansine (3.6 mg/kg q3w) on the QT interval in patients with HER2-positive LABC or MBC. A subgroup of patients (n = 20) who developed early disease progression while receiving single-agent trastuzumab emtansine (i.e., within 6 cycles or 18 weeks from study start) were eligible to receive combination treatment with trastuzumab emtansine plus pertuzumab in subsequent cycles. Two patients who received the combination therapy achieved partial response. Safety data are summarized in the pooled analysis for trastuzumab emtansine plus pertuzumab (Section 1.2.3).

Study TDM4788g/BO22589 (MARIANNE) is a randomized three-arm, Phase III study of trastuzumab emtansine combined with pertuzumab versus trastuzumab emtansine combined with pertuzumab-placebo (blinded for pertuzumab) versus trastuzumab plus taxane as a first-line treatment in patients with HER2-positive progressive or recurrent

LABC or MBC. The primary objectives of the study are to compare the efficacy (PFS) and safety across the three arms. *A* total of 1095 patients *were enrolled in this study.*

Efficacy and safety data were recently described (Ellis et al. 2015). For the primary endpoint of PFS based on independent review facility (IRF) assessment, both trastuzumab emtansine +placebo and trastuzumab emtansine + pertuzumab were non-inferior to trastuzumab +taxane: the upper bounds of the 97.5% CIs for the stratified HRs were below the pre-specified non-inferiority margin of HR 1.1765: 1.13 for trastuzumab emtansine +placebo (HR =0.91; 97.5% CI: 0.73, 1.13) and 1.08 for trastuzumab emtansine +pertuzumab (HR =0.87; 97.5% CI: 0.69, 1.08), each versus trastuzumab +taxane. The addition of pertuzumab to trastuzumab emtansine did not result in a statistically significant increase in PFS in the ITT population. Median PFS was 13.7 months for trastuzumab +taxane, 14.1 months for trastuzumab emtansine +placebo and 15.2 months for trastuzumab emtansine +pertuzumab.

The safety profile of trastuzumab emtansine as a single agent or in combination with pertuzumab was consistent with prior experience, with no new safety signals identified compared with those already known for these study drugs. Trastuzumab emtansine as a single agent or in combination with pertuzumab was more tolerable than trastuzumab +taxane, with respect to a numerical lower incidence and/or severity of certain clinically important and/or symptomatic toxicities, fewer Grade ≥3 AEs and fewer AEs leading to treatment discontinuation (Ellis et al. 2015).

Study TDM4652g/*GO01355 wa*s a Phase Ib/IIa open-label study to evaluate the safety, tolerability, and pharmacokinetics of trastuzumab emtansine weekly (qw) or q3w with paclitaxel, with or without pertuzumab, in patients with HER2-positive LABC or MBC who have previously received HER2-directed therapy. A total of 104 patients were enrolled in the study. The Phase Ib dose-escalation portion of the study was to determine the maximum tolerated dose (MTD) of the combination regimen(s). The MTD of trastuzumab emtansine q3w was 3.6 mg/kg with paclitaxel 80 mg/m^2 qw. The addition of the pertuzumab 840-mg loading dose followed by 420 mg q3w to the regimen was feasible (Modi et al. 2012).

The Phase IIa portion of this study was to further evaluate trastuzumab emtansine with paclitaxel with or without pertuzumab at the MTD in order to determine the safety and feasibility of delivering at least 12 doses of qw paclitaxel in combination with trastuzumab emtansine with or without pertuzumab within the first 15 weeks after Cycle 1 Day 1. Enrollment in the Phase IIa portion was completed in January 2013, with 22 patients in Group A (paclitaxel + trastuzumab emtansine) and 22 patients in Group B (paclitaxel + trastuzumab emtansine + pertuzumab). All patients enrolled had received prior trastuzumab, and 36 of 44 (81.8%) had received previous taxane therapy. As of 23 May 2013, in Groups A and B, 23 of 42 evaluable patients (54.8%) were able to receive at least 12 doses of paclitaxel within 15 weeks after Cycle 1 Day 1. Exposure data demonstrated that the median dose intensities achieved for trastuzumab emtansine,

paclitaxel, and pertuzumab were 93.95%, 50.12%, and 100.00%, respectively. The most commonly observed Grade 3 or 4 adverse events (peripheral neuropathy, neutropenia, fatigue, and thrombocytopenia) were consistent with the known safety profiles of the three study agents. However, the incidence rate of Grade ≥ 3 peripheral neuropathy increased compared with the use of single-agent trastuzumab emtansine in patients with MBC. Peripheral neuropathy was the major reason for paclitaxel dose reduction and/or discontinuation.

1.2.1.2 Trastuzumab Emtansine Clinical Experience in Early Breast Cancer

Study TDM4874g/BO22857 was a single-arm Phase II study to assess the safety and feasibility of administering trastuzumab emtansine at a dose of 3.6 mg/kg IV q3w for up to 17 cycles following anthracycline-based chemotherapy for patients with early-stage HER2-positive breast cancer, in neoadjuvant and/or adjuvant settings. Radiation therapy (RT) was administered after the first four cycles of trastuzumab emtansine to patients in whom it was indicated. Four cycles of trastuzumab/docetaxel (given after the first four cycles of trastuzumab emtansine) were optional. The primary objectives of the study are to evaluate the safety profile of trastuzumab emtansine and to evaluate the rate of prespecified cardiac events (death from cardiac cause or severe congestive heart failure [CHF]; New York Heart Association [NYHA] Class III or IV) following initiation of trastuzumab emtansine treatment.

*The final analysis (clinical cutoff 12 June 2013) indicated that there were n*o prespecified cardiac events occurred and there were no reports of symptomatic left ventricular systolic dysfunction (LVSD) or heart failure. Overall, 123 (83.1%) patients completed the planned course of trastuzumab emtansine treatment, 119 (80.4%) of whom had no dose reduction. Twenty patients (13.5%) had adverse events leading to trastuzumab emtansine discontinuation: in 11 of these patients, the adverse events were laboratory abnormalities requiring discontinuation (none were Grade 4), and in 9 patients, discontinuation was because of symptomatic adverse events (2 were Grade 3 [fatigue, joint crepitation]; none were Grade 4). Of the 148 patients, 32.4% had Grade 3 trastuzumab emtansine–related adverse events and 2.7% had Grade 4 trastuzumab emtansine–related adverse events (1 patient each: febrile neutropenia and pancytopenia, atrial fibrillation, decreased platelet count, and hypokalemia); no deaths occurred. The adverse events observed to date are consistent with the known safety profile of trastuzumab emtansine. There were no cases of portal hypertension/nodular regenerative hyperplasia (NRH) reported. *For additional safety details for this study, please refer to the trastuzumab emtansine Investigator's Brochure.*

Of the 116 patients receiving RT, 39 received it concurrently with trastuzumab emtansine and 77 received it sequentially. The percentage of patients who completed the planned RT dose without delay was similar to the percentage who received concurrent or sequential treatment (90% and 92%, respectively). Radiation pneumonitis occurred in 3 patients (1 in concurrent and 2 in sequential treatments).

Fifty patients (Stage I, 8%; Stage II, 56%; Stage III, 36%) received neoadjuvant trastuzumab emtansine and underwent surgery. The pathological complete response (pCR) rate (ypT0/is ypN0) was 56.0% (95% CI: 41.3%, 69.6%).

Study BP22572 is a Phase Ib/II study designed to assess the safety, feasibility, and/or efficacy of combining docetaxel with trastuzumab emtansine with or without pertuzumab in patients with HER2-positive MBC or newly diagnosed LABC.

The feasibility of combining these agents in patients with HER2-positive MBC and LABC was demonstrated in the Phase Ib portion of the study. A total of 70 patients with LABC have been treated with the following combinations:

- Trastuzumab emtansine 3.6 mg/kg + docetaxel 75 mg/m^2 q3w (n = 15)
- Trastuzumab emtansine 3.6 mg/kg + docetaxel 100 mg/m^2 q3w (with primary granulocyte colony-stimulating factor [G-CSF]) (n = 22)
- Trastuzumab emtansine 3.6 mg/kg + docetaxel 60 mg/m^2 + pertuzumab 840-mg loading dose, then 420 mg q3w (n = 11)
- Trastuzumab emtansine 3.6 mg/kg + docetaxel 75 mg/m^2 (with primary G-CSF) + pertuzumab 840-mg loading dose, then 420 mg q3w (n = 22)

As of 2 May 2013, 97.3% of the patients have received five or more cycles of the doublet combination and 87.8% of the patients have received four or more cycles of the triplet combination. Grade 2 or worse skin toxicity was observed, including a Grade 4 dermatomyositis. Incidences of increased ALT and thrombocytopenia observed with the docetaxel combination were higher than expected on the basis of the known safety profile of the individual agents. One patient treated in the cohort of docetaxel 100 mg/m^2 (starting docetaxel dose at 100 mg/m^2 and dose reduced to 75 mg/m^2 after the first dose) combined with trastuzumab emtansine died, with a reported *SAE* of pneumonitis.

In the MBC population (n = 25), the ORR was 80.0% (95% CI: 59.3, 93.2). In the overall LABC population (n = 73), the pCR rate was 60.3% (95% CI: 48.1, 71.5). In LABC patients receiving trastuzumab emtansine + docetaxel (n = 40), the pCR rate was 60.0%, and in those receiving trastuzumab emtansine + docetaxel + pertuzumab (n = 33), it was 60.6%.

Study WSG-ADAPT is a Phase II study evaluating trastuzumab emtansine with or without endocrine therapy in comparison to trastuzumab + endocrine therapy as neoadjuvant treatment in HER2+/HR+ EBC patients. After 4 cycles of either neoadjuvant trastuzumab + endocrine therapy or neoadjuvant trastuzumab emtansine with or without endocrine therapy, patients underwent definitive breast surgery with total pCR serving as the primary endpoint. Notable therapeutic activity was observed at the planned interim analysis (January 2015) among 130 patients. Total pCR (ypT0/is, ypN0) rates after 4 cycles of neoadjuvant trastuzumab + endocrine therapy,

trastuzumab emtansine + endocrine therapy, or trastuzumab emtansine alone were 6.7%, 45.8%, and 40.5%, respectively (Harbeck et al. 2015).

Study BO27938 (KATHERINE) is a randomized, multinational, multicenter, open-label Phase III study, evaluating adjuvant treatment with trastuzumab emtansine compared with trastuzumab in patients with EBC who have not achieved a pCR following neoadjuvant treatment with chemotherapy and trastuzumab. The primary objective of this trial, which started in April 2013, is to compare invasive disease–free survival (IDFS) between treatment arms. *As of 11 May 2015, unblinded safety and efficacy data were not available to the Sponsor, but the independent Data Monitoring Committee (iDMC), which reviews data from the trial, had thus far recommended that the study continue as planned.*

Study BO28408/TRIO021 (KRISTINE) is a randomized, multicenter, open-label Phase III study, evaluating neoadjuvant treatment with trastuzumab emtansine +pertuzumab compared with chemotherapy +trastuzumab and pertuzumab in patients with EBC. The primary objective of this trial, which started in June 2014, is to compare the pCR rate (ypT0/is, ypN0) using local evaluation between treatment arms.

1.2.1.3 Pooled Safety Analysis of Single-Agent Trastuzumab Emtansine

Pooled safety data are available for 884 patients with MBC treated with single-agent trastuzumab emtansine at a dose of 3.6 mg/kg q3w. The most common adverse events associated with single-agent trastuzumab emtansine (in ≥25% of patients) were fatigue (*46.4*%), nausea (*43.0*%), thrombocytopenia (*29.6*%), headache (*29.4*%), and constipation (26.*5*%). Most of these events were Grade 1 or 2 in intensity. The most common Grade ≥3 adverse events (occurring in >2% of patients) were thrombocytopenia (*10.*7%), increased AST (4.3%), fatigue (3.2%), increased ALT (3.1%), hypokalemia (2.9%), and anemia (2.*9*%). *Sixty-two* patients (*7.0*%) experienced adverse events that resulted in their trastuzumab emtansine treatment being discontinued: The most common adverse events leading to discontinuation were blood and lymphatic system disorders (primarily thrombocytopenia [1.5%]) and investigations system organ classes (SOCs) (increased AST [0.8%] and increased ALT [0.5%]).

*Selected a*dverse events for all patients include hepatotoxicity, peripheral neuropathy, thrombocytopenia, infusion-related reactions (IRR)/hypersensitivity, cardiac dysfunction, and pneumonitis. Table 1 provides an overview of these adverse events.

Table 1 Overview of *Selected* Adverse Events with Trastuzumab Emtansine *Alone* (n=884)

Type of Event	No (%) of Patients with AE of Special Interest			
	Any	Grade > 3	SAE	AE Leading to Withdrawal
Thrombocytopenia	285 (32.2%)	105 (11.9%)	8 (0.9%)	15 (1.7%)
Hemorrhage	*323 (36.5%)*	*18 (2.0%)*	*14 (1.6%)*	*0*
Hepatotoxicity[a]	292 (33.2%)	81 (9.2%)	10 (1.1%)	18 (2.0%)
Peripheral neuropathy	257 (29.1%)	22 (2.5%)	2 (0.2%)	4 (0.5%)
Infusion-related reactions/hypersensitivity	61 (6.9%)	1 (0.1%)	2 (0.2%)	1 (0.1%)
Cardiac dysfunction[b]	14 (1.6%)	2 (0.2%)	—	2 (0.2%)
Pneumonitis/ILD	10 (1.1%)	3 (0.3%)	3 (0.3%)	4 (0.5%)

Single-agent pooled analyses: cut-off date of 31 July 2012

AE = adverse event; CHF = congestive heart failure; ILD = interstitial lung disease; LVEF = left ventricular ejection fraction; NRH = nodular regenerative hyperplasia; SAE = serious adverse event.

[a] Hepatotoxicity includes increases in serum AST or ALT and NRH of the liver.

[b] Cardiac dysfunction refers to left ventricular dysfunction including CHF and decreases in LVEF.

Please refer to the Investigator's Brochure for a full description of the trastuzumab emtansine safety profile, warnings, and precautions.

1.2.2 Pertuzumab

Pertuzumab is a fully humanized IgG1$_\kappa$ monoclonal antibody that targets HER2 by inhibiting HER2 heterodimerization with other HER family members such as HER1/epidermal growth factor receptor (EGFR), HER3, and HER4. HER2 functions as a co-receptor and is frequently activated by forming heterodimers with another HER family receptor when activated in a HER ligand–dependent manner.

Like trastuzumab, pertuzumab is directed against the extracellular domain of HER2. However, pertuzumab binds to an epitope within subdomain 2 of HER2, whereas the epitope for trastuzumab is localized to subdomain 4 (Cho et al. 2003, Franklin et al. 2004). As a result of heterodimerization inhibition, pertuzumab inhibits ligand-initiated intracellular signaling through two major signaling pathways: MAP-kinase and PI3-kinase. Inhibition of these signaling pathways can result in growth arrest and apoptosis, respectively (Hanahan and Weinberg 2000). In vitro studies have shown that heregulin-activated HER3-HER2 heterodimers elicit the strongest proliferative and transformation responses of any possible receptor combination. Consequently, ligand-activated downstream signaling is blocked more effectively by pertuzumab than by trastuzumab. Therefore, as a result of their complementary modes

of action, there is a potential role for the combination of pertuzumab and trastuzumab in HER2-overexpressing diseases, which has been demonstrated in clinical trials (Section 1.2.2.1 and Section 1.2.2.2).

Pertuzumab as a single agent has been studied in several Phase I or II clinical trials in solid tumors, including breast, prostate, ovarian, and lung cancer. Low clinical activity has been observed in Phase I/II studies conducted in patients with HER2 low-expressing tumors receiving single-agent pertuzumab; complete responses have not been observed in any of these trials.

Pertuzumab has also been evaluated in Phase II and III studies in combination with trastuzumab and has demonstrated clinical efficacy with acceptable safety profile in patients with HER2-positive MBC. Pertuzumab is approved in several countries for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive MBC who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

A summary of the pertuzumab safety profile is provided in Section 5.1.1.2. Clinical trials of pertuzumab relevant to the design of the current trial are listed in the following subsections. Please refer to the most recent version of the Pertuzumab Investigator's Brochure for further information.

1.2.2.1 Pertuzumab Clinical Experience in MBC

Phase III Study WO20698/TOC4129g (CLEOPATRA) was a randomized, multicenter, double-blind, placebo-controlled trial of 808 patients with HER2-positive MBC, in which patients were randomized 1:1 to receive either placebo plus trastuzumab and docetaxel or pertuzumab plus trastuzumab and docetaxel.

The primary endpoint of this randomized trial was PFS as assessed by an IRF. The randomized trial demonstrated a statistically significant improvement in IRF-assessed PFS in the pertuzumab-treated group compared with the placebo-treated group (HR = 0.62 [95% CI: 0.51, 0.75]; $p < 0.0001$) and an increase in median PFS of 6.1 months (median PFS of 18.5 months in the pertuzumab-treated group vs. 12.4 months in the placebo-treated group) (Baselga et al. 2012c). *The final analysis of OS took place when 389 deaths had occurred, after a median follow-up of 50 months. Despite crossover, OS benefit in favor of the pertuzumab-treated group was maintained (HR =0.68; 95% CI: 0.56, 0.84; p =0.0002). The median OS was longer by 15.7 months in the pertuzumab-treated group (median 56.5 months) compared to the placebo-treated group (median 40.7 months)* (Swain et al. *2015*).

In this study, the addition of pertuzumab to trastuzumab did not increase the rates of symptomatic or asymptomatic cardiac dysfunction. Adverse events (any grade) of diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin were reported more frequently in the pertuzumab group than in the control group. The events were

mostly Grade 1 or 2 and occurred during the period of concomitant docetaxel administration. Grade 3 or worse febrile neutropenia (13.8% vs. 7.6%) and diarrhea (7.9% vs. 5%) were increased in the pertuzumab group.

1.2.2.2 Pertuzumab Clinical Experience in Early Breast Cancer

Pertuzumab in combination with trastuzumab and docetaxel has been generally well tolerated and has improved pCR rates in neoadjuvant therapy of EBC (Gianni et al. 2012, Schneeweiss et al. 2013).

Neoadjuvant Study WO20697 (NEOSPHERE) evaluated patients with newly diagnosed HER2-positive breast cancer (n = 417) who were randomized to receive in the neoadjuvant setting the treatments specified in Table 2. As seen in Table 2, the pCR rate (ypT0/is ypN0) improved with the addition of pertuzumab.

Table 2 Early Breast Cancer and pCR Rates in Study WO20697

	Treatment Arm A (trastuzumab and docetaxel) [a]	Treatment Arm B (trastuzumab, docetaxel and pertuzumab) [b]	Treatment Arm C (trastuzumab and pertuzumab, without chemotherapy)	Treatment Arm D (pertuzumab and docetaxel)
pCR rates (ypT0/is ypN0)	21.5%	39.3%	11.2%	17.7%

pCR = pathological complete response.

[a] Reference treatment.

[b] Primary comparison arm.

The safety analysis for the neoadjuvant treatment period showed that the tolerability of pertuzumab in combination with trastuzumab and docetaxel was acceptable. The most frequently occurring adverse events in the neoadjuvant period (in ≥ 25% of patients in any arm) were alopecia, neutropenia, diarrhea, nausea, fatigue, rash, and mucosal inflammation. The majority of Grade ≥ 3 adverse events were blood and lymphatic system disorders SOC (neutropenia, leukopenia, and febrile neutropenia). The rates of severe neutropenia for trastuzumab with docetaxel and for trastuzumab with docetaxel and pertuzumab were 57% and 44.9%, respectively, with corresponding rates of febrile neutropenia of 7.5% and 8.5%, respectively. In the principal arms of the study (Arms A and B), there was no substantial difference in the occurrence of cardiac events during the neoadjuvant treatment period.

Results from the post-treatment follow-up period (up to the third clinical cutoff of 12 July 2013) showed that there were no clinically relevant, long-term toxicities.

Five-year pre-planned analyses of pertuzumab in combination with trastuzumab and docetaxel compared with trastuzumab and docetaxel showed 81% and 82% PFS (similar to event-free survival) and 88% and 84% DFS rate, respectively. These analyses showed that these results are consistent with breast pCR results and shows long-term

benefits of adding pertuzumab to trastuzumab and docetaxel as neoadjuvant therapy (Gianni et al. 2015).

Neoadjuvant Study BO22280 (TRYPHAENA) evaluated cardiac safety and pCR rates when pertuzumab was administered concurrently or sequentially with anthracycline-based therapy (epirubicin, FEC regimen) or with a non–anthracycline-based regimen (TCH regimen) in a neoadjuvant setting (Schneeweiss et al. 2013). A total of 225 patients were randomized to receive the treatments specified in Table 3. The pCR rate (ypT0/is ypN0) is reported in Table 3.

Table 3 Cardiac Safety and pCR Rates in Study BO22280

	Treatment Arm A[a]		Treatment Arm B[b]		Treatment Arm C[c]
	Cycles 1–3	Cycles 4–6	Cycles 1–3	Cycles 4–6	Cycles 1–6
	FECHP	THP	FEC	THP	TCHP
pCR rates (ypT0/is ypN0)	56.2%		54.7%		63.6%

FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; FECHP = 5-fluorouracil, epirubicin, cyclophosphamide, trastuzumab, and pertuzumab; H = trastuzumab; pCR = pathological complete response; P = pertuzumab; T = docetaxel; TCH = docetaxel, carboplatin, and trastuzumab.

[a] Trastuzumab and pertuzumab given from Cycles 1 to 3 concurrently with FEC and given from Cycles 4 to 6 concurrently with docetaxel (FECHP × 3→THP × 3).

[b] Trastuzumab and pertuzumab given from Cycles 4 to 6 concurrently with docetaxel following three cycles of FEC (FEC × 3→THP × 3).

[c] TCH + pertuzumab (TCHP × 6).

The safety analysis showed that the combination of pertuzumab with trastuzumab with standard anthracycline-based chemotherapy or non–anthracycline-based chemotherapy was generally well tolerated.

The cardiac safety outcomes were similar across all three arms of the study in both the anthracycline-based regimens and the non–anthracycline-based regimen. There was a low incidence of left ventricular dysfunction (Grades 1 to 4) in all arms of the study (Arm A, 5.6%; Arm B, 4%; Arm C, 2.6%) in the neoadjuvant treatment period.

The most common adverse event in the neoadjuvant period was diarrhea (in 61% to 72% of patients). Other common adverse events (> 20% incidence in any arm) included alopecia, nausea, neutropenia, vomiting, fatigue, anemia, mucosal inflammation, constipation, dyspepsia, leukopenia, decreased appetite, and headache. Grade ≥ 3 events were predominately blood and lymphatic system disorders SOC.

The following rates were seen across Arms A, B, and C in the neoadjuvant treatment period: Grade ≥ 3 neutropenia, 47.2%, 42.7%, and 46.1%, respectively; and febrile neutropenia, 18.1%, 9.3%, and 17.1%, respectively.

Study BO25126 (APHINITY) is a Phase III, randomized trial designed to demonstrate the superiority of adjuvant pertuzumab + trastuzumab + standard chemotherapy treatment (anthracycline and non–anthracycline based regimens) compared with placebo and trastuzumab –containing regimens in early-stage HER2-positive breast cancer. The primary endpoint is IDFS. Secondary endpoints include DFS, OS, and safety.

The main selection criteria include patients with newly diagnosed, HER2-positive primary invasive breast cancer who have undergone definitive surgery and are intended to receive adjuvant systemic chemotherapy (either node-positive or node-negative and tumor size > 1 cm or node-negative and tumor size 0.5–1.0 cm with at least one high-risk feature [histologic/nuclear Grade 3, both estrogen receptor (ER)– and progesterone receptor (PR)–negative, or age < 35 years]). The investigator chooses either an anthracycline-based chemotherapy or a non–anthracycline-based chemotherapy according to local practice guidelines. Eligible patients are randomized to receive chemotherapy plus trastuzumab and placebo or chemotherapy plus trastuzumab and pertuzumab. As of *14 January 2015*, unblinded safety and efficacy data were not available to the Sponsor, but the iDMC, which reviews data from the trial, had thus far recommended that the study continue as planned.

1.2.3 Pooled Safety Analysis of Trastuzumab Emtansine in Combination with Pertuzumab

Pooled safety data are available for 87 patients treated with trastuzumab emtansine and pertuzumab (Studies TDM4373g*/BO22495* [n = 67] and TDM4688g [n = 20]; including follow-up data for any patients continuing to receive treatment in the extension study [TDM4529g/BO25430]). The most common adverse events of any grade (in ≥ 20% of patients) were fatigue (52.9%), nausea (42.5%), diarrhea (3*5.6*%), cough (33.3%), decreased appetite (31%), thrombocytopenia (27.6%), constipation (26.4%), vomiting (*27.6*%), pyrexia (26.4%), increased AST (26.4%), chills (25.3%), epistaxis (*25.3*%), increased ALT (23%), headache (23%), dyspnea (23%), dysgeusia (20.7%), and rash (2*1.8*%), with most of these events being Grade 1 or 2. The most common Grade ≥ 3 adverse events (occurring in > 2 patients [2.5%]) were *fatigue (11.5%),* thrombocytopenia (10.3%), increased AST (9.2%), dyspnea (*9.2*%), increased ALT (6.9%), anemia (5.7%), cellulitis (4.6%), peripheral sensory neuropathy (4.6%), pleural effusion (3.4%), and pneumonia (3.4%).

Selected adverse events *of relevance to trastuzumab emtansine* for all patients include hepatotoxicity, peripheral neuropathy, thrombocytopenia, infusion reactions, cardiac dysfunction, and pneumonitis. Table 4 provides an overview of these adverse events.

Table 4 Overview of *Selected* Adverse Events with Trastuzumab Emtansine in Combination with Pertuzumab (n = 87)

	No (%) of Patients with AE of Special Interest			
Type of Event	Any	Grade > 3	SAE	AE Leading to Withdrawal
Thrombocytopenia	25 (28.7%)	9 (10.3%)	1 (1.1%)	—
Hemorrhage	*35 (40.2%)*	*5 (5.7%)*	*5 (5.7%)*	*4 (4.6%)*
Hepatotoxicity[a]	28 (32.2%)	13 (14.9%)	2 (2.3%)	3 (3.4%)
Peripheral neuropathy	29 (33.3%)	*5 (5.7%)*	—	1 (1.1%)
Infusion reactions	*3 (3.4%)*	—	—	—
Cardiac dysfunction[b]	3 (3.4%)	1 (1.1%)	—	1 (1.1%)
ILD	1 (1.1%)	1 (1.1%)	1 (1.1%)	—

Trastuzumab emtansine plus pertuzumab pooled analyses: cut-off date of 30 September 2013

AE = adverse event; CHF = congestive heart failure; ILD = interstitial lung disease; LVEF = left ventricular ejection fraction; NRH = nodular regenerative hyperplasia; SAE = serious adverse event.

[a] Hepatotoxicity includes increases in serum AST or ALT, and NRH of the liver.

[b] Cardiac dysfunction refers to left ventricular dysfunction including CHF and decreases in LVEF.

*Based on new safety data from Study TDM4788g/BO22589 (MARIANNE), t*he safety profile of trastuzumab emtansine in combination with pertuzumab is consistent with this *pooled* analysis, with no new safety signals identified. *Overview of adverse events for Study TDM4788g/BO22589 (MARIANNE) for safety population is described below in* Table 5.

Table 5 *Overview of Adverse Events (Safety Population)*

	Trastuzumab + taxane (N=353)	T-DM1 + Placebo (N=361)	T-DM1 + Pertuzumab (N=366)
Any AE	348 (98.6%)	357 (98.9%)	361 (98.6%)
Any Grade ≥ 3 AE	191 (54.1%)	164 (45.4%)	169 (46.2%)
AE leading to discontinuation			
Taxane	97 (27.5%)	0	0
Trastuzumab	19 (5.4%)	1 (0.3%)	0
T-DM1	0	63 (17.5%)	67 (18.3%)
Pertuzumab/Placebo	0	32 (8.9%)	40 (10.9%)
Any treatment component	105 (29.7%)	66 (18.3%)	70 (19.1%)
Deaths	123 (34.8%)	114 (31.6%)	116 (31.7%)
Deaths due to PD	116 (32.9%)	106 (29.4%)	106 (29.0%)
Deaths due to AEs	6 (1.7%)	4 (1.1%)	7 (1.9%)
Deaths due to other causes	1 (0.3%)	4 (1.1%)	3 (0.8%)
SAEs	80 (22.7%)	77 (21.3%)	85 (23.2%)
Selected AEs			
Hepatotoxicity	20 (5.7%)	98 (27.1%)	71 (19.4%)
Pulmonary Toxicity	7 (2.0%)	8 (2.2%)	11 (3.0%)
Left Ventricular Dysfunction	38 (10.8%)	10 (2.8%)	18 (4.9%)
Pregnancy/Fetal Harm	3 (0.8%)	5 (1.4%)	5 (1.4%)
Peripheral Neuropathy	211 (59.8%)	132 (36.6%)	151 (41.3%)
Thrombocytopenia	0	50 (13.9%)	53 (14.5%)
IRR/Hypersensitivity (Type 1)	54 (15.3%)	105 (29.1%)	153 (41.8%)
IRR/Hypersensitivity Symptoms	44 (12.5%)	97 (26.9%)	140 (38.3%)
Hemorrhage	76 (21.5%)	142 (39.3%)	167 (45.6%)
Rash	155 (43.9%)	112 (31.0%)	142 (38.8%)
Diarrhea	172 (48.7%)	91 (25.2%)	176 (48.1%)
Neutropenia	103 (29.2%)	45 (12.5%)	33 (9.0%)
Mucositis	122 (34.6%)	89 (24.7%)	108 (29.5%)
Venous Thromboembolism	10 (2.8%)	5 (1.4%)	4 (1.1%)

Source: Synopsis of Clinical Study Report 1056171 (Protocol TDM4788G/BO22589)

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.3.1 Study Rationale

Despite improved DFS and OS with trastuzumab-containing adjuvant systemic therapy, a significant number of patients remain at risk for relapse and death from their disease. Given the curative intent of adjuvant therapy, there is the potential to further improve outcomes, with manageable toxicity, using newer HER2-directed agents, particularly in higher-risk patient populations.

The combination of two HER2-targeted therapies with complementary mechanisms of action, such as pertuzumab and trastuzumab, has been shown to further improve efficacy for HER2-positive breast cancer with a manageable safety profile in a first-line metastatic setting (Study WO20698/TOC4129g [CLEOPATRA]) and neoadjuvant setting (Study WO20697 [NEOSPHERE] and Study BO22280 [TRYPHAENA]) (see Section 1.2.2 for details). Dual HER2-blockade therapy with trastuzumab and lapatinib has also improved pCR rates over the use of trastuzumab combined with

chemotherapy (Baselga et al. 2012a). Therefore, it is anticipated that there will be a future change in the SoC for HER2-positive EBC to include pertuzumab on the basis of the results of Study BO25126 (APHINITY) (see Section 1.2.2.2 for details). Please see Section 3.3.3 for further details on rationale of the selection of trastuzumab combined with pertuzumab as control arm.

The highly potent chemotherapeutic agent DM1 should complement the HER2 signaling pathway inhibition caused by the combination of trastuzumab and pertuzumab. Furthermore, DM1 may provide higher dose intensity and longer duration when delivered as a HER2-targeted chemotherapy with potentially less systemic toxicity compared with conventional chemotherapy. Therefore, trastuzumab emtansine *may* reduce the risk of recurrence and increase the likelihood of DFS in HER2-positive EBC, with an acceptable safety profile compared with the current or anticipated future SoC.

The Phase III EMILIA study demonstrated improved efficacy (PFS and OS), with a favorable safety profile and QoL, with trastuzumab emtansine as a single agent compared with lapatinib plus capecitabine in patients with recurrent/metastatic HER2-positive breast cancer who have previously received taxanes and trastuzumab. *Furthermore, this benefit was seen both in patients treated as first-line therapy for MBC who had progressed early as well as those who received therapy in second line and later* (Section 1.2.1.1.1; Blackwell et al. 2012; Verma et al. 2012).

The Phase III TH3RESA study also showed improved efficacy in PFS and a trend for OS benefit at the first interim analysis, with a favorable safety profile for single-agent trastuzumab emtansine compared with TPC in patients who received at least two prior regimens of HER2-directed therapies, including trastuzumab and lapatinib, in the metastatic or unresectable locally advanced/recurrent setting (Section 1.2.1.1.1; Krop et al. 2014).

A randomized Phase II study, TDM4450g/*BO21976* (Section 1.2.1.1.1), demonstrated improvements in PFS, safety, and QoL with trastuzumab emtansine compared with trastuzumab combined with docetaxel in the first-line recurrent/metastatic setting (Hurvitz et al. 2013).

The Phase III MARIANNE study demonstrated that trastuzumab emtansine as single agent or in combination with pertuzumab were non-inferior to taxane + trastuzumab with respect to PFS as assessed by independent review, with numerical improvements in tolerability and QoL; however, neither of the trastuzumab emtansine-containing arms showed superiority over taxane plus trastuzumab (Section 1.2.1.1.2; Ellis et al. 2015).

These results*, taken in context with the totality of data from all the MBC studies described above,* demonstrated the therapeutic potential of trastuzumab emtansine, as an ADC, to improve *or at least provide similar* benefit and decrease safety risk

compared with trastuzumab *or lapatinib* plus a concurrent systemic *chemotherapy/*taxane *in the MBC setting*.

In Study TDM4874g/*BO22857*, trastuzumab emtansine following anthracycline-based chemotherapy showed acceptable safety as neoadjuvant and/or adjuvant treatment in HER2-positive early-stage breast cancer. Furthermore, clinical activity in the neoadjuvant setting *(pCR [ypT0/is, ypN0] rate of 56%)* was also demonstrated (Section 1.2.1.2).

In the WSG-ADAPT Study MO23078 (Section 1.2.1.2), a planned interim analysis demonstrated clinically meaningful pCR (ypT0/is, ypN0) rates (>40%) in HER2+/HR+ EBC patients treated with 4 cycles of neoadjuvant trastuzumab emtansine alone or with endocrine therapy, versus a pCR rate of 6.7% treated with trastuzumab +endocrine therapy. These interim pCR results observed in the WGS-ADAPT trial are among the highest reported for ER+, HER2+ EBC and are an improvement over the previously reported 22% total pCR rate observed with 4 cycles of docetaxel, trastuzumab, and pertuzumab in subset of patients with ER+ breast cancer treated in the WO20697 (NEOSPHERE) study (Gianni et al. 2012). With the acknowledged caveats regarding cross trial comparisons, these promising pCR data from the TDM4874g/BO22857 and WSG-ADAPT studies indicate that trastuzumab emtansine is an active agent in HER2-positive EBC, regardless of hormonal receptor status, and further supported developing trastuzumab emtansine +pertuzumab as a treatment option for the EBC population.

Synergy has been demonstrated in the nonclinical setting between trastuzumab emtansine and pertuzumab. Studies with three HER2-positive mouse xenograft models in vivo consistently showed enhanced anti-tumor activity when trastuzumab emtansine was administered in combination with pertuzumab compared with trastuzumab emtansine administered as a single agent. Furthermore, the combination of trastuzumab emtansine and pertuzumab has shown clinical activity and acceptable tolerability in patients with recurrent LABC/MBC in the Phase Ib/II Studies TDM4373g/BO22495 and TDM4688g (see details in Section 1.2.1.1.2 and Section 1.2.3).

In MARIANNE, no clinically or statistically significant synergy between trastuzumab emtansine and pertuzumab was observed in the ITT population. Uncertainties exist regarding the translation of results of MBC trials where equivalent or inferior outcomes are observed into results of adjuvant studies due to differences in tumor biology (e.g., less intratumor heterogeneity in EBC due to temporal variaions in cancer evolution, bulky disease in MBC vs. microscopic disease in the adjuvant setting, and the hypothesized potential pre-existing suppression of anti-cancer immunoresponse in the metastatic tumor microenvironment), study endpoints (imaging based PFS vs. IDFS), as well as the mechanism of action of trastuzumab emtansine and pertuzumab (e.g., potential MOA as immunotherapy) (Liakou et al. 2007; Stagg et al. 2011; Loi et al 2013; Apolo et al. 2014; Bianchini et al. 2014; Perez et al. 2015). As an

example, the Phase III study comparing docetaxel, doxorubicin, and cyclophosphamide (TAC) to 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) as the first-line chemotherapy for MBC patients demonstrated similar time to tumor progression (HR =1.0380; p =0.51) (Mackey et al. 2002). However, it was reported in the BCIRG001 study that adjuvant TAC showed improved DFS rates compared to FAC (HR =0.72, p =0.0020) (Mackey et al. 2013). Therefore, the lack of clinically meaningful synergy between trastuzumab emtansine and pertuzumab in the MBC setting may not be of full predictive value on whether there would be a potential synergy between trastuzumab emtansine and pertuzumab in the adjuvant setting.

*In the adjuvant setting, it may be of particular clinical importance to e*valuat*e* trastuzumab emtansine without concurrent taxane*, which may* utilize the full potential of this ADC in efficacy and safety improvement *or demonstrating numerically equivalent efficacy with better tolerability or different safety profile in EBC* and avoid compromised safety and dose intensity observed in Studies TDM4652g and BP22572 (Section 1.2.1). The combination of trastuzumab emtansine and pertuzumab without a taxane will therefore be compared with trastuzumab and pertuzumab plus taxane in this study. The goal is to assess whether trastuzumab emtansine–based adjuvant regimens will improve the benefit-risk outcome of high-risk patients with HER2-positive EBC*. This study question remains clinically and scientifically important since MARIANNE results in the MBC setting may not fully predict the outcome of the combination of trastuzumab emtansine and pertuzumab in the adjuvant setting.*

Further rationales for the study design *and study design changes* can be found in Section 3.3.

1.3.2 Benefit-Risk Assessment

Trastuzumab emtansine has shown a favorable benefit-risk profile in patients whose disease has progressed after prior HER2-directed therapies for MBC (*Krop et al. 2014),* Blackwell et al. 2012, Verma et al. 2012). Trastuzumab emtansine also appears to have a*n acceptable or* favorable benefit-risk profile in patients who have not received prior chemotherapy for metastatic disease, including patients who have previously received trastuzumab in the adjuvant setting (Hurvitz et al. 2013*; Ellis et al. 2015*). Trastuzumab emtansine monotherapy has demonstrated a favorable or tolerable toxicity profile across studies conducted to date in patients with breast cancer, including a Phase II cardiac safety study of trastuzumab emtansine in patients with EBC (Study TDM4874g/BO22857, see Section 1.2.1.2) *and the WSG-ADAPT Study, see Section 1.2.1.2). Furthermore, Studies TDM4874g and WSG-ADAPT indicate that trastuzumab emtansine is an active agent in HER2-positive EBC, regardless of hormonal receptor status.*

In the curative treatment setting, certain acute adverse events and/or potential chronic accumulative organ effects (e.g., cardiac, hepatic, and pulmonary toxicities) may constitute a specific concern for trastuzumab emtansine. With all available safety data, there does not appear to be an increased risk for cardiac adverse events with

trastuzumab emtansine compared with other HER2-directed therapies. Increases in transaminases are observed with the administration of trastuzumab emtansine, but the potential for severe acute drug-induced liver injury (DILI) is not clear due to confounding factors in patients who experienced DILI (e.g., the use of concomitant medication that is known to induce DILI). Cases of NRH of the liver have been identified from liver biopsies in patients treated with trastuzumab emtansine presenting with signs and symptoms of portal hypertension. NRH is a rare liver condition characterized by widespread benign transformation of hepatic parenchyma into small regenerative nodules. NRH may lead to the development of non-cirrhotic portal hypertension and potentially fatal hepatic failure. Severe pulmonary events, including cases of interstitial lung disease (ILD) such as pneumonitis, some leading to acute respiratory distress syndrome or a fatal outcome, have been reported in clinical trials with trastuzumab emtansine. Patients with dyspnea at rest due to complications of advanced malignancy and comorbidities may be at an increased risk of pulmonary events. In patients with EBC in Study TDM4874g/BO22857, 148 patients had received trastuzumab emtansine and 112 patients (76%) had received at least 13 cycles of trastuzumab emtansine therapy. No protocol- prespecified cardiac events or portal hypertension/NRH have been reported. Radiation pneumonitis occurred in 3 patients (with 1 patient having a Grade 3 event).

Although safety data to date involving trastuzumab emtansine in previously untreated patients in both the adjuvant (Dang et al. 2012) and the metastatic setting (Hurvitz et al. 2013; *Ellis et al. 2015*) appear acceptable, the long-term safety of trastuzumab emtansine in the EBC setting is not fully known. A safety plan for this study, including appropriate eligibility criteria, dose modification guidelines, interim safety analyses for overall deaths and hepatic events defined as confirmed Hy's law cases, and regular monitoring of accumulating patient safety data by an iDMC, has been put into place to minimize any potential risk in the trial patient population. Furthermore, iDMC recommendations and available safety *and efficacy* data from Study MARIANNE (TDM4788g/BO22589; see Section 1.2.1.1.2) *have been provided to the iDMC; and iDMC recommendations and available safety and efficacy data from* Study BO25126 (APHINITY; see Section 1.2.2.2) will be *provided as applicable* to the iDMC for consideration during the conduct of Study BO28407.

The combination of trastuzumab emtansine and pertuzumab following systemic anthracyclines has the potential to further improve the efficacy outcome in high-risk patients with HER2-positive EBC. *The totality of data regarding trastuzumab emtansine and pertuzumab (see Sections 1.2.1, 1.2.2, and 1.3.1), support that the experimental arm (trastuzumab emtansine and pertuzumab following anthracyclines) in this study is highly likely to demonstrate a risk/benefit profile at least equivalent to the current anthracycline-trastuzumab based adjuvant SoC for patients with HER2-positive EBC. Specifically, the efficacy in MARIANNE is at least equivalent to taxane and trastuzumabin the MBC setting with AE profile that may be more tolerable*

than taxane and trastuzumab which is the current EBC adjuvant SoC. In addition the interim data from WGS-ADAPT demonstrated clinically meaningful pCR rates (> 40%) with single agent trastuzumab emtansine, which is better than or comparable to pCR rates achieved with trastuzumab containing regimens with concurrent systemic chemotherapy in the EBC setting. (Harback et al, 2015).

Toxicities observed in studies with combination of trastuzumab emtansine and pertuzumab appear to be manageable, on the basis of final Phase II study results (TDM4373g/BO22495 and TDM4688g) and Phase III MARIANNE Study TDM4788g/BO22589. On the basis of available data, the safety of trastuzumab emtansine when combined with pertuzumab appears consistent with the known toxicity profiles of each drug as a single agent (see Section 1.2.3). *MARIANNE data suggested that the combination of trastuzumab emtansine and pertuzumab may be more tolerable than trastuzumab +taxane, which may be of particular importance to the EBC population(see Sections 1.2.1, 1.2.2, and 1.3.1).*

*Overall, c*onsidering the known *tolerable* safety profiles of these *study* drugs, *the totality of efficacy data in the MBC and EBC settings, a potential better efficacy outcome of the combination of trastuzumab emtansine and pertuzumab in the adjuvant setting compared to the MBC setting due to the long treatment duration of additional HER2 targeted DM1 and biology differeneces between EBC and MBC (see Section 1.3.1 for more details), and the known benefit-risk for the current anthracycline-trastuzumab–based adjuvant SOC,* it is anticipated that the combination regimen*s in this study* will have a manageable safety profile and has an acceptable benefit-risk assessment for the conduct of the study. *It is important and justified to evaluate the benefit-risk of trastuzumab emtansine plus pertuzumab following anthracyclines, compared with the anticipated new SOC (taxane +trastuzumab +pertuzumab following anthracyclines), in the adjuvant clinical trial setting.*

2. OBJECTIVES

2.1 EFFICACY OBJECTIVES

The co-primary efficacy objectives for this study are as follows:

- To compare IDFS (1) in the node-positive subpopulation and (2) in the overall protocol-defined population of patients with HER2-positive breast cancer randomized to receive either a taxane and 1 year of trastuzumab plus pertuzumab following anthracycline-based chemotherapy or 1 year of trastuzumab emtansine plus pertuzumab following anthracycline-based chemotherapy

The secondary efficacy objectives for this study are as follows:

- To compare IDFS plus second non-breast primary cancers, DFS, and distant recurrence–free interval (DRFI) (1) in the node-positive subpopulation and (2) in the overall protocol-defined population between the two treatment arms

- To compare OS (1) in the node-positive subpopulation and (2) in the overall protocol-defined population between the two treatment arms

2.2 SAFETY OBJECTIVE

The safety objective for this study is as follows:

- To compare overall safety, cardiac safety, hepatic, and pulmonary safety in the overall protocol-defined population between the two treatment arms

2.3 PATIENT-REPORTED OUTCOME OBJECTIVES

PRO objectives in the overall protocol-defined population for this study are as follows:

- To compare PROs of treatment-related symptoms, patient functioning, and health-related quality of life (HRQoL) to better understand treatment impact and tolerability, as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) and the modified EORTC Breast Cancer module (Quality of Life Questionnaire–Breast Cancer 23 [QLQ-BR23]), between 'Trastuzumab + Pertuzumab + Taxane following Anthracyclines' and 'Trastuzumab Emtansine + Pertuzumab following Anthracyclines' treatment arms.

2.4 EXPLORATORY OBJECTIVES

The exploratory biomarker objectives for this study are as follows:

- To evaluate the impact of HER2 mRNA level on treatment benefit using the efficacy endpoints
- To evaluate the impact of the PIK3CA mutation status on prognosis and treatment benefit using the efficacy endpoints
- To assess correlations between candidate biomarkers or biomarker panels and efficacy and/or safety in the overall protocol-defined population
- To identify whether changes in expression levels of biomarker or biomarker panels during treatment correlate with treatment efficacy in the overall protocol-defined population

Efficacy endpoints considered for these objectives will include IDFS and OS, as appropriate.

The exploratory anti-therapeutic antibodies (ATAs) objective in the trastuzumab emtansine–treated patient population for this study is as follows:

- To assess the incidence of ATAs to trastuzumab emtansine and the effect of ATAs on safety and efficacy

The health economic exploratory objective is as follows:

- To assess health status as measured using the EuroQol 5-Dimension Questionnaire (EQ-5D) questionnaire for health economic modeling

3. STUDY DESIGN

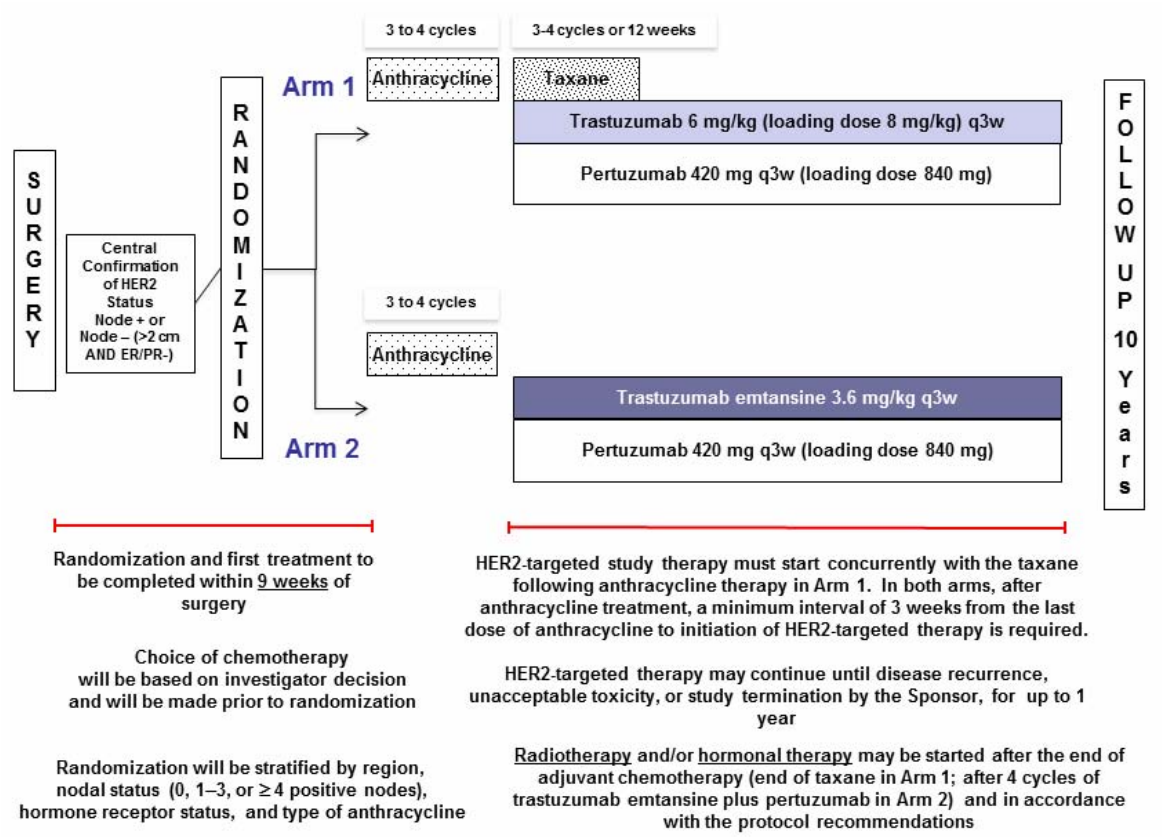
3.1 DESCRIPTION OF STUDY

This is a prospective, two-arm, Phase III, randomized, multicenter, multinational, open-label study in patients with newly diagnosed HER2-positive primary invasive breast cancer who have had curative-intent surgery of their primary tumor and are candidates for adjuvant systemic chemotherapy following surgery. HER2-positive status of the primary tumor will be confirmed by the central pathology laboratory prior to enrollment of the patient in the study. Approximately *1850* patients *are anticipated to* be randomized to one of the two treatment arms listed below in a 1:1 ratio (see Section 4.2 for stratification factors).

- Arm 1: Anthracycline chemotherapy of choice (see Table 6) followed by trastuzumab at 6 mg/kg q3w (8-mg/kg loading dose) in combination with pertuzumab 420 mg q3w (840-mg loading dose) and paclitaxel (80 mg/m^2) qw or docetaxel q3w (see Table 5 for dose and duration). After the taxane-concurrent phase, HER2-targeted therapy (i.e., trastuzumab at 6 mg/kg q3w in combination with pertuzumab 420 mg q3w) will continue for up to 1 year.
- Arm 2: Anthracycline chemotherapy of choice (see Table 6) followed by trastuzumab emtansine 3.6 mg/kg q3w in combination with pertuzumab 420 mg q3w (840-mg loading dose). HER2-targeted therapy (i.e., trastuzumab emtansine at 3.6 mg/kg q3w in combination with pertuzumab 420 mg q3w) will continue for up to 1 year.

The study schema is illustrated in Figure 1. The investigator should select one of the protocol-approved adjuvant anthracycline-based chemotherapy regimens (FEC; epirubicin, cyclophosphamide [EC]; doxorubicin, cyclophosphamide [AC]; or dose-dense AC/EC) followed by either paclitaxel or docetaxel (choice of taxane applies only to Arm 1; Arm 2 is taxane free) as described in Table 6 for each patient prior to randomization. Choice of adjuvant chemotherapy must be recorded by the investigator on the electronic Case Report Form (eCRF), and this choice should be maintained throughout adjuvant chemotherapy whenever possible.

Figure 1 Study Schema



ER = estrogen receptor; HER2 = human epidermal growth factor–2; PR = progesterone receptor; q3w = every 3 weeks.

Table 6 Protocol-Approved Chemotherapy Regimens (Investigator's Choice)—Taxane is for Arm 1 Only

Regimen	Dose	Frequency
Anthracycline Therapy: FEC→T		
3 cycles or 4 cycles FEC →3 cycles or 4 cycles docetaxel[a]	F: 500–600 mg/m^2 E: 90–100 mg/m^2 C: 500–600 mg/m^2	q3w
	Followed by: Docetaxel[a]: 100 mg/m^2 for 3 cycles OR 75 mg/m^2 for 4 cycles[a] OR Docetaxel: 75 mg/m^2 in Cycle 1, escalating to 100 mg/m^2 in subsequent cycles, for a total of 3 cycles	q3w
3 cycles or 4 cycles FEC→12 weeks of paclitaxel	F: 500–600 mg/m^2 E: 90–100 mg/m^2 C: 500–600 mg/m^2	q3w
	Followed by paclitaxel[a]: 80 mg/m^2	qw
Anthracycline Therapy: AC (or EC) → T		
4 cycles of AC[b] (or EC[b])→ 3 cycles or 4 cycles of docetaxel	A: 60 mg/m^2 or E: 90–100 mg/m^2 C: 500–600 mg/m^2	q3w
	Followed by: Docetaxel[a]: 100 mg /m^2 for 3 cycles OR 75 mg/m^2 for 4 cycles[a] OR Docetaxel: 75 mg/m^2 in Cycle 1, escalating to 100 mg/m^2 in subsequent cycles, for a minimum of 3 total docetaxel cycles	q3w
4 cycles of AC[b] (or EC[b])→12 weeks of paclitaxel[a]	A: 60 mg/m^2 or E: 90–100 mg/m^2 C: 500–600 mg/m^2	q3w
	Followed by paclitaxel[a] 80 mg/m^2	qw

A = doxorubicin; C = cyclophosphamide; E = epirubicin; ESMO = European Society for Medical Oncology; F = 5-fluorouracil; G-CSF = granulocyte colony-stimulating factor; NCCN = National Comprehensive Cancer Network; qw = weekly; q3w = every 3 weeks; T = taxane.

[a] Choice of taxane applies only to the control arm (Arm 1). If docetaxel 75 mg/m^2 is used and not escalated to 100 mg/m^2, then four cycles should be given. Prophylactic use of G-CSF should be in accordance with NCCN, ESMO, or local guidelines.

[b] AC or EC can be given every 2 weeks (dose dense) with G-CSF support for a total of four cycles.

In Arm 1, HER2-targeted study therapy with trastuzumab plus pertuzumab must start concurrently with the taxane component of chemotherapy following anthracycline therapy. In both arms, after anthracycline treatment, a minimum interval of 3 weeks from the last dose of anthracycline to initiation of HER2-targeted therapy is required. Prior to commencing the HER2-targeted therapy, patients must have a left ventricular ejection fraction (LVEF) ≥ 50% and must not have experienced any clinical symptoms suggesting

heart failure or asymptomatic LVEF declines of 15 percentage points or more from baseline *and below the lower limit of normal*.

Patients will receive up to 1 year of HER2-targeted therapy. Study treatment will be discontinued in the event of invasive disease recurrence, unacceptable toxicity, withdrawal of consent, or study termination by the Sponsor.

Adjuvant radiotherapy is to be given as clinically indicated at the end of chemotherapy (end of taxane in Arm 1; after four cycles of trastuzumab emtansine plus pertuzumab in Arm 2, to be consistent with Arm 1 in terms of timing of initiation) while receiving HER2-targeted therapy (Section 4.5.1.1 and Appendix 4). For patients with ER-positive and/or PR-positive tumors, hormonal agents should be administered at the end of chemotherapy (end of taxane in Arm 1; after four cycles of trastuzumab emtansine plus pertuzumab in Arm 2, to be consistent with Arm 1 in timing of initiation) (Section 4.5.1.2).

Each patient will be followed for disease status and survival according to the Schedule of Assessments for approximately 10 years after the first patient initiation (FPI) (i.e., first patient randomized). Evaluations of efficacy and safety and a detailed Schedule of Assessments are provided in the study assessment section (Section 4.7) and in Appendix 1.

3.1.1 Data Monitoring Committee

An iDMC will monitor accruing patient safety data at least once every 6 months during the study until the last patient has completed study treatment. In addition, safety data reports related to concurrent radiotherapy and/or hormonal therapy, SAEs, and deaths will be monitored by the iDMC at least once every 3 months during the study. At each iDMC review, relevant safety information from ongoing trastuzumab emtansine and/or pertuzumab studies will also be provided to the iDMC. The iDMC will also assess safety and efficacy as part of the planned interim efficacy and safety analyses as pre-specified in the protocol.

An independent Data Coordination Center (iDCC) will perform unblinded analyses to support the periodic iDMC review of safety data and the interim analysis. Additional details will be provided in an iDMC Charter. The iDMC members will review and sign off the charter before the first data review.

3.1.2 Clinical Events Committee

An independent Clinical Events Committee (CEC) will adjudicate prespecified safety events of interest (cardiac and hepatic dysfunction events) in a blinded fashion. A separate charter will outline committee composition, meeting timelines, and the roles and responsibilities of members. The committee members will review all potential cases of CHF and cardiac death as well as all potential cases of hepatic dysfunction and Hy's law. Ad hoc members may be added to the CEC to review/adjudicate other safety

events if a new safety signal emerges. Adjudicated cases by the CEC will be forwarded to the iDMC on a regular basis as part of ongoing safety reviews of the study.

3.2 END OF STUDY

To enable long-term follow-up for survival and safety information, the study is planned to end approximately 10 years after the first patient is randomized.

The Sponsor has the right to terminate this study*, including long-term follow-up,* at any time (e.g., if emerging safety signals indicate a potential health hazard to patients).

3.3 RATIONALE FOR STUDY DESIGN

It is anticipated that there will be a future change in the SoC for HER2-positive EBC to include pertuzumab, on the basis of the results of Study BO25126 (APHINITY). Trastuzumab emtansine has the potential to increase cure rates in high-risk patients with EBC and also improve safety during the traditional taxane-concurrent phase when combined with pertuzumab following anthracycline-based chemotherapy. The design of this study will allow the evaluation of a taxane-sparing approach with trastuzumab emtansine as part of an anthracyline-based pertuzumab-containing adjuvant regimen. The objective is to determine whether trastuzumab emtansine is a more effective treatment than trastuzumab plus taxane, as part of the adjuvant regimen described above, while sparing the taxane-associated toxicities.

3.3.1 Rationale for Test Product Dosage

In a Phase I study (TDM3569g), the MTD of trastuzumab emtansine administered by IV infusion q3w was 3.6 mg/kg. Clinical efficacy has been demonstrated at a dose of 3.6 mg/kg q3w in studies of single-agent trastuzumab emtansine, with a favorable safety profile in both pretreated and previously untreated HER2-positive MBC. In the adjuvant or neoadjuvant setting following anthracycline therapy, trastuzumab emtansine 3.6 mg/kg q3w has been tolerated as a single agent (see details in Section 1.2.1.1.1).

The dose of 3.6 mg/kg of trastuzumab emtansine has been combined with pertuzumab (loading dose of 840 mg with a subsequent dose of 420 mg) q3w in the Phase I/II Studies TDM4373g/BO22495 and TDM4688g and in the Phase III Study TDM4788g/BO22589 (MARIANNE). Toxicities in these studies appear to be manageable*/tolerable*, on the basis of final study results (Studies TDM4373g/BO22495*,* TDM4688g*, and* TDM4788g/BO22589*)* (see details in Section 1.2.1.1).

Please refer to the Trastuzumab Emtansine and Pertuzumab Investigator's Brochures for further information.

3.3.2 Rationale for Patient Population

Despite improved DFS and OS with trastuzumab-containing adjuvant systemic therapy, there remains a substantial risk for recurrence and breast cancer–related death in HER2-positive EBC, especially in the higher-risk subpopulation. Factors such as lymph

node status, hormone receptor status, and tumor size can be used to define a subgroup of patients at substantial risk of recurrence who may require more effective therapies. This study is designed to enroll patients with a sufficiently high risk of disease recurrence in order to achieve a clinically meaningful improvement in absolute treatment effect with a positive benefit-risk profile. This study will enroll a population of patients with newly diagnosed HER2-positive EBC who are node-positive or node-negative AND ER/PR-negative AND have a tumor size >2 cm.

This study population is a higher-risk subset of the patient population selected in ongoing Study BO25126 (APHINITY; see Section 1.2.2.2) as well as in adjuvant trastuzumab trials (e.g., BCIRG 006). Study BO25126 (APHINITY) includes a broader group of node-negative patients with lower overall risk (i.e., tumor size >1 cm regardless of hormonal receptor status or tumor size of 0.5 cm to 1.0 cm with at least one high-risk feature [histologic/nuclear Grade 3, negative for ER and PR, or age <35 years]), compared with the node-negative subpopulation selected for this study (ER/PR-negative AND tumor size >2 cm). The node-negative subpopulation proposed for this study would have an estimated 3-year IDFS rate of 91.8% with AC-TH treatment on the basis of the results of the BCIRG 006 study, which is similar to that for node-positive patients with 1–3 nodes (91.1%, unpublished data). Therefore, the risk of recurrence at 3 years and the benefit-risk considerations for the node-negative subset are expected to be similar to those for the node-positive subset (with one to three nodes).

Assuming that Study BO25126 (APHINITY) is positive and that the target HR of that study (0.75) is observed, the proposed overall population (node positive plus protocol defined node negative) in this study is estimated to have a 3-year IDFS rate of 89.5% in the control arm with the added effect from pertuzumab. Therefore, even with presumed additional treatment effect of pertuzumab, the recurrence rate in the overall population proposed for Study BO28407 is estimated to remain approximately 10% at 3 years, with a continued risk of recurrence and breast cancer–related death with longer follow-up (e.g., estimated 5-year IDFS rate of 82.2%).

3.3.2.1 Rationale for Capping Subgroup Enrollment

Capping *was planned to* be implemented to ensure that an appropriately high-risk patient population is enrolled. The proportions of subgroups enrolled in the BCIRG 006 study that form the basis for assumptions on IDFS rates in the proposed study will be utilized to guide capping. Hence, the proportion of node-positive patients with one to three nodes will be capped at 50% of the study population, and the proportion of node-negative patients will be capped at 10% of the study population. Given the small size of the node-negative subset in the BCIRG 006 study, there may be considerable variability in the 3- and 5-year IDFS rate estimates for this subgroup, and the 3–year IDFS rate may not be an ideal late recurrence risk indicator for lower-risk population(s). Therefore, these two subsets *were planned to* be capped independently.

The capping as of Protocol Version 2 will not be implemented since the study enrollment is stopped earlier than planned. Therefore, the planned proportion of node-positive patients with one to three nodes and/or node-negative patients may not be achieved as described above.

3.3.2.2 Rationale for Powering for Node-Positive Subgroup

Given the relatively broad range of recurrence rates in the target population among subpopulations with four or more nodes, one to three nodes, and node-negative disease, descriptive analyses are planned to assess overall benefit versus risk within each of the subgroups. Furthermore, the node-positive subgroup is sufficiently powered to support a co-primary efficacy objective to assess IDFS in both the overall protocol-defined population and the node-positive subpopulation.

3.3.2.3 *Rationale for Sample Size Reduction*

The MARIANNE study results (see Section 1.2.1.1.1) have further informed the assumptions that drove the original study design (i.e., trastuzumab emtansine improves both PFS and safety and a synergy between trastuzumab emtansine and pertuzumab will be demonstrated clinically in the first-line MBC setting). Therefore, the likelihood of this study meeting its primary efficacy endpoint for superiority has decreased. A sample size reduction is warranted to mitigate the risk of this study not meeting its primary efficacy endpoint. However, due to the uncertainty of translating MBC results to the adjuvant setting (see details in Section 1.3.1), the study question of whether the regimen of trastuzumab emtansine in combination with pertuzumab following anthracyclines may be superior to the regimen of trastuzumab in combination with a taxane and pertuzumab following anthracyclines in the adjuvant setting remains unanswered and is of clinical/scientific importance. With a sample size reduction from 2500 to approximately 1850 patients, the study objectives can still be adequately addressed with the original statistical power and validity with the prolonged analyses timing (see Table 19 in Section 6.1).

3.3.3 Rationale for Control Group

The ongoing Phase III Study BO25126 (APHINITY; see Section 1.2.2.2) has been designed to demonstrate the superiority of adjuvant pertuzumab + trastuzumab + standard chemotherapy (anthracycline and non–anthracycline-based regimens) compared with standard trastuzumab-containing regimens in HER2-positive EBC. Assuming Study BO25126 (APHINITY) is positive, it is expected that adjuvant pertuzumab + trastuzumab + standard chemotherapy will become the new SoC for the adjuvant treatment of HER2-positive EBC before the results from this study become available. On the basis of this rationale and the observed safety and efficacy profiles in neoadjuvant Studies WO20697 (NEOSPHERE) and BO22280 (TRYPHAENA; Section 1.2.2.2), anthracycline-based chemotherapy followed by trastuzumab + pertuzumab + taxane has been selected as the comparator.

3.3.4 Rationale for Adjuvant Regimens and Duration of Therapy

Several studies demonstrated that adding complementary and dual HER2-targeted agents, such as pertuzumab and trastuzumab, further improves outcomes in patients with HER2-positive MBC or EBC with an acceptable safety profile (see Section 1.2). The efficacy and safety profiles of pertuzumab in combination with trastuzumab and chemotherapy shown in the neoadjuvant Study WO20697 (NEOSPHERE) and Study BO22280 (TRYPHAENA) indicate that treatment with pertuzumab + trastuzumab + standard chemotherapy (including anthracycline- and taxane-based regimens) is the likely direction of further significant efficacy improvements in EBC.

Proof of concept has been established in the randomized *MBC* Studies TDM4450g*/BO21976*, TDM4370g*/BO21977* (EMILIA)*, and TDM4997g/BO25734 (TH3RESA)* that trastuzumab emtansine as a single agent can improve efficacy and safety compared with a combination of a HER2-directed agent and traditional chemotherapy. *The TDM4788g/BO22589 (MARIANNE) study supports trastuzumab emtansine+pertuzumab as a non-inferior regimen to trastuzumab +taxane, with a more tolerable safety profile in the first-line MBC setting.* In addition, the pCR rates observed in the single-arm Study TDM4874g*/BO22857 and WGS-ADAPT Study MO23078* suggest robust clinical activity of trastuzumab emtansine in EBC. Furthermore, a meta-analysis (EBCTCG 2013) of long-term outcome among 100,000 patients with EBC in 123 randomized trials has shown that in trials adding four cycles of taxane to a fixed anthracycline-based control regimen, extending treatment duration, mortality due to breast cancer was reduced (RR = 0.86, SE = 0.04, two-sided significance p = 0.0005). However, in trials with four such extra cycles of taxane, counterbalanced in controls by extra cycles of other cytotoxic drugs, roughly doubling non-taxane dosage, there was no significant difference (RR = 0.94, SE = 0.06, two-sided significance p = 0.33). On the basis of this analysis, *the totality of data for trastuzumab emtansine and/or pertuzumab in the MBC and EBC setting, and the uncertainties regarding the translation of results of trastuzumab emtansine plus pertuzumab in the MARIANNE study into results of this combination in this adjuvant study,* it is anticipated that 1 year of *trastuzumab emtansine +pertuzumab, with* the HER2-targeted chemotherapeutic agent DM1 (i.e., with higher dose intensity and longer duration than four cycles of concurrent taxane) will provide risk reduction that is the same as or better than that provided by the four cycles of concurrent taxane *and 14 cycles of trastuzumab +pertuzumab* in the control arm. Therefore, this study will evaluate whether trastuzumab emtansine without concurrent taxane as a replacement for trastuzumab plus taxane, in combination with pertuzumab following anthracyclines, can provide an improved benefit-risk ratio in high-risk patients with HER2-positive EBC. Systemic anthracyclines will mitigate potential efficacy risk due to *intra*tumor heterogeneity. The cardiac safety of both pertuzumab and trastuzumab emtansine following anthracycline-based regimens appears acceptable to date on the basis of data

from Study BO22280 (TRYPHAENA; see Section 1.2.2.2) and
Study TDM4874g/BO22857 *EBC safety study;* (see Section 1.2.1.1.1).

On the basis of the rationale provided above, anthracycline-based chemotherapy (Section 3.3.4.1) followed by trastuzumab emtansine + pertuzumab has been selected as the trastuzumab emtansine–based adjuvant regimen in this study.

The 1-year duration of HER2-directed therapy is based on current standard guidelines as well as data from both the PHARE and HERA trials, in which neither shorter nor longer durations of HER2-directed therapy were demonstrated to have an advantage (Goldhirsch et al. 2013, Pivot et al. 2013).

3.3.4.1 Rationale for Selection of Anthracycline Regimens

Doxorubicin at 60 mg/m^2 and epirubicin at approximately 100 mg/m^2 are considered to be equally efficacious with overlapping but different safety profiles (Kaklamani and Gradishar 2003; Glück 2005; Khasraw and Bell 2012; *Khasraw et al. 2012*). Regimens such as FEC, EC, AC, or dose-dense AC/EC with G-CSF support are included to allow for differences in local practice. Epirubicin at doses between 90 and 100 mg/m^2 is also included to allow for differences in local SoC. These anthracycline-based regimens are included in practice guidelines such as those of the National Comprehensive Cancer Network (NCCN) and the St. Gallen Early Breast Cancer Guidelines.

3.3.4.2 Rationale for Selection of Taxane Dose and Schedule

The use of paclitaxel in combination with trastuzumab is supported by a number of studies in the adjuvant and neoadjuvant settings (Buzdar et al. 2005, Romond et al. 2005, Paluch-Shimon et al. 2008). Both Studies NCCTG N9831 and NSABP B31 utilized q3w or qw paclitaxel in combination with trastuzumab. Following anthracycline-based chemotherapy, paclitaxel 80 mg/m^2 qw is better tolerated and more active than paclitaxel 175 mg/m^2 q3w (Sparano et al. 2008). Weekly paclitaxel (12 doses) following anthracycline therapy is a preferred regimen for the adjuvant treatment of EBC, according to the NCCN Guidelines (NCCN 2012).

It is recognized that docetaxel at a dose of 100 mg/m^2 in combination with trastuzumab has been associated with a positive benefit-risk ratio in patients with HER2-overexpressing MBC when compared with docetaxel alone (100 mg/m^2 q3w; Marty et al. 2005). The clinical utility of docetaxel 100 mg/m^2 in combination with trastuzumab, used in sequence with an anthracycline and cyclophosphamide, has been previously demonstrated in the BCIRG 006 EBC study (Slamon et al. 2011). The risks and benefits associated with a variety of single-agent docetaxel doses (60–100 mg/m^2 q3w) have been established in randomized studies in breast cancer (Harvey et al. 2006, Bono et al. 2009). To allow for differences in local SoC, alternative docetaxel dose and duration are permitted in this study. Four cycles of docetaxel at 75 mg/m^2 following anthracycline-based chemotherapy is an acceptable adjuvant treatment option that

confers superior efficacy over a non-taxane regimen (Nitz et al. 2008) and is recognized by the NCCN guidelines (NCCN 2012). Alternatively, the dose of docetaxel may be started at 75 mg/m^2 in the first cycle and escalated to 100 mg/m^2 in subsequent cycles according to individual tolerability; a minimum of three cycles will be given for this dosing regimen.

3.3.5 Rationale for Patient-Reported Outcome Assessments

EBC is often asymptomatic, especially after tumor removal; therefore, it is important to assess treatment impact and tolerability in order to inform the benefit-risk ratio for a patient on adjuvant therapy.

PRO measures will contextualize a patient's experience on trial, elucidating symptom and treatment burden between 'Trastuzumab + Pertuzumab + Taxane following Anthracyclines' and 'Trastuzumab Emtansine + Pertuzumab following Anthracyclines' treatment arms. Because treatment-related side effects (e.g., peripheral neuropathy, joint/muscle pain, and skin problems) have the potential to affect patient functioning and HRQoL, it is crucial to characterize not only the incidence of these side effects but also the associated trends and burden from the patient's perspective, which would contribute to a more comprehensive understanding of treatment impact and tolerability. The EORTC QLQ-C30 and QLQ-BR23 demonstrate strong psychometric properties, of both reliability and validity, and meet the requirements for this study. The QLQ-BR23 will be modified to include validated items on peripheral neuropathy (1 item), joint/muscle pain (1 item), and skin problems (2 items) in order to characterize these symptoms of special interest (Appendix 8).

3.3.6 Rationale for Biomarker Assessments

This study includes mandatory collection of tumor tissue and plasma samples. Apart from HER2 expression, there are no known additional predictors of response to trastuzumab, pertuzumab, or trastuzumab emtansine, nor are there accurate predictors of resistance to these therapies. Tumor tissue will be collected to centrally assess HER2 status and hormonal receptor status and to assess potential predictive and prognostic candidate markers. Additional biomarker assessments potentially related to the mechanism of action of trastuzumab emtansine, pertuzumab, or trastuzumab; HER signaling; or breast cancer biology may be performed. For example, expression of other receptors of the HER family (e.g., HER1/EGFR or HER3), which may affect HER2, could be explored. HER2 signaling is known to be modulated by expression levels of other HER family members and their ligands, the expression of which may correlate with response or resistance to HER2-targeted therapies (Wiseman et al. 2005, Robinson et al. 2006). Additionally, alterations in the HER2 intracellular signaling pathway (e.g., activating mutations in PI3K) and its regulation (e.g., loss of negative regulation by phosphatase and tensin homolog [PTEN]) may also affect responsiveness of tumors to HER2-directed therapies (Berns et al. 2007, Mellinghoff et al. 2007).

Level of HER2 mRNA expression in tumor tissue has been explored in prior clinical trials with trastuzumab emtansine, pertuzumab, and trastuzumab. The WO20698 (CLEOPATRA) MBC trial showed that increased levels of HER2 mRNA (above median cutoff) were associated with longer PFS outcome in both treatment arms (Baselga et al. 2012b). The TDM4370g (EMILIA) MBC trial, similar to previous Phase II and single-agent trastuzumab emtansine MBC studies, showed that the degree of HER2 mRNA expression correlated with ORR and/or PFS outcome (LoRusso 2011, Perez 2012, Baselga et al. 2013). In the TDM4370g (EMILIA) trial, this correlation was present in both treatment arms for PFS but apparent only in the trastuzumab emtansine–treated patients when correlated to OS. HER2 mRNA expression level may be predictive for trastuzumab emtansine benefit in the adjuvant setting and will be explored in this study.

Additionally, activating PIK3CA mutations have been evaluated as a resistance marker for HER2-targeted therapies in prior trials. In metastatic HER2-positive breast cancer (the CLEOPATRA study), worse outcome was observed in patients with PIK3CA mutations than in those without (Baselga et al. 2012b). Lower pCR rates were observed in the neoadjuvant setting in HER2-positive breast cancer with PIK3CA mutations (Schneeweis et al. 2012, Baselga et al. 2012a). The role of PIK3CA mutations in the adjuvant setting in HER2-positive breast cancer is, however, unknown. Data from the BCIRG 006 trial suggest that PIK3CA mutations are associated with worse DFS when treatment arms were pooled (Gardner et al. 2009). This study will explore the prognostic value of PIK3CA mutations and the potential predictive value for predicting efficacy with trastuzumab emtansine.

Identification of possible markers of benefit or resistance to therapy could have significant future clinical impact upon patient treatment decisions. Additional candidate markers of response to treatments that emerge from other clinical or nonclinical studies may also be assessed in this study.

The study also requires mandatory plasma/serum samples for biomarker research, which may include, among other analyses, the assessment of circulating tumor DNA. There is increasing evidence that circulating DNA can be obtained from the blood specimens of patients with cancer, which represents the DNA and mutational status of tumor cells (Diehl et al. 2008, Maheswaran et al. 2008, Punnoose et al. 2012, Rosell et al. 2012, Dawson et al. 2013, Murtaza et al. 2013). Another example of markers that could be assessed in serum or plasma are circulating ligands of HER family members. The serial sampling gives the opportunity to evaluate changes in circulating biomarker levels over time that may allow further understanding of potential resistance mechanisms or of (early) indicators of recurrence.

Additional candidate markers of response to treatments that emerge from other clinical or nonclinical studies may also be assessed in this study and can be assessed with different types of technologies.

In addition, a mandatory whole-blood sample for clinical genotyping will be collected. Both safety and efficacy questions will be explored with the clinical genotyping analyses. The following are examples describing potential questions that could be explored by clinical genotyping.

For example, reversible thrombocytopenia has been observed in completed and ongoing studies with trastuzumab emtansine in a subset of patients. It is hypothesized that this effect may be related to an interaction between trastuzumab emtansine and proteins expressed in megakaryocytes and/or platelets: Fcγ receptor (FcγRIIa). FcγRIIa is the only FcγR expressed in platelets, and it has been shown to bind to and internalize IgG (Cassel et al. 1993, Anderson et al. 1995, Worth et al. 2006). The H131R polymorphism in FcγRIIa has been associated with differential affinity for binding of IgG Fc and, in some cases, with heparin-induced thrombocytopenia (Bachelot-Loza et al. 1998, Chen et al. 2003).

One possible hypothesis to explain the observation of trastuzumab emtansine–induced thrombocytopenia in some but not all patients is a differential ability of megakaryocytes and/or platelets to bind to and internalize the drug conjugate. In relationship to efficacy, it has been hypothesized that the mechanism of action of antibody therapeutics, such as rituximab and trastuzumab, could include Fc-mediated attraction of immune effector cells known as antibody-dependent cell-mediated cytotoxicity (ADCC). The affinity of IgG to the Fcγ receptors is influenced by the FcγRIIa and FcγRIIIa polymorphisms and may cause a difference in the efficacy of trastuzumab, trastuzumab emtansine, or pertuzumab or the efficacy of the combination of trastuzumab emtansine and pertuzumab, as a result of different FcγR-mediated ADCC (Shields et al. 2001).

P-glycoprotein (P-gp), which is encoded in the *ABCB1* (also known as *MDR1*) gene, is known to act as an energy-dependent drug efflux pump for various chemotherapeutic drugs, such as anthracyclines, vinca alkaloids, and taxanes (Gottesman et al. 2002). Previous studies showed that *ABCB1* 3435CC genotype carriers had significantly higher P-gp expression in the duodenum and in breast cancer tissue (Taheri et al. 2010), which may result in a decreased drug concentration in cells. Additional data support the theory that *ABCB1* polymorphisms may predict PFS after first-line trastuzumab and taxane therapy in patients with HER2-positive MBC (Kim et al. 2012). Polymorphisms in this gene and their correlation to efficacy in this trial may also be explored.

Examples of other safety markers may also include polymorphisms in the human leukocytic antigen or genes involved in trastuzumab emtansine metabolism to evaluate their correlation to hepatotoxicity (Andrade et al. 2009, Xu et al. 2010).

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

3.4.1.1 Primary Efficacy Outcome Measures

The primary efficacy outcome measures for this study are listed below.

- IDFS, defined as the time from randomization until the date of the first occurrence of 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)

  Contralateral or ipsilateral second primary invasive breast cancer

  Distant recurrence (i.e., evidence of breast cancer in any anatomic site [other than the three sites mentioned above]) that has either been histologically confirmed or clinically/radiographically diagnosed as recurrent invasive breast cancer

  Death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause

3.4.1.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- IDFS plus second primary non-breast cancer, excluding 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 any of the IDFS events described above, second primary non-breast cancer event (excluding non-melanoma skin cancers and CIS of any non-breast site), and contralateral or ipsilateral ductal carcinoma in situ (DCIS)
- DRFI, defined as the time between randomization and the first occurrence of distant breast cancer recurrence
- OS, defined as the time from randomization to death due to any cause

3.4.2 Safety Outcome Measures

Clinical and laboratory adverse events will be reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0. LVEF will be assessed using either echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scans.

The safety outcome measures for this study are as follows:

- Incidence, type, and severity of all adverse events based on NCI CTCAE v4.0
- Incidence, type, and severity of SAEs
- Incidence, type and severity of $\geq$ Grade 3 adverse events

- Incidence and type of adverse events leading to dose discontinuation, modification, or delay
- Cause of death
- Abnormal laboratory values
- Decrease in LVEF from baseline over time
- Cardiac safety outcome measures

  Primary cardiac endpoints: cardiac events defined as death from cardiac cause or severe CHF (NYHA Class III or IV) with a decrease in LVEF of $\geq$10 percentage points from baseline to an LVEF of $<$50%

  Secondary cardiac endpoints: other cardiac-related events (e.g., any mild symptomatic CHF [NYHA Class II] associated with a $\geq$10% drop in LVEF to $<$50%; asymptomatic declines in LVEF requiring dose delay or discontinuation)
- Hepatic safety outcome measures

  Death from hepatic cause

  Severe DILI (Hy's law cases)

  NRH
- Pulmonary safety outcome measures

  Death from pulmonary cause

  Pneumonitis and ILD

3.4.3 Patient-Reported Outcome Measures

The PRO measures for this study are as follows:

- HRQoL, including bothersome side effects of therapy (e.g., peripheral neuropathy, joint/muscle pain, or skin problems), and patient functioning as measured using the EORTC QLQ-C30 and the modified breast cancer module QLQ-BR23 (Appendix 8)
- Time from first HER2-targeted treatment, ± a taxane, to *clinically meaningful deterioration in the* global health status/QoL *and functional (physical, role, and cognitive)* subscale*s* of the QLQ-C30. The event of worsening of global health status/QoL for a given patient is defined as a decrease in *baseline* mean score by 10 points or more at two consecutive timepoints. A 10-point or greater change in mean score is defined as being a "moderate" to "very much" *and* perceived *an* important change from the patient's perspective (Osoba et al. 1998). *Deterioration in function will be assessed using the published corresponding MIDs by Cocks et al. (2011).*

3.4.4 Exploratory Biomarker Outcome Measures

The exploratory biomarker outcome measures for this study are the relationship between molecular markers and efficacy and/or safety outcomes. Efficacy outcomes considered for this analysis will include IDFS and OS, as appropriate.

Correlations between biomarker status and efficacy and/or safety will include but not be limited to the following:

- Level of HER2 mRNA expression assessed by quantitative real-time polymerase chain reaction (qRT-PCR) with efficacy outcome
- Status of PIK3CA mutations assessed by PIK3CA allele–specific polymerase chain reaction assay with efficacy outcome
- Level of *HER2* gene amplification assessed by in situ hybridization (ISH) with efficacy outcome
- Level of HER2 protein expression assessed by immunohistochemistry (IHC) with efficacy outcome
- Level of HER3 mRNA expression assessed by qRT-PCR with efficacy outcome
- Changes in expression levels of biomarker or biomarker panels over time with efficacy outcome

3.4.5 Exploratory Anti-Therapeutic Antibody Outcome Measures

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

- Incidence of ATAs to trastuzumab emtansine
- Effect of ATAs on safety and efficacy

3.4.6 Exploratory Health Economic Outcome Measures

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

The EQ-5D is a generic, preference-based health utility measure with questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that are used to build a composite of the patient's health status. A single summary index from the EQ-5D health states will be utilized in this study for economic modeling, and the results will not be reported in the Clinical Study Report (CSR).

4. MATERIALS AND METHODS

4.1 PATIENTS

The target population for this study will be patients with newly diagnosed primary invasive breast cancer that is HER2 positive (as determined by the central pathology laboratory) and who will be treated with adjuvant systemic chemotherapy following definitive surgery. *Approximately 1850* patients *are anticipated to* be enrolled at approximately 350 sites worldwide.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Age ≥ 18 years
- Eastern Cooperative Oncology Group Performance Status ≤ 1
- Non-metastatic histologically confirmed primary invasive breast carcinoma that was operable
- HER2-positive breast cancer prospectively determined on the primary tumor by a central pathology laboratory and defined as follows:

  IHC score (see Appendix 6) of 3+ and/or positive by ISH (see Appendix 7), as defined by ISH ratio of ≥ 2.0 for the number of *HER2* gene copies to the number of chromosome 17 copies. Both IHC and ISH assays will be performed; however, only one positive result is required for eligibility.

  Availability of formalin-fixed paraffin-embedded (FFPE) tissue block or partial block (for minimum dimensions, see laboratory manual) with a representative invasive part of the tumor for central pathology laboratory confirmation of HER2 eligibility, hormonal receptor status, and additional biomarker analysis is required.

- Known hormone receptor status of the primary tumor determined by a central pathology laboratory

  Hormone receptor-positive status can be determined by either known positive ER or known positive PR status. Hormone receptor–negative status must be determined by both known negative ER and known negative PR.

- Adequately excised: Patients must have undergone either breast-conserving surgery or mastectomy/nipple- or skin-sparing mastectomy.

  For patients who undergo breast-conserving surgery, the margins of the resected specimen must be histologically free of invasive tumor and 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.

  For patients who undergo mastectomy/nipple- or skin-sparing mastectomy, margins must be free of gross residual tumor. It is recommended that patients should have a negative microscopic margin in accordance with local pathology protocol. Patients with a microscopic positive deep margin are eligible (see RT requirements in Appendix 4).

- Pathological tumor-node-metastasis staging (Union for International Cancer Control/American Joint Committee on Cancer [UICC/AJCC], 7th edition): Patients must have had sentinel lymph node biopsy (SLNB) and/or axillary lymph node dissection for evaluation of pathologic nodal status (minimum requirements for patients undergoing SLNB are provided in Section 4.4.1). Pathological classification

of regional lymph node micrometastases (tumor deposits > 0.2 mm and ≤ 2 mm) is considered to be pN1, and isolated tumor cells are considered to be pN0.

Eligible patients must have one of the following:

Node-positive disease (pN ≥ 1), any tumor size except T0, and any hormonal receptor status

Enrollment of patients with 1–3 nodes *was planned to* be limited to no more than 50% of the total number of randomized patients. *However, no formal capping of enrollment will be implemented (see Section 3.3.2.1 for details).*

There is no prespecified limit for the enrollment of patients with ≥ 4 nodes.

Node-negative disease (pN0) with pathologic tumor size > 2.0 cm by standard local assessment AND negative for ER and PR as determined by a central pathology laboratory

Enrollment of patients with node-negative disease *was planned to* be limited to no more than 10% of the total number of randomized patients. *However, no formal capping of enrollment will be implemented (see Section 3.3.2.1 for details).*

- Patients with synchronous bilateral invasive disease are eligible only if both lesions are HER2 positive.
- No more than 9 weeks (63 days) may elapse between definitive breast surgery (or the last surgery if additional resection required for breast cancer) and randomization.
- Baseline LVEF ≥ 55% measured by ECHO (preferred) or MUGA scans
- Documentation of hepatitis B virus (HBV) and hepatitis C virus (HCV) serologies is required. This includes hepatitis B surface antigen (HBsAg) and/or total hepatitis B core antibody (HBcAb) in addition to HCV antibody testing. The most recent serologic testing must have occurred within 3 months prior to randomization. If such testing has not been done, it must be performed during screening.

  Patients who have positive HBV or HCV serologies without known active disease must meet the eligibility criteria for ALT, AST, total bilirubin (TBILI), INR, activated partial thromboplastine time (aPTT), and alkaline phosphatase (ALP) on at least two consecutive occasions, separated by at least 1 week, within the 30-day screening period. The second of these evaluations must be performed within 3 days prior to the first administration of study drug. *Note: positive serology markers that indicate immunity will not be considered as clinically meaningful positive serology to trigger these tests.*
- Female patients of childbearing potential must be willing to use one highly effective form of nonhormonal contraception or two effective forms of nonhormonal contraception. For male patients with partners of childbearing potential, one highly effective form of contraception or two effective forms of contraception must be used (see Appendix 10 for descriptions of highly effective and effective contraception). Contraception must continue for the duration of study treatment and for 7 months after the last dose of study treatment.

The above contraception is not a requirement in the case of any of the following:

The patient or partner of the patient is surgically sterilized.

The female patient is >45 years of age and is postmenopausal (has not menstruated for at least 12 consecutive months; for additional details, see Section 4.5.1.2 on definition of postmenopausal status).

The patient truly abstains from sexual activity and when this is the preferred option to avoid conception and contraception and/or usual lifestyle of the patient.

- Male patients whose partners are pregnant must use condoms or truly refrain from sexual activity for the duration of the pregnancy
- Willing and able to comply with the requirements of the protocol
- Signed informed consent

4.1.2 Exclusion Criteria

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

- History of any prior (ipsilateral and/or contralateral) invasive breast carcinoma
- History of non-breast malignancies within the 5 years prior to randomization, except for the following:

  CIS of the cervix

  CIS of the colon

  Melanoma in situ

  Basal cell and squamous cell carcinomas of the skin
- Any clinical T4 tumor as defined by tumor-node-metastasis classification in UICC/AJCC, 7th edition, including inflammatory breast cancer
- For the currently diagnosed breast cancer, any previous systemic anti-cancer treatment (e.g., neoadjuvant or adjuvant), including but not limited to chemotherapy, anti-HER2 therapy (e.g., trastuzumab, trastuzumab emtansine, pertuzumab, lapatinib, neratinib, or other tyrosine kinase inhibitors), hormonal therapy, OR anti-cancer RT (intraoperative radiotherapy as a boost at the time of primary surgery is acceptable)
- Previous therapy with anthracyclines, taxanes, or HER2-targeted therapy for any malignancy
- History of DCIS and/or LCIS that was treated with any form of systemic chemotherapy, hormonal therapy, or RT to the ipsilateral breast where invasive cancer subsequently developed. Patients who had their DCIS/LCIS treated with only surgery and/or contralateral DCIS treated with radiation are allowed to enter the study.
- Patients with contraindication to RT while adjuvant RT is clinically indicated
- Concurrent anti-cancer treatment in another investigational trial

- Cardiopulmonary dysfunction as defined by any of the following prior to randomization:

  History of NCI CTCAE Version 4.0 Grade ≥ 3 symptomatic CHF or 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 atrioventricular [AV]-block [second degree AV-block Type 2 [Mobitz 2] or third degree AV-block])

  Significant symptoms (Grade ≥ 2) relating to left ventricular dysfunction, cardiac arrhythmia, or cardiac ischemia

  Myocardial infarction within 12 months prior to randomization

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

  Evidence of transmural infarction on ECG

  Requirement for oxygen therapy

- Other concurrent serious diseases that may interfere with planned treatment, including severe pulmonary conditions/illness, uncontrolled infections, uncontrolled diabetes, or known infection with HIV
- Any known active liver disease, including but not limited to disease due to HBV, HCV, autoimmune hepatic disorders, or sclerosing cholangitis. For patients who are known carriers of HBV/HCV, active hepatitis B/C infection must be ruled out on the basis of negative serologic testing and/or determination of HBV DNA/HCV RNA viral load per local guidelines.
- Any of the following abnormal laboratory tests prior to randomization:

  Serum TBILI >1.0 times the upper limit of normal (ULN). In cases of known Gilbert's syndrome, direct bilirubin should be within the normal range.

  ALT and/or AST $>$ ULN

  ALP $>1.5\times$ ULN

  Serum creatinine $>1.5\times$ ULN

  Total WBC $<2500/\mu L$ ($<2.5\times10^9$/L)

  ANC $<1500/\mu L$ ($<1.5\times10^9$/L)

  Platelets $<100{,}000/\mu L$ ($<100\times10^9$/L)

  INR or aPTT $>1.5\times$ ULN

- Pregnant or lactating women or women of childbearing potential without a negative serum pregnancy test result, within 7 days prior to randomization, regardless of the method of contraception used

- Hypersensitivity to any of the study medications or any of the ingredients or excipients of these medications, including hypersensitivity to benzyl alcohol
- Chronic immunosuppressive therapies, including systemic corticosteroids

4.2 METHOD OF TREATMENT ASSIGNMENT

After written informed consent has been obtained and eligibility has been established and approved, the study site will obtain the patient randomization number and treatment assignment from the interactive voice response system/interactive web response system (IVRS/IWRS). Patients should receive their first dose of study treatment the day of randomization, if possible, but no later than 7 days after randomization. Patients will be randomized in a 1:1 ratio by a permuted block randomization scheme to one of the two treatment arms through use of the IVRS/IWRS.

Randomization will be stratified by the following stratification factors:

- World region (United States/Canada, Western Europe/Australia/New Zealand, Asia, or rest of the world)
- Nodal status (0, 1–3, or ≥4 positive nodes)
- Centrally assessed hormonal receptor status (ER- and/or PR-positive or both ER- and PR-negative)
- Type of anthracycline (doxorubicin or epirubicin)

4.3 STUDY TREATMENT

Study treatment is defined as non-hormonal systemic adjuvant (post-operative) treatment. Trastuzumab emtansine, pertuzumab, and trastuzumab are considered investigational medicinal products (IMPs) in this study. Paclitaxel and docetaxel are also considered IMPs in this study; however, paclitaxel and docetaxel may be considered non-IMPs on the basis of local legislation.

Doxorubicin, epirubicin, cyclophosphamide, and 5-fluorouracil are considered non-IMPs in this study. Depending on local legislation, doxorubicin, epirubicin, cyclophosphamide, and 5-fluorouracil may be considered IMPs. If considered an IMP, then appropriate information on formulation, packaging, handling, and administration will be provided.

Concomitant therapy and premedication (Section 4.5) are defined as non-IMPs.

The choice of which adjuvant chemotherapy regimen (see Table 6 in Section 3.1) is given will be determined by the investigator prior to randomization. Randomization will determine whether a patient receives adjuvant therapy with trastuzumab plus pertuzumab plus taxane OR trastuzumab emtansine plus pertuzumab.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Trastuzumab Emtansine

The formulation, packaging, and handling should be performed according to the current Trastuzumab Emtansine Investigator's Brochure. For further details, see the Study Pharmacy Binder and/or local prescribing information for Kadcyla®.

4.3.1.2 Pertuzumab

The formulation, packaging, and handling should be performed according to the current Pertuzumab Investigator's Brochure. For further details, see the Study Pharmacy Binder and/or local prescribing information for Perjeta®.

4.3.1.3 Trastuzumab for Intravenous Administration

For information on the formulation, packaging, and handling of trastuzumab, see the most recent version of the Trastuzumab Investigator's Brochure as well as local prescribing information.

4.3.1.4 Doxorubicin, Epirubicin, Cyclophosphamide, 5-Fluorouracil, Paclitaxel, and Docetaxel

Please refer to local prescribing information for details on drug formulation, packaging, and handling.

4.3.2 Dosage, Administration, and Compliance

SoC chemotherapy backbone treatments should include three to four cycles of an anthracycline-based regimen. In Arm 1, three to four cycles or 12 weeks of taxane will also be administered. Administration of HER2-targeted therapy will be up to 1 year (up to 18 cycles). Adjuvant study treatment will be discontinued in the event of invasive disease recurrence, unacceptable toxicity, withdrawal of consent, or study termination by the Sponsor. Patients diagnosed with in situ breast cancer or a second primary cancer not requiring systemic therapy and with no evidence of invasive breast cancer recurrence should continue with adjuvant study treatment, if considered by the investigator to be in the patient's best interest, whenever possible.

4.3.2.1 Anthracycline Treatment Phase

Either FEC (see Table 7) or AC/EC (see Table 8) regimens as described in following subsections may be selected at the discretion of the investigator in this study. Please refer to local prescribing information/institutional guidelines for detailed guidelines on administration, premedications, dose delays/reductions for toxicities, contraindications, requirements for duration of contraception, and concomitant medications.

Table 7 5-Fluorouracil, Epirubicin, and Cyclophosphamide (FEC)

Drug	Dose	Dosing Interval	Planned Duration
5-Fluorouracil (F)	500–600 mg/m^2 IV bolus or infusion, according to local policy; dose should be capped at 1200 mg for BSA > 2 m^2	Day 1 of q3w cycle	3–4 cycles
Epirubicin (E)	90–100 mg/m^2 IV infusion over 15–30 minutes or infuse according to local policy	Day 1 of q3w cycle	3–4 cycles
Cyclophosphamide (C)	500–600 mg/m^2 IV infusion over 30 minutes or infuse according to local policy	Day 1 of q3w cycle	3–4 cycles

BSA = body surface area; IV = intravenous; q3w = every 3 weeks.

Table 8 Doxorubicin OR Epirubicin, and Cyclophosphamide (AC/EC)

Drug	Dose	Dosing Interval	Planned Duration
Doxorubicin (A)	60 mg/m^2 IV over 15–30 minutes or infuse according to local policy	Day 1 of q3w cycle or q2w cycle (dose dense)	4 cycles
Epirubicin (E)	90–100 mg/m^2 IV infusion over 15–30 minutes or infuse according to local policy	Day 1 of q3w cycle or q2w cycle (dose dense)	4 cycles
Cyclophosphamide (C)	500–600 mg/m^2 IV infusion over 30 minutes or infuse according to local policy	Day 1 of q3w cycle or q2w cycle (dose dense)	4 cycles

IV = intravenous; q2w = every 2 weeks; q3w = every 3 weeks.

The dose-dense (every 2 weeks [q2w]) AC/EC regimen may be administered with G-CSF support (e.g., pegfilgrastim 6 mg subcutaneously on Day 2 of q2w cycle).

Anti-emetic regimens may be used as premedication at the physician's discretion.

4.3.2.2 Concurrent Taxane Phase and/or HER2 Targeted Only Phase

Concurrent taxane phase applies only to treatment Arm 1 (control arm). Trastuzumab plus pertuzumab must start concurrently with the taxane component of chemotherapy following anthracycline therapy in the control arm. After anthracycline treatment, a minimum interval of 3 weeks from the last dose of anthracycline to initiation of HER2-targeted therapy is required. Prior to commencing the HER2-targeted component of therapy, patients must have an LVEF ≥ 50% and must not have experienced any clinical symptoms suggesting heart failure or asymptomatic LVEF declines by an absolute point of > 15% from baseline *and below the lower limit of normal*.

HER2-targeted treatment will continue for up to a total duration of 1 year and will be discontinued in the event of invasive disease recurrence, unacceptable toxicity, withdrawal of consent, or study termination by the Sponsor.

A ±3-day window is allowed for q3w dosing, and a +3-day window is allowed for qw dosing. This time window does not apply when dose delay is indicated due to toxicities.

4.3.2.2.1 Trastuzumab plus Pertuzumab plus Taxane Treatment (Arm 1)

During the taxane-concurrent phase, either docetaxel q3w (at 100 mg/m^2 for three cycles; at 75 mg/m^2 for four cycles; or start at 75 mg/m^2 in the first cycle and escalate to 100 mg/m^2 if no DLT occurs, for a total of three cycles at minimum) or 12 weeks of paclitaxel 80 mg/m^2 qw will be administered concurrently with trastuzumab in combination with pertuzumab. Please refer to local prescribing information/institutional guidelines for detailed guidelines on docetaxel or paclitaxel administration, premedications, dose delays/reductions for toxicities, contraindications, requirements for duration of contraception, and concomitant medications.

After the concurrent phase, only administration of only trastuzumab plus pertuzumab will continue, for up to a total duration of 1 year (up to 18 cycles).

Trastuzumab will be given at a loading dose of 8 mg/kg and pertuzumab at 840 mg. For subsequent cycles, trastuzumab will be given as a maintenance dose of 6 mg/kg and pertuzumab at 420 mg q3w. The dose of trastuzumab does not need to be recalculated unless the body weight has changed by ±10% or greater from baseline. Dose must be readjusted for ± 10% or greater weight change based on the previous weight used for dose recalculation. *The Investigator may choose to re-calculate dose at every cycle using actual weight at that time according to their local practice.* If the patient misses a dose of trastuzumab for any cycle (i.e., the two sequential administration times are 6 weeks or more apart), a re-loading dose of 8 mg/kg of trastuzumab should be given. If the patient misses a dose of pertuzumab for any cycle and the time between doses is 6 weeks or more, a re-loading dose of pertuzumab (840 mg) should be given. *Re-loading of doses for trastuzumab per local prescribing information may be followed.* Patients who experience trastuzumab or pertuzumab infusion–related symptoms may be pre-medicated with paracetamol and anti-histamines for subsequent infusions.

The sequence of administration for this treatment arm should follow that outlined in Table 9 (sequence from top to bottom).

Table 9 Treatment Regimen for Arm 1

Drug		Infusion Period[a]	Observation Period	Planned Duration
Pertuzumab	First dose	60 minutes	60 minutes	Up to 18 cycles
	Subsequent doses	30–60 minutes according to tolerability	30 minutes if well tolerated	
Trastuzumab[b]	First dose	90 minutes (first dose)	See national prescribing information	Up to 18 cycles
	Subsequent doses	30–90 minutes according to tolerability		
Taxane	Docetaxel	60 minutes	See national prescribing information	4 cycles
	OR Paclitaxel	30–60 minutes		12 weeks

[a] At the investigator's discretion, infusion period may be longer than described here, for patient safety.

[b] Trastuzumab infusion to start only after observation period for pertuzumab is completed.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.3 and Section 5.1.4.

4.3.2.2.2 Trastuzumab Emtansine plus Pertuzumab Treatment (Arm 2)

Taxane will not be administered in patients in treatment Arm 2. Trastuzumab emtansine plus pertuzumab will continue for up to a total duration of 1 year (up to 18 cycles).

Trastuzumab emtansine will be given at a dose of 3.6 mg/kg by IV infusion in combination with pertuzumab at an initial loading dose of 840 mg IV followed by a maintenance dose of 420 mg IV q3w. The dose of trastuzumab emtansine does not need to be recalculated unless the body weight has changed by ±10% or greater from baseline. Dose must be readjusted for ±10% or greater weight change based on the previous weight used for dose recalculation. *The Investigator may choose to re-calculate dose at every cycle using actual weight at that time according to local practice.* If the patient misses a dose of pertuzumab for any cycle and the time between doses is 6 weeks or more, a re-loading dose of pertuzumab (840 mg) should be given. Patients who experience pertuzumab infusion–related symptoms may be pre-medicated with paracetamol and anti-histamines for subsequent infusions.

The sequence of administration for this treatment arm should follow that outlined in Table 10 (sequence from top to bottom).

Table 10 Treatment Regimen for Arm 2

Drug		Infusion Period	Observation Period	Planned Duration
Pertuzumab	First dose	60 minutes	60 minutes	Up to 18 cycles
	Subsequent doses	30–60 minutes according to tolerability	30 minutes if well tolerated	
Trastuzumab emtansine[a]	First dose	90 minutes	90 minutes	Up to 18 cycles
	Subsequent doses	30–90 minutes according to tolerability	30 minutes if well tolerated	

[a] Trastuzumab emtansine infusion to start only after observation period for pertuzumab is completed.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.3 and Section 5.1.4.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (trastuzumab emtansine, pertuzumab, trastuzumab, docetaxel, and paclitaxel) will be provided by the Sponsor, with the exception of trastuzumab, docetaxel, and paclitaxel, which may be sourced locally in some countries. The investigational site will acknowledge receipt of IMPs, using the IVRS/IWRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will be either disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log or a similar document at the site.

4.3.4 Post-Trial Access to Trastuzumab Emtansine and Pertuzumab

The Sponsor does not intend to provide trastuzumab emtansine, pertuzumab, or other study interventions to patients after conclusion of the study or any earlier patient withdrawal.

4.4 PRIOR THERAPY

Prior anti-cancer therapy for this study population includes primary surgery. Date and extent of primary surgery should be collected in the eCRF.

4.4.1 Minimum Requirements for Patients Undergoing Sentinel Lymph Node Biopsy

Patients with positive SLNB must undergo axillary dissection unless all of the following characteristics apply (Giuliano et al. 2011):

- No palpable nodes
- No more than two positive lymph nodes
- Breast-conserving surgery
- Tangential whole breast irradiation
- Clinical tumor size ≤T2 (5 cm)

In the event that all of the above are applicable, it is not mandatory to have the axillary dissection, but it is left to the discretion of the investigator as per site standard practice.

4.5 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, or nutritional supplements) used by a patient from 7 days prior to randomization to the end-of-treatment visit.

All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. All concomitant medications are to be reported until the end-of-treatment visit. In addition, adjuvant hormonal therapy will be reported in the eCRF until hormonal therapy completion or study completion.

4.5.1 Permitted Therapy

Permitted therapy includes adjuvant radiotherapy and adjuvant hormonal therapy or any medication that the investigator deems necessary for the supportive management of the patient.

The following treatments are permitted throughout the duration of the study treatment phase and during follow-up:

- Standard therapies for preexisting medical conditions unless listed as prohibited therapy in Section 4.5.2. Any medication intended solely for supportive care (e.g., analgesics, anti-diarrheals, and anti-depressants) may be used at the investigator's discretion. Patients on anti-coagulant treatment should have their platelet count monitored closely during treatment with trastuzumab emtansine.
- Hematopoietic growth factors (e.g., G-CSF) may be used at the investigator's discretion for the primary prophylaxis and/or management of treatment-emergent neutropenia and/or for secondary prophylaxis as per NCCN/European Society for Medical Oncology guidelines (Crawford et al. 2010, 2013) or local standard practice.
- Bisphosphonate or denosumab therapy (to be used in accordance with the approved labeled indication and/or nationally recognized treatment guidelines)

4.5.1.1 Adjuvant Radiotherapy

Before actively enrolling patients, each center must define a radiotherapy policy for treating patients in the trial. Guidelines are given in Appendix 4.

Radiotherapy is to be given at the end of systemic chemotherapy (end of taxane in Arm 1; after four cycles of trastuzumab emtansine plus pertuzumab in Arm 2, to be consistent with Arm 1 in timing of initiation) while HER2-targeted therapy is being administered.

Any locoregional RT (extent or volume and total dose) must be reported in the eCRF.

4.5.1.2 Concomitant Hormonal Therapy

Concomitant hormonal therapy should be administered after systemic chemotherapy (end of taxane in Arm 1; after four cycles of trastuzumab emtansine plus pertuzumab in Arm 2, to be consistent with Arm 1 in timing of initiation) according to the following recommendations.

Female patients must be classified according to one of the following menopausal status definitions on the basis of their prechemotherapy status:

- Premenopausal

  $<$12 months since last menstrual period AND no prior bilateral ovariectomy AND not receiving estrogen replacement OR biochemical evidence of premenopausal status, according to local guidelines

- Postmenopausal

  $>$12 months since last menstrual period with no prior hysterectomy OR prior bilateral ovariectomy OR biochemical evidence of postmenopausal status, according to local guidelines

Female hormonal receptor–positive patients should be treated according to local guidelines. A minimum of 5 years of hormonal therapy should be planned.

Endocrine therapy in male patients is to be given according to local guidelines (see Table 11).

Table 11 Recommendations for Hormonal Therapy

Clinical Scenario	Hormonal Therapy
Hormone receptor negative[a]	Not recommended[a]
Hormone receptor positive[a] (premenopausal[b])	Tamoxifen for 5–10 years with or without ovarian suppression as per local policy
Hormone receptor positive[a] (postmenopausal[b])	Any one of the following: Aromatase inhibitor for 5 years Aromatase inhibitor for 2–3 years, followed by tamoxifen to complete a total of 5–10 years Tamoxifen for 2–3 years, followed by aromatase inhibitor to complete a total of 5 years Tamoxifen for 5–10 years Tamoxifen for 5 years, followed by aromatase inhibitor for 5 years

ER = estrogen receptor; PR = progesterone receptor.

[a] Hormone receptor negative is defined as negative for both ER and PR, and hormone receptor positive is defined as positive for either ER or PR, on the basis of the preoperative or postoperative tumor pathology per central laboratory analysis. The investigator may decide on the treatment policy according to local laboratory receptor status if receptor status is centrally "negative" and locally "positive."

[b] Patients who are initially premenopausal may become postmenopausal over the course of the study, in which case hormonal therapy can be adjusted according to local policy.

4.5.2 Prohibited Therapy

Explicitly prohibited therapies prior to disease recurrence include anti-cancer therapies other than protocol-approved therapies administered in this study.

- Anti-cancer therapies other than those administered in this study, including cytotoxic chemotherapy, radiotherapy (except for adjuvant radiotherapy for breast cancer after completion of chemotherapy), immunotherapy, and biological or targeted (e.g., lapatinib or neratinib) anti-cancer therapy
- Any systemically active oral, injected, or implanted hormonal method of contraception except for previously implanted progesterone-coated intrauterine devices
- Estrogen-replacement therapy
- Chronic immunosuppressive therapies, including systemic corticosteroids
- Any investigational agent, except those used in this study

Concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole and itraconazole) with trastuzumab emtansine should be avoided. An alternate medication with no or minimal potential to inhibit CYP3A4/5 should be considered. If a strong CYP3A4/5 inhibitor is co-administered with trastuzumab emtansine, patients should be closely monitored for adverse reactions.

Excessive alcohol intake should be avoided. Occasional to moderate alcohol use is permitted.

4.6 TREATMENTS DURING FOLLOW-UP

After the end-of-treatment visit, only medications and therapies applicable for long-term reporting must be reported, including the following:

- Breast cancer treatments (e.g., hormone therapy)
- Anti-cancer treatments for recurrence(s)
- Bisphosphonate or denosumab therapy
- Medications related to the treatment of SAEs that are applicable for long-term reporting

All systemic therapies (including but not limited to drug name and duration of treatment for breast cancer for the first recurrence and all subsequent recurrences/disease progression), including chemotherapy, biologic therapy (antibody and small molecule therapies), hormonal therapy (including ovarian ablation and drug-induced ovarian suppression), or surgery/radiation will be collected during study follow-up.

4.7 STUDY ASSESSMENTS

Patients will be assessed for safety, efficacy, biomarker, and QoL during the study. All patients will be closely monitored for safety and tolerability during study treatment. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable. In this study, one cycle is defined as 3 weeks (21 ± 3 days) unless otherwise stated (e.g., for AC/EC dose-dense regimens). Study treatment will be administered in 21-day/3-week cycles if no additional time is required for reversal of toxicity.

If the timing of a protocol-mandated procedure coincides with a holiday and/or weekend that precludes performance of the procedure within the allotted window, the procedure should be performed on the nearest following date. Study assessments are outlined in this section and in Appendix 1 and Appendix 2.

4.7.1 Description of Study Assessments

4.7.1.1 Medical History and Demographic Data

Medical history includes past or current clinically significant conditions, surgeries, breast cancer surgery and diagnosis, non-breast cancer history, reproductive status, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) used by the patient within 7 days prior to randomization.

Demographic data will include age, sex, and self-reported race/ethnicity and may include local HER2 and hormonal receptor test information.

4.7.1.2 Physical Examinations

A complete physical examination, including height and weight, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, GI, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations focusing on organ systems related to adverse events or disease should be performed. Weight is to be measured on Day 1 of the specified cycles and compared with baseline. If ±10% or greater variation occurs, then study treatment doses will be recalculated. Dose must be readjusted for ± 10% or greater weight change based on the previous weight used for dose recalculation. *The investigator may choose to re-calculate dose at every cycle using actual weight at that time according to local practice. For anthracyclines and taxanes, local standards for dose calculations will be followed.*

Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Physical examination, including breast examination and evaluation of local-regional lymphatics, if applicable, should be conducted as part of disease status assessments per Section 4.7.1.5.1.

4.7.1.3 Vital Signs

Vital signs will include measurements of pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position, as well as temperature.

4.7.1.4 Radiographic Assessments

Bone scan, chest X-rays/diagnostic computed tomography (CT), magnetic resonance imaging (MRI), liver imaging, 18-fluoro-deoxyglucose positron emission tomography (PET) scans, and/or other radiographic modalities may be performed as clinically indicated according to NCCN or national guidelines. A baseline chest X-ray will be obtained.

These radiographic assessments may be considered when clinically indicated to exclude metastatic disease at baseline or assess distant disease recurrence status during study treatment and follow-up.

4.7.1.5 Disease Recurrence Status

All patients should be followed to assess disease recurrence, second primary cancer, and survival. Disease recurrence or status based on all available clinical assessments should be evaluated and documented every 3 months during study treatment and for up

to 2 years following completion of treatment, at intervals of every 6 months from 3 to 5 years following completion of treatment, and annually thereafter until approximately 10 years from FPI.

4.7.1.5.1 Recurrence of Disease—Recommended Procedures for Confirmation

The diagnosis of a breast cancer recurrence or second primary tumor should be confirmed histologically whenever possible. Some patients may have a suspicious recurrence that leads to death quite quickly without the possibility of confirming relapse of disease. Efforts should be made to obtain an autopsy report in such cases. The earliest date of diagnosis of recurrent disease should be used and recorded. This date should be based on objective clinical, radiological, histological, or cytological evidence.

Recurrent disease includes local, regional, or distant recurrence and contralateral or ipsilateral second primary invasive breast cancer. Patients who have a diagnosis of in situ breast disease or second, non-breast malignancies should be maintained on a regular follow-up schedule wherever possible in order to fully capture any subsequent recurrent invasive disease events.

A tumor biopsy at recurrence for exploratory biomarker research should be taken if the tumor is accessible for biopsy without significant risk to the patient (in the investigator's opinion). These analyses are done in order to gain better understanding of resistance mechanisms and tumor biology at recurrence. A blood sample for biomarker analysis should also be collected at this time.

The definitions of and procedures for confirming invasive disease recurrence, death, and other noteworthy events on follow-up are as follows:

- 1) Local invasive recurrence

    Ipsilateral breast after previous lumpectomy

        Defined as evidence of invasive tumor (except DCIS and LCIS) in the ipsilateral breast after lumpectomy. Patients who develop clinical evidence of tumor recurrence in the remainder of the ipsilateral breast should have a biopsy of the suspicious lesion to confirm the diagnosis.

        Confirmed by positive histology or cytology

    Ipsilateral after previous mastectomy

        Defined as evidence of invasive tumor in any soft tissue or skin of the ipsilateral chest wall. This includes the area bounded by the midline of the sternum, extending superiorly to the clavicle and inferiorly to the costal margin. Soft tissue recurrences in this area extending into the bony chest wall or across the midline will be considered as evidence of local recurrence.

        Confirmed by positive histology or cytology

- 2) Regional recurrence

  Defined as the development of tumor in the ipsilateral internal mammary lymph nodes, ipsilateral axillary lymph nodes, or supraclavicular lymph nodes and in the extranodal soft tissue of the ipsilateral axilla. Regional recurrence does not include tumor in the opposite breast.

  Confirmed by positive histology or cytology, or radiologic evidence (especially in case of PET activity or visible internal mammary lymph nodes on CT or MRI if no biopsy was performed)

- 3) Contralateral or ipsilateral second primary invasive breast cancer

  Confirmed by positive cytology or histology

- 4) Distant recurrence

  Defined as evidence of tumor in all areas, with the exception of those described in 1), 2), and 3) above

  Confirmed by the following criteria:

  Skin, subcutaneous tissue, and lymph nodes (other than local or regional)

  Positive cytology, aspirate, or biopsy OR radiologic (CT scan, MRI, PET, or ultrasound) evidence of metastatic disease

  Bone

  X-ray, CT scan, or MRI evidence of lytic or blastic lesions consistent with bone metastasis, OR bone scan (requires additional radiologic investigation; alone not acceptable in case of diagnostic doubt) OR biopsy proof of bone metastases or cytology

  Bone marrow

  Positive cytology or histology or MRI scan

  Lung

  Radiologic evidence of multiple pulmonary nodules consistent with pulmonary metastases

  Positive cytology or histology (in practice, rarely performed except in the case of solitary nodules)

  Note: For solitary lung lesions, cytologic or histologic confirmation should be obtained in case of diagnostic doubt. Proof of neoplastic pleural effusions should be established by cytology or pleural biopsy.

  Liver

  Radiologic evidence consistent with liver metastases OR liver biopsy or fine needle aspiration

  Note: If radiologic findings are not definitive (especially in the case of solitary liver nodules), a liver biopsy is recommended; however, if a biopsy is not performed, serial scans should be obtained, if possible, to document stability or progression.

Central nervous system

Positive MRI or CT scan, usually in a patient with neurologic symptoms, OR biopsy or cytology (e.g., for a diagnosis of meningeal involvement). However, meningeal involvement may also be diagnosed by CT scan or MRI and, depending on the general status of the patient, additional investigations (including cytology of the cerebrospinal fluid).

- 5) Second primary malignancy (non-breast)

  Any positive diagnosis of a second (non-breast) primary cancer other than basal or squamous cell carcinoma of the skin or CIS of the cervix will be considered an event in the analysis of the IDFS, including second primary non-breast cancer endpoint; however, such diagnoses will not be included in the IDFS primary endpoint.

  Myelodysplastic syndrome is not considered a progression event. The diagnosis of a second primary cancer must be confirmed histologically.

  All second primary malignancies are to be reported whenever they occur during the study.

  Note: Patients diagnosed with a second primary malignancy not requiring systemic therapy (i.e., chemotherapy, hormonal therapy, targeted therapy, etc.) and with no evidence of breast cancer recurrence should continue, whenever possible, with study drug treatment and Schedule of Assessments, if considered by the investigator to be in the patient's best interest.

- 6) Death without recurrence

  Any death occurring without prior breast cancer recurrence or second (non-breast) malignancy is considered an event for the following endpoints: IDFS, IDFS including second primary non-breast cancer, DFS, and OS.

- 7) Other noteworthy events

  The following events should be recorded on the eCRF:

  Ipsilateral and contralateral LCIS

  Ipsilateral and contralateral DCIS

  Note: These events are not considered recurrent invasive disease but must be recorded.

4.7.1.6 Laboratory Assessments

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis according to the Schedule of Assessments:

- Hematology (complete blood counts with differential) including hemoglobin, hematocrit, platelet count, WBC count, and differential including absolute neutrophil count

- Serum chemistry

  At baseline: sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein (if available), albumin, TBILI (and direct bilirubin when TBILI > ULN), ALT, AST, and ALP

  At subsequent timepoints: potassium, TBILI (and direct bilirubin when TBILI > ULN), ALT, AST, ALP, and other assessments when clinically indicated

- Viral serology at screening and as clinically indicated

  HBsAg

  HBcAb and/or HBV DNA for known HBV carrier per local guidelines

  HCV antibody and/or HCV RNA for known HCV carrier per local guidelines

- Pregnancy test

  All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

- Coagulation (INR and aPTT) at screening; otherwise, as clinically indicated

Samples for the following laboratory tests will be sent to one or several central laboratories or to the Sponsor for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

- Prospective central testing for HER2-positive status by IHC and ISH

  Central laboratory confirmation of a positive HER2 status is required prior to randomization to the study. The outcome of this assessment will be communicated to the investigator.

  After completion of HER2 testing for eligibility criteria, with use of prespecified HER2 tests, patient samples may also be tested with other HER2 assays to establish performance characteristics of these assays for diagnostic development. Testing may be performed on all screened patients (screen-failed and enrolled patients). These testing data will have no impact on eligibility, and testing will be performed only after eligibility is established for each patient.

- Prospective central testing for hormonal receptor (ER/PR) status by IHC
- Assessment of potential candidate biomarkers (see Section 4.7.1.9)
- Analysis of serum, plasma, and whole blood samples collected as part of the optional biomarker program
- Analysis of serum samples for trastuzumab emtansine pharmacokinetic (PK) and ATA assessments

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

These samples will be stored until the end of the study, with the following exceptions:

- Mandatory biomarker samples will be destroyed no later than 5 years after the date of final closure of the clinical database.

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

4.7.1.7 Cardiac Assessments

4.7.1.7.1 Electrocardiograms

Single 12-lead ECGs will be performed locally and assessed at screening and otherwise as clinically indicated.

For safety monitoring purposes, any abnormalities on any of the ECGs will be documented on the eCRF. The investigator or designee must review, sign, and date all ECG tracings. Paper copies will be kept as part of the patient's permanent study file at the site. For ECG tracings that will fade over time (e.g., ECGs on thermal paper), lasting, legible copies should be filed together with the original.

4.7.1.7.2 Left Ventricular Ejection Fraction

LVEF cardiac monitoring will be assessed by ECHO or MUGA in all patients. LVEF assessment by ECHO is preferred, but LVEF can also be assessed by MUGA. The same modality should be used throughout the study for each patient and, preferably, performed and assessed by the same assessor. Results of ECHO/MUGA will be collected in the eCRF.

4.7.1.8 Patient-Reported Outcomes

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

The EORTC QLQ-C30 and the modified Breast Cancer module QLQ-BR23 questionnaires (Appendix 8) will be used to assess HRQoL, including side effects of therapy (e.g., peripheral neuropathy, joint/muscle pain, skin issues) and patient functioning (refer to Schedule of Assessments for detailed description of timepoints).

The EORTC QLQ-C30 is a validated and reliable self-report measure (Aaronson et al. 1993; *Osoba et al. 1997*) that consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social); three symptom scales (fatigue; nausea, vomiting, and pain); the global health/QoL *scale*; and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial

difficulties), within a recall period of ”the last week.” Scale scores can be obtained for each of the multi-item scales, the global health status/QoL scale, and the six single items by using a liner transformation for standardization of the calculated raw score.

The EORTC QLQ-BR23 breast cancer module was first validated for use in 1995, uses a recall period of ”the past week,“ and is intended for use across multiple treatment modalities (i.e., surgery, chemotherapy, radiotherapy, and hormonal treatment; *Sprangers et al. 1998*). As peripheral neuropathy (1 item), joint/muscle pain (1 item), and skin problems (2 items) are key symptoms of therapy not assessed by currently available tools, validated items from the EORTC Item Bank will be added to assess the presence and bothersomeness of these treatment-related side effects. Data analysis will be performed on the final modified BR23 data set *outside of the protocol* in parallel with the final data analysis to confirm the psychometric properties of the modified instrument. Scale scores can be obtained for each of the multi-item and single-item scales by using a linear transformation for standardization of the calculated raw score.

4.7.1.9 Mandatory Samples for HER2 Testing and Biomarker Analysis

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual. The mandatory tissue and blood samples will be stored for up to 5 years after final database lock, unless the patient consents to long-term storage as part of the optional biomarker research program (OBRP) for 15 years.

Tumor Tissue Samples

As a requirement for study enrollment, tumor tissue samples in the form of a FFPE tumor tissue block or a partial block (for minimal dimensions, see Sample Handling and Logistics Manual) from the primary tumor (definitive surgery sample) must be submitted to a Sponsor-designated central pathology laboratory for assessment of HER2 status by IHC (see Appendix 6) and ISH (see Appendix 7) and hormone receptor status by IHC. Tissue that has been submitted for HER2, hormonal receptor testing, and mandatory biomarker analysis may also be used for the assessment of additional in situ methods, or newly available alternative diagnostic technologies may also be applied on these samples from all screened patients.

Tumor Biopsy at Recurrence

There is a need to further understand the relapse of the tumor during or after adjuvant therapy. Molecular characterization of the tumor at time of relapse will help to further our understanding of the underlying resistance mechanisms and tumor biology at recurrence. A tumor biopsy at recurrence for exploratory biomarker research should be taken if the tumor is accessible for biopsy without significant risk (in the investigator’s opinion) to the patient.

Biomarker Analysis

Tumor samples will be used to assess the potential prognostic or predictive value of candidate markers or biomarker panels, improve diagnostic tests, improve

understanding of breast cancer biology, or discover new biomarker profiles related to treatment benefit and/or safety or disease characteristics. Tumor tissue from the tumor block or partial block will be used to assess the potential relationship between the degree of *HER2* gene amplification and the level of HER2/3 mRNA and response to study treatment. Other markers that may be selected for exploratory analyses are, for example, other HER family members—markers that are involved in downstream signaling of HER2, belong to a group of related receptor tyrosine kinases that could serve as salvage routes for an inhibited HER2 pathway (e.g., PIK3CA mutations, PTEN), or are ligands of HER family proteins that induce activation of the HER pathway.

Analysis of the tissue block will include the following markers for all patients in screening:

- HER2 eligibility testing, including hematoxylin and eosin stain, IHC, and ISH (6–8 slides)
- ER/PR status (2–3 slides)

Analysis of the tissue block of all randomized patients will include, but not be limited to, the following markers:

- RNA extraction to allow, for example, for the analysis of HER2/3 mRNA levels using qRT-PCR (2–3 slides)
- DNA extraction to allow, for example, for the analysis of PIK3CA mutations (1–2 slides)
- PTEN (2 slides for IHC)
- Additional markers or alternative technologies (based on scientific developments and/or novel technologies) to explore potential prognostic or predictive candidate markers/panels or markers related to treatment benefit and/or safety, to improve diagnostic tests, or to understand breast biology

After initial HER2, ER/PR, and mandatory biomarker testing, the tissue blocks will be used for tissue microarray (TMA) construction (after study enrollment) before they are returned to sites to allow for additional biomarker analysis. Analysis of additional markers may be required, because science is rapidly and constantly evolving, and therefore the definitive list of biomarkers that will be analyzed remains to be determined and may include additional markers as well as novel or alternative technologies to be evaluated. These TMAs will be destroyed no later than 2 years after the date of final closure of the clinical database, unless the patient gives specific consent for the remainder of the samples to be stored for optional exploratory research in the study biosample repository (see Section 4.7.1.10).

There is a need to further understand the relapse of the tumor during or after adjuvant therapy. Molecular characterization of the tumor at time of relapse will be conducted if tumor sample is available at disease recurrence.

The implementation and use of the study biomarker specimens is governed by the study Steering Committee (SC) (Section 9.4), with guidance from a dedicated translational research committee to ensure the appropriate use of the study specimens. All biomarker specimens will be retained for new research related to this study and/or disease in accordance with the recommendations and approval of the study SC.

Blood Samples

Blood samples for collection of serum (6 mL) and plasma (2 × 6 mL) will be collected as shown in the Schedule of Assessments for all patients. These specimens will be used for research purposes to identify biomarkers that are predictive of response to study treatment (in terms of dose, safety, and tolerability) and will help to better understand the pathogenesis, course, and outcome of EBC and related diseases. The serial sampling gives the opportunity to evaluate changes in circulating biomarker levels, which may give further understanding of potential resistance mechanisms. Measurement of these samples may include, but not be limited to, circulating ligands of HER family members, such as transforming growth factor−alpha, epidermal growth factor, betacellulin, amphiregullin, or neuregulin-1/heregulin or circulating tumor DNA. Somatic mutations in known oncogenes and tumor suppressor genes (i.e., *PIK3CA*) and other genes related to the mechanism of action or resistance mechanism of the investigational genes will be determined.

Candidate markers of response to treatments that emerge from other clinical or nonclinical studies may also be assessed in this study and can be assessed with use of different types of technologies.

Clinical Genotyping

At baseline (Cycle 1 Day 1 of anthracyclines), an approximate 3-mL whole blood sample will be taken for genetic biomarker analysis (polymorphisms). If, however, the genetic blood sample is not collected during the scheduled visit, it may be collected at any time (after randomization) during the treatment phase of the clinical study.

Clinical genotyping analysis will be used to investigate genetic markers in correlation to efficacy and safety of trastuzumab emtansine. Several hypotheses may be evaluated in this trial, and some example hypotheses are further described in Section 3.3.6.

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

Samples will be destroyed no later than 2 years after the date of final closure of the clinical database.

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

4.7.1.10 Optional Biomarker Research Samples and Study Biosample Research Repository

There will be an OBRP for which samples will be stored in a study biosample repository for the long term. The collection and analysis of biomarker specimens as part of the OBRP will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

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

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

Approval by the Institutional Review Board or Ethics Committee

Sampling for the OBRP is contingent upon the review and approval of the exploratory research and long term storage in the study biosample repository portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for ORBP sampling, this section of the protocol will not be applicable at that site.

Sample Collection

Patients who are enrolled in the study will be asked to consent to allow the remainders of mandatory tissue and blood/plasma/serum samples as described above to also be used for exploratory biomarker research.

In addition, the following sample will be collected for patients who consent to Optional Biomarker Research for identification of genetic (inherited) biomarkers:

- Whole blood samples for DNA extraction to assess for biomarkers

For all samples, dates of consent and specimen collection should be recorded on the associated page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

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

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

Confidentiality

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

Data generated from OBRP specimens in the study biosample repository must be available for inspection upon request by representatives of national and local health authorities and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with OBRP specimens is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from OBRP specimen analysis on individual patients will not generally be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using specimens in the study biosample repository will be available via study data publication.

Any inventions and resulting patents, improvements, and/or knowhow originating from the use of specimens in the study biosample repository data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

Consent to Participate in the Optional Biomarker Research Program

The Informed Consent Form will contain a separate section that addresses participation in the OBRP. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the OBRP. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be

required to document a patient's agreement to provide the optional biomarker specimen. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the OBRP Informed Consent eCRF.

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

A separate, specific signature is not required for the following mandatory biomarker samples, which will be stored until 2 years after final closure of the database:

- Tumor tissue collection for HER2 testing and biomarker analyses
- Clinical genotyping blood sample
- Blood samples for plasma/serum

Withdrawal from the Optional Biomarker Research Program

Patients who give consent to provide specimens for the OBRP have the right to withdraw their specimens from this program at any time and for any reason. If a patient wishes to withdraw consent for the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes using the OBRP Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the OBRP Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study BO28407 does not, by itself, constitute withdrawal of specimens from the OBRP. Likewise, a patient's withdrawal from the OBRP does not constitute withdrawal from Study BO28407.

Monitoring and Oversight

OBRP specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality and adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the OBRP for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the OBRP samples.

4.7.1.11 Samples for ATA

Serum samples for ATA and pharmacokinetics will be taken from all patients receiving trastuzumab emtansine as indicated in Schedule of ATA Assessments (Appendix 2). The ATAs to trastuzumab emtansine will be measured and characterized using validated assays. The PK samples will be analyzed using validated assays.

For details of sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

4.7.2 Timing of Study Assessments

4.7.2.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before any study-specific screening tests or evaluations are performed. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site. Screening tests and evaluations will be performed within 30 days prior to enrollment unless otherwise specified. Results of SoC tests or examinations performed prior to obtaining informed consent and within 30 days prior to enrollment may be used; such tests do not need to be repeated for screening. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Central HER2 testing to confirm patient HER2 status and hormonal receptor status will be performed at a Sponsor-designated central laboratory. In addition, local HER2 test information, baseline demographic, and disease-related characteristic data for all screened patients may be collected in order to support potential registration of a companion diagnostic assay for trastuzumab emtansine.

Pretreatment tests and evaluations will be performed within 7 days prior to enrollment after confirmation of other eligibility criteria, unless otherwise specified.

Please see Appendix 1 for the schedule of screening and pretreatment assessments.

4.7.2.2 Assessments during Treatment

During adjuvant therapy, patients will be assessed for safety and efficacy. All assessments must be performed on the day of the specified visit, unless a time window is specified in the Schedule of Assessments (see Appendix 1 and Appendix 2). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the Schedule of Assessments.

Please see Appendix 1 and Appendix 2 for the Schedule of Assessments performed during the treatment period.

4.7.2.3 Assessments at Study End-of-Treatment Visit

Patients who complete the study treatment (defined as completion of 1 year of HER2 targeted therapy) or discontinue from the study treatment early will be asked to return to the clinic 28–42 days after the last dose of study drug for a follow-up visit.

Please see Appendix 1 for the Schedule of Assessments performed at the study completion/early termination visit.

4.7.2.4 Follow-Up Assessments

The follow-up period begins from the date of the end-of-treatment visit. Visit windows are ±28 days for quarterly and semiannual assessments and ±42 days for annual assessments (see Appendix 1).

After the end-of-treatment visit, adverse events should be followed as outlined in Section 5.5 and Section 5.6.

All patients must be followed up for approximately 10 years from the date of randomization of the first patient (or until sites are notified that the study is closed by the Sponsor) according to the Schedule of Assessments, even if the assigned treatment is discontinued permanently.

The schedule of follow-up visits and tests for this study is the minimum required; investigators may see their patients more frequently according to their routine practice.

In cases of disease recurrence that is defined as an IDFS event in Section 3.4.1, diagnosed at any time during the study, patients will be out of the study schedule and will be followed up once a year (starting 1 year after first recurrence) for approximately 10 years from the date of randomization of the first patient for survival (or until sites are notified that the study is closed by the Sponsor), and new recurrence/disease progression events.

Please see Appendix 1 for the schedule of follow-up assessments.

4.8 PATIENT, STUDY, AND SITE DISCONTINUATION

4.8.1 Patient Discontinuation

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Completion of all assessments, including 10 years of follow-up
- The study is closed by the Sponsor

4.8.1.1 Discontinuation from Study Drug

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

- Invasive disease recurrence
- Unacceptable toxicity (Section 5.1.3 and Section 5.1.4)
- Pregnancy
- Intercurrent, non–cancer-related illness that prevents continuation of protocol therapy or follow-up
- Major protocol violation that may jeopardize the patient's safety according to the Sponsor
- Repeated patient noncompliance with protocol requirements
- Changes in the patient's condition or study drug–related toxicity such that in the opinion of the investigator, continued participation in the protocol would compromise the patient's well-being
- Withdrawal of patient consent

Patients who discontinue study drug prematurely will be asked to return to the clinic for an end-of-treatment visit (see Schedule of Assessments) and may undergo follow-up assessments. The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug prematurely will not be replaced.

4.8.1.2 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

Withdrawal from Entire Study

Should a patient decide to withdraw from the study, all efforts will be made to complete and report the observations for that patient as thoroughly as possible. No further data will be collected after the date of the patient's withdrawal from study. The investigator should contact the patient or a legally authorized relative by telephone or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made, along with an explanation of why the patient is withdrawing from the study.

Partial Withdrawal from Study

All of the above provisions regarding withdrawal from the entire study are applicable to partial withdrawal from the study, except that the patient must agree to be contacted for further information on recurrence as per the primary study endpoint and survival status. Whenever possible, information on recurrence should be documented through review of medical records as well as patient contact. It should be documented in both the medical

records and the eCRF that the patient agreed to be contacted for information on survival despite the patient's withdrawal of informed consent.

In the case of patients who miss scheduled visits, site staff should make at least three attempts within a reasonable period of time after a missed visit to contact these patients for follow-up information. The collection of follow-up data is extremely important for the reliable estimation of study endpoints.

If a patient is lost to follow-up, contact will initially be attempted through the trial research nurse and the lead investigator at each study site. If these attempts are unsuccessful, the patient's physician will be contacted and asked to contact the patient or the patient's family and provide follow-up information to the recruiting study site.

Only after sufficient unsuccessful attempts at contact have been made may a patient be declared lost to follow-up.

4.8.2 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the study is placed on hold or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety monitoring plan for patients in this study is based on the known safety profiles of trastuzumab emtansine, pertuzumab, trastuzumab, and protocol-approved chemotherapy agents.

5.1.1 Study Drugs Associated Risks, Warnings, and Precautions

5.1.1.1 Trastuzumab Emtansine

Identified and potential risks of treatment with trastuzumab emtansine are based on all available nonclinical and clinical data relating to trastuzumab emtansine and clinical toxicities related to its components (trastuzumab and DM1, a derivative of maytansine) and to other DM1-containing ADCs.

Pulmonary toxicity, hepatotoxicity, cardiac toxicity (left ventricular dysfunction), IRR/hypersensitivity, thrombocytopenia (including thrombocytopenia associated with severe hemorrhage), and peripheral neuropathy are important identified risks of trastuzumab emtansine and are detailed in the subsections below. Fetal harm and impaired fertility are important potential risks with trastuzumab emtansine.

Guidance on dose modifications and discontinuation upon toxicities are provided in Section 5.1.3 and Section 5.1.4.

Please refer to the Investigator's Brochure for full description of the trastuzumab emtansine safety profile, warnings, precautions, and guidance for investigators.

5.1.1.1.1 Pulmonary Toxicity

Cases of ILD, including pneumonitis, some leading to acute respiratory distress syndrome or fatal outcome, have been reported in clinical trials with trastuzumab emtansine. Signs and symptoms include dyspnea, cough, fatigue, and pulmonary infiltrates. These events may or may not occur as sequelae of infusion reactions. Treatment has included administration of steroids and oxygen, as well as study drug discontinuation.

5.1.1.1.2 Hepatotoxicity

Hepatotoxicity, predominantly in the form of asymptomatic increases in the concentrations of serum transaminases (Grade 1–4 transaminitis), has been observed in patients while on treatment with trastuzumab emtansine in clinical trials. Transaminase elevations were generally transient with peak elevation at Day 8 after therapy administration and subsequent recovery to Grade 1 or lower prior to the next cycle. The incidence of increased AST was substantially higher than that for ALT. A cumulative effect of trastuzumab emtansine on transaminases has been observed: the proportion of patients with Grade 1 or 2 elevated transaminases increases with successive cycles; however, no increase in the proportion of Grade 3 abnormalities over time was observed. The majority of patients with elevated transaminases improved to Grade 1 or normal within 30 days of the last dose of trastuzumab emtansine.

Rare cases of severe hepatotoxicity, including death due to DILI and associated hepatic encephalopathy, have been observed in patients treated with trastuzumab emtansine. Some of the observed cases may have been confounded by concomitant medications with known hepatotoxic potential and/or underlying conditions. Nevertheless, a

contributory role of trastuzumab emtansine in these cases cannot be excluded. Therefore, acute severe liver injury (Hy's law) is an important risk with trastuzumab emtansine. A Hy's law case has the following components:

- Aminotransferase enzymes are greater than $3 \times$ ULN with concurrent elevation of serum TBILI to $> 2 \times$ ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase).

- No other reason can be found to explain the combination of increased aminotransferases and serum TBILI, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

Cases of NRH of the liver have been identified from liver biopsies in patients treated with trastuzumab emtansine and presenting with signs and symptoms of portal hypertension. NRH confirmed by biopsy was observed leading to fatal hepatic failure. NRH is a rare liver condition characterized by widespread benign transformation of hepatic parenchyma into small regenerative nodules; NRH may lead to non-cirrhotic portal hypertension (Hartleb et al. 2011). NRH should be considered in patients who develop clinical symptoms of portal hypertension and/or a cirrhosis-like pattern seen on CT scan of the liver but with normal transaminases and no other manifestations of cirrhosis or liver failure following long-term treatment with trastuzumab emtansine. Diagnosis of NRH can be confirmed only by histopathology.

5.1.1.1.3 Cardiac Toxicity

Patients treated with trastuzumab emtansine are at risk of developing left ventricular dysfunction. LVEF $< 40\%$ has been observed in patients treated with trastuzumab emtansine.

5.1.1.1.4 Infusion-Related Reactions/Hypersensitivity

IRRs (anaphylactoid/cytokine release reactions) and hypersensitivity (anaphylactic/allergic reactions) may occur with the administration of monoclonal antibodies and have been reported with trastuzumab emtansine. Treatment with trastuzumab emtansine has not been studied in patients who had trastuzumab permanently discontinued because of an IRR/hypersensitivity; treatment with trastuzumab emtansine is not recommended for these patients.

IRRs, characterized by one or more of the following symptoms—flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia—have been reported in clinical trials of trastuzumab emtansine. In general, these symptoms were not severe. In most patients, these reactions resolved over the course of several hours to a day after the infusion was terminated. Serious hypersensitivity (anaphylactic-like reactions) has been observed in clinical trials of trastuzumab emtansine.

Administration of trastuzumab emtansine will be performed in a setting with access to emergency facilities and staff who are trained to monitor and respond to medical emergencies. Patients will be observed closely for infusion-related/hypersensitivity reactions during and after each trastuzumab emtansine infusion. Premedication is allowed according to standard practice guidelines. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), trastuzumab emtansine treatment must be permanently discontinued.

5.1.1.1.5 Thrombocytopenia

Thrombocytopenia, or decreased platelet count, was reported in patients in clinical trials of trastuzumab emtansine. The majority of these patients had Grade 1 or 2 events ($\geq$50,000/mm^3), with the nadir occurring by Day 8 and generally improving to Grade 0 or 1 ($\geq$75,000/mm^3) by the next scheduled dose. In clinical trials, the incidence and severity of thrombocytopenia were higher in Asian patients. Among Asian patients, the incidence of thrombocytopenia was higher (52.5%) compared with the overall population (30.4%) in Study TDM4370g. However, the incidence rate of Grade $\geq$2 hemorrhage did not increase in Asian patients compared with the overall population.

Cases of bleeding events with a fatal outcome have been observed. Independent of race, cases of severe hemorrhagic events, including central nervous system hemorrhage, have been reported in clinical trials with trastuzumab emtansine. In some of the observed cases, the patients were also receiving anti-coagulation therapy. Patients on anti-coagulant treatment have to be monitored closely during treatment with trastuzumab emtansine. Platelet counts will need to be monitored prior to each trastuzumab emtansine dose.

5.1.1.1.6 Neurotoxicity

Peripheral neuropathy, mainly Grade 1 and predominantly sensory, has been reported in clinical trials of trastuzumab emtansine. Patients should be examined for signs of peripheral neuropathy prior to each dose of trastuzumab emtansine.

5.1.1.1.7 Extravasation

In trastuzumab emtansine clinical studies, reactions secondary to extravasation have been observed. These reactions were usually mild and comprised erythema, tenderness, skin irritation, pain, or swelling at the infusion site. Rare reports of more severe events, such as cellulitis, pain (tenderness and burning sensation), and skin irritation, have been received as part of the continuing surveillance of trastuzumab emtansine safety. These reactions have been observed more frequently within 24 hours of infusion. Specific treatment for trastuzumab emtansine extravasation is unknown at this time. The infusion site should be closely monitored for possible subcutaneous infiltration during drug administration.

5.1.1.2 Pertuzumab

Overall, safety data indicates that pertuzumab is well tolerated as monotherapy and that it can be given in combination with trastuzumab and a range of other therapeutic agents with manageable toxicities. No unexpected toxicities of pertuzumab were encountered other than those known for agents that target the HER family of receptors (see details in Section 5.1.1.2.1 and Section 5.1.1.2.2). IRRs (chills, fatigue, headache, nausea, and pyrexia), hypersensitivity reactions and anaphylaxis, neutropenia/febrile neutropenia, diarrhea, mucositis, rash, and left ventricular dysfunction are adverse events (AEs) of particular clinical relevance for this study. Diarrhea has been observed in approximately 60% of patients (treatment-related diarrhea in 50% of patients) being treated with pertuzumab in Phase II single-agent studies and in up to 90% of patients in combination therapy studies. Diarrhea was Grade 1 or 2 in the majority of cases. Rash has been observed in approximately 17% of patients receiving pertuzumab in Phase II single-agent studies and up to 73% of patients in combination studies. The rash was generally Grade 1 or 2 in severity. The toxicities described above are to be closely monitored during the course of the study as detailed in Section 5.1.4 and/or in the Pertuzumab Investigator's Brochure.

Serious or severe infusion-associated symptoms have been observed rarely in patients receiving pertuzumab. A low level of cardiac AEs, predominantly asymptomatic declines in LVEF, has been reported. In the pivotal Phase III Study WO20698/TOC4129g, the rates of symptomatic and asymptomatic LVSD were lower in patients receiving pertuzumab than in those receiving placebo.

Because of pertuzumab's role in inhibiting heterodimerization with EGFR, there is a potential risk of ILD with pertuzumab treatment. However, few reports of ILD have been received from patients receiving pertuzumab, and, in all cases, these indicated alternative possible causes for the events (e.g., concomitant medication, preceding/concurrent neutropenia with potential infection, relevant medical history). In Study WO20698/TOC4129g, 2.2% of patients receiving pertuzumab developed pneumonitis/ILD, compared with 1.5% of patients receiving placebo. The incidence of Grade ≥ 3 AEs was similar in both treatment arms (0.7% in the pertuzumab-treated arm vs. 0.5% in the placebo-controlled arm).

5.1.1.2.1 Single-Agent Pertuzumab

The most commonly reported AEs in patients ($n = 386$) receiving single-agent pertuzumab were diarrhea, fatigue, nausea, vomiting, and decreased appetite. The majority of AEs reported were Grade 1 or 2 in severity, and the proportion of patients across the pertuzumab program who have discontinued study medication as a result of AEs is low.

5.1.1.2.2 Pertuzumab in Combination with Trastuzumab and Docetaxel

Pertuzumab was well tolerated in combination with trastuzumab (Study WO20697 and Study BO17929), with an increase in the incidence but not severity of the common AEs

seen with single-agent pertuzumab (notably diarrhea, rash, and fatigue). Pertuzumab also added little toxicity (predominantly diarrhea and febrile neutropenia) to the AE profile of trastuzumab and docetaxel when all three drugs were used concurrently (Study WO20698/TOC4129g and Study WO20697), and had minor impact on the doses received, interruptions, discontinuations, or treatment-related mortality. Diarrhea, rash, mucosal inflammation, febrile neutropenia, pruritus, and dry skin were more common (>5% difference) in patients receiving the pertuzumab+trastuzumab+docetaxel regimen than in patients in the placebo-controlled arm in Study WO20698/TOC4129g.

Importantly, despite targeting the same HER2 pathway, pertuzumab adds no significant cardiac toxicity when given with trastuzumab (with or without chemotherapy).

An increased incidence of febrile neutropenia was observed for Asian patients in both treatment arms compared with patients of other races and from other geographic regions. Among Asian patients, the incidence of febrile neutropenia was higher in the pertuzumab-treated group (26%) compared with the placebo-treated group (12%) in Study WO20698/TOC4129g.

Please refer to the Investigator's Brochure for full description of the pertuzumab safety profile, warnings, precautions, and guidance for investigators.

5.1.1.3 Trastuzumab and Adjuvant Chemotherapy Agents

For adverse reactions, warnings, precautions, contraindications, requirements for contraception duration, and concomitant medications for trastuzumab, doxorubicin, epirubicin, cyclophosphamide, 5-fluorouracil, paclitaxel, and docetaxel, refer to local prescribing information.

Dose modifications for overlapping toxicities with study drugs are detailed in Section 5.1.4.

5.1.2 Safety Considerations for Eligibility and Safety Assessments

To mitigate the potential for treatment-related toxicities in the study, patients with the following characteristics will be excluded from participation in the study because of the risks associated with the study drugs as described in Section 5.1.1:

- Inadequate organ function as indicated by abnormal laboratory tests specified in Section 4.1.2
- Known active liver disease
- LVEF <55%, cardiopulmonary dysfunction including history of past symptomatic CHF, myocardial infarction within 12 months
- Pregnant or lactating women

All patients will be closely monitored for safety and tolerability during study treatment and during follow-up if they meet the criteria for long-term safety follow-up. LVEF will be

monitored up to 5 years of survival follow-up. Abnormal platelet count, ALT, AST, and total and/or direct bilirubin will be followed at a minimum of every 4 weeks (monthly) until normalization or until they are clinically stable as assessed by the investigator. Any AE that is believed to be related to prior study drug treatment will be followed beyond study completion. The investigator will be instructed to notify the Sponsor of any death, SAE, or other AE of concern occurring at any time after a patient has discontinued study participation, if the event is believed to be related to prior study drug treatment, even after the completion of this study (see Appendix 1 and Section 5.5 and Section 5.6 for details). Patients will be assessed for toxicity before each dose. Dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

Clinical and laboratory AEs will be reported according to the NCI CTCAE v4.0. In addition, cardiovascular side effects will be reported according to predefined criteria (NCI CTCAE and NYHA).

The study will also utilize iDMC and CEC (Section 3.1.1 and Section 3.1.2) to routinely monitor accruing patient safety data. The CEC will adjudicate prespecified safety events of interest (cardiac and hepatic dysfunction events) and communicate their findings regarding cardiac and hepatic events to the iDMC to aid iDMC review.

An interim safety analysis (Section 6.8.2) is planned to evaluate protocol-specified hepatic events and overall death rate to ensure patient safety.

5.1.3 General Guidance for Dose Modifications and Delays

Chemotherapy and trastuzumab emtansine doses may be delayed and/or reduced and trastuzumab and pertuzumab may be delayed as a result of toxicities. No dose reductions are allowed for trastuzumab or pertuzumab.

Patients will be instructed to notify their physician immediately for any and all toxicities. NCI CTCAE v4.0 must be used to grade the severity of AEs. Assessment of causality (chronology, confounding factors, concomitant medications, diagnostic tests, and previous experience with the study treatment) should be conducted by the investigator prior to dose modification and/or delay whenever possible.

As a general approach, it is suggested that all AEs be managed with supportive care, when possible, at the earliest signs of toxicity. Should this be ineffective, a dose delay or dose reduction may be considered to avoid worsening toxicity.

All dose modifications should be based on the AE requiring the greatest modification and should be properly documented in source documents. Investigators may take a more conservative approach than the guidelines outlined in the protocol on the basis of clinical judgment that this is in the best interest of their patients.

For protocol-approved anthracyline regimens (i.e., FEC, AC/EC, or dose-dense AC/EC), please refer to local prescribing information for AE management and dose delay/modifications.

For taxane, trastuzumab, pertuzumab, and trastuzumab emtansine, general guidelines on dose delay and modifications are detailed in the following subsections. Please refer to Section 5.1.4 for guidance on management of specific AEs related to study treatment safety profiles. Local prescribing information for taxane may be followed in case of discrepancy between the local prescribing information and the general guidelines provided in the protocol. Please refer to local prescribing information for taxane for dose delay and modifications details that are not specified in the protocol.

5.1.3.1 Dose Delays and Dose Reductions

General guidelines on dose delays for study treatment–related toxicity, other than those specified in Section 5.1.4, are as follows:

- If the patient has not recovered from significant treatment-related toxicities to Grade 1 or baseline, the next scheduled dose may be delayed for up to 42 days from last dose for the q3w regimen or 28 days from the last dose for qw paclitaxel (Arm 1 only). The definitions of “significant” and “related” will be based on the judgment of the investigator (in consultation with the Sponsor’s Medical Monitor or designee, when appropriate). For example, alopecia, even if considered related, would most likely not be considered to be significant. Fatigue may or may not be considered related or significant.
- After a treatment delay, study therapy should be resumed as soon as possible. In general, when the significant and related toxicity (or any other toxicity for which the investigator has chosen to delay dosing) resolves to Grade 1 or baseline, the patient may resume study treatment if the delay has not exceeded the timeframe defined above for corresponding dosing schedule. Patients should be re-evaluated at least qw during the delay, whenever possible. If dosing resumes, a patient may receive study treatment at the previous dose or at a reduced dose per investigator’s clinical judgment if applicable (unless a reduced dose is required as described in Section 5.1.4). If a patient requires a dose reduction, dosing will be reduced by one dose level at a time (see Table 12).
- In the event that any of the individual study drugs in a regimen is delayed as a result of toxicity, the administration of other agents may be continued based on the following guidelines:

  If trastuzumab or trastuzumab emtansine is delayed, pertuzumab should also be withheld.

  If pertuzumab is withheld, trastuzumab or trastuzumab emtansine may continue. Do not make up missed pertuzumab dose.

  During the taxane-concurrent phase (Arm 1 only), taxane treatment may continue if trastuzumab and/or pertuzumab is withheld. If taxane is withheld,

trastuzumab and pertuzumab may continue. Whether to make up for missed taxane dose is at the investigator's clinical discretion.

- During each 3-week cycle, 3 weeks of qw paclitaxel should be given. If a paclitaxel dose is missed during a cycle, the subsequent cycle should not be delayed for trastuzumab and pertuzumab.

Table 12 Dose Reduction Levels for Taxane (Arm 1) and Trastuzumab Emtansine (Arm 2)

Drug	Dose Level 0 (Starting Dose)	Dose Level –1	Dose Level –2	Dose Level –3
Docetaxel (mg/m^2)	100	75	60	Discontinue
Docetaxel (mg/m^2)	75	60	50	Discontinue
Paclitaxel (mg/m^2)	80	65	Discontinue	NA
Trastuzumab emtansine (mg/kg)	3.6	3.0	2.4	Discontinue

A = doxorubicin; C = cyclophosphamide; E = epirubicin; F = 5-fluorouracil; NA = Not applicable.

Note: Please refer to local prescribing information for dose reduction levels for protocol-approved anthracyline regimens (i.e., FEC, AC/EC, or dose-dense AC/EC).

5.1.3.2 Dose Discontinuation

In case of unacceptable toxicity, the following general rules should apply to determine study treatment discontinuation/continuation:

- If toxicity does not resolve within the timeframe defined in the protocol or does not resolve after level(s) of dose reduction per the protocol (see Table 12), the patient will discontinue the study drug(s) that caused dose delay/reduction.
- Patients who discontinue chemotherapy (one or more agents) because of toxicity should not be systematically withdrawn from all study treatments. The remaining study treatment should be continued based on the following guidelines:

  Patients who discontinue anthracyclines because of toxicity before completion of anthracycline dosing period may start taxanes and/or HER2-targeted treatment at the investigator's discretion, as long as criteria defined in Section 4.3.2.2 are met to start taxane and/or HER2-targeted agents following anthracyclines.

  During the taxane-concurrent phase (Arm 1), patients who discontinue taxanes because of toxicity should complete 1 year of HER2-targeted treatment if possible.

- For patients who discontinue one or more HER2-targeted agents because of toxicity, the rules listed below will apply.

  During the taxane-concurrent phase (Arm 1 only), taxane treatment should be continued to complete 3-4 cycles/12 weeks if possible.

Trastuzumab (Arm 1) or trastuzumab emtansine (Arm 2) may be continued if pertuzumab has been discontinued because of pertuzumab-specific toxicity (e.g., diarrhea or rash).

In Arm 1, if trastuzumab is discontinued because of toxicity, then pertuzumab must also be discontinued. Patients will continue to have safety, efficacy, and survival follow-up per the protocol.

In Arm 2, in the case of trastuzumab emtansine–specific toxicity (e.g., thrombocytopenia or hepatotoxicity), trastuzumab should be considered to replace trastuzumab emtansine for up to 1 year of HER2-targeted therapy, if considered appropriate by the investigator. Pertuzumab may be continued with trastuzumab treatment.

In Arm 2, if trastuzumab emtansine is discontinued because of toxicity that precludes the substitution to trastuzumab (such as cardiac toxicity or infusion reaction), then pertuzumab must also be discontinued. Patients will continue to have safety, efficacy, and survival follow-up per the protocol.

5.1.4 Dose Modifications/Management for Specific Adverse Events

Please refer to local prescribing information/institution guidelines for AE management and dose modifications for protocol-approved anthracyline regimens (i.e., FEC, AC/EC, or dose-dense AC/EC).

Please refer to local prescribing information for docetaxel, paclitaxel, trastuzumab, and/or pertuzumab for managing toxicities that are not described in detail in the protocol, including reversible chemotherapy-induced myelosuppression.

Guidance on management of specific AEs related to study treatment safety profiles is provided in the following subsections for HER2-targeted agents and taxanes.

5.1.4.1 Specific Adverse Events for Multiple Agents

During study treatment, some toxicity may be attributable to multiple agents. It is important to evaluate the possible cause of toxicity and weigh risk versus benefit for each agent to determine the schema of dose modifications (e.g., which agent to prioritize for maintaining dose level and the sequence of dose modifications).

General guidelines are provided in the following subsections based on the known safety profile of study drugs.

5.1.4.1.1 Infusion-Related Reactions

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with trastuzumab, trastuzumab emtansine, and pertuzumab. Refer to Table 13 for guidance on management of IRR/allergic/hypersensitivity reactions.

Table 13 Management of Infusion-Related Reactions/Hypersensitivity Reactions

Event	Action to be Taken with HER2-Directed Therapy
Grade 4 IRR/allergic/hypersensitivity reaction	Stop infusion. Study treatment should be permanently discontinued. Supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids may be used, as appropriate, at the investigator's discretion. Patients should be monitored until complete resolution of symptoms.
Grade 3 IRR/allergic/hypersensitivity reaction	Stop infusion. Supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids may be used, as appropriate, at the investigator's discretion. Patients should be monitored until complete resolution of symptoms. May re-treat at investigator's discretion. **In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), study treatment should be permanently discontinued**. Premedication with corticosteroids, antihistamines, and antipyretics may be used before subsequent infusions, at the investigator's discretion.
Grade 2 IRR/allergic/hypersensitivity reaction	Decrease infusion rate by 50% or interrupt infusion. Supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids may be used as appropriate at the investigator's discretion. Patients should be monitored until complete resolution of symptoms. When symptoms have completely resolved, infusion may be restarted at ≤50% of prior rate and increased in 50% increments every 30 minutes as tolerated. Infusions may be restarted at the full rate at the next cycle, with appropriate monitoring. **In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), study treatment must be permanently discontinued.** Premedication with corticosteroids, antihistamines, and antipyretics may be used before subsequent infusions, at the investigator's discretion.

HER2 = human epidermal growth factor-2; IRR = infusion-related reaction.

5.1.4.1.2 Pneumonitis/Interstitial Lung Disease

Pneumonitis/ILD has been reported with trastuzumab emtansine, trastuzumab, pertuzumab, docetaxel, paclitaxel, or radiation. Guidance on dose modifications/delays for pneumonitis/ILD is provided in Table 14.

Table 14 Dose Modification/Delays for Pneumonitis/Interstitial Lung Disease Adverse Events

Adverse Event (NCI CTCAE v4.0)	Docetaxel/Paclitaxel, Trastuzumab Emtansine, Trastuzumab/Pertuzumab, or Radiation
Interstitial lung disease/pneumonitis Grade 1 or 2	Discontinue study treatment permanently if not radiotherapy-related and suspected to be caused by study treatment. For symptomatic (Grade 2) radiotherapy- related pneumonitis, discontinue if not resolving with standard treatment (e.g., steroids). Relationship to radiotherapy should be determined on the basis of timing and location of radiographic abnormalities relative to the radiation treatment. Patients discontinued from trastuzumab emtansine for pneumonitis may not continue study treatment with trastuzumab.
Interstitial lung disease/pneumonitis Grade 3 or 4	Discontinue all study treatment permanently regardless of attribution.

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

5.1.4.1.3 Neuropathy

Neuropathy has been reported with trastuzumab emtansine, paclitaxel, and docetaxel. Guidance on dose modifications/delays for neuropathy is provided in Table 15.

Table 15 Dose Modification/Delays for Neuropathy

Paresthesias/Dysesthesias Persistent for > 7 Days or Causing the Next Cycle to be Delayed	Docetaxel/Paclitaxel	Trastuzumab Emtansine
Grade 1 paresthesias/dysesthesias that do not interfere with function	Maintain dose	Maintain dose
Grade 2 paresthesias/dysesthesias that interfere with function but not activities of daily living	Continue to treat with dose reduced one level	Maintain dose
Grade 3 paresthesias/dysesthesias with pain or with function impairment that interfere with activities of daily living	Withhold therapy dose until neuropathy < Grade 3. Reduce one dose level.	Withhold therapy dose until neuropathy < Grade 3. May consider reducing one dose level.
Grade 4 persistent paresthesias/dysesthesias that are disabling or life-threatening	Discontinue therapy.	Discontinue therapy if event does not resolve to Grade < 3 within 42 days.

5.1.4.1.4 Cardiovascular Safety Assessments and Dose Modifications Due to Cardiovascular Events

All patients will undergo scheduled LVEF assessments: ECHO or MUGA scans (Schedule of Assessments). The results of the LVEF assessments will be used to determine whether trastuzumab, pertuzumab, and trastuzumab emtansine administration can be continued (Schedule of Assessments).

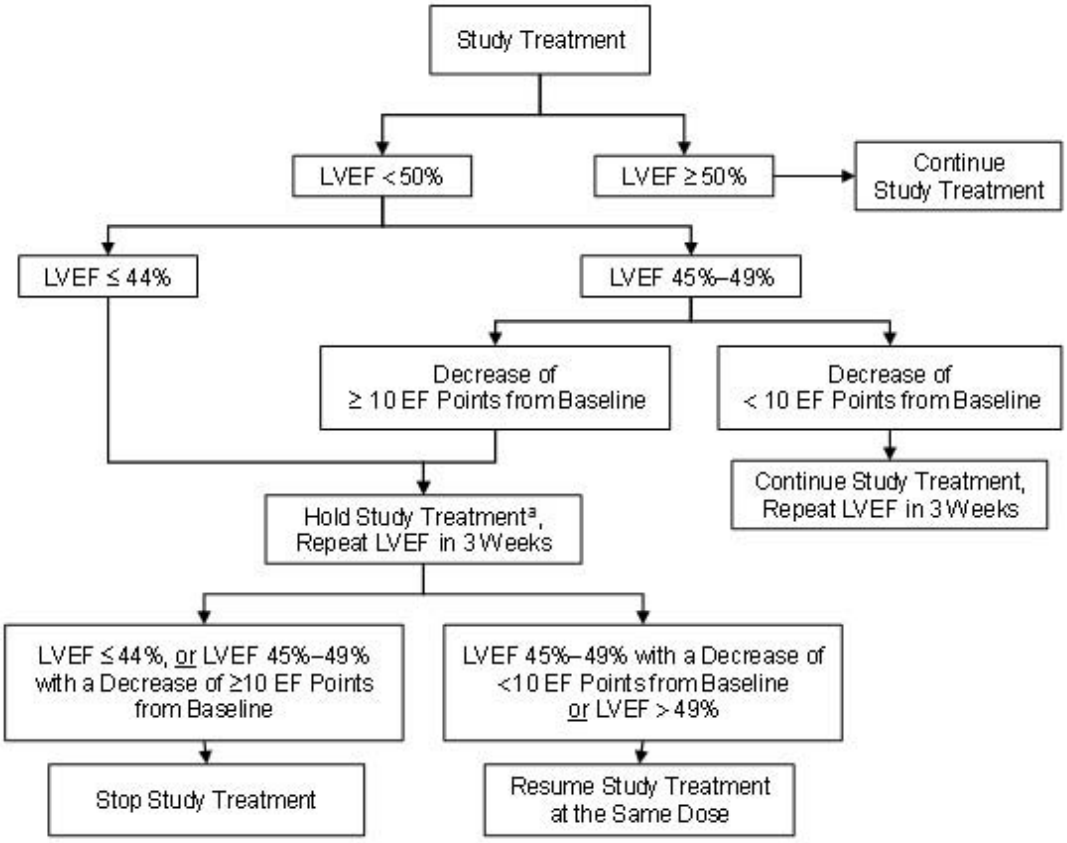
Asymptomatic Decrease in LVEF

Refer to Figure 2 for the algorithm for continuation and discontinuation of study treatment on the basis of asymptomatic LVEF assessment.

Grade 3–4 LVSD; Grade 3–4 Heart Failure; or Grade 2 Heart Failure Accompanied by LVEF <45%

Patients should be permanently discontinued from HER2-targeted treatment. An SAE should be reported.

Figure 2 HER2-Directed Therapy Management Based on LVEF Assessments



EF = ejection fraction; LVEF = left ventricular ejection fraction.

Note: Baseline refers to the screening LVEF.

[a] Three intermittent holds of study treatment will lead to discontinuation.

5.1.4.2 Specific Adverse Events for Individual Agents

For toxicities that have not been described in Section 5.1.3.1 and are likely to be attributable to trastuzumab, docetaxel, or paclitaxel on the basis of known safety profiles of these drugs, please refer to local prescribing information/institution guidelines for AE management and dose modifications.

For toxicities that are likely to be attributable to trastuzumab emtansine or pertuzumab, please refer to the following subsections. For some of the toxicities listed below, the investigator may consider modifying the dose of other agent(s) as well, on the basis of *the investigator's* clinical judgment (e.g., rash and diarrhea may be attributed to both pertuzumab and chemotherapy).

For neutropenia that is likely to be attributable to taxanes, please refer to local prescribing information in case of discrepancy between local prescribing information and the general guidelines (see Table 17) provided in the protocol.

5.1.4.2.1 Trastuzumab Emtansine

Guidelines for managing trastuzumab emtansine specific AEs are provided in Table 16. Please refer to the Investigator's Brochure for a full description of trastuzumab emtansine-related AE management and dose modification guidelines.

Table 16 Dose Modification/Delays for Trastuzumab Emtansine–Specific Adverse Events

Event	Action to Be Taken
Hepatotoxicity	
ALT	For a Grade 2–3 increase in ALT that occurs on the laboratory evaluation for cycle Day 1 or the planned day of dosing, hold trastuzumab emtansine until ALT recovers to ≤ Grade 1. Resume with dose reduction by one level for Grade 2 or 3 elevations. Grade 2 or 3 ALT elevations that are noted between cycles do not require dose delay or reduction unless ALT remains elevated (≥ Grade 2) at the time of planned dosing. For a Grade 4 increase in ALT, discontinue trastuzumab emtansine. A repeat laboratory evaluation (within 24 hours) may be done to exclude laboratory error prior to discontinuing study treatment.

Event	Action to Be Taken
AST	For a Grade 2 increase in AST on the laboratory evaluation for cycle Day 1 or the planned day of dosing, hold trastuzumab emtansine until AST recovers to $\leq$ Grade 1. Resume without dose reduction when AST has recovered. For Grade 3 increase in AST on the laboratory evaluation for cycle Day 1 or the planned day of dosing, hold trastuzumab emtansine until AST recovers to $\leq$ Grade 1. Resume with dose reduction by one level when AST has recovered. For Grade 4 increase in AST, discontinue trastuzumab emtansine. A repeat laboratory evaluation (within 24 hours) may be done to exclude laboratory error prior to discontinuing study treatment.
TBILI	For TBILI $> 1.0 \times$ ULN to $\leq 2.0 \times$ ULN that occurs on the laboratory evaluation for cycle Day 1 or the day of planned dosing, hold trastuzumab emtansine until TBILI recovers to $\leq 1.0 \times$ ULN (or direct bilirubin recovers to $\leq 1.0 \times$ ULN for patients with Gilbert's syndrome). For TBILI elevations $> 1.0 \times$ ULN to $\leq 2.0 \times$ ULN, resume when recovered, with a one-level dose reduction. For TBILI $> 2 \times$ ULN at any time (or direct bilirubin $> 2 \times$ ULN for patients with Gilbert's syndrome), discontinue trastuzumab emtansine and report the event as an SAE (if applicable) or non-serious expedited AE (if applicable).
NRH	For any clinical signs of liver dysfunction, discontinue trastuzumab emtansine and have the patient evaluated by a hepatologist. If there are signs of portal hypertension (e.g., ascites and/or varices) and a cirrhosis-like pattern is seen on CT scan of the liver, the possibility of NRH should be considered. For liver biopsy guidelines, please see Appendix 5. Trastuzumab emtansine should be permanently discontinued in the event of a diagnosis of NRH. Note: Assess AST, ALT, and TBILI qw or as medically indicated until recovery. Allow a maximum dose delay of 42 days from the last administered dose to recovery as described above or otherwise discontinue study treatment. For ALT or AST $> 3.0 \times$ ULN concurrent with TBILI $> 2.0 \times$ ULN, discontinue trastuzumab emtansine permanently.
Thrombocytopenia	
Grade 2 or 3 on day of scheduled treatment	Assess platelet counts qw or as medically indicated until recovery. Hold study treatment until Grade ≤ 1. Resume treatment without dose reduction. If a patient requires two delays due to thrombocytopenia, consider reducing dose by one level.
Grade 4 at any time	Assess platelet counts qw or as medically indicated until recovery. Hold trastuzumab emtansine until Grade ≤ 1, then resume with one-level dose reduction (i.e., from 3.6 to 3 mg/kg or from 3 to 2.4 mg/kg) in subsequent cycles. If event occurs with 2.4 mg/kg dose, discontinue study treatment.
Other Hematologic Toxicity	

Event	Action to Be Taken
Grade ≥ 3	Withhold study treatment until recovery to ≤ Grade 2. Weekly CBC assessments should be done until recovery, or as medically indicated. A maximum dose delay of 42 days from the last administered dose to Grade ≤ 2 or baseline will be allowed; otherwise, patient must be discontinued from study treatment.

AE = adverse event; CT = computed tomography; NRH = nodular regenerative hyperplasia; qw = weekly; SAE = serious adverse event; TBILI = total bilirubin; ULN = upper limit of normal.

5.1.4.2.2 Pertuzumab

Pertuzumab dose may be delayed because of toxicities. Pertuzumab dose modifications are not permitted.

Diarrhea and rash are considered EGFR-related risks on the basis of the mechanism of action of pertuzumab. To prevent dehydration, early treatment of diarrhea with anti-diarrheal medication should be considered, and patients should be treated with fluids and electrolyte replacement, as clinically indicated. Treatment recommendations for EGFR-associated rash include topical or oral antibiotics, topical pimecrolimus, and topical or (for severe reactions) systemic steroids. These agents may be used in patients experiencing pertuzumab-related rash, as clinically indicated; although they have not been studied in this context.

Please refer to the Investigator's Brochure for full description of pertuzumab-related AE management and dose delay guidelines.

5.1.4.2.3 Taxane

General guidelines on managing taxane-related neutropenia are provided in Table 17. Please refer to local prescribing information in case of discrepancy between local prescribing information and the general guidelines provided in the protocol.

Table 17 Dose Modifications and Delays for Docetaxel- or Paclitaxel-Related Neutropenia

For AEs that occur during a cycle but resolve prior to the next treatment cycle	For Grades 2–4 Maintain dose
For AEs that require a delay in administration of the treatment cycle	For Grades 2–4 For docetaxel: Hold until ≥ 1500/mm^3. If recovery takes 1–3 weeks, maintain dose and add G-CSF. If receiving G-CSF and recovery takes 1 week: maintain dose 2–3 weeks: reduce one dose level For paclitaxel: Hold until ≥ 1000/mm^3. If recovery takes 1–3 weeks, maintain dose and add G-CSF. If receiving G-CSF and recovery takes 1 week: maintain dose 2–3 weeks: reduce one dose level

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

5.1.4.3 Radiotherapy Toxicity

For radiotherapy-related skin toxicity Grade 3–4 (e.g., moist desquamation), study treatment should be held until recovery to Grade ≤ 1.

For radiotherapy pneumonitis, refer to Table 14.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A SAE is any AE that meets any of the following criteria:

- Fatal (i.e., the AE actually causes or leads to death)
- Life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any AE that, had it occurred in a more severe form or was allowed to continue, might have caused death.

- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10).
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

SAEs are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

AEs of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). AEs of special interest for this study include the following:

- Potential cases of DILI as assessed by laboratory criteria for Hy's law regardless of seriousness criteria and causality. The following laboratory abnormalities define potential Hy's Law cases:

  Treatment-emergent serum ALT and/or AST $> 3 \times$ ULN concurrent with serum TBILI $> 2 \times$ ULN

  Treatment-emergent serum ALT and/or AST $> 3 \times$ ULN concurrent with clinical jaundice

- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a medicinal product. This term applies ONLY when a contamination of the study drug is suspected, NOT for infections supported by the mode of action (e.g., immunosuppression.)

5.2.4 Selected Adverse Events

Additional data will be collected for the selected AEs described below.

5.2.4.1 Cardiac General

Symptomatic LVSD should be reported as an SAE. If the diagnosis is heart failure, it should be reported as such and not in terms of the individual signs and symptoms thereof.

Heart failure should be graded according to NCI CTCAE v4.0 for "heart failure" (Grade 2, 3, 4, or 5) and in addition according to the NYHA classification.

Heart failure occurring during the study and post-study (Section 5.6) must be reported, irrespective of causal relationship, and followed until one of the following occurs: resolution or improvement to baseline status, no further improvement can be expected, or death.

5.2.4.2 Asymptomatic Left Ventricular Systolic Dysfunction

Asymptomatic declines in LVEF should generally not be reported as AEs because LVEF data are collected separately in the eCRF. Exceptions to this rule are as follows:

- An asymptomatic decline in LVEF $\geq$10 percentage-points from baseline to an LVEF $<$50% must be reported as an AE with the term "ejection fraction decreased" as per NCI CTCAE v4.0, and, in addition, a comment in the AE comments field should confirm that this was asymptomatic.
- An asymptomatic decline in LVEF requiring treatment delay or leading to discontinuation of trastuzumab emtansine, pertuzumab, or trastuzumab must also be reported.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4–Section 5.6.

For each AE recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on AEs at each patient contact. All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only SAEs caused by a protocol-mandated intervention should be reported (e.g., SAEs related to invasive procedures such as biopsies).

After initiation of study drug, all AEs, regardless of relationship to study drug, will be reported until 28 days after the last dose of study drug. After this period, investigators should report any deaths, SAEs, or other AEs of concern that are believed to be related to prior treatment with study drug (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The AE severity grading scale for the NCI CTCAE (v4.0) will be used for assessing AE severity. Table 18 will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

Table 18 Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living[a]
3	Severe or medically significant, but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living[b,c]
4	Life-threatening consequences or urgent intervention indicated[d]
5	Death related to AE[d]

AE = adverse event; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the NCI CTCAE (v4.0), which can be found at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a SAE (see Section 5.4.2 for reporting instructions), per the definition of SAE in Section 5.2.2.

[d] Grade 4 and Grade 5 events must be reported as SAEs (see Section 5.4.2 for reporting instructions), per the definition of SAE in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one AE term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

Infusion-Related Reactions

AEs that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., infusion-related reaction" or "allergic reaction", "hypersensitivity," "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and a systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

Other Adverse Events

For AEs other than IRRs, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously

reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. *The initial severity (intensity or grade) of the event should be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, then the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any increases in severity should be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, then it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.*

A recurrent AE is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin $5 \times$ ULN associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Hepatotoxicity

The finding of an elevated ALT or AST ($>3\times$ ULN value) in combination with either an elevated TBILI ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ ULN value in combination with TBILI $>2\times$ ULN
- Treatment-emergent ALT or AST $>3\times$ ULN value in combination with clinical jaundice

NRH, whether or not accompanied by liver laboratory abnormalities, should be reported to the Sponsor as a SAE.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a SAE or a non-SAE of special interest (see Section 5.4.2).

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified AE reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of breast cancer should be recorded only on the Study Completion/Early Discontinuation eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or

without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Recurrence/Progression of Breast Cancer

Events that are clearly consistent with the expected pattern of recurrence/progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of recurrence/progression will be based on both clinical and laboratory findings (physical examination, biopsy, breast imaging, radiologic evidence, etc). In rare cases, the determination of clinical recurrence/progression will be based on symptomatic deterioration. However, every effort should be made to document recurrence/progression using objective criteria. If there is any uncertainty as to whether an event is due to disease recurrence/progression, it should be reported as an AE.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE (per the definition of SAE in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

The patient has not suffered an AE

- Hospitalization due solely to recurrence or progression of the underlying cancer

The following hospitalization scenarios are not considered to be SAEs and should be reported as AEs instead:

- Hospitalization for a minor condition for which the patient suffers an AE, but does not meet the definition of an overnight admission (e.g., tooth extraction)

5.3.5.11 Overdoses

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

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

5.3.5.12 Patient-Reported Outcome Data

AE reports will not be derived from PRO data. However, if any patient responses suggestive of a possible AE are identified during site review of the PRO questionnaires, site staff will alert the investigator, who will determine if the criteria for an AE have been met and will document the outcome of this assessment in the patient's medical record per site practice. If the event meets the criteria for an AE, it will be reported on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- SAEs
- AEs of special interest
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor: [redacted], M.D. (primary)

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Alternate Medical Monitor Contact Information for All Sites:

Medical Monitor: [redacted], M.D., *M.S.*

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

For reports of SAEs and non-SAEs of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event/Non-Serious Adverse Event of Special Interest CRF and fax cover sheet should be completed and faxed to Roche Safety Risk Management or its designee immediately

(i.e., no more than 24 hours after learning of the event), with use of the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 7 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC systemsystem. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, a Pregnancy Report worksheet and Pregnancy fax cover sheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via this system.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 7 months after the last dose of study drug. Male patients whose partners are pregnant must use condoms for the duration of the pregnancy.

A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

Additional information on any trastuzumab, pertuzumab, or and trastuzumab emtansine–exposed pregnancy and infant will be requested by Roche Drug Safety at specific timepoints (i.e., after having received the initial report, at the end of the second trimester, 2 weeks after the expected date of delievery, and at 3, 6, and 12 months of the infant's life.)

5.4.3.3 Abortions

Any spontaneous abortion should be classified as a SAE (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as a SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For SAEs, non-serious AEs of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case. Pathologic material, if already obtained to

evaluate the event, may be requested for review by the Sponsor or designee such as CEC.

5.6 POST-STUDY ADVERSE EVENTS

At the study completion/early termination visit, the investigator should instruct each patient to report to the investigator any subsequent AEs that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

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 participation if the event is believed to be related to prior study drug treatment or study procedures. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient who participated in this study.

The investigator should report these events to Roche Safety Risk Management on the Adverse Event eCRF. If the Adverse Event eCRF is no longer available, the investigator should report the event directly to Roche Safety Risk Management via telephone (see "Protocol Administrative and Contact Information & List of Investigators").

During post-study survival follow-up, deaths attributed to progression of breast cancer should be recorded only on the Survival eCRF *or Study Completion/Early Discontinuation eCRF.*

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all SAEs and non-serious AEs of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs/ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Trastuzumab Emtansine Investigator's Brochure
- Pertuzumab Investigator's Brochure
- Trastuzumab Investigator's Brochure
- Summary of Product Characteristics and U.S. and other approved national prescribing information for doxorubicin, epirubicin, cyclophosphamide, 5-fluorouracil, docetaxel, and paclitaxel

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

The iDMC will monitor the incidence of these expected events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The statistical considerations and analysis plan are summarized below. Further details of the analyses will be described in the Statistical Analysis Plan (SAP) as part of the Data Analysis Plan (DAP). The SAP overrides the analyses as described in the study protocol, as applicable.

6.1 DETERMINATION OF SAMPLE SIZE

The sample size of the study is primarily driven by the analysis of IDFS in both the node-positive subpopulation and the overall protocol-defined population. The statistical assumptions for the sample size calculations are summarized in Table 19.

The IDFS analysis is powered at 80% for the node-positive subpopulation. Additionally, the IDFS analysis with the assumptions stated below is powered at *82.5*% for the overall protocol-defined population. It is assumed that the overall protocol-defined population has approximately 10% more patients and 6% more IDFS events than the node-positive subpopulation. These percentages were observed in the BCIRG 006 (Slamon et al. 2006, 2009, 2011) trial after subsetting for the respective populations in this study.

To detect a target HR of 0.64 in IDFS in the overall protocol-defined population and the node-positive subpopulation, approximately 171 and 160 IDFS events will be required to achieve *82.5*% and 80% power, respectively, in the two populations, at a two-sided significance level of 5% using a log-rank test. Approximately *1850 and 1665* patients will be enrolled in the overall protocol-defined population and node-positive subpopulation, respectively, including a dropout/ineligibility rate of 8% for both arms as estimated from previous trials in this setting. The assumed 3-year IDFS rate for the control arms for both the populations were based on the IDFS rate from the BCIRG 006 data for the proposed populations and the assumed target HR from Study BO25126. The six piecewise Kaplan-Meier estimates of the IDFS function in the control group for the overall protocol-defined population and the node-positive subpopulation were 99.6% and 99.5% during the first 6 months, 98.2% and 98.0% during the second 6 months, 93.7% and 93.1% during Year 2, 89.5% and 89.1% during Year 3, 87.7% and 87.1% during

Year 4, and 86.2% and 85.5% during Year 5. With the assumed target HR of 0.64, the estimated 3-year IDFS rate for the experimental arms in each of the two populations is shown in Table 19.

Table 19 Summary of Sample Size Assumptions for IDFS

Population	BCIRG 006 3-Year IDFS for the proposed population AC-TH	Control Group (Study BO25126 [APHINITY]) 3-Year IDFS HR = 0.75 AC-THP	Experimental Group (Study BO28407 [KAITLIN]) 3-Year IDFS HR = 0.64 AC-KP	Power AC-T HP vs. AC-K P	No. IDFS Events	Sample Size
Overall protocol–defined population	86.3%	89.5%	93.2%	*82.5%*	*171*	*1850*
Node-positive subpopulation	85.8%	89.1%	92.9%	*80.0%*	*160*	*1665*

AC-T = doxorubicin + cyclophosphamide followed by docetaxel; H = trastuzumab; HR = hazard ratio; IDFS = invasive disease–free survival; K = trastuzumab emtansine; P = pertuzumab.

A total of approximately 1850 patients are anticipated to be enrolled. The study is expected to be fully enrolled approximately *17* months after FPI. The final IDFS analysis will be performed after at least *160* events have occurred in the node-positive subpopulation and approximately *171* events have occurred in the overall protocol-defined population, which is projected to be approximately *57* months after FPI.

The sample size calculations are performed using EAST v*6* software (Cytel Inc.).

6.2 SUMMARIES OF CONDUCT OF STUDY

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 violations and eligibility violations will be summarized by treatment arm.

6.3 SUMMARIES 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, and medical history. 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.

6.4 EFFICACY ANALYSES

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

6.4.1 Primary Efficacy Endpoint

The primary efficacy variable is IDFS, defined as the time between randomization and date of first occurrence of an IDFS event as described in the Efficacy Outcome Measures section. Data from patients who have not had an event at the time of data analysis will be censored on the date on which they are last known to be alive and event free, on or before the clinical data cutoff date of the respective analysis.

The log-rank test, stratified by the protocol-defined stratification factors (excluding region), will be used to compare IDFS between the two treatment arms. Region will be excluded because of the potential that some of the strata may have very few patients, which would result in a loss of power. The unstratified log-rank test results will also be provided for sensitivity analysis. If, at the time of analysis, it is deemed that the smallest stratum per arm necessary to conduct robust stratified analyses contains <5 events, unstratified analyses will be used as the primary analysis. The Cox proportional hazards model, stratified by the previously noted stratification factors, excluding region, will be used to estimate the HR between the two treatment arms and the corresponding 95% CI. The Kaplan-Meier approach will be used to estimate 3-year IDFS rates and corresponding 95% CIs for each treatment arm.

6.4.2 Secondary Efficacy Endpoints

Secondary endpoints are IDFS plus second primary non-breast cancer, DFS, DRFI (defined in the Efficacy Outcomes Measures section), and OS.

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. Data from patients who have not had an event at the time of data analysis will be censored at the date on which they are last known to be alive and event free or prior to the clinical data cutoff date for the respective analysis.

The Kaplan-Meier approach will be used to estimate 5-year IDFS rates and corresponding 95% CIs for each treatment arm using both the overall protocol-defined population and the node-positive subpopulation.

6.4.3 Hierarchical Testing Procedure

A hierarchical testing procedure will be used in the order given below, on the primary and secondary endpoints to control the overall study type I error rate at 5%.

1. Primary endpoint of IDFS in the node-positive subpopulation
2. Primary endpoint of IDFS in the overall protocol-defined population
3. Secondary endpoint of OS in the node-positive subpopulation
4. Secondary endpoint of OS in the overall protocol-defined population

Details of IDFS and OS interim analyses are specified in the Interim Analyses section.

6.5 SAFETY ANALYSES

Patients who receive any dose of study treatment will be included in the safety analyses. Safety results will be summarized according to actual treatment received. In particular, a patient assigned to trastuzumab who inadvertently receives a dose of trastuzumab emtansine will be analyzed in the trastuzumab emtansine safety group.

The safety of trastuzumab emtansine in combination with pertuzumab and chemotherapy will be assessed through treatment exposure, summaries of AEs (including hepatic and cardiac events), SAEs, LVEF measurements, and laboratory test results, including platelet count, transaminases, and total/direct bilirubin.

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.

Verbatim descriptions of AEs will be mapped to the MedDRA thesaurus terms and graded according to the NCI CTCAE v4.0. All AEs, SAEs, AEs leading to death, and AEs leading to study treatment discontinuation that occur upon or after the first dose of study treatment (i.e., treatment-emergent AEs) 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.

Laboratory abnormalities for each treatment arm will be summarized by NCI CTCAE grade using shift tables.

Incidence of cardiac events, defined as death from cardiac cause or severe CHF (NYHA Class III or IV) with a decrease in LVEF of $\geq$10% or more from baseline to an LVEF of $<$50%, will be summarized for each treatment arm. Other cardiac-related events (e.g., any mild symptomatic CHF [NYHA Class II] associated with a $\geq$10% drop in LVEF to $<$50%; asymptomatic declines in LVEF requiring dose delay or discontinuation) will also be summarized. Change in LVEF from baseline over time will be summarized for each treatment arm.

Incidence of hepatic AEs, pulmonary AEs, pneumonitis, ILD, NRH, and Hy's law cases will be summarized for each treatment arm. Additional analyses of transaminases and liver function laboratory tests will also be performed.

Subgroup safety analyses (e.g., incidence of AEs during radiotherapy for the subgroup of patients who receive radiotherapy) may be performed and will be detailed in the SAP.

6.6 PATIENT-REPORTED OUTCOME ANALYSES

HRQoL data will be captured using the following questionnaires: the EORTC QLQ-C30 and the modified breast cancer module, QLQ-BR23 (Appendix 8).

Summary statistics (mean, SD, median, 25th and 75th percentiles, and range) of linear transformed scores will be reported for all the subscales (including peripheral neuropathy, joint/muscle pain, and skin problems) of the EORTC QLQ-C30 questionnaire and the modified BR23 *for each assessment time-point* according to the EORTC scoring manual guidelines for each assessment timepoint. The mean change of the linear transformed scores from baseline (and 95% CI*s* using the normal approximation) will also be assessed. Line charts depicting the mean changes (and standard errors) of subscales over time will be provided for each treatment arm from the baseline assessment.

Completion and compliance rates will be summarized at each timepoint for each measure by treatment arm with reasons for missing data. Only patients with a baseline assessment and at least one post-treatment assessment will be included in the analyses.

The number and proportion of patients *reporting clinically meaningful differences in treatment-related symptoms based on the threshold reported by Cocks et al. (2011) at each time-point will be the primary analysis. In addition, the proportion of patients reporting "a little" or "quite a bit" for each of the neuropathy, joint/muscle pain and skin single items will be reported by treatment arm.*

The proportion of patients with clinically meaningful deterioration in global health status/HRQoL and function (physical, role, and cognitive) scales will also be assessed. The deterioration will be based on the respective thresholds reported by Osaba et al (1998) and Cocks et al. (2011).

Analysis will be performed to compare the two treatment arms at the "Cycle 1 Day 1 (C1D1) of anthracycline treatment period" timepoint and the "C1D1 of HER2-targeted treatment period" timepoint to descriptively assess treatment group comparability between the two treatment arms. The "'C1D1 of HER2-targeted treatment" timepoint will be utilized as the reference for time-to-event Kaplan-Meier analysis, provided that the treatment groups are comparable at this timepoint.

The time to clinically meaningful deterioration in the global health status/HRQoL subscale (question 29 and 30 of the QLQ-C30) will be used to *assess* the time from first HER2-targeted treatment to worsening in HRQoL. An event for a given patient is a decrease in mean score by 10 points or more, at two consecutive time points, with a 10-point or greater change in mean score defined as a "moderate" to "very much" perceived important change from the patient's perspective (Osoba et al. 1998). *Time-to-event analyses to investigate the time to clinically meaningful deterioration in function (physical, role, and cognitive function scales) will also be assessed using the published thresholds by Cocks et al. (2011).* A stratified log-rank test will be used to test the differences between treatment arms.

Additionally, in order to elucidate if the taxane-sparing arm reduces patient treatment burden, analyse*s* of covariance (*repeated* mixed *effects* model) will be used to compare change from baseline in *the global health status/HRQoL and functional scales of the EORTC QLQ-C30.* In each mixed model, change from baseline will be the response variable; treatment, visit, and treatment by visit interaction terms will be the fixed *factors*; and *the* patient will be *denoted as a repeated factor. If substantial interaction effect is present, pair-wise comparison will be conducted.*

6.7 EXPLORATORY ANALYSES

The relationship between molecular markers (e.g., HER family receptors; see Section 3.4.4) and efficacy outcomes will be evaluated as exploratory analyses. Efficacy outcomes considered for this analysis will include IDFS and OS, as appropriate.

Analyses will also be performed to explore the correlation between biomarkers, ATAs to trastuzumab emtansine, and clinical outcomes as appropriate.

The EQ-5D is a generic, preference-based health utility measure with questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that are used to build a composite of the patient's health status. A single summary index is calculated from the EQ-5D health states after application of a weighted formula and will be utilized in this study for economic modeling. The results will not be reported in the CSR.

6.7.1 Subgroup Analyses for Efficacy

Exploratory analyses (e.g., for subgroups per nodal status, hormonal receptor status, HER2 mRNA expression level status [high vs. low], PIK3CA mutation status, or other important prognostic factors) will be performed for IDFS and OS, as appropriate, in the overall protocol-defined population and node-positive subpopulation to assess the robustness and consistency of treatment effect of trastuzumab emtansine plus pertuzumab.

6.8 INTERIM ANALYSES

6.8.1 Interim Efficacy Analyses

One interim analysis of IDFS and three interim analyses of OS in both the node-positive subpopulation and the overall protocol-defined population are planned.

A futility analysis may be incorporated to evaluate lack of superiority for the treatment arm of trastuzumab emtansine +pertuzumab following anthracyclines. The timing and details of this futility analysis will be described in the SAP and aligned with the availability of information from other relevant studies (e.g., KRISTINE and/or APHINITY).

Interim IDFS Analyses

An interim efficacy analysis of IDFS will be performed after approximately 75% of the targeted IDFS events are observed in the overall protocol-defined population (i.e. 128 of the 171 target events) and node-positive population (i.e. 120 of 160 target events) and is projected to occur approximately *43* months from FPI (see Table 20). A hierarchical testing procedure will be used for the primary endpoint IDFS for the node-positive subpopulation and the overall protocol-defined population as defined in Section 6.4.3. The type I error will be controlled at the 5% level at the interim and final analyses within the node-positive subpopulation and the overall protocol-defined population using a Lan-DeMets α-spending function with an O'Brien-Fleming boundary.

The interim analysis will be performed by the iDCC statistician, and the results will be presented to the iDMC by the iDCC statistician. If the interim analyses in both populations cross the interim efficacy boundaries of the O'Brien-Fleming design, on the basis of the totality of both efficacy and safety data, the iDMC may recommend releasing the primary endpoint results before the targeted number of 160 and 171 events have occurred in the node-positive subpopulation and overall protocol-defined population, respectively. In this case, the Sponsor will be unblinded to study results, and a full data package including the first OS interim analysis results will be prepared for discussion with the regulatory authorities. The study will continue until 10 years of follow-up from FPI have occurred, and the IDFS analysis will be updated descriptively. If the IDFS interim analyses fail to cross the statistical efficacy boundaries of the O'Brien-Fleming design, then the study will continue as planned. The Sponsor will conduct the final analyses.

Table 20 summarizes the planned IDFS analyses in the overall protocol-defined population and the node-positive subpopulation; the efficacy stopping boundaries based on the expected number of events; and the estimated timing of these analyses. The boundaries to be used at each interim and final IDFS analysis will depend on the number of IDFS events actually included in the analyses and so may vary from the numbers shown below.

Table 20 Summary of Planned Analyses of IDFS in Overall Protocol-Defined Population and Node-Positive Subpopulation

Analysis of IDFS	Overall Population		Node-Positive Population		Estimated Timing[c]
	No. of Events	Efficacy Stopping Boundary[a,b]	No. of Events	Efficacy Stopping Boundary[a,b]	
Interim	128	$p < 0.0193$ or observed HR < 0.6618	120	$p < 0.0193$ or observed HR < 0.6528	43 months
Final	171	$p < 0.0442$ or observed HR < 0.7353	160	$p < 0.0442$ or observed HR < 0.7279	57 months

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

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

[b] Efficacy stopping boundaries follow O'Brien-Fleming design.

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

Interim OS Analyses

Three interim OS analyses and one final OS analysis are planned in both the overall protocol-defined population and the node-positive subpopulation. The assumed 3-year OS rate for the control arms for both populations were based on the OS rate from the BCIRG 006 data for the proposed population and the assumed target HR from Study B025126. The five piecewise Kaplan-Meier estimates of the OS function in the control group for the overall protocol-defined population and the node-positive subpopulation were 99.7% and 99.7% during Year 1, 98.6% and 98.5% during Year 2, 96.1% and 95.7% during Year 3, 94.1% and 93.9% during Year 4, and 92.1% and 91.9% during Year 5. The estimated 3-year OS rate for the experimental arms in each of the two populations is shown in Table 21, with an assumed target HR of 0.80 between the control arm (AC-THP) and the experimental arm (AC-KP).

Table 21 Summary of Assumptions for Overall Survival Analyses

Population	BCIRG 006 3-Year OS for the proposed populations AC-TH	Control Group (Study BO25126 [APHINITY]) 3-Year OS AC-THP HR = 0.80	Experimental Group (Study BO28407 [KAITLIN]) 3-Year OS AC-KP HR = 0.80
Overall protocol–defined population	95.2%	96.1%	96.9%
Node-positive subpopulation	94.7%	95.7%	96.6%

AC-T = doxorubicin + cyclophosphamide followed by docetaxel; H = trastuzumab; HR = hazard ratio; IDFS = invasive disease–free survival; K = trastuzumab emtansine; OS = overall survival P = pertuzumab.

For the OS interim analyses and final OS analysis, the Lan-DeMets α-spending function with an O'Brien-Fleming boundary will be used such that the overall type I error will be controlled at the 5% level for the OS endpoint. With the study sample size and approximately 10 years of follow-up from FPI, this study has 38% power in the overall protocol-defined population and 35% power in the node-positive subpopulation to detect an HR of 0.8. This in the overall protocol-defined population corresponds to a 0.8% improvement in 3-year OS, from 96.1% in the control arm to 96.9% in the experimental arm and in the node-positive subpopulation to a 0.9% improvement in 3-year OS, from 95.7% in the control arm to 96.6% in the experimental arm, at a two-sided significance level of 5%.

All OS interim and final analyses will be performed by the Sponsor subsequent to the primary IDFS analysis and after the Sponsor is unblinded. If the interim IDFS analyses in both the node-positive subpopulation and the overall protocol-defined population cross the statistical efficacy boundaries, the first OS interim analysis will be performed in both populations hierarchically at that time (approximately at 43 months from FPI). If the final IDFS analysis crosses the statistical boundaries, then the second interim OS analysis will be performed hierarchically at the time of the final IDFS analysis (approximately 57 months from FPI), followed by the third and the final OS analyses performed hierarchically in both populations (planned to occur at 84 months [7 years] and 120 months [10 years], respectively, from FPI). If, at any OS interim analysis, the O'Brien-Fleming efficacy boundary is crossed, that analysis of OS will be considered as confirmatory and all subsequent analyses of OS will be considered as descriptive.

Table 22 summarizes the planned OS analyses in the overall protocol-defined population and the node-positive subpopulation, respectively; the efficacy stopping boundaries based on the expected number of events; and the estimated timing of these analyses. The boundaries to be used at each interim and final IDFS analysis will depend on the number of IDFS events actually included in the analyses and may vary from the numbers shown below.

Table 22 Summary of Planned Analyses of Overall Survival in Overall Protocol-Defined Population and Node-Positive Subpopulation

	Overall Population		Node-Positive Population		
Analysis of OS	No. of Events	Efficacy Stopping Boundary [a,b]	No. of Events	Efficacy Stopping Boundary [a,b]	Estimated Timing [c]
Interim 1 (Interim IDFS)	*50*	p < 0.*0000033* or observed HR < 0.*2647*	*50*	p < 0.*000013* or observed HR < 0.*2908*	*43* months
Interim 2 (Final IDFS)	*87*	p < 0.*000643* or observed HR < 0.*4811*	*83*	p < 0.*000908* or observed HR < 0.*4827*	*57* months
Interim 3	*153*	p < 0.*01316* or observed HR < 0.*6697*	*138*	p < 0.*01281* or observed HR < 0.*6545*	84 months
Final	*224*	p < 0.*04585* or observed HR < 0.*7658*	*203*	p < 0.*04591* or observed HR < 0.*7556*	120 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] Efficacy stopping boundaries follow O'Brien-Fleming design.

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

6.8.2 Interim Safety Analyses

An iDMC will monitor accruing patient safety data at least once every 6 months during the study until the last patient has completed study treatment. In addition, safety data related to concurrent radiotherapy and/or hormonal therapy, SAEs, and deaths will be monitored by the iDMC at least once every 3 months during the study until the last patient has completed study treatment. At each iDMC review, relevant safety information from ongoing trastuzumab emtansine and/or pertuzumab studies will also be provided to the iDMC.

After the first 600 patients have been randomized and followed for 3 months (anticipated to occur at approximately 13 months after FPI), the iDMC will perform an interim safety analysis regarding overall numbers of deaths (all causes, including cardiac deaths) and hepatic events defined as confirmed Hy's law cases. The CEC will communicate their findings to the iDMC to aid iDMC review.

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

If the true difference in the percentage of death is >3% (e.g., 2% vs. 6%), then there is approximately a 70% chance of observing an absolute difference of >3% at the interim with 600 patients. Table 23 presents the probability of observing an increase of >3% in the percentage of deaths in the trastuzumab emtansine + pertuzumab arm compared with the trastuzumab + pertuzumab arm, with different assumptions for the percentage of deaths in the two treatment arms.

Table 23 Probability of Observing >3% Increase of Death

Percentage of Deaths		
Trastuzumab + Pertuzumab (n=300)	Trastuzumab Emtansine + Pertuzumab (n=300)	Probability of Observing True Treatment Difference >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 CEC) is observed in the trastuzumab emtansine + pertuzumab arm compared with the trastuzumab + pertuzumab arm, the iDMC will consider a recommendation of pausing enrollment for further data review, stopping the trial, 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 a 54% chance of observing an absolute difference of >3% at the interim with 600 patients. Table 24 presents the probability of observing a >3% increase in the percentage of Hy's law cases in the trastuzumab emtansine + pertuzumab arm compared with the trastuzumab + pertuzumab arm, with different assumptions for the number of Hy's law cases in the two treatment arms.

Table 24 Probability of Observing >3% Increase in Confirmed Hy's Law Cases

Number of Confirmed Hy's Law Cases (%)		
Trastuzumab +Pertuzumab (n = 300)	Trastuzumab Emtansine + Pertuzumab (n = 300)	Probability of Observing True Treatment Difference > 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 guidelines defined in the iDMC Charter. The iDMC Charter will contain details regarding frequency of meetings, guidelines for decision making, and processes for requesting further information. The iDMC members will review and sign off the charter before the first iDMC review.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

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

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Data from paper PRO questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the

electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the European Union/EEA will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor’s sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child’s Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the “Consent Forms”) before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

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

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last patient, last visit).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This study will have an SC that will provide guidance on the protocol and study design and the SAP and will provide guidance on the review of any relevant study-related documents or procedures to ensure that the data will be collected in a timely fashion and will be accurate and complete. A separate SC charter will outline the committee's composition, meeting timelines, and members' roles and responsibilities. Additionally, the SC will be kept apprised of all relevant efficacy and safety data from this and related clinical trials.

In addition, the study will have an iDMC and CEC (see Section 3.1.1 and Section 3.1.2).

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

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

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound..,

The investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

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

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Assessments

	Screening[a] (30 days)	Anthracycline Treatment Period	HER2-Targeted Treatment Period within 3 Days of Day 1 of Cycle Number X				End-of-Treatment Visit[b]	Follow-Up[c] (±28 days)		Follow-Up[c] (±42 days)
		Cycles 1[a]–3 or Cycle 4	Cycles 1–4 (concurrent taxane in Arm 1 only)			Cycles 5–18		Year 1–2	Year 3–5	Year 6–10
		Day 1	Day 1	Day 8	Day 15	Day 1				
Informed consent[d]	x									
Mandatory tumor tissue sample for determination of HER2, ER/PR; and exploratory biomarkers[e]	x	x[e] (at disease recurrence)								
Bilateral mammogram[f,g]	x (within 6 months)	x (q12mo)								
Chest X-ray[h]	x (within 2 months)	As clinically indicated								
Demography, medical history	x									
Disease status assessment[g]	x	x (q3mo)						x (q3mo)	x (q6mo)	x (q12mo)
Physical examination[g,i]	x	x (Cycle 1)	x			x	x	x (q3mo)	x (q6mo)	x (q12mo)
Vital signs[j]	x	x	x	x (for paclitaxel only)	x (for paclitaxel only)	x				
ECOG Performance	x						x			

Appendix 1
Schedule of Assessments (cont.)

	Screening[a] (30 days)	Anthracycline Treatment Period	HER2-Targeted Treatment Period within 3 Days of Day 1 of Cycle Number X				End-of-Treatment Visit[b]	Follow-Up[c] (±28 days)		Follow-Up[c] (±42 days)
		Cycles 1[a]–3 or Cycle 4	Cycles 1–4 (concurrent taxane in Arm 1 only)			Cycles 5–18		Year 1–2	Year 3–5	Year 6–10
		Day 1	Day 1	Day 8	Day 15	Day 1				
Status										
ECG	x	As clinically indicated					x			
ECHO/MUGA[k]	x	x[k] (end of last cycle)	x[k] (in last week of Cycle 2, and every 4 cycles thereafter)				x[k]	x[k]	x[k]	
PRO HRQoL assessment[l]		x[l]	x[l]			x[l]	x	x[l] (q6mo)		
Hematology[m]	x[n]	x[o]	x[o]	x[o] (for paclitaxel only)[p]	x[o] (for paclitaxel only)[p]	x[o]	x	x[m]		
Serum chemistry[q]	x[n]	x[o]	x[o]			x[o]	x	x[q]		
HBV and HCV serology[r]	x	As clinically indicated								
INR and aPTT	x[n]	As clinically indicated								
Pregnancy test[s]	x[n]		x[o,s] (C1D1 then every 3 cycles thereafter)					x[s]		
Clinical genotyping whole blood sample[t]		x[t]								
Mandatory serum and plasma sample for exploratory biomarker analysis[u,v]		x (C1D1 predose)	x (C1D1 predose)				x	x[s]		
		x[u] (at disease recurrence)								

Appendix 1
Schedule of Assessments (cont.)

	Screening[a] (30 days)	Anthracycline Treatment Period	HER2-Targeted Treatment Period within 3 Days of Day 1 of Cycle Number X				End-of-Treatment Visit[b]	Follow-Up[c] (±28 days)		Follow-Up[c] (±42 days)
		Cycles 1[a]–3 or Cycle 4	Cycles 1–4 (concurrent taxane in Arm 1 only)			Cycles 5–18		Year 1–2	Year 3–5	Year 6–10
		Day 1	Day 1	Day 8	Day 15	Day 1				
OBRP whole blood sample for genetic analysis (optional)[v]		x[v](to be done at baseline if possible)								
Adverse events[w]	x	x	x	x (for paclitaxel only)	x (for paclitaxel only)	x	x	x[w]		
Concomitant medications[x]	x	x	x	x (for paclitaxel only)	x (for paclitaxel only)	x	x			
Record post-recurrence anti-cancer–related therapies[y]		As required								
Survival post-recurrence[y]		q12mo								

AE = adverse event; ALP = alkaline phosphatase; aPTT = activated partial thromboplastine time; ATA = anti-therapeutic antibody; C1D1 = Cycle 1 Day 1; CT = computed tomography; eCRF = electronic Case Report Form; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D = EuroQol 5-Dimension Questionnaire; FFPE = formalin-fixed paraffin-embedded; FPI = first patient initiation; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCG = human chorionic gonadotropin; HCV = hepatitis C virus; HER2 = human epidermal growth factor-2; HRQoL = health-related quality of life; IDFS = invasive disease–free survival; IVRS/IWRS = interactive voice response system/interactive web response system; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; OBRP = optional biomarker research program; pac = paclitaxel; PK = pharmacokinetic; PR = progesterone receptor; PRO = patient-reported outcome; QLQ-BR23 = Quality of Life Questionnaire–Breast Cancer 23; QLQ-C30 = Quality of Life Questionnaire–Core 30; qw = weekly; SAE = serious adverse event; SoC = standard of care; TBILI = total bilirubin; ULN = upper limit of normal.

[a] Screening to be performed within 30 days prior to randomization. The randomization visit may be combined with anthracycline Cycle 1 Day 1 visit. Patients should receive their first dose of study treatment on the day of randomization, if possible, but no later than 7 days after randomization. No more than 9 weeks (63 days) may elapse between definitive breast surgery (or the last surgery if additional resection required for breast cancer) and randomization.

[b] End-of-treatment visit or early termination visits will optimally be scheduled within 28 to 42 days following the last dose of study treatment.

[c] The follow-up period begins from the date of the end-of-treatment visit, with a duration of up to 10 years from the date of randomization of the first patient.

[d] 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 SoC prior to obtaining informed consent and within 30 days prior to randomization may be used rather than repeating required tests unless the tests are required to be within 7 days prior to randomization.

[e] FFPE tumor tissue must be obtained for central laboratory assessment of HER2 status for eligibility. ER/PR determination will also be evaluated by a central laboratory. A tissue block (FFPE material) collected at definitive breast cancer surgery is acceptable. Sections and/or slides are not acceptable. Biomarker analysis will only be performed on tissue from randomized patients. At recurrence, tumor biopsy sample should be taken if the tumor is accessible for biopsy sample collection without (in the investigator's opinion) significant risk to the patient. In case tissue becomes available at time of recurrence, this tissue will be used for exploratory biomarker analysis. 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.

[f] Bilateral mammogram (or breast MRI if indicated) is to be performed within 6 months prior to randomization. *If mammogram is not available, then it could be performed after surgery.* During treatment and follow-up, mammograms of any remaining breast tissue should be performed at least annually *(±28 days)* since the previous mammogram. *If there is no remaining breast tissue, then mammograms are not mandated.*

[g] Disease status based on all available clinical assessments should be documented from the date of randomization at the following timepoints: every 3 months *(±3 days)* during study treatment and for the first 2 years after study treatment completion/early termination, every 6 months *(±7 days)* from Years 3 to 5 after study treatment completion, and annually (±28 days) from Year 6 up to Year 10 after study treatment completion, unless a recurrence that is defined as an IDFS event in Section 3.4.1 has occurred. Patients who have a diagnosis of in situ breast cancer or second non-breast cancer should be maintained on a regular follow-up schedule as described above wherever possible in order to fully capture any subsequent recurrent invasive disease events. Such patients should continue with adjuvant study treatment, if not yet completed and considered by the investigator to be in the patient's best interest, whenever possible. In addition to physical examinations and mammograms, liver function tests, bone scans, chest X-rays/diagnostic CT, liver imaging, or other radiographic modality may be considered when clinically indicated to exclude metastatic disease and within a timeline as per current local standard of practice. Whenever possible, disease recurrence should be confirmed histopathologically. In cases of first disease recurrence (an IDFS event as defined in Section 3.4.1) diagnosed at any time during the study, patients will be out of the study schedule and will be followed annually starting 1 year after first recurrence until Year 10 from FPI for survival, anti-cancer medications, and new relapse (recurrence or disease progression) events.

[h] If a CT scan is already available within 2 months prior to randomization, it may be used in lieu of chest X-ray.

[i] A complete physical examination, including height and weight, should be measured at baseline. Throughout the study, limited symptom-directed physical examination focusing on organ systems related to AE or disease may be performed. Weight is to be measured on Day 1 of the specified cycles and compared to baseline. If ±10% or greater variation occurs, then study treatment doses will be recalculated. Dose must be readjusted for ±10% or greater weight change based on the previous weight used for dose recalculation. *For anthracyclines and taxanes, local standards for dose calculations will be followed.*

[j] Vital signs include blood pressure, pulse rate, and body temperature. Vital signs should be obtained and reviewed, but it is not required that they should always

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.

[k] Cardiac monitoring (ECHO/MUGA) will be performed to assess LVEF. LVEF assessment by ECHO is preferred. The same method should be used throughout the study for each patient and, preferably, performed and assessed by the same assessor. At baseline, LVEF must be done within 14 days prior to randomization. At the end of anthracycline therapy, LVEF should be assessed to determine if patient can start HER2-targeted therapy. During HER2-targeted study treatment, ECHO/MUGA should be obtained at Cycle 2, and every 4 cycles thereafter (Cycles 6, 10, 14, and 18). All assessments will be performed within the last week of the treatment cycle to allow evaluation of the results before the next treatment cycle. ECHO/MUGA should be obtained at the end-of-treatment visit if not performed within the previous 6 weeks and at 3, 6, 12, 18, 24, 36, 48, and 60 months of follow-up regardless of the occurrence of invasive disease recurrence. Note: Cardiac signs/symptoms and an additional LVEF assessment must be completed after the last cycle of anthracycline is administered, but prior to the first cycle of targeted therapy. Patients treated with anthracyclines must have an LVEF $\geq 50\%$ and must have not experienced any clinical symptoms suggesting heart failure or asymptomatic LVEF declines by an absolute point of $> 15\%$ from baseline *and below the lower limit of normal* prior to commencing the HER2-targeted component of therapy.

[l] The PRO questionnaires (EORTC QLQ-C30, modified QLQ-BR23) and EQ-5D will be completed by the patients at the investigational site. Assessments are to be completed on Cycle 1 Day 1 of the anthracycline treatment period; Day 1 of Cycles 1 through 5, Cycle 9, and Cycle 14 of the HER2-targeted treatment period; at treatment completion/treatment discontinuation visit; and at the 6- and 12-month follow-up visits after the end-of-treatment visit regardless of the occurrence of invasive disease recurrence. All PRO questionnaires are required to be completed by patients prior to administration of study drug and prior to any other study assessment(s) or health care provider interactions to ensure that the validity of the instrument is not compromised and to ensure that data quality meets regulatory requirements. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site, and the hard copy originals of the questionnaires must be maintained as part of the patient's medical record at the site for source data verification.

[m] Hematology tests (complete blood count with differential) including hemoglobin, hematocrit, counts of WBCs, platelets, and differential including absolute neutrophils. Abnormal CBC, including platelet counts, will be followed until resolution, until they are stable as assessed by the investigator, until the patient is lost to follow-up, or until the patient withdraws consent. Only if abnormal platelets have not returned to $\geq 100{,}000/mm^3$ at the time of end-of-treatment visit, it should be checked at a minimum of every four weeks (monthly) during the follow-up period until $\geq 100{,}000/mm^3$, until they are clinically stable as assessed by the investigator, until the patient is lost to follow-up, or until the patient withdraws consent, regardless of the occurrence of invasive disease recurrence. Clinicians should consider more frequent evaluation (qw, etc.) for increasing grade of toxicity.

[n] Screening laboratory tests 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. Results must be reviewed and documented prior to administration of first dose of study treatment. (Local laboratory [hematology, biochemistry, INR, and aPTT assessments] to be used for these assessments.)

[o] Prior to the first dose of study treatment (i.e., antracycline treatment), screening tests within 7 days prior to randomization will be utilized. Protocol-specified subsequent tests will be performed within 72 hours preceding administration of study treatment; results must be reviewed and documented prior to administration of study treatment. (Local laboratory [hematology, biochemistry, INR, and aPTT assessments] to be used for these assessments.)

[p] For patients receiving paclitaxel, sample for hematology should be collected qw during treatment. Paclitaxel will be administered every $7 + 3$ days.

[q] Serum chemistry tests at baseline include sodium, potassium, chloride, glucose, BUN or urea, creatinine, TBILI (and direct bilirubin when TBILI > ULN), total protein, albumin, ALT, AST, and ALP. Patients who have positive HBV or HCV serology without known active disease must meet the eligibility criteria for ALT, AST, TBILI, INR, aPTT, and ALP on at least two consecutive occasions, separated by at least 1 week, within the 30 day screening period. Assessments at each treatment and at the end-of-treatment visit include potassium, TBILI, ALT, AST, and ALP; other assessments may be obtained as clinically indicated. For patients who have positive HBV or HCV serology without known active disease, ALT, AST, TBILI, INR, aPTT, and ALP need to be assessed within 72 hours prior to the first dose on C1D1. Abnormal ALT, AST, and total and/or direct bilirubin will be re-tested at a minimum of every 4 weeks (monthly) until normalization (i.e., until they are clinically stable for at least 3 months, as assessed by the investigator), until the patient is lost to follow-up or until the patient withdraws consent, regardless of the occurrence of invasive disease recurrence. Clinicians should consider more frequent evaluation (qw, etc.) for increasing grade of toxicity. *Note: positive serology markers that indicate immunity will not be considered as clinically meaningful positive serology to trigger these tests.*

[r] Documentation of HBV and HCV serologies is required: This includes HBsAg and/or total HBcAb in addition to HCV antibody testing. The most recent serologic testing must have occurred no more than 3 months prior to randomization. If such testing has not been done, it must be performed during screening. For patients who are known carriers of HBV and/or HCV, active hepatitis B infection and active hepatitis C infection must be ruled out on the basis of negative serologic testing and/or determination of HBV DNA viral load/HCV RNA load per local guidelines.

[s] For all women of childbearing potential and for those who do not meet the definition of postmenopausal status (see definition in Section 4.5.1.2) or who have not undergone surgical sterilization, a serum β-HCG must be performed within 7 days prior to randomization. During the treatment period, in all treatment arms, a urine pregnancy test must be performed in women of childbearing potential within 72 hours prior to C1D1 of HER2-targeted therapy, then every 3 cycles thereafter during study treatment, at 3 and 6 months after the end-of-treatment visit, and as clinically indicated regardless of the occurrence of invasive disease recurrence. All positive urine pregnancy tests must be confirmed by a serum β-HCG test.

[t] A whole blood sample for DNA isolation will be collected at baseline or at any time (after randomization) during the conduct of the clinical study.

[u] Collection of serum and plasma samples for biomarker analysis is mandatory. After the end-of-treatment visit, these samples will be collected once a year for 5 years, whenever possible, unless a recurrence that is defined as an IDFS event in Section 3.4.1 has occurred. Biomarker samples (or processed samples) will be stored for up to 5 years after final database lock unless the patient consents to long-term storage for 15 years.

[v] If the patient gives OBRP consent, the serum and plasma samples for biomarker analysis will undergo long-term storage in the study biosample repository for use in future exploratory biomarker analyses. For patients that consented to the OBRP, a whole blood sample for DNA analysis will be collected as well at baseline if possible or any time after randomization.

[w] AE and SAEs will be recorded from the start of study screening procedures if related to protocol-mandated intervention. All non-serious AEs occurring prior to Day 1 (administration of study treatment) will be reported in the medical history, unless AE reporting is deemed more appropriate. AEs are to be monitored continuously during study treatment. All AEs occurring during the study and until the end-of-treatment/treatment discontinuation visit 28 days after the last dose of study treatment are to be recorded; thereafter, only drug-related SAEs and AEs/SAEs that qualify for long-term reporting should continue to be collected. 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.

[x] Concomitant medication will be recorded in the interval beginning 7 days prior to the patient being randomized into the study until the end of the treatment period, except for medications that are also collected during follow-up (Section 4.6).

[y] In cases of invasive disease recurrence (an IDFS event as defined in Section 3.4.1) diagnosed at any time during the study, patients will be out of the study schedule for disease status assessments and will be followed annually $(\pm 28\ days)$ starting 1 year after first recurrence until 10 years after FPI for survival, anti-cancer medications, and new relapse (recurrence or disease progression) events. If a patient has a recurrence, any anti-cancer medication given after the date of diagnosis must be recorded on the post-treatment anti-cancer medication page.

Appendix 2
Schedule of Anti-Therapeutic Antibody Assessments

Study Visit	Time	Sample Acquisition[a]
Cycle 1, Day 1 and Cycle 4, Day 1	Before infusion of trastuzumab emtansine	Serum sample for trastuzumab emtansine concentration Serum sample for ATA to trastuzumab emtansine
Cycle 1, Day 1	15–30 minutes after infusion of trastuzumab emtansine	Serum sample for trastuzumab emtansine concentration
Study treatment termination	Any point during study visit	Serum sample for trastuzumab emtansine concentration Serum sample for ATA to trastuzumab emtansine
3 months after last dose of trastuzumab emtansine	Any point during study visit	Serum sample for ATA to trastuzumab emtansine

ATA=anti-therapeutic antibody; PK=pharmacokinetic.

Note: These samples will be collected in all patients receiving trastuzumab emtansine.

[a] Blood sample for PK/ATA should not be obtained using the same line through which trastuzumab emtansine is infused. Please see the Sample Handling and Logistics Manual for details.

Appendix 3
New York Heart Association Classifications

Table 1 Clinical Evaluation of Functional Capacity of Patients with Heart Disease in Relation to Ordinary Physical Activity

NYHA Class	Functional Class	Description	Objective Assessment
I	Mild	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea	No objective evidence of cardiovascular disease
II	Mild	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea	Objective evidence of minimal cardiovascular disease
III	Moderate	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea	Objective evidence of moderately severe cardiovascular disease
IV	Severe	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased	Objective evidence of severe cardiovascular disease

NYHA = New York Heart Association.

Appendix 4
Adjuvant Radiotherapy Guidelines

I. BREAST-CONSERVING THERAPY

MANDATORY: Breast radiotherapy (RT) after complete local excision

Breast RT may be contraindicated in patients with significant comorbidity (e.g., scleroderma and systemic lupus erythematosus). Patients with contraindication to RT while adjuvant RT is clinically indicated are not eligible for this study.

Target volume

- Whole breast including the primary tumor bed
- Primary tumor bed boost in conjunction with whole breast RT may be used as per local policy.
- Partial breast RT may be used as per local policy declared by the center prior to local activation.
- Regional nodal RT: Refer to Item III below.

Dose fractionation

- Whole breast recommended schedules:

  50 Gy in 25 fractions, 5 fractions per week; or

  42.5 Gy in 16 fractions, 5 fractions per week; or

  40 Gy in 15 fractions, 5 fractions per week
- Other schedules may be used as per local policy declared by the center prior to local activation.

  Primary tumor bed boost in conjunction with whole breast RT: as per local policy declared by the center prior to local activation

  Partial breast RT: as per local policy declared by the center prior to local activation

Treatment planning

- Computer tomography (CT)–based treatment planning is strongly recommended for whole breast RT and tumor bed boost.
- CT-based treatment planning is mandatory for partial breast irradiation delivered using external beam RT.

II. POSTMASTECTOMY RADIOTHERAPY

MANDATORY:

- 4 or more positive axillary nodes or pathologic T4 disease
- “Non-resectable” microscopic positive deep margin (invasive carcinoma or ductal carcinoma in situ)

OPTIONAL:

- 1–3 positive axillary nodes or higher risk node-negative disease (for example, T3 primary in the presence of high histologic grade and/or lymphovascular invasion)

Target Volume

- Whole chest wall
- Primary tumor bed boost in conjunction with chest wall RT may be used as per local policy declared by the center prior to local activation.
- Regional nodal RT: Refer to Item III below.

Dose Fractionation

- Whole breast: Recommended schedule is 50 Gy in 25 fractions, 5 fractions per week. Other schedules may be used as per local policy declared by the center prior to local activation.
- Primary tumor bed boost in conjunction with chest wall RT: as per local policy declared by the center prior to local activation

Treatment planning

- CT–based treatment planning is strongly recommended for chest wall RT.

III. REGIONAL NODAL RT

For patients who have completed SNB alone or ALND as per protocol:

- RECOMMENDED: Any breast surgery, 4 or more positive axillary nodes
- OPTIONAL: Any breast surgery, 0–3 positive axillary nodes, pathological T4 (pT4) disease

Target volume

- Required:

  Supraclavicular fossa if there are 4 or more positive axillary nodes

- Optional:

  Supraclavicular fossa if there are 0-3 positive axillary nodes;

  Axilla as per local policy declared by the centre prior to local activation (for example, known or high risk of residual axillary disease postsurgery);

  Internal mammary nodes if there is a high risk of tumor involvement as per local policy.

Dose fractionation

- Recommended schedule: 50 Gy in 25 fractions, 5 fractions per week. Other schedules may be used as per local policy.

Treatment planning

- CT–based treatment planning is strongly recommended for supraclavicular fossa and/or axillary RT.
- CT-based treatment planning is mandatory for internal mammary nodal RT.

Appendix 5
Guidelines for Liver Biopsy

Because nodular regenerative hyperplasia (NRH) can be a very subtle diagnosis to make on liver biopsy, every attempt should be made to maximize the amount of tissue obtained.

The needle used should be at least 18 gauge, and percutaneous biopsies of length at least 1.5 cm are recommended, if clinically appropriate. In order to diagnose NRH, reticulin and trichrome stains are necessary.

Smaller biopsies obtained via a transjugular approach and smaller biopsy gun needle biopsies are discouraged. Small wedge biopsies should also be discouraged.

Appendix 6
Ventana HER2 IHC Assay

The PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody (PATHWAY HER2 [4B5]) is a rabbit monoclonal antibody intended for laboratory use for the semi-quantitative detection of HER2 antigen in sections of formalin-fixed, paraffin-embedded breast cancer tissue to determine tumor HER2 immunohistochemistry (IHC) status and to select HER2-positive patients for enrollment in study BO28407. The 4B5 IHC assay is currently being developed by Ventana Medical Systems as a companion diagnostic to trastuzumab emtansine and will be used for investigational purposes only.

Device Description

The PATHWAY HER2 (4B5) IHC assay is an automated immunohistochemical staining assay system comprising a pre-dilute, ready-to-use, rabbit monoclonal primary antibody (clone 4B5) directed against the internal domain of HER2, the BenchMark ULTRA automated slide staining platform, and ultraView universal DAB detection kit. The reagents and the IHC procedure are optimized for use on the BenchMark ULTRA automated slide stainer, utilizing VSS software (Ventana System Software). Details of the staining protocol and scoring criteria can be found in instruction for use and interpretation guide published by Ventana.

Appendix 7
Ventana HER2 ISH Assay

Probe Cocktail is intended to determine the ratio of the HER2 gene to chromosome 17 using two-color chromogenic in situ hybridization (ISH) in formalin-fixed, paraffin-embedded human breast cancer tissue to determine tumor HER2 gene status and select HER2-positive patients for enrollment in study BO28407. The INFORM HER2 Dual ISH DNA Probe Cocktail is currently being developed by Ventana Medical Systems as a companion diagnostic to trastuzumab emtansine and will be used for investigational purposes only for Study BO28407.

The Ventana INFORM HER2 Dual ISH assay consists of a dinitrophenyl (DNP)-labeled double stranded probe that targets the HER2 gene region of chromosome 17 and a digoxigenin (DIG)-labeled double stranded probe that hybridizes to repetitive sequences in the centromeric region of chromosome 17 (INFORM Chromosome 17 probe). The probes are packaged as a mixture and require the use of Ventana's *ultra*View™ SISH DNP Detection Kit, *ultra*View Red DIG Detection Kit, and other accessory reagents to stain routinely processed, formalin-fixed paraffin-embedded tissue sections on Ventana automated slide stainer instruments.

Appendix 8
PRO Measures: QLQ-C30 and Modified QLQ-BR23

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

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

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

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

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ - BR23

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

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

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

Please go on to the next page


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Appendix 9
EuroQoL EQ-5D

E -5

Health Questionnaire

English version for the US

1

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

Mobility

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

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

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

Pain/Discomfort

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

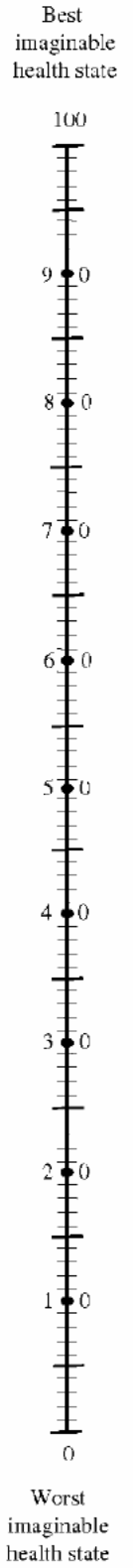
Anxiety/Depression

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

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

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

Your own health state today



Appendix 10
Acceptable Contraception Methods

For female patients of childbearing potential (who have not undergone surgical sterilization), agreement must be obtained to use one highly effective nonhormonal form of contraception or two effective forms of nonhormonal contraception. Specific country and/or local requirements for contraception will be followed.

Highly Effective Contraception

Methods of birth control that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are considered highly effective forms of contraception.

The following nonhormonal methods of contraception are acceptable:

- True abstinence when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [e.g., calendar, ovulation, symptothermal postovulation methods] and withdrawal are not acceptable methods of contraception).
- Male sterilization (with appropriate postvasectomy documentation of the absence of sperm in the ejaculate). For female patients, the vasectomized male partner should be the sole partner.
- Female surgical sterilization
- Placement of a nonhormonal intrauterine device. Consideration should be given to the type of device being used, as there *are* higher failure rates quoted for certain types, (e.g., steel or copper wire). Patients who have had a progesterone-coated device in place prior to screening are not required to have it removed. However, newly inserted devices after screening should not contain estrogen or progesterone.

OR

Effective Nonhormonal Contraception

Alternatively two of the following effective forms of contraception may be used instead:

- Condom with spermicidal foam/gel/film/cream/suppository.
- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:

- Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore, the use of additional spermicides does confer additional theoretical contraceptive protection.
- However, spermicides alone are ineffective at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and should not be used alone.

It should be noted that two forms of effective contraception are required. A double barrier method defined as condom and occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream /suppository is acceptable.

For partners of male patients of childbearing potential (who have not undergone surgical sterilization), agreement must be obtained to use hormonal contraception, or one highly effective nonhormonal, or two effective forms of nonhormonal contraception. Specific country and/or local requirements for contraception will be followed.