NI PASS PROTOCOL (Primary data collection)

TITLE:	**UK – A DISEASE REGISTRY STUDY TO PROSPECTIVELY OBSERVE TREATMENT PATTERNS AND OUTCOMES IN PATIENTS WITH HER2-POSITIVE UNRESECTABLE LOCALLY ADVANCED OR METASTATIC BREAST CANCER**
PROTOCOL NUMBER:	ML29659
VERSION NUMBER:	4.1
EU PAS REGISTER NUMBER:	EUPAS23334
STUDIED DISEASE:	HER2-positive metastatic breast cancer
MARKET AUTHORISATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany
DATE FINAL:	Version 1: 15th September 2014
DATES AMENDED	Version 2.0: 13th November 2014 Version 3.0: 29th January 2015 Version 4.0: 16th May 2016 Version 4.1: 19th October 2018

Observational Disease Registry Study—Roche Products Ltd
Protocol ML29659, Version 4.1
19th October 2018

Based on protocol template Version 2.0 released on 14-Mar-2016

PROTOCOL AMENDMENT FINALISATION SIGNATURE PAGE

TITLE:	UK- A DISEASE REGISTRY STUDY TO PROSPECTIVELY OBSERVE TREATMENT PATTERNS AND OUTCOMES IN PATIENTS WITH HER2-POSITIVE UNRESECTABLE LOCALLY ADVANCED OR METASTATIC BREAST CANCER
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DATE AMENDED:	19th Oct 2018

This protocol amendment was finalized on the date shown above.

[redacted]

26 October 2018

Date

PROTOCOL AMENDMENT, VERSION 4.1:
RATIONALE

Protocol 4.1 has been amended to implement the following changes:

1. Updated cover pages to reflect PDC NI-PASS and EU PAS registration
2. Site inspection wording updated as per guidance from MHRA following inspection in 2018 (section 9.2)
3. Updated the Responsible Parties table (page 17-18) with Roche contacts
4. Corrected cross-referencing in protocol to Appendices
5. Update to protocol recruitment numbers to 300 as per agreement with Global Medical Affairs

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**UK – A DISEASE REGISTRY STUDY TO PROSPECTIVELY OBSERVE TREATMENT PATTERNS AND OUTCOMES IN PATIENTS WITH HER2-POSITIVE UNRESECTABLE LOCALLY ADVANCED OR METASTATIC BREAST CANCER**
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I agree to conduct the non-interventional study in accordance with the current protocol.

_____

Treating Physician's Name (print)

_____ _____

Treating Physician's Signature Date

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CI	confidence interval
CR	complete response
CRO	contract research organisation
CTCAE	common terminology criteria for adverse events
DoR	Duration of response
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ePRO	electronic patient-reported outcome
EQ-5D	EuroQol 5-Dimensions questionnaire
FACT-B	Functional Assessment of Cancer Therapy – Breast
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HER2	human epidermal growth factor receptor 2
ICF	Informed consent form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
LA	locally advanced
LVEF	left ventricular ejection fraction
mBC	metastatic breast cancer
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PR	partial response
PRO	patient-reported outcome
QoL	quality of life
SAE	serious adverse event
SOC	system organ class

Abbreviation	Definition
T-DM1	trastuzumab emtansine
WPAI	Work Productivity and Activity Impairment Questionnaire
ULN	upper limit of normal

RESPONSIBLE PARTIES

Study Contacts	Contact Name/Address	Telephone/Fax Number and Email
Sponsor	Roche Products Ltd Hexagon Place Shire Park 6 Falcon Way AL7 1TW	[redacted]
Sponsor Contact Person and Project Director	[redacted]	[redacted]
Study Project Manager	[redacted]	[redacted]
Drug Safety and Pharmacovigilance	[redacted]	[redacted]

Contract Research Organisation	N/A	Note: Roche UK Country Clinical Operations outsource monitoring to Quintiles as per global study structure – not study specific.
Main Author	[redacted]	[redacted]
Principal Investigator	[redacted]	[redacted]

HER2-POSITIVE MBC DISEASE REGISTRY STUDY SYNOPSIS

TITLE:	**UK– A DISEASE REGISTRY STUDY TO PROSPECTIVELY OBSERVE TREATMENT PATTERNS AND OUTCOMES IN PATIENTS WITH HER2-POSITIVE UNRESECTABLE LOCALLY ADVANCED OR METASTATIC BREAST CANCER**
PROTOCOL NUMBER:	ML29659
VERSION	4.1
EU PAS REGISTER NUMBER:	EUPAS23334
PHASE	IV
INDICATION	HER2-positive unresectable locally advanced or metastatic breast cancer
DATE OF PROTOCOL	19th October 2018
MARKET AUTHORISATION HOLDER:	Roche Registration GmbH Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen Germany

Study Objectives

Primary Objective

In patients with unresectable locally advanced (LA) or metastatic breast cancer (mBC), to observe the different anti-cancer treatment regimens and their sequencing throughout the course of the disease and to describe the clinical outcome for each treatment regimen measured as progression-free survival (PFS).

Secondary Objectives

The secondary objectives for this study are as follows:

Safety objectives

- To observe the safety of different anti-cancer treatment regimens through the reporting of serious adverse events (SAEs), specific adverse events relevant to HER2-targeted therapies (potential medicine-induced liver injury, suspected transmission of an infectious agent by study medicine, cardiac dysfunction and serious and non-serious pneumonitis; refer to Section 5.1.1.2 for more detail)and AEs leading to discontinuation or dose modification of an anti-cancer therapy
- To observe and describe the incidence of and reasons for anti-cancer treatment modifications
- To observe and describe the treatment of populations of special interest by estimating the incidence and prevalence of cardiac events related to left ventricular dysfunction; pregnancy; and pregnancy outcomes.

Effectiveness objectives

- To observe regional differences in anti-cancer treatment regimens
- To observe overall survival (OS)
- To observe objective response rate (ORR) per anti-cancer treatment regimen
- To observe duration of response (DoR) per anti-cancer treatment regimen
- To evaluate time to treatment failure (to when treatment is stopped or switched or death)

Other objectives

- To observe patients' demographics and breast cancer histories for each anti-cancer treatment regimen
- To document the incidence (during the observation period) of pregnancy and pregnancy outcomes
- To examine utilisation or adherence to predefined clinical guidelines regarding anti-cancer treatment regimen decisions
- To evaluate quality of life (QoL) using patient-reported outcomes (PROs), where collected as part of routine clinical practice
- To evaluate CNS disease as related to: CNS as the site of first progression, and CNS-only disease progression.
- To observe patient characteristics, treatment patterns and outcomes in patients with oligometastatic disease

Health Economic Assessment Objectives

- To examine the healthcare resource utilisation associated with various anti-cancer treatment regimens including the resource requirement of treating associated adverse events (AEs)

Study Design

Description of the Study

This disease registry is a prospective, multicentre non-interventional study designed to observe anti-cancer treatment regimens and clinical outcomes with these regimens in patients with human epidermal growth factor receptor 2 (HER2)-positive unresectable LA/mBC. Patients can be enrolled in the study irrespective of the anti-cancer treatment they are prescribed. Once a patient is enrolled in the study, she/he will be followed until death, withdrawal of consent or study termination, whichever occurs first.

Number of Patients

All eligible patients can be invited to participate in the study and should be enrolled sequentially. No other pre-selection criteria should be applied.

This study will enroll approximately 300 patients over approximately 3 years from the time this protocol is approved by the UK Ethics Committee.

Target Population

The target population for inclusion in this study is patients with HER2-positive unresectable LA/mBC, where the initial diagnosis of LA/mBC has been made no more than 6 months prior to enrolment. Patients may have had prior diagnosis with early breast cancer, which was treated with curative intent and has now relapsed.

Inclusion criteria

Patients must meet the following criteria for study entry:

- Male or females
- Initially diagnosed with HER2-positive unresectable LA/mBC no more than 6 months prior to enrolment, although they can have received anti-cancer treatment during that time
- Age ≥18 years
- Able and willing to provide written informed consent and to comply with the study protocol.

Exclusion criteria

There are no exclusion criteria for entry into this study.

Length of Study

The study will recruit for at least 3 years followed by a minimum period of 5 years follow-up after the last patient is enrolled. Patient enrolment may be staggered according to study timelines.

End of Study

The end of study is defined as the date of the last follow-up visit of the last patient enrolled and will occur 5 years after the last patient enrolls in the study.

Data Sources and Data Collection

Source data for patient data and healthcare resource utilisation data will be taken from the patient's chart and other medical records and reported by means of a web-based electronic data collection system.

Where PRO self-completed questionnaires are collected as part of routine clinical practice, these data will be entered into the eCRF by site staff and will be analysed centrally by the sponsor.

Follow-up visits with the treating physician will be made at a frequency following local medical standards of care.

Anti-Cancer Treatment Pattern Measures

At study entry, all prior anti-cancer treatments for HER2-positive breast cancer (including the neoadjuvant, adjuvant and advanced settings) will be captured retrospectively. All anti-cancer treatments will then be captured prospectively during the observation period. Anti-cancer treatments (and the associated data collected) include:

- Radiation treatment (including date, body site, dose and type of radiation)
- Chemotherapy (including drug name, administration route, date, dose, number of cycles per regimen and reasons [if any] for discontinuation)
- Hormonal treatment (including agent name, administration route, date, dose and reasons [if any] for discontinuation)
- Immunotherapy (including agent name, administration route, date, dose, number of cycles per regimen and reasons [if any] for discontinuation)
- Other anti-cancer treatments including targeted therapy (including agent name, administration route, date, dose, number of cycles per regimen and reasons [if any] for discontinuation)
- Surgery (including date, body site and type of procedure)

Effectiveness Outcome Measures

Effectiveness will be measured as follows:

- PFS for each anti-cancer treatment regimen: PFS will be calculated from the start date of a treatment regimen to the date of either disease progression or death. Progression will be evaluated by the Investigator according to site-specific medical practice.

A treatment regimen is defined as: any anti-cancer medication, used as a single agent or as part of a combination of medications, given from the date of initiation until the date of disease progression. If during the time elapsed between two disease-progression events a sequence of medications is used, this will count as one regimen. For example, a patient diagnosed with metastatic disease receives trastuzumab and docetaxel. After 3 cycles the docetaxel must be discontinued and the patient continues with trastuzumab and tamoxifen therapy. The use of trastuzumab, docetaxel and antihormonal therapy will be considered as one regimen.

- OS: defined as the date from initiation of treatment for HER2-positive unresectable LA/mBC to the date of death from any cause.
- ORR for each anti-cancer treatment regimen: defined as the proportion of patients with either a complete response (CR) or partial response (PR), based on their overall response. Response will be evaluated by the Investigator according to site-specific medical practice.
- DoR for each treatment regimen: defined as the time from date of first response (CR or PR) to the date of disease progression, as per Investigator assessment.
- Time to treatment failure: defined as the time from initiation of treatment regimen to when the treatment regimen is stopped, OR a new treatment regimen is started (change of regimen), OR death.
- CNS as first site of progression

Safety Outcome Measures

The following safety parameters will be evaluated:

- SAEs
- Specific adverse events relevant to HER2-targeted therapies (potential medicine-induced liver injury, suspected transmission of an infectious agent by study medicine, cardiac dysfunction and serious and non-serious pneumonitis; refer to Section 5.1.1.2 for more detail)AEs leading to discontinuation or dose modification[1] of an anti-cancer therapy
- Pregnancy and pregnancy outcomes

Quality of Life Measures

PRO measures that capture QoL data will be used in this study where it is routine clinical practice. PROs will be collected at study enrolment and periodically throughout study participation, including at the clinic visit at approximately at 3-month intervals throughout the study period and during clinic visits that are determined by the treating physician (no specific visits will be mandated for collecting these data). The following PROs will be used in this study:

[1]Dose modification refers to any change in the prescribed quantity of drug and/or the dosing interval including withholding or delaying doses.

- EuroQol 5-Dimensions questionnaire (EQ-5D; Rabin and de Charro 2001)
- Functional Assessment of Cancer Therapy Breast (FACT-B), assessing overall health status (Brady 1997)

The following PRO measures may be included for specific patients and specific therapies.

- Work Productivity and Activity Impairment (WPAI) questionnaire (Reilly Associates 2002)

Health Economic Outcome Measures

- Healthcare resource utilisation (e.g. hospitalisations, emergency room attendances and outpatient visits) associated with various anti-cancer treatment regimens including the resource requirement associated with treatment of associated AEs

Study Treatments

No treatment regimen is mandated by this protocol.

This is an observational study in which clinical decisions concerning the optimum management strategy for a particular patient are taken independent of and/or prior to any decision by the physician to invite a patient to participate in the study. The treating physician will make all treatment decisions according to his/her regular practice independent of this study.

Statistical Methods

The study will be analysed according to the separate Statistical Analysis Plan.
The full analysis set will comprise all enrolled patients; this will be the primary analysis population for safety and efficacy parameters. Other analysis populations may be defined based on more restrictive criteria, such as patients receiving a particular anti-cancer treatment.

The analysis of the present study will be exploratory and primarily make use of descriptive statistical methods. In addition, exploratory statistical testing and modelling will be used to highlight interesting aspects of the data. Any test performed will be two-sided and carried out with a 5% α error rate without correction for multiplicity.

A descriptive analysis of safety will be performed. The main safety parameter is the incidence of SAEs. The proportion of patients experiencing at least one event with each anti-cancer treatment regimen will be estimated with 95% Clopper–Pearson confidence intervals (CIs).

The analysis of PFS and OS is based on the survivor function, which is the probability of remaining event free beyond a certain point in time. The survival function will be

estimated using Kaplan–Meier methodology and summarised using the range, the 25th and 75th percentiles, the median overall survival and a 95% CI for the median. The plot of Kaplan–Meier estimates for each treatment regimen will be presented.

Efficacy measures will be analysed for parameters as described in the study objectives. Efficacy analyses will include CNS as the site of first progression, and CNS-only progression, OS and PFS; as well as ORR, DoR, and time to treatment failure

PRO outcomes measures will be analysed.

Health economic outcome measures will be analysed.

Pre-specified subgroup analyses will include comparisons between:

- Efficacy and PRO measures for patients with access to non HTA-funded medicines vs those without
- Efficacy and PRO measures for patients >65 years versus <65 years of age
- Efficacy and PRO measures for patients who are hormone receptor positive versus hormone receptor negative
- Efficacy and PRO measures for patients with performance status 0-1 versus performance status >2

Determination of Sample Size

This study has a planned sample size of approximately 300 patients. This sample size is intended to provide a sufficient number of patients to allow characterisation of treatments in a broad population and to measure overall trends by subgroups of common treatment regimens.

Interim Analyses

For this study, there will be annual interim analyses for: safety reporting and presentation of safety results; presentation of the different treatment regimens and their sequencing. These annual reporting events will start 1 year after first patient first visit and will continue until study end.

1 BACKGROUND

1.1 HER2-POSITIVE METASTATIC BREAST CANCER

Breast cancer is the most common cancer in women globally, in both the developed and the developing world, with approximately 1.38 million new cases diagnosed in 2008 (World Health Organization 2011). It is also the leading cause of cancer death in women, accounting for 458,400 deaths (14% of all cancer deaths) in 2008 (Jemal et al. 2011). Each year approximately 2,000 people in the United Kingdom die of HER2-positive (HER2+) metastatic breast cancer. The majority of the people diagnosed are women, with an average age at diagnosis of 55 years (Marty, 2005; Baselga, 2012).

With current treatments, 50% of women die within approximately three years of developing metastatic disease (Baselga, 2012).

The primary objective of the management of HER2+ metastatic breast cancer is to extend length of life, whilst maintaining or improving quality of life. People with metastatic disease are unlikely to be cured.

The HER tyrosine kinase receptor family comprises four receptors: HER1, HER2, HER3 and HER4. These receptors are important mediators of cell growth, survival and differentiation (Sundaresan et al. 1999). Activation of HER receptors leads to receptor dimerisation and cell signalling through the phosphatidylinositol 3-kinase/AKT pathway for promotion of tumour cell survival and through the mitogen-activated protein kinase pathway for cellular proliferation.

Overexpression of HER2 is observed in approximately 15–20% of human breast cancers (Owens et al. 2004). Several lines of scientific and clinical evidence support a direct role for HER2 overexpression in the aggressive growth and poor clinical outcomes associated with these tumours (Slamon et al. 1987).

1.2 TREATMENT OPTIONS FOR HER2-POSITIVE METASTATIC BREAST CANCER

The number of anti-cancer treatment options available to patients with HER2-positive breast cancer is broad and may vary between countries, in terms of both the drugs used and the sequence in which they are used.

The majority of patients diagnosed with HER2+ breast cancer are diagnosed at an early stage of disease (HER2+ eBC) (Lyratzopoulos, 2012). For these patients the standard

treatment is surgery followed by chemotherapy and trastuzumab (Herceptin) (NICE TA107). The primary aim of this treatment is curative.

For a proportion of patients this treatment will not be curative and their disease will recur as advanced/metastatic breast cancer. In addition to these patients with recurrent disease, a high proportion of patients diagnosed with mBC will present with *'de novo'* disease (disease that hasn't been previously diagnosed in an earlier setting) (Lyratzopoulos, 2012).

The standard first-line treatment (first treatment for metastatic disease) for HER2+ mBC has historically been trastuzumab in combination with taxane (docetaxel or paclitaxel). Following the recent EMA approval of pertuzumab, first-line treatment may evolve to include a combination of pertuzumab, trastuzumab and docetaxel.

After progressing on one of these 'first-line' therapies a patient will then typically receive a 'second-line' treatment. The treatments typically considered in this setting include lapatinib in combination with capecitabine, monotherapy capecitabine or vinorelbine or continued use of trastuzumab with an alternative chemotherapy agent. Following the recent EMA approval of trastuzumab emtansine (T-DM1), second-line treatment may evolve to include single-agent trastuzumab emtansine.

For those patients who progress rapidly (<6 months) following, or during, their adjuvant therapy with trastuzumab and/or a taxane, a clinician may typically move directly to the second-line treatment options listed above.

Following progression on second line treatment a patient may be offered a third line treatment which typically consists of monotherapy capecitabine or vinorelbine (usually the alternative therapy to that given in second line).

The treatment of HER2-positive mBC will continue to evolve as new agents become available.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

There are limited published data concerning treatment patterns for patients with HER2-positive unresectable locally advanced (LA)/mBC. However, clinicians and reimbursement agencies may require such information to inform decision-making regarding the best treatment strategies for patients throughout the course of their disease.

This study will allow descriptive analyses to identify associations between patient characteristics, treatments and outcomes. Additionally, as new information becomes available on potential risk factors and as new treatments become available, the study will provide an opportunity to gain an insight into the evolving treatment landscape.

As no therapeutic intervention is mandated by this protocol and no investigational product is used in the study, with only routine care being observed, there are no additional risks for participating patients. The study is non-interventional; initial treatment decisions will be made independent of a patient's participation in the study. Hence, no explicit additional potential benefits are expected from participation. The benefit is not for the individual patient but instead may be for the broader patient population as the disease and its treatment will be better understood. Other than possibly requiring additional patient time at routine clinic attendances, there are no anticipated costs associated with a patient's participation. Therefore, the benefit–risk balance for this study is considered to be neutral for an individual patient but overall it is considered favourable for the wider patient population with HER2-positive LA/mBC.

2 OBJECTIVES

This observational disease registry is a prospective, multicentre non-interventional study designed to observe clinical outcomes, patient-reported outcomes (PROs), QoL and health economics across anti-cancer treatment regimens and sequences during the course of HER2-positive unresectable LA/mBC.

2.1 PRIMARY OBJECTIVE

In patients with unresectable LA/mBC, to observe the different anti-cancer treatment regimens and their sequencing throughout the course of the disease and to describe clinical outcome for each anti-cancer treatment regimen measured as progression-free survival (PFS).

2.2 SECONDARY OBJECTIVES

The secondary objectives for this study are as follows:

Safety objectives

- To observe the safety profiles of different anti-cancer treatment regimens through the reporting of serious adverse events (SAEs), specific adverse events relevant to HER2-targeted therapies and AEs leading to discontinuation or dose modification of an anti-cancer therapy
- To observe and describe the incidence of and reasons for anti-cancer treatment modifications
- To observe and describe the treatment of populations of special interest by estimating the incidence and prevalence of cardiac events related to left ventricular dysfunction; pregnancy; and pregnancy outcomes.

Effectiveness objectives

- To observe regional differences in anti-cancer treatment regimens
- To observe overall survival (OS)
- To observe objective response rate (ORR) per anti-cancer treatment regimen
- To observe duration of response (DoR) per anti-cancer treatment regimen
- To evaluate time to treatment failure (to when treatment is stopped or switched or death)

Other objectives

- To observe patients' demographics and breast cancer histories for each anti-cancer treatment regimen
- To document the incidence (during the observation period) of pregnancy and pregnancy outcomes
- To evaluate quality of life (QoL) using patient-reported outcomes (PROs), where collected
- To evaluate CNS disease as related to: CNS as the site of first progression, and CNS-only disease progression.
- To observe patient characteristics, treatment patterns and outcomes in patients with oligometastatic disease
- To examine the healthcare resource utilisation associated with various anti-cancer treatment regimens including the resource requirement of treating associated adverse events (AEs)

3 STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

Roche Products Ltd (UK) will conduct this study.

3.1.1 Overview

This observational disease registry is a prospective, national, multicentre, non-interventional study designed to enrol patients who have an initial diagnosis of unresectable LA/mBC made up to 6 months prior to registry enrolment. These patients will be prospectively followed for at least 5 years after study enrolment to evaluate their anti-cancer treatments. Data on patients' previous anti-cancer treatments for breast cancer will be collected retrospectively at study entry.

3.1.2 Overall Number of Patients

All eligible patients can be invited to participate in the study and should be enrolled sequentially. No other pre-selection criteria should be applied.

This study will enroll approximately 300 patients over approximately 3 years from the time this protocol is approved by the UK Ethics Committee.

3.1.3 Enrolment of Countries and/or Centres

The study will be performed at approximately 28 sites. An appropriate number of sites will be opened to ensure that the recruitment target is reached within 3 years.

For this study, the type of healthcare site (e.g. specialty care, private practice, teaching institution, etc.) will be collected and documented only once in the electronic Case Report Form (eCRF) for each participating site.

3.1.4 Enrolment of Patients

Enrolled patients will receive treatment and clinical assessments for their HER2-positive unresectable LA/mBC as determined by their treating physician, according to the standard of care and routine clinical practice at each site.

Data regarding patient characteristics, breast cancer history and prior anti-cancer treatments for their breast cancer (including neoadjuvant, adjuvant and advanced settings) will be collected at enrolment.

Patients may also be concurrently enrolled in an interventional clinical trial in which case their study treatment(s) will be recorded, if open label and known, otherwise they will be recorded as "investigational treatment".

Follow-up visits will be determined by the treating physician, but data will be collected approximately every 3 months from patient charts, clinical notes, and diagnostic and

laboratory test results. All anti-cancer treatment changes, clinical outcomes (including disease progression), AEs and survival status will be collected.

Patient source data and healthcare resource utilisation data (hospitalisations, emergency admissions, outpatient visits) will be taken from the patient's medical records and reported by means of a web-based electronic data collection (EDC) system. Where collected as part of routine clinical practice, PROs will be collected by a self-completed questionnaire during routine clinical visits at approximately 3-month intervals throughout study participation. Patients will be considered "on study" until death, withdrawal of consent, loss to follow-up, or end of study, whichever comes first. This study will be analysed according to the separate study Statistical Analysis Plan.

The Investigator should maintain a log of patient information (hospital/clinic identification numbers, names, addresses, telephone numbers, and hospital numbers, if applicable) for both patients who choose to participate and those who choose not to participate in the study. The purpose of recording patients who choose not to participate is to prevent those patients who have been approached from being asked again at a later date to enter the study. The log document should be maintained in strict confidence by the Investigator and will not be submitted to the Sponsor.

3.2 STEERING OR ADVISORY COMMITTEES

A scientific advisory committee composed of experts will be set up to advise the Sponsor on the global conduct and analysis of this study. The composition of this committee and their remit will be outlined in a separate charter.

3.3 LENGTH OF STUDY

The study will recruit for at least 3 years followed by a minimum period of 5 years' follow-up after the last patient is enrolled. Patient enrolment may be staggered according to study timelines.

3.4 END OF STUDY

The end of study is defined as the date of the last follow-up visit of the last patient enrolled and will occur 5 years after the last patient enrolls in the study.

3.5 MILESTONES

A summary of study milestones is presented in Table 1.

Table 1. Observational Study Milestones

Milestone	Target date
Protocol approval by an Institutional Review Board/Ethics Committee	December 2014
Start of data collection	16/03/2015
End of data collection	16/03/2023
Study progress report(s)	Annually to Ethics Committee
Interim report(s) of study results	Annually
Final report of study results	01/08/2023; no later than 4 months after last patient last visit

3.6 RATIONALE FOR OBSERVATIONAL STUDY DESIGN

As the objective of this observational disease registry is to observe patterns of treatment for patients with unresectable LA/mBC, the study does not stipulate any specific treatments or dosing regimens. The specific treatment, dose and treatment duration will be decided by the Investigator independent of a patient's participation in the study and according to the approved product information, local treatment guidelines and/or routine clinical practice.

This observational disease registry will capture important data on the clinical characteristics of patients and their breast cancer at study enrolment. Patients will then be followed throughout the course of their disease to capture both the sequence of anti-cancer treatments, and their corresponding treatment-specific, as well as overall, outcomes.

The data captured will allow both descriptive and inferential comparative analyses to be made to evaluate associations between patient risk factors, treatments and outcomes.

This registry will provide an opportunity to gain a better understanding of decision-making regarding treatments across various stages of LA/mBC and how these might be influenced by patient factors (e.g. presence or absence of central nervous system metastases). It will also allow insight into the treatment landscape as it evolves.

3.7 OUTCOME MEASURES

3.7.1 Anti-Cancer Treatment Pattern Measures

At study entry, all prior anti-cancer treatments for HER2-positive breast cancer (including in the neoadjuvant, adjuvant and advanced settings) will be captured retrospectively. All anti-cancer therapies will then be captured prospectively during the observation period. Anti-Cancer treatments (and the associated data collected) include:

- Radiation treatment (including date, body site, dose and type of radiation)
- Chemotherapy (including names, dates, doses, number of cycles per regimen and reasons [if any] for discontinuation)

- Hormonal treatment (including agent name, administration route, date, dose and reasons [if any] for discontinuation)
- Immunotherapy (including agent name, administration route, date, dose, number of cycles per regimen and reasons [if any] for discontinuation)
- Other anti-cancer treatments including targeted therapy (including agent name, administration route, date, dose, number of cycles per regimen and reasons [if any] for discontinuation)
- Surgery (including date, body site and type of procedure)

3.7.2 Effectiveness Outcome Measures

Effectiveness will be measured as follows:

- PFS for each treatment regimen: PFS will be calculated from the start date of an anti-cancer treatment regimen to the date of either disease progression or death. Progression will be evaluated by the Investigator according to site specific medical practice.

  A treatment regimen is defined as: any anti-cancer medication, used as a single agent or as part of a combination of medications given from the date of initiation until the date of disease progression. If during the time elapsed between two disease-progression events a sequence of medications is used, this will count as one regimen. For example, a patient diagnosed with metastatic disease receives trastuzumab and docetaxel. After 3 cycles the docetaxel must be discontinued and the patient continues with trastuzumab and tamoxifen therapy. The use of trastuzumab, docetaxel and antihormonal therapy will be considered as one regimen.

- OS: defined as the date from initiation of treatment for HER2-positive unresectable LA/mBC to the date of death from any cause.
- ORR for each treatment regimen: defined as the proportion of patients with either complete response (CR) or partial response (PR), based on their overall response. Response will be evaluated by the Investigator according to site-specific medical practice.
- DoR for each anti-cancer treatment regimen: defined as the time from date of first response (CR or PR) to the date of disease progression, as per Investigator assessment.
- Time to treatment failure: defined as the time from initiation of treatment regimen to when the treatment regimen is stopped, OR a new treatment regimen is started (change of regimen), OR death.
- CNS as first site of progression

3.7.3 Safety Outcome Measures

The following safety parameters will be evaluated:

- SAEs
- Specific adverse events relevant to HER2-targeted therapies (potential medicine-induced liver injury, suspected transmission of an infectious agent by study medicine, cardiac dysfunction and serious and non-serious pneumonitis; refer to Section 5.1.1.2 for more detail)
- AEs leading to discontinuation or dose modification[2] of an anti-cancer therapy
- Pregnancy and pregnancy outcomes

3.7.4 Quality of Life Measures

PRO measures that capture QoL data will be used in this study where it is routine clinical practice. PROs will be collected at study enrolment and periodically throughout study participation, including at the clinic visit at approximately at 3-month intervals throughout the study period and during clinic visits that are determined by the treating physician (no specific visits will be mandated for collecting these data). The following PROs will be used in this study:

- EuroQol 5-Dimensions questionnaire (EQ-5D; Rabin and de Charro 2001)
- Functional Assessment of Cancer Therapy Breast (FACT-B), assessing overall health status (Cella 1997)

The following PRO measures may be included for specific patients and specific therapies:

- Work Productivity and Activity Impairment (WPAI) questionnaire (Reilly Associates 2002)

3.7.5 Health Economic Outcome Measures

- Healthcare resource utilisation (e.g. hospitalisations, emergency room attendances and outpatient visits) associated with various anti-cancer treatment regimens including the resource requirement associated with treatment of associated AEs.

4 MATERIALS AND METHODS

4.1 PATIENT POPULATION

The target population for inclusion in this study is patients with HER2-positive unresectable LA/mBC, where the initial diagnosis of LA/mBC has been made no more than 6 months prior to enrolment.

[2]Dose modification refers to any change in the prescribed quantity of drug and/or the dosing interval including withholding or delaying doses.

To minimise patient selection bias, the Investigator (or sub-Investigator) should invite all eligible consecutive patients or else implement a fixed sampling method, e.g. to include every n^{th} patient. The sites are asked to maintain a screening log which will not have to be submitted to the Sponsor.

This is an observational study in which clinical decisions concerning the optimal management strategy for a particular patient are taken independent of and prior to any decision by the physician to invite a patient to participate in the study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Males or females
- Initially diagnosed with HER2-positive unresectable LA/mBC no more than 6 months prior to enrolment, although they can have received anti-cancer treatment during that time
- Age ≥18 years
- Able and willing to provide written informed consent and to comply with the study protocol.

4.1.2 Exclusion Criteria

There are no exclusion criteria for entry into this study.

4.2 ANTI-CANCER TREATMENTS

All anti-cancer treatments will be prescribed according to local treatment guidelines and/or routine clinical practice. The treating physician will make all treatment decisions and will provide prescriptions for his/her patients – which will need to be paid for, or reimbursed, according to routine local practice. The Sponsor will not supply any medications as part of this study.

4.3 CONCOMITANT THERAPY

Any treatment necessary for the patient's well-being may be administered as required in the opinion of the treating physician. There are no excluded therapies and interventional/surgical treatments are permitted.

4.4 DATA COLLECTION

The following data will be collected.

4.4.1 Healthcare Provider Information

The treating physician will provide details of the type of healthcare provider operating at their site (e.g. specialty care, private practice, teaching institution, etc.).

4.4.2 Informed Consent and Patient Enrolment

An Eligibility Screening Form is to be completed by the Investigator to document their assessment of each patient with regard to the protocol's inclusion criteria(Section 4.1.1).

Patients must read, understand, sign and date the most current independent EC-approved written Informed Consent Form (ICF) before any data are collected for the study.

Patients willing and able to participate in the study will be assigned from a list supplied by the Sponsor an individual study patient number in the order of enrolment. Each participating centre will be identified by a unique centre number assigned by Roche or its designee.

4.4.3 Demographics

Demographic data will be collected as per routine clinical practice and will include date of birth, sex and self-reported ethnicity.

4.4.4 Patient Medical History

Medical history will be collected as per routine clinical practice and, if available, recorded in the eCRF pages:

- Past medical history includes surgeries, cardiovascular risk factors, comorbid medical conditions and their treatments, and other relevant medical history
- Past breast cancer history
    - At initial diagnosis: stage of disease; histology; hormone (oestrogen and progesterone) receptor status; metastatic sites (if stage IV at diagnosis); staging diagnostic work-up; and HER2 diagnostic method (*in situ* hybridisation or immunohistochemistry) with results
    - Prior to diagnosis of unresectable LA/mBC: anti-cancer treatments in the early breast cancer setting (including radiotherapy; surgical treatments; hormonal treatments; chemotherapies; and/or other anti-cancer therapies, such as targeted therapies), reasons that led to treatment discontinuation or modification, and other clinical relevant information
- Breast cancer history after diagnosis of unresectable LA/mBC:
    - Sites of metastases
    - Number of lesions (isolated or multiple) per site
    - Disease status as assessed by the Investigator
    - Anti-cancer treatment history for unresectable LA/mBC including:
        - Radiation treatment (including date, body site, dose and type of radiation)

- § Chemotherapy (including names, dates, doses, number of cycles per regimen and reasons [if any] for discontinuation)
- § Hormonal treatment (including agent name, administration route, date, dose and reasons [if any] for discontinuation)
- § Immunotherapy(including agent name, administration route, date, dose, number of cycles per regimen and reasons [if any] for discontinuation)
- § Other anti-cancer treatments including targeted therapies (including agent name, administration route, date, dose, number of cycles per regimen and reasons [if any] for discontinuation)
- § Surgery (including date, body site and type of procedure)

4.4.5 Anti-Cancer and Concomitant Medications

Data on all anti-cancer and concomitant medications will be collected and recorded in the eCRF. This will include:

- All anti-cancer treatments received by the patient for breast cancer including during the period prior to enrolment
  - Patients enrolled in an interventional clinical trial will have their study treatment(s) recorded, if open label and known, otherwise they will be recorded as “investigational treatment”
- All other medications (e.g. prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient within 14 days prior to enrolment and during the observation period

4.4.6 Performance Status

Routine clinical assessments of patient performance status (e.g. Eastern Cooperative Oncology Group [ECOG] performance status) will be collected.

This also includes weight and height collection at screening and when deemed necessary by the investigator (unscheduled visits). This also includes other routine assessment deemed necessary by the investigator to routinely assess the patient status at any visit (e.g., physical examination, vital signs, ECG, etc).

4.4.7 Quality of Life and Patient-Reported Outcomes

QoL PROs will be collected and measured using the following questionnaires, where this is collected as routine practice:

- EQ-5D (Rabin and de Charro 2001)
- FACT-B (Brady 1997)

The following PRO measures may be included for specific patients and specific therapies:

- WPAI questionnaire (Reilly 2002)

4.4.8 Health Economic Outcome Measurements

Health economic outcome measurements (see Section 3.7.5 for details) will be collected at study entry for the 6-month period prior to enrolment and prospectively during the observation period.

4.4.9 Safety Assessment Measurements

SAEs, specific adverse events relevant to HER2-targeted therapies, and AEs leading to discontinuation or dose modification of an anti-cancer therapy (see Section 5.1.1.2) will be collected prospectively throughout the duration of the observation period. Dose modification refers to any change in the prescribed quantity of drug and/or the dosing interval, including the withholding or delaying of doses.

Clinical AEs meeting the above definitions, serious and non-serious, that will be collected in the disease registry, will be recorded in the eCRF during the total observation period, with physician's assessment of severity (mild, moderate, severe or in oncology studies using the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]) and relationship to therapy (i.e., related or unrelated) as described in Appendix 2.

4.4.10 Pregnancy Status and Pregnancy Outcomes

For this study, the pregnancy status of female patients and the outcome of any pregnancy will be collected at screening and during the observation period. Local laboratory pregnancy testing data (e.g. human β-chorionic gonadotropin) will be collected if available and may be used to determine pregnancy status.

4.5 TIMING OF DATA COLLECTION

The complete schedule of data collected during the observation period is provided in Appendix 1. A summary of data to be collected is provided in Table 2. Data will be recorded at patient enrolment and then approximately every 3 months throughout the study or according to the local medical standard of care.

Table 2. Summary of Data Collected During the Observation Study

Prior to the start of study-related data collection	At enrolment	Periodic data collection at approximately 3 months, at death, or study discontinuation
Informed consent (Section 4.4.2)	Demographic data (Section 4.4.3)	
	Patient past medical history, including surgeries, cardiovascular risk factors, comorbid medical conditions and their treatments, and other relevant medical history (Section 4.4.4)	Changes in medical history (Section 4.4.4)
	Breast cancer specific history (from initial diagnosis) including details regarding early breast cancer (Section 4.4.4)	Changes in breast cancer history (e.g. interval surgeries, site of metastases, disease status; Section 4.4.4)
	Anti-Cancer treatments (radiation, chemotherapy, hormonal, and/or other anti-cancer therapy such as targeted therapy) for unresectable LA/mBC along with reasons for changes (Section 4.4.4 and Section 4.4.5)	Anti-Cancer treatments (radiation, chemotherapy, hormonal, and/or other anti-cancer therapy such as targeted therapy) along with reasons for changes (Section 4.4.4 and Section 4.4.5)
	Characteristics of the investigational site, e.g. type of healthcare provider, type and size of hospital (Section 4.4.5) Concomitant medications (Section 4.4.5)	Concomitant medications (Section 4.4.5)
	Disease and performance status (Section 4.4.6)	Disease and performance status (Section 4.4.6)
	Patient-reported outcomes (Section 4.4.7)	Patient-reported outcomes (Section 4.4.7)
	Healthcare resource utilisation (Section 4.4.8)	Healthcare resource utilisation (Section 4.4.8)
	Pregnancy status (Section 4.4.10)	Pregnancy status and pregnancy outcome (Section 4.4.10)
		SAEs, specific adverse events and AEs leading to discontinuation or modification of an anti-cancer therapy (Section 4.4.9) (continuous reporting)
Abbreviations: AE = adverse event; BC = breast cancer; SAE = serious adverse event;		

4.5.1 Prior to Study-Related Data Collection

Patients must read, understand, sign and date the most current independent EC-approved written ICF before any data are collected for the study (see Section 4.4.2).

4.5.2 Data Collected at Enrolment

Once the patient has been enrolled into the study, the following routine clinical data will be collected at the enrolment visit:

- Demographic data (Section 4.4.3)
- Past medical history (Section 4.4.4)
- Breast cancer history (Section 4.4.4)
- Anti-cancer treatment history for early breast cancer, unless the patient presented *de novo* with advanced breast cancer (Section 4.4.4)
- Anti-cancer treatment history for advanced disease and reasons for changes (Section 4.4.5)
- Concomitant medications (Section 4.3 and Section 4.4.5)
- Performance status (Section 4.4.6)
- Patient-reported outcomes (Section 3.7.4 and Section 4.4.7)
- Healthcare resource utilisation within 6 months prior to enrolment (Section 4.4.8)
- Pregnancy status (Section 4.4.10)

4.5.3 Data Collected During Observation Period or at Completion/Early Termination Visit

It is recommended that the following data are collected approximately every 3 months at routine clinic visits.

- Changes in medical history (Section 4.4.4)
- Changes in breast cancer history (e.g. surgical procedures, sites and number of metastases, disease status; Section 4.4.4)
- Anti-cancer treatments (Section 4.2, Section 4.4.4 and Section 4.4.5), including any changes and reasons for them
- Concomitant medications (Section 4.3 and Section 4.4.5)
- Performance status (Section 4.4.6)
- Patient-reported outcomes (Section 3.7.4 and Section 4.4.7)
- Healthcare resource utilisation within 6 months prior to enrolment (Section 4.4.8)
- Pregnancies and pregnancy outcomes (Section 4.4.10)

- SAEs, specific adverse events relevant to HER2-targeted therapies, and AEs leading to discontinuation or dose modification of an anti-cancer therapy (see Section 5.1.1.2) .

4.6 PATIENT, STUDY AND SITE DISCONTINUATION

4.6.1 Patient Withdrawal

The Investigator has the right to discontinue a patient from any anti-cancer treatment or to withdraw a patient from the study at any time.

Patients have the right to voluntarily discontinue any anti-cancer treatment or concomitant medication at any time and for any reason. In addition, patients enrolled in the study are free to withdraw their informed consent for the use and disclosure of health information at any time and, when asked, patients are not obliged to provide a reason.

Discontinuation of anti-cancer treatment will not be considered to be a reason for study discontinuation and patients will continue to be followed. The treating clinician is encouraged to follow the patient for as long as possible, until patient death or through to study end.

The date of study withdrawal and final status (i.e. withdrawal of consent, loss to follow-up or death) for a patient who withdraws from the study should be recorded in the eCRF.

4.6.2 Study Discontinuation

The Sponsor has the right to terminate the study at any time and for any reason. The Sponsor will notify the Investigator if the study is placed on hold or if the Sponsor decides to discontinue the study.

The Sponsor may also decide to close recruitment and/or follow-up at a particular investigational site. Reasons for doing so include, but are not limited to, the following:

- Excessively slow recruitment
- Treating clinician does not adhere to the protocol or applicable regulatory guidelines in conducting the study
- Inaccurate or incomplete data recording

5 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

5.1 SAFETY REPORTING REQUIREMENTS FOR STUDIED MEDICINAL PRODUCTS

5.1.1 Safety Parameters and Definitions

The reporting requirements in this section apply to all studied medicinal products (observational products of interest, as specifically stated in the study Objectives). For safety reporting requirements for non-studied medicinal products, see Section 5.2.

Safety assessments will consist of monitoring and recording SAEs and non-serious AEs (those leading to dose modification/treatment discontinuation and specific AEs relevant to HER2-targeted therapies), performing safety laboratory assessments, measuring vital signs, and conducting other tests that are deemed critical to the safety evaluation of the study as per standard medical practice.

5.1.1.1 Adverse Events

According to the International Conference of Harmonisation (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation patient 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 Appendix 2.3.10
- 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., electrocardiogram [ECG], X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.

5.1.1.2 Assessment of Serious Adverse Events (Immediately Reportable to the Marketing Authorization Holder), non-serious adverse events of specific relevance to HER2-targeted therapies, non-serious adverse events leading to dose modification or treatment discontinuation and Other Non-serious Adverse Events

Serious Adverse Events

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

- Is fatal (i.e., the AE actually causes or leads to death)

- Is life-threatening (NOTE: The term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires or prolongs inpatient hospitalization (see Appendix 2.3.11)
- 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)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study medicine
- Is a significant medical event in the physician'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 (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Appendix 2); 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 CRF (for detailed instructions, see Appendix 2).

For reporting requirements for SAEs, please refer to Section 5.1.3.1

Non-Serious Adverse Events

For this disease registry study, all non-serious AEs leading to dose modification or dose discontinuation or the following specific adverse events must be collected as per protocol Appendix 2. Dose modification refers to any change in the prescribed quantity of drug and/or the dosing interval, including the withholding or delaying of doses.

Specific AEs relevant to HER2-targeted therapies will also be collected:

- Cases of potential medicine-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 9.4.1.2).
- Suspected transmission of an infectious agent by the study medicine, 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 that indicate an infection in a patient exposed to a medicinal product. This term only applies when a contamination of the study medicine is suspected and DOES NOT apply to infections supported by the mode of action, e.g. immunosuppression.
- Cardiac dysfunction, including one or more of the following:
    - Any fall in LVEF equal to or below 50% and/or clinically significant in the opinion of the treating physician and/or where a change in LVEF requires specific cardiovascular treatment and/or leads to discontinuation or delay of an anti-cancer treatment.

- Congestive heart failure
- Cardiac arrest
- Cardiac ischemia/infarction

- Serious and non-serious pneumonitis

For the reporting of non-serious adverse events please refer to Section 5.1.3.2.

Rationale for not collecting all non-serious adverse events

The primary objective of this disease registry is to observe the different anti-cancer treatment regimens and their sequencing throughout the course of the disease and to describe clinical outcome for each anti-cancer treatment regimen. The registry will capture patients on multiple different therapies and is not targeted at any specific treatments. Given the nature of metastatic breast cancer, it is expected that each patient's condition will worsen over the course of their participation in the registry, eventually leading to death. Each patient will experience many adverse events, whether related to the prescribed anti-cancer therapy or to the progression of the disease, and it is therefore not practical to request the participating sites to collect and report all adverse events in such a disease registry.

The standard of care of HER2-positive metastatic breast cancer disease mainly includes the use of targeted therapies, such as trastuzumab, pertuzumab, and trastuzumab emtansine. The safety profile of all three above mentioned products is well established with cumulative exposures of tens of thousands of patients. There have been multiple studies reported in this patient population, and the occurrence of adverse events has been generally similar. Hence there is a reasonable basis to conclude that the occurrence of adverse events in the population to be studied will be similar to previously observed rates.

Although not all non-serious adverse events will be collected from patients participating in this disease registry, safety is an important indicator of the course of the disease and of the wellbeing of the patients. The following safety categories will therefore be collected and reported, as described earlier in this section:

- All Serious Adverse Events
- Non-serious adverse events of specific relevance to HER2-targeted therapies;
- All adverse events leading to the discontinuation or dose modification of any anti-cancer treatment

5.1.2 Methods and Timing for Capturing and Assessing Safety Parameters

The physician is responsible for ensuring that all AEs collected as per protocol (see Section 5.1.1.1 for definition) are recorded in the AE section of the CRF and reported to the marketing authorization holder in accordance with instructions provided in this section and in Section 5.1.3.

For each AE recorded in the AE section of the CRF, the physician will make an assessment of seriousness (see Section 5.1.1.2), severity (see Appendix 2.1), and causality (see Appendix 2.2).

5.1.2.1 Adverse Event Reporting Period

Physicians will seek information on AEs at each patient contact. All AEs subject to the collecting and reporting requirements outlined in this protocol, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and in the AE section of the CRF.

Once the patient is enrolled in the study, AEs will be collected until the end of his or her observation period. After this period, the physician is not required to actively monitor patients for AEs but if the treating physician becomes aware of any related AEs to any medicinal product they should be notified to the competent authority in the Member State where the reactions occurred or to the marketing authorization holder of the suspected medicinal product, but not to both (to avoid duplicate reporting).

5.1.2.2 Procedures for Recording Adverse Events

Physicians should use correct medical terminology/concepts when recording AEs in the AE section of the CRF. Colloquialisms and abbreviations should be avoided.

Only one AE term should be recorded in the event field of the CRF.

See Appendix 2 for further specific instruction regarding:

- Infusion-Related or Injection Reactions
- Diagnosis versus signs and symptoms
- Adverse Events occurring secondary to other Adverse Events
- Persistent or recurrent Adverse Events
- Abnormal Laboratory Values
- Abnormal Vital Sign Values
- Abnormal Liver Function Tests
- Deaths
    - All events with an outcome or consequence of death should be classified as serious adverse events (SAEs) and reported to the marketing authorization holder immediately.

In certain circumstances, however, suspected adverse reactions with fatal outcome may not be subject to expedited reporting (see Section 8.3). All deaths that occur during the protocol-specified AE reporting period, regardless of relationship to study medicine, must be recorded in the AE section of the CRF and immediately reported to the marketing authorization holder

- Pre-existing Medical Conditions
- Lack of Therapeutic Efficacy or worsening of metastatic breast cancer
- Hospitalization or Prolonged Hospitalization
- Overdoses, Misuses, Abuses, Off-Label Use, Occupational Exposure, or Medication Error
- Quality Defects and Falsified Medicinal Products
- Drug Interactions

5.1.3 Reporting Requirements from Physician to Marketing Authorisation Holder

5.1.3.1 Immediate Reporting Requirements from Physician to Marketing Authorization Holder

Certain events require immediate reporting to allow the Marketing Authorization Holder and the regulatory authorities to take appropriate measures to address potential new risks associated with the use of the medicine. The physician must report such events to the marketing authorization holder immediately; under no circumstances should reporting take place more than 24 hours after the physician learns of the event. The following is a list of events that the physician must report to the marketing authorization holder within 24 hours after learning of the event, regardless of relationship to study medicine:

- SAEs
- Pregnancies

The physician must report new significant follow-up information for these events to the marketing authorization holder 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

For reports of SAEs, including follow-up, physicians should record all case details that can be gathered immediately (i.e., within 24 hours) in the AE page of the CRF and submit the report via the EDC system. A report will be generated and sent to Roche Drug Safety by the EDC system.

In the event that the EDC system is temporarily unavailable please refer to Section 5.1.3.3.

Physicians must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

5.1.3.2 Reporting Requirements for Non-Serious Adverse Events

For all non-serious AEs leading to dose modification or dose discontinuation, and specific adverse events described in Section 5.1.1.2, including follow-up reports, physicians must record all case details that can be gathered within 30 calendar days of learning of the event on the AE section of the CRF and submit the report via the EDC system. A report will be generated and sent to Roche Drug to allow appropriate reporting to relevant competent authorities.

In the event that the EDC system is temporarily unavailable please refer to Section 5.1.3.3.

5.1.3.3 If EDC System is Temporarily Unavailable or not Used

In the event that the EDC system is temporarily unavailable, a completed paper reporting form and fax coversheet should be faxed/scanned to Roche Drug Safety or its designee immediately (i.e. no more than 24 hours after learning of the event) or within 30 days for non-serious AEs, using the fax number or email address provided to physicians.

Once the system is available again, all information should additionally be entered and submitted via the EDC system.

5.1.3.4 Reporting Requirements for Pregnancies/Breastfeeding

Pregnancies/Breastfeeding in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the physician if they become pregnant during the study, either whilst receiving anti-cancer medication or for a defined period after the last dose of medicine. The national prescribing information (Summary of Product Characteristics) for the medicine will typically define the period of time following the last dose during which specific measures or precautions are required. A Pregnancy Report should be completed by the physician immediately (i.e., no more than 24 hours after learning of the pregnancy) and sent to Roche Drug Safety. Pregnancy should not be recorded on the AE CRF. The physician should refer to the prescribing information for the medicine for pregnancy-specific recommendations, and considercounselling the patient, discussing the risks of the pregnancy and the possible effects on the foetus. 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 AE section of the CRF.

Suspected adverse reactions that occur in infants following exposure to a medicinal product from breast milk should be reported to Roche Drug Safety.

Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the physician if their partner becomes pregnant during the study, either whilst receiving anti-cancer medication or for a defined period after the last dose of medicine. The national prescribing information (Summary of Product Characteristics) for the medicine will typically define the period of time following the last dose during which specific measures or precautions are required. A Pregnancy Report should be completed by the physician immediately (i.e., no more than 24 hours after learning of the pregnancy) and sent to Roche Drug Safety. 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 medicine. 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 with additional information on the course and outcome of the pregnancy. A physician 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.

Abortions

Any abortion should be classified as an SAE (as the marketing authorization holder considers abortions to be medically significant), recorded in the AE section of the CRF, and reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event; see Section 5.1.3.1).

Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to the medicine {or the female partner of a male patient exposed to the medicine} should be classified as an SAE, recorded in the AE section of the CRF, and reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event; see Section 5.1.3.1).

5.1.4 Follow-Up of Patients after Adverse Events

5.1.4.1 Physician Follow-Up

The physician should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the physician, 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 studied medicinal product until a final outcome can be reported or until close of the study.

During the study period, resolution of AEs (with dates) should be documented in the AE section of the CRF to facilitate SDV.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.1.4.2 Marketing Authorization Holder Follow-Up

For all AEs, the marketing authorization holder or a designee may follow up by telephone, fax and/or electronic mail, to obtain additional case details and outcome information from the disease registry in order to perform an independent medical assessment of the reported case.

5.2 SAFETY REPORTING REQUIREMENTS FOR NON-STUDIED MEDICINAL PRODUCTS

In the context of this disease registry, all medicinal products used to treat the disease are considered studied products. Any other products should be considered as non-studied products.

Although adverse event information is not being actively solicited for non-studied medicinal products, the physician/consumers are reminded to report any adverse reactions (for which they suspect a causal role of a medicinal product) that come to their attention to the marketing authorization holder of the suspected medicinal product, or to the concerned competent authorities via the national spontaneous reporting system (www.mhra.gov.uk/yellowcard).

In addition, the following should also be reported if occurring during exposure to a marketed medicinal product, even in the absence of adverse events:

- Pregnancy
- Breastfeeding
- Abnormal laboratory findings
- Overdose, abuse, misuse, off-label use, medication error or occupational exposure
- Reports of lack of efficacy
- Product quality defects and falsified medicinal products
- Data related to a suspected transmission of an infectious agent via a medicinal product
- Drug interactions (including drug/drug, drug/food, drug/device and drug/alcohol)

When a patient is not exposed to a marketed medicinal product, but the physician/consumer becomes aware of the potential for a medication error, or an intercepted medication error, this should also be reported.

6 STATISTICAL METHODS

For this study, a detailed data analysis plan will be included in the Statistical Analysis Plan.

6.1 DETERMINATION OF SAMPLE SIZE

The emphasis of this study is to observe trends in treatment regimens and their sequencing throughout the disease course, clinical outcomes (PFS, OS), and safety outcomes (incidence of SAEs, specific adverse events relevant to HER2-targeted therapies, AEs leading to discontinuation or dose modification of an anti-cancer therapy, and pregnancies) in patients with HER2-positive unresectable LA/mBC. Where possible, and if allowed by the number of patients enrolled receiving various anti-cancer treatment regimens, a comparative analysis of these clinical and safety outcomes across various HER2-targeted treatment regimens will also be performed.

The primary objective of the study is to observe treatment regimens and their sequencing and to describe clinical outcomes in individual treatment groups. The planned sample size is intended to provide a sufficient number of patients to assess overall trends according to subgroups of common treatment regimens.

6.1.1 Study Population Size

This study will enrol a minimum of 300 patients over a 3-year period. Enrolled patients will receive various anti-cancer treatment regimens as determined by their treating physicians and according to the standard of care and/or clinical practice at each study site.

The primary objective of the study is to observe treatment regimens and their sequencing and to describe treatment outcomes in individual treatment groups. The planned sample size is intended to provide a sufficient number of patients to allow the assessment of overall trends by subgroups of common anti-cancer treatment regimens.

In order to assess the adequacy of the sample size for the precision of median PFS time – the primary measure of efficacy – simulated exponential survival times were generated and evaluated 1000 times for sample sizes ranging from 100 to 1000 (with a 3-year enrolment period and 5-year follow-up period from the last patient enrolled). The sample size is also based on practical considerations.

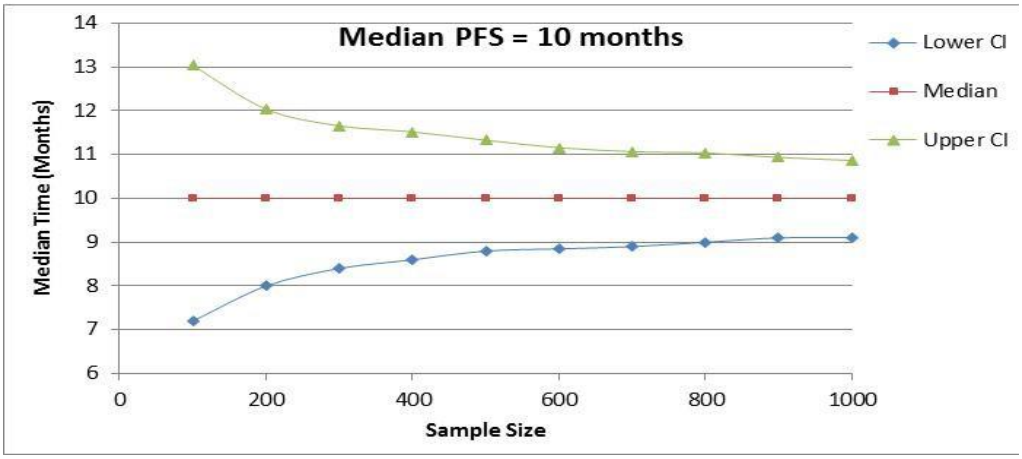
The median PFS time used in the simulations was approximately 10 months. The results show that with 600 patients the expected 95% confidence interval (CI) for the median will extend from 8.85 to 11.16 months (a width of 2.32 months). The precision of this estimate is deemed sufficient to draw valid conclusions around this measure of efficacy. Table 5 and Figure 1 show the expected estimates of the 95% CIs for the median PFS using different sample sizes.

Table 5. Estimated 95% CIs for a Median Progression-free Survival of 10 Months

No. of patients	Lower 95% CI (months)	Upper 95% CI (months)	Width of CI (months)
400	8.59	11.52	2.93
500	8.80	11.33	2.53
600	8.85	11.16	2.31
700	8.93	11.07	2.14
800	9.02	11.04	2.02
900	9.09	10.94	1.85
1000	9.11	10.87	1.76

Abbreviation: CI = confidence interval.

Figure 1. Estimated Median PFS Times and Their 95% CIs as a Function of Sample Sizes



Abbreviations: CI = confidence interval; PFS = progression-free survival.

Figure 1 suggests that an increase in sample size up to 300 patients results in noticeably increased precision (tighter 95% CI) of measuring PFS of up to 10 months when a study sizes of 100 to 1000 were examined. Increasing the sample size beyond 300 does not yield a substantial increase in precision. For instance, in measuring a median PFS time of 10 months, the width of the estimated 95% CI is 4.02 months for a sample size of 200 versus 2.02 months for a sample size of 800.

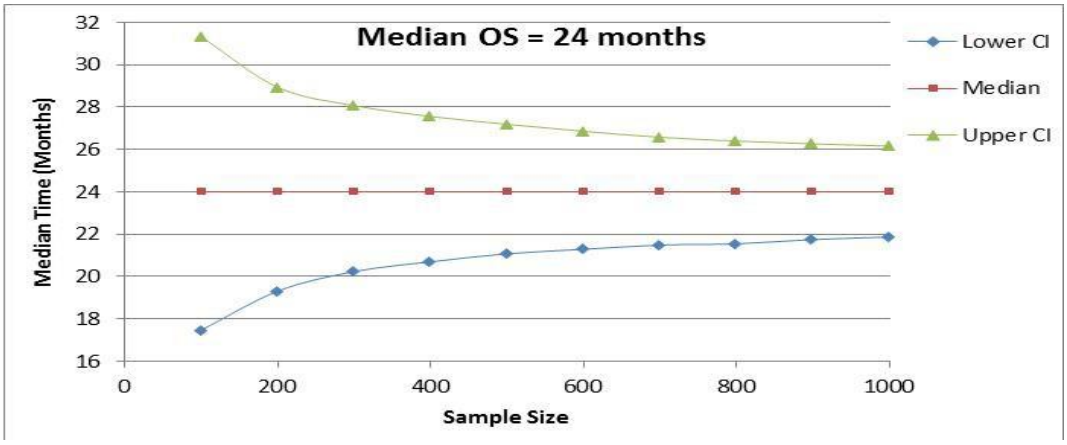
An additional simulation study was performed to evaluate the precision of median OS time for sample sizes from 100 to 1000. The median OS time used in this simulation was 24 months. With 600 patients, the expected CI for median OS will extend from 21.3 to 26.9 months (a width of 5.6 months). Table 6 and Figure 2 show the expected estimates of the 95% CIs for the median OS using different sample sizes.

Table 6. Estimated 95% Confidence Intervals for a Median Overall Survival of 24 Months

No. of patients	Lower 95% CI (months)	Upper 95% CI (months)	Width of CI (months)
400	20.70	27.56	6.86
500	21.08	27.19	6.11
600	21.29	26.86	5.57
700	21.49	26.58	5.09
800	21.55	26.40	4.85
900	21.75	26.27	4.52
1000	21.87	26.16	4.29

CI = confidence interval.

Figure 2. Estimated Median OS Times and Their 95% Confidence Intervals as a Function of Sample Sizes



Abbreviations: CI = confidence interval; OS = overall survival.

In relation to the measures of safety, assuming that a specific event occurs in 1% of patients in the study (e.g. a specific SAE), with 600 patients the 95% Clopper–Pearson CI around that incidence will extend from 0.37% to 2.2%. For events occurring in 10% of patients, the CI will extend from 7.7% to 12.7%. The precision of these CIs and the probability to detect rare events is deemed sufficient to draw valid conclusions concerning the events of interest.

Table 7 shows the estimated 95% CIs for different event rates.

Table 7. Estimated 95% Confidence Intervals for Different Event Rates

		Event rate				
No. of Patients		**0.1% (1/1000)**	**1% (1/100)**	**2% (2/100)**	**5% (5/100)**	**10% (1/10)**
200	95% CI, %	0.0–2.0	0.12–3.6	0.05–5.0	2.4–9.0	6.2–15.0
400	95% CI, %	0.0–1.1	0.2–2.5	0.87–3.9	3.1–7.6	7.2–13.4
600	95% CI, %	0.0–0.8	0.37–2.2	1.0–3.5	3.4–7.1	7.7–12.7
800	95% CI, %	0.0–0.65	0.4–2.0	1.1–3.2	3.6–6.7	8.0–12.3
1000	95% CI, %	0.0–0.5	0.48–1.8	1.2–3.1	3.7–6.5	8.2–12.0

Table 8 shows the probability of detecting occurrences for different event rates with different sample sizes.

Table 8. Probability of Detecting Occurrences for Different Event Rates

		Event rate				
No.of patients		**0.1% (1/1000)**	**1% (1/100)**	**2% (2/100)**	**5% (5/100)**	**10% (1/10)**
200	Probability of detecting at least one event	0.18	0.87	0.98	1.0	1.0
400	Probability of detecting at least one event	0.33	0.98	1.0	1.0	1.0
600	Probability of detecting at least one event	0.45	1.0	1.0	1.0	1.0
800	Probability of detecting at least one event	0.55	1.0	1.0	1.0	1.0
1000	Probability of detecting at least one event	0.63	1.0	1.0	1.0	1.0

A Statistical Analysis Plan will be developed to provide further detail on statistical analyses and a schedule for interim analyses.

7 SUMMARIES OF THE CONDUCT OF THE STUDY

Based on the enrolled patients, the numbers and proportions of patients completing or starting treatments or withdrawing from the study will be summarised. For patients who withdraw, the reasons for discontinuation will be summarised by types of reasons.

For descriptive summaries, continuous variables will be summarised using descriptive statistics (i.e. number, mean, median, standard deviation and range). If applicable, analysis of variance (*t* test or F test) or non-parametric testing, such as Wilcoxon's rank-sum test or Kruskal–Wallis test, will be used to test group difference on the continuous variables.

Categorical variables will be summarised by numbers and proportions. If applicable, a chi-squared test will be used to test group differences for categorical variables.

7.1 Demographics and Enrolment Characteristics Analysis

Demographic and enrolment characteristics will be summarised overall and by the most common treatment regimens received among the final enrolled patient population.

7.2 SUMMARIES OF TREATMENT-GROUP COMPARABILITY

Where possible, and if allowed by the number of enrolled patients receiving various treatment regimens, a comparative analysis of the outcomes across various HER2-targeted treatment regimens will also be performed.

7.3 EFFICACY ANALYSIS

7.3.1 Primary Effectiveness Variable

The primary objective for this study is to observe treatment regimens and their sequencing, and to describe treatment outcomes in patients with HER2-positive unresectable LA/mBC in the setting of normal clinical practice.

The numbers and proportions of patients receiving each unique treatment regimen overall and as first-line versus subsequent-line therapy will be summarised. First-line treatment regimens will be defined as therapies received after initial diagnosis of HER2-positive unresectable LA/mBC and before a patient experiences their first disease progression event.

For patients who receive more than one treatment regimen while on study, the proportion of patients receiving each unique treatment regimen sequence will also be summarised. Temporal changes in treatment patterns will be summarised across 6-month intervals.

7.3.2 Secondary Effectiveness Variables

Where available, the following efficacy parameters will be documented:

- Patient characteristics associated with receipt of particular anti-cancer treatment regimens
- The sequencing of anti-cancer treatment regimens across the stages of unresectable LA/mBC
- OS for the overall population
- The number of treatment regimens received by patients
- The presence of CNS disease as the site of first progression

7.4 SAFETY ANALYSES

- To observe the safety of different anti-cancer treatment regimens through the reporting of serious adverse events (SAEs), specific adverse events relevant to HER2-targeted therapies and AEs leading to discontinuation or dose modification of an anti-cancer therapy
- To observe and describe the incidence of and reasons for anti-cancer treatment modifications

- To observe and describe the treatment of populations of special interest by estimating the incidence and prevalence of cardiac events related to left ventricular dysfunction; pregnancy; and pregnancy outcomes.

7.5 OUTCOMES AND ANALYSES

7.5.1 Quality of Life Outcome Analysis

Describe QoL PROs for each of the sequential treatment regimens using the following questionnaires: EQ-5D and FACT-B (see Section 3.7.4 and Section 4.4.7).

7.5.2 Patient-Reported Outcomes Analysis

Describe symptom burden, ability to perform activities of daily living and work productivity for each of the sequential treatment regimens using PROs

- Work Productivity and Activity Impairment (WPAI) questionnaire (Reilly Associates 2002)

7.5.3 Healthcare Utilisation and Cost Analysis

Healthcare resource utilisation prior to unresectable LA/mBC diagnosis and sequencing of anti-cancer treatment regimens will be described:

- Utilisation or adherence to predefined clinical guidelines regarding treatment regimen decisions Healthcare resource utilisation associated with the treatment of AEs, including associated procedures, hospitalisations, emergency room attendances and outpatient visits

7.6 INTERIM ANALYSES

In addition to the primary analysis, there will be annual interim analyses for safety reporting and presentation of safety results; presentation of the different treatment regimens and their sequencing; and effectiveness data at appropriate timepoints. These annual reporting events will start 1 year after first patient first visit and will continue annually until study end.

7.7 STUDY ANALYSIS METHODS

The following is an outline of the statistical methodology that will be used to report and analyse data from this study. A more detailed description will be provided in a separate Statistical Analysis Plan, which may include additional exploratory analyses not explicitly mentioned below.

All enrolled patients who received at least one dose of an anti-cancer medication for HER2-positive unresectable LA/mBC will be included in the full analysis set, which will be the primary analysis population for safety and efficacy parameters. Other analysis populations may be defined based on more restrictive criteria.

The analysis of the present study will be exploratory and primarily make use of descriptive statistical methods. In addition, exploratory statistical testing and modelling will be used to highlight interesting aspects of the data. Any test performed will be two-sided and carried out with a 5% α error rate without correction for multiplicity.

A descriptive analysis of safety will be performed. The main safety parameter is the incidence of SAEs. The proportion of patients experiencing at least one event within each line of treatment will be estimated with 95% Clopper–Pearson CIs.

The analysis of PFS and OS is based on the survivor function, which is the probability of remaining event free beyond a certain point in time. The survival function will be estimated using Kaplan–Meier methodology and summarised using the range, the 25th and 75th percentiles, the median overall survival and a 95% CI for the median. The plot of Kaplan–Meier estimates for the single treatment group will be presented.

Efficacy measures will be analysed for parameters as described in the study objectives. Efficacy analyses will include CNS as the site of first progression, and CNS-only progression, OS and PFS; as well as ORR, DoR, and time to treatment failure.

PRO outcomes measures will be analysed.

Health economic outcome measures will be analysed.

Pre-specified subgroup analyses will include comparisons between:

- Efficacy and PRO measures for patients with access to non HTA-funded medicines vs those without
- Efficacy and PRO measures for patients >65 years versus <65 years of age
- Efficacy and PRO measures for patients who are hormone receptor positive versus hormone receptor negative
- Efficacy and PRO measures for patients with performance status 0-1 versus performance status >2.

7.8 DATA COLLECTION AND MANAGEMENT

This study will collect data from patients enrolled at each site. Patient medical records and patient-reported questionnaires will be used as data sources in this study. Local site staff will also provide appropriate patient information.

These data will be anonymised and entered into the eCRF via a secure web-based EDC system.

The Sponsor or designated contract research organisation (CRO), as appropriate, will be responsible for data management of this study, including quality checking. Data entered manually will be captured via EDC using eCRFs. The sites will be responsible for data entry into the EDC system. PROs will be collected on standard paper or electronic questionnaires, whichever is normally used in standard practice at the study site, and the data from these questionnaires will be entered into the eCRF by the site staff and will be analysed centrally.

In the event of discrepant data, the Sponsor or a designated CRO will request data clarification from the sites, which the sites will resolve electronically within the EDC system. eCRFs and correction documentation will be maintained in the EDC system's audit trail.

The EDC system should meet approved established standards for the security of health information and be validated. The system should also meet the ICH guideline E6R1 regarding electronic study data handling and be available for audit upon request. Patient confidentiality will be strictly maintained.

The Sponsor maintains high data quality standards and utilises processes and procedures to repeatedly ensure that the data are as clean and as accurate as possible when presented for analysis. Data quality is enhanced through a series of programmed data quality checks that automatically detect and prevent the entry of out of range or anomalous data. A remote data quality audit will be performed on collected data at various times throughout the study.

7.9 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed, as applicable, and submitted using the EDC system. Sites will receive training and have access to a user manual to assist in proper eCRF completion. These eCRFs will be submitted electronically to the Study Sponsor and should be handled in accordance with instructions from the Study Sponsor.

All eCRFs should be completed by designated trained site staff. These 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.

7.10 PATIENT-REPORTED OUTCOME DATA

In this study, PRO data will be elicited from the patients to more fully characterise the clinical profile of anti-cancer treatments if this is as part standard practice at the study site. The PRO instruments should be validated in the local language and authorised for use. The validated and approved PRO instrument will be distributed by the

Investigator's staff and completed in their entirety by the patient at specified timepoints during the study. Patients will use standard paper or electronic questionnaires, whichever is normally used in standard practice at the study site.

Once the study is complete, the PRO (paper or electronic if applicable) data, audit trail and local information and system documentation will be archived. The Study Sponsor will provide each site Investigator with patient data for their site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required.

7.11 SOURCE OF DATA VALIDATION

Source documents (paper or electronic) are documents 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.

Screening lists of those who chose to participate and those who declined participation in the study will be kept at the study site.

PRO questionnaires are anticipated to be paper based, however if sites collect PRO data electronically as standard this is acceptable.

A monitoring plan will be developed for this study describing how data are managed.

7.12 USE OF COMPUTERISED SYSTEMS

When clinical observations are entered directly into an investigational site's computerised medical record system (i.e. in lieu of original paper records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerised systems used in clinical research. An acceptable computerised 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.

7.13 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of anti-cancer treatment, including eCRFs, ePRO data (if applicable), ICFs, laboratory test

results and medication inventory records, must be retained securely 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 time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Study Sponsor. Written notification should be provided to the Study 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

The Investigator will ensure that this study is conducted in full compliance with the principles of the Declaration of Helsinki and Good Pharmacoepidemiology Practices (GPP), as well as the laws and regulations of the country in which the research is conducted, whichever affords greater protection to the individual patient.

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by the applicable local and regional laws and regulations.

This study will also comply with the definition of the non-interventional (observational) study provided in Article 2(c) of Directive 2001/20/EC (available at http://eur-lex/europa/eu) and its refinement provided in Chapter 1.7 Section 1 of Volume 9A of the Rules Governing Medicinal Products in the European Union (available at http://ec.europa.eu/health/documents/eudralex/vol-9/index_en.htm), the amended definition for Post-Authorisation Safety Studies to Directive 2001/83/EC in Article 1(c) of Directive 2001/83/EU (available at http://ec.europa.eu/health/documents/eudralex/vol-9/index_en.htm), and its refinement provided in Guideline of Good Pharmacovigilance Practices (GVP) Module VIII – Post-Authorisation Safety Studies (available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf).

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki (available at http://www.wma.net/en/30publications/10policies/b3/) and will be consistent with the Council for International Organizations of Medical Sciences International Ethical Guidelines for Biomedical Research Involving Human Subjects (available at http://www.cioms.ch/publications/layout_guide2002.pdf) and the GCP guidelines (available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf). The study will also follow the International Society of Pharmacoepidemiology Guidelines on GPP (available at http://www.pharmacoepi.org/resources/guidelines_08027.cfm), the International Ethical

Guidelines for Epidemiological Studies (available at http://www.ufrgs.br/bioetica/cioms2008.pdf), as well as all other applicable regulatory requirements. The study will also abide by the European Federation of Pharmaceutical Industries and Associations Code on the Promotion of Prescription-only Medicines to and Interactions With, Healthcare Professionals (available at: http://transparency.efpia.eu/uploads/Modules/Documents/efpia-hcp-code---2013-consolidated-final-2.pdf).

Study personnel involved in conducting this trial will be qualified by education, training and experience to perform their respective task(s).

8.2 INFORMED CONSENT FORM

The Study Sponsor's sample ICF will be provided to each site and will be supplied in a certified translation of the local language. The Study Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICF or any alternative consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. In countries where IRB/EC ICF review and approval are required for non-interventional observational studies, the final IRB/EC approved Consent Forms must be provided to the Study Sponsor for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or the patient's legally authorised 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.
Patients may decline the invitation to participate in the study and refuse consent without giving a reason and without prejudice to any treatment that is proposed.

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 Study Sponsor for submission to health authorities in countries where IRB/EC ICF review and approval are required for observational studies.

Patients must be re-consented using 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 authorised 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.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

Participating physicians must obtain EC approval of the protocol, ICF and other required study documents prior to starting the study

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 8.7).

In addition to the requirements for reporting AEs to the Study Sponsor, Investigators must comply with requirements for reporting SAEs to the local health authority and IRB/EC. Investigators may receive written safety-related communications and reports from the Roche Affiliate 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

Access to the EDC system will be controlled via hierarchical username and password control.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorisation 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 regulatory agencies (e.g. European Medicines Agency) and other national and local health authorities, Study Sponsor monitors, representatives and collaborators, and the IRB/EC for each study site, as appropriate.

8.4.1 Patient De-Identification Process

The Study 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 the Study Sponsor or any other Sponsor location.

Patient data will be anonymised through design of data entry fields that do not permit the entry of identifying information such as initials or centre-assigned patient identifiers. Only site staff will enter data into eCRFs. The patient's age in whole years and date of birth will be entered. No patient identifiers used by centres will be entered; instead patients will be assigned a study-specific identification number. The anonymised data, as entered into the EDC system, will be visible to the CRO and the Study Sponsor, but only centre staff will be able to trace a case identification number back to a patient's true identity, a necessary measure to allow centre staff to respond to data queries raised by the CRO later. Detailed explanation of data protection and patient confidentiality measures will be included in each application for local ethics approval.

8.5 FINANCIAL DISCLOSURE

Within this study, Investigators will provide the Study Sponsor with sufficient accurate financial information in accordance with local regulations to allow the Study Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory 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.

9 STUDY DOCUMENTATION, MONITORING AND ADMINISTRATION

Study monitors may perform ongoing source data verification to confirm that critical protocol data (i.e. source data) entered into the eCRFs by authorised site personnel are accurate, complete and verifiable from source documents.

9.1 STUDY DOCUMENTATION

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Study 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 as detailed in the policy for retention of records (see Section 6.7).

To facilitate source data verification, the Investigators and institutions must provide the Study Sponsor with 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.

9.2 SITE INSPECTIONS

The physician will permit the marketing authorization holder to audit facilities and records relevant to this study.

The physician will also permit national and local health authorities to inspect facilities and records relevant to this study.

9.3 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by Roche Products Ltd. Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 28 sites in the UK will participate to enroll approximately 300 patients.

Enrollment will occur through a manual management system.

Accredited local laboratories are required to be used for routine monitoring; local laboratory ranges will be collected.

All laboratory tests will be performed by the Investigator according to clinical judgement and routine clinical practice.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

9.4.1 Publication of Primary Study

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Study 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 only support publication of multicentre trials in their entirety and not as individual centre data. In this case, a co-ordinating 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 the 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.

9.4.2 Interim Analysis Reporting

For this study, there will be annual interim analyses for: safety reporting and presentation of safety results; presentation of the different treatment regimens and their sequencing; and effectiveness analyses where relevant. These annual reporting events will start 1 year after first patient first visit and will continue annually until study end.

9.4.3 Final Analysis Reporting

For this study, a Final Analysis Report will be generated and will include data for all patients enrolled across sites.

9.4.4 Use of Study Information and Publications

Results of this disease registry study will be disclosed by posting a summary online at www.clinicaltrialsregister.eu within 12 months of the close of this study.

Roche intends to submit a manuscript/paper or abstract for publication, or otherwise publicly disclose information, concerning the study.

Proposals for publications arising from this study may be submitted to the Roche Global Medical Affairs team for review. If the Roche Global Medical Affairs team determines that patentable matters are disclosed in any proposed publications, it shall be withheld for a period of time considered convenient.

9.5 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Investigators are responsible for promptly informing the IRB/EC of any amendments to the protocol. Approval must be obtained from the IRB/EC 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 Data Collected During the Observational Study

Assessment	Timepoint		
	Prior to start of study-related data collection	**Enrol-ment**	**Approximately every 3 months, at death, or discontinuation[a]**
Informed consent	X		
Demographic data		X	
Healthcare provider type	X		
Medical history			
Cardiovascular risk factors		X	
Other relevant medical history		X	X[b]
Selected laboratory tests		X	X[b]
LVEF value		X	X[b]
BC-specific cancer history[c]		X	X[b]
BC treatments		X	X[b,d]
Interval surgical and radiotherapy administration			X[b,d]
Interval anti-cancer therapy administration			X[b]
Disease status		X	X
Selected concomitant medications		X	X[b,d]
ECOG performance status		X	X
Quality of life assessments[e, f]		X	X[b,e,f]
Safety events[g]			Continuous
Pregnancy and pregnancy outcome		X	X[h]
Optional PRO and healthcare resource utilisation[f]		X	X[b,f]

Abbreviations: AE = adverse event; BC = breast cancer; ECOG = Eastern Cooperative Oncology Group; EQ-5D = EuroQol 5-Dimensions questionnaire; HER2 = human epidermal growth factor receptor 2; LVEF = left ventricular ejection fraction; SAE = serious adverse event.

a Data will be collected at approximately 3-month intervals throughout the study period during clinic visits that are determined by the treating physician (no specific visit will be mandated for collecting these data).

b Reporting of changes in patient history, BC-specific history, selected tests, LVEF values, BC treatments and concomitant medications during the course of this observational study.

c To include stage (at time of initial diagnosis and enrolment), histology, oestrogen receptor/progesterone receptor status, HER2 status (fluorescence *in situ* hybridization/immunohistochemistry) and BC archival HER2 status, staging diagnostic work-up, metastatic sites, and presence or absence of central nervous system metastases.

d All cancer treatments, including any changes to them, as well as treatments for any AEs

e The following quality of life assessments (where it is routine clinical practice) will be collected on-site: EQ-5D. FACT-B

f Additional patient-reported outcomes may be collected, including Work Productivity and Activity Impairment (WPAI) questionnaire (Reilly Associates 2002)

g Including all SAEs, specific adverse events relevant to HER2-targeted agents (see Section 3.7.3), and AEs leading to treatment discontinuation or modification. SAEs must be reported to Sponsor within 24 hours of learning of the events.

h Pregnancy Report should be completed and sent to Roche Drug Safety by the Investigator within 24 hours after learning of pregnancy in a female patient or the partner of a male patient

Appendix 2
Methods for Assessing and Recording Adverse Events

2.1 Assessment of Severity of Adverse Events

2.2 Assessment of Causality of Adverse Events

2.3 Procedures for Recording Adverse Events

Appendix 2.1 Assessment of Severity of Adverse Events

The AE severity grading scale for the NCI CTCAE (v4.03) will be used for assessing AE severity. The table below will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

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]

Note: Based on the NCI CTCAE (v4.03), which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[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 oneself, 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 an SAE (see Section 5.1.3.1 for reporting instructions), per the definition of SAE in Section 5.1.1.2.

[d] Grade 4 and 5 events must be reported as SAEs (see Section 5.1.3.1 for reporting instructions), per the definition of SAE in Section 5.1.1.2.

Appendix 2.2 Assessment of Causality of Adverse Events

Physicians 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 medicine, indicating “yes” or “no” accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study medicine
- Course of the event, considering especially the effects of dose reduction, discontinuation of study medicine, or reintroduction of study medicine (when applicable)
- Known association of the event with the study medicine 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 of the medicinal product.

Appendix 2.3 Procedures for recording Adverse Events

Appendix 2.3.1 Infusion-Related or Injection Reactions

AEs that occur during or within 24 hours after studied medicinal product administration should be captured as individual signs and symptoms in the AE section of the CRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related or anaphylactic reaction.

Appendix 2.3.2 Diagnosis versus Signs and Symptoms

For AEs, other than infusion-related or injection reactions (see Section 3.3.1) a diagnosis (if known) should be recorded in the AE section of the CRF 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 in the AE section of the CRF. 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.

Appendix 2.3.3 Adverse Events Occurring Secondary to Other Events

In general, AEs that are 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. A medically significant secondary AE that is separated in time from the initiating event should be recorded as an independent event in the AE section of the CRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the CRF.
- If vomiting results in severe dehydration, both events should be reported separately on the CRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the CRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the CRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the CRF.

All AEs should be recorded separately in the AE section of the CRF if it is unclear as to whether the events are associated.

Appendix 2.3.4 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 in the AE section of the CRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent AE becomes more severe, the most extreme severity should also be recorded in the AE section of the CRF. If the event becomes serious, it should be reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.1.3.1for reporting instructions). The AE section of the CRF 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's evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded separately in the AE section of the CRF.

Appendix 2.3.5 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:

- Is accompanied by clinical symptoms meeting the definition of an SAE;
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

Note: For oncology studies, certain abnormal values may not qualify as AEs.

It is the physician'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., alkaline phosphatase and bilirubin 5 x the upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded in the AE section of the eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded in the AE section of the CRF, 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 only be recorded once in the AE section of the eCRF (see Appendix 2.3.4 for details on recording persistent AEs).

Appendix 2.3.6 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:

- Is accompanied by clinical symptoms meeting the definition of an SAE;
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

It is the physician'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 in the AE section of the CRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once in the AE section of the CRF (see Appendix 2.3.4 for details on recording persistent AEs).

Appendix 2.3.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 x the ULN) in combination with either an elevated total bilirubin (> 2 x the 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, physicians must report as an AE the occurrence of either of the following:

Treatment-emergent ALT or AST > 3 x ULN in combination with total bilirubin > 2 x the ULN

Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded in the AE section of the CRF (see Appendix 2.3.5) and reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event) either as an SAE or a non-serious AE of special interest (see Section 5.1.3.1).

Appendix 2.3.8 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.1.3.1), regardless of relationship to study medicine, must be recorded in the AE section of the eCRF and immediately reported to the marketing authorization holder (see Section 5.1.3.1).

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 AE section of the CRF. Generally, only one such event should be reported. The term **"sudden death"** should only be used 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 after 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 AE section of the CRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

Appendix 2.3.9 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 in the CRF.

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 in the AE section of the CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Appendix 2.3.10 Lack of Therapeutic Efficacy or Worsening of HER2-positive unresectable locally advanced or metastatic breast cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as effectiveness assessment data only. In most cases, the expected pattern of progression will be based on clinical criteria such as physical examination, surgical and/or imaging. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE. This exception from reporting includes events of disease progression with a fatal outcome which are clearly attributable to disease progression.

Appendix 2.3.11 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 5.1.1.2), except as outlined below.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for respite care
- 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 progression of the underlying cancer

Appendix 2.3.12 Overdoses, Misuses, Abuses, Off-Label Use, Occupational Exposure, or Medication Error

Any overdose, misuse, abuse, off-label use, occupational exposure, medication error (including intercepted or potential), or any other incorrect administration of medicine under observation should be noted in the Drug Administration section of the CRF. Any overdose, abuse, misuse, inadvertent/erroneous administration, medication error (including intercepted or potential), or occupational exposure reports must be forwarded to the marketing authorization holder with or without an AE.

Reports with or without an AE should be forwarded to the marketing authorization holder as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event, see Section Section 5.1.3.1).

For the purpose of reporting cases of suspected adverse reactions, an occupational exposure to a medicine means an exposure to a medicine as a result of one's professional or non-professional occupation.

Appendix 2.3.13 Quality Defects and Falsified Medicinal Products

Reports of suspected or confirmed falsified medicinal product or quality defect of a medicinal product, with or without an associated AE, should be forwarded to the marketing authorization holder as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event, see Section 5.1.3.1).

Appendix 2.3.14 Drug Interactions

Reports of suspected or confirmed drug interactions, including drug/drug, drug/food, drug/device and drug/alcohol, should be forwarded to the marketing authorization holder as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event, see Section 5.1.3.1).