NI PASS PROTOCOL (PRIMARY DATA COLLECTION)

TITLE:	**A EUROPEAN DISESE REGISTRY STUDY TO PROSPECTIVELY OBSERVE TREATMENT PATTERNS AND OUTCOMES IN PTIENTS WITH HER2 POSITIVE UNRESECTABLE LOCALLY ADVANCED OR METASTATIC BREAST CANCER**
PROTOCOL NUMBER:	MO39146
VERSION NUMBER:	3.0
AUTHOR:	[redacted] *Roche Austria GmbH* *Engelhorngasse 3* *1211 Wien*
DATE FINAL:	Version 1.0: 25 May 2016
DATES AMENDED:	Version 2.0: 9 Sep 2016 Version 3.0: 16 Feb 2018

EU PAS REGISTER NUMBER:	22426
ACTIVE SUBSTANCES:	Not applicable (see studied medicinal products)
STUDIED MEDICINAL PRODUCTS:	Nationally authorized products according to physician's choice
PRODUCT REFERENCE NUMBERS:	Not applicable (see studied medicinal products)
PROCEDURE NUMBERS:	Not Applicable
JOINT PASS:	Yes

PROTOCOL AMENDMENT APPROVAL

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Approver's Name	Title	Date and Time (UTC)
[redacted]		16-Feb-2018 16:40:29
		16-Feb-2018 14:36:42

RESEARCH QUESTION AND OBJECTIVES:	Clinical outcome, patient-reported outcomes, QoL and health economics across anti-cacer treatment regimens and sequences during the course of HER2-positive unresectable LA/mBC in Europe
COUNTRIES OF STUDY POPULATION:	Austria Bulgaria Italy Portugal Romania
MARKETING AUTHORIZATION HOLDERS (MAH):	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom
MAH CONTACT PERSON:	[redacted] Engelhorngasse 3 1211 Vienna Austria

PROTOCOL AMENDMENT, VERSION 3:
RATIONALE

Study MO39146 has been reassessed as a NI-PASS. Protocol amendment has been created according to respective template.

Protocol MO39146 has been amended to include additional patients and sites which came as a consequence of Romania joining the study.

Additional changes to the protocol are as follows:

Protocol version and date is updated throughout the document.

Patient number is updated from 465 to 635 patients throughout the document

Number of study sites is updated from 54 to 64 throughout the document

In section 7.7.5, the following text has replaced the older text in order to account for the change in sample size

- "*The results show that with 635 patients the expected 95% confidence interval (CI) for the median will extend from 8.89 to 11.15 months (a width of 2.26 months)*" has replaced this text "The results show that with 465 patients the expected 95% confidence interval (CI) for the median will extend from 8.66 to 11.34 months (a width of 2.68 months)."
- Table 1 updated to include 635 patients

No. of patients	Lower 95% CI (months)	Upper 95% CI (months)	Width of CI (months)
100	7.23	13.04	6.01
200	8.02	12.04	4.02
300	8.41	11.66	3.25
315	8.46	11.67	3.21
400	8.59	11.52	2.93
465	8.66	11.34	2.68
500	8.80	11.33	2.53
600	8.85	11.16	2.31
635	**8.89**	**11.15**	**2.26**
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

- "*With 635 patients, the expected CI for median OS will extend from 21.39 to 26.69 months (a width of 5.30months)*." replaced this older text "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 2 updated to include 635 patients¨

No. of patients	Lower 95% CI (months)	Upper 95% CI (months)	Width of CI (months)
100	17.48	31.31	13.83
200	19.32	28.93	9.61
300	20.24	28.07	7.83
400	20.70	27.56	6.86
465	*20.84*	*27.28*	*6.44*
500	21.08	27.19	6.11
600	21.29	26.86	5.57
635	**21.39**	**26.69**	**5.30**
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

- *"Confidence intervals for the median times (PFS and OS) were constructed using the method described by Klein and Moeschberger (1997) with a log-log transformation."* was added.
- "*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 635 patients the 95% Clopper–Pearson CI around that incidence will extend from 0.39% to 2.134%. For events occurring in 10% of patients, the CI will extend from 7.784% to 12.6%*" replaced this text "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%."
- Table 3 updated to include 635 patients

		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
465	*95% CI, %*	*0.0 – 1.0*	*0.3 – 2.4*	*0.9 – 3.7*	*3.2 – 7.4*	*7.4 - 13.1*
600	95% CI, %	0.0–0.8	0.37–2.2	1.0–3.5	3.4–7.1	7.7–12.7
635	**95% CI, %**	**0.0 – 0.76**	**0.39 – 2.13**	**1.06 – 3.42**	**3.45 – 7.0**	**7,78 – 12.6**
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 4 updated

		Event rate				
No.of patients		**0.1% (1/1000)**	**1% (1/100)**	**2% (2/100)**	**5% (5/100)**	**10% (1/10)**
200	Probability of observing at least one event	0.18	0.87	0.98	1.0	1.0
400	Probability of observing at least one event	0.33	0.98	1.0	1.0	1.0
465	Probability of observing at least one event	0.37	0.99	0.99	1.0	1.0
600	Probability of observing at least one event	0.45	1.0	1.0	1.0	1.0
635	**Probability of observing at least one event**	**0.47**	**1.0**	**1.0**	**1.0**	**1.0**
800	Probability of observing at least one event	0.55	1.0	1.0	1.0	1.0
1000	Probability of observing at least one event	0.63	1.0	1.0	1.0	1.0

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 3:
SUMMARY OF CHANGES

GLOBAL CHANGES

- Protocol version and date is updated throughout the document.
- Patient number is updated from 465 to 635 patients throughout the document
- Number of study sites is updated from 54 to 64 throughout the document

PROTOCOL SYNOPSIS

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

SECTION 7.7.5: Determination of Sample Size

"*The results show that with 635 patients the expected 95% confidence interval (CI) for the median will extend from 8.89 to 11.15 months (a width of 2.26 months)*" has replaced this text ~~"The results show that with 315 patients the expected 95% confidence interval (CI) for the median will extend from 8.46 to 11.67 months (a width of 3.21 months)."~~

"*With 635 patients, the expected CI for median OS will extend from 21.39 to 26.69 months (a width of 5.3 months)*." replaced this older text ~~"With 600 patients, the expected CI for median OS will extend from 21.3 to 26.9 months (a width of 5.6 months)."~~

"*Confidence intervals for the median times (PFS and OS) were constructed using the method described by Klein and Moeschberger (1997) with a log-log transformation."* was added.

"*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 635patients the 95% Clopper–Pearson CI around that incidence will extend from 0.39% to 2.134%. For events occurring in 10% of patients, the CI will extend from 7.784% to 12.6%*" replaced this text ~~"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%."~~

Section 7.6.1

PROs will be collected on paper Case Report Forms and will be entered at a central facility, as determined by the Study Sponsor" was replaced with the text „*PROs will be collected on paper and will be entered in Case Report Forms by site staff, as determined by the Study Sponsor*.".

The text „ „Paper PRO questionnaires will be faxed or sent by courier from the site to a data-entry center.collected on paper and will be entered into EDC system by site staff." was replaced with this text: *„Paper PRO questionnaires will be collected on paper and will be entered into EDC system by site staff."*

Section 7.5.1: Patient discontinuation

The caption has been changes from *"Study Discontinuation"* to "Patient Discontinuation" the text "*Patients have the right at any time and for any reason to withdraw their consent that their data are collected and used for the study. Reasons for discontinuation of treatment with the medicinal product or withdrawal from the study may include, but are not limited to, the following:*

Patient withdrawal of consent at any time

Patient is lost to follow-up."

When a patient faces end of life and decides to enter the hospice for end of life cares, the patient shouldn't be considered as discontinued from the registry, although the patient does not receive any anti-cancer treatment anymore. Instead data from patient's charts and note will continue to be transferred into the CRF until registry discontinuation.

The date of patient discontinuation and final status (i.e. withdrawal of consent, physician's decision, loss to follow up or death) for a patient who discontinues from the registry should be recorded in the eCRF." replaces this text "Patients have the right at any time and for any reason to withdraw their consent that their data are collected and used for the study.
When a patient faces end of life and decides to enter the hospice for end of life cares, the patient shouldn't be considered as discontinued from the study, although the patient does not receive any anti cancer treatment anymore. Instead data from patient's charts and note will continue to be transferred into the CRF until study discontinuation.

The data of study discontinuation and final status (i.e. withdrawal from consent, physician's decision, loss to follow up or death for a patient who discontinues from the study should be recorded in the eCRF."

7.5.2: Withdrawal from registry

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

7.5.3 Registry and Site Discontinuation

The Marketing Authorization Holder has the right to terminate this registry at any time.

7.5.4 Discontinuation from Anti-Cancer Treatment

has been formatted.

7.8.1: Study Documentation

The Marketing Authorization Holder shall ensure that the dataset and statistical programs used for generating the data included in the final report are kept in electronic format and are available for auditing and inspection.

TABLE 1

Table 1 has been revised to include the new patient number

TABLE 2

Table 2 has been revised to include the new patient number

TABLE 3

Table 3 has been revised to include the new patient number

TABLE 4

Table 4 has been revised to include the new patient number

SAMPLE INFORMED CONSENT FORM

The sample Informed Consent Form has been revised to reflect the changes to the protocol.

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A EUROPEAN DISEASE REGISTRY STUDY TO PROSPECTIVELY OBSERVE TREATMENT PATTERNS AND OUTCOMES IN PATIENTS WITH HER2 POSITIVE UNRESECTABLE LOCALLY ADVANCED OR METASTATIC BREAST CANCER**
PROTOCOL NUMBER:	MO39146
VERSION NUMBER:	3.0
EU PAS REGISTER NUMBER:	22426
STUDIED MEDICINAL PRODUCTS:	Nationally authorized products according to physician's choice
MARKETING AUTHORIZATION HOLDERS (MAH):	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom

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

_____
Treating Physician's Name (print)

_____ _____
Treating Physician's Signature Date

Please return a copy of this form {as instructed by function} {to the contact provided below}. Please retain the signed original for your study files.

- {Name}
  {Address}

TABLE OF CONTENTS

LIST OF TABLES

No table of figures entries found.

LIST OF APPENDICES

No table of figures entries found.

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CI	confidence interval
CR	complete response
CRO	contract research organization
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
EORTC	European Organisation for Research and Treatment of Cancer
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
PASS	post-authorization safety study
PFS	progression-free survival
PR	partial response
PRO	patient-reported outcome
QoL	quality of life

Abbreviation	Definition
SAE	serious adverse event
SOC	system organ class
T-DM1	trastuzumab emtansine
ULN	upper limit of normal

2. RESPONSIBLE PARTIES

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3. SYNOPSIS

Rationale and Background

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). Metastatic breast cancer (mBC) is incurable, with the primary goal of treatment being to extend life and palliate symptoms while preserving quality of life (QoL). Annually, almost 100,000 breast cancer-related deaths occur in patients whose tumors overexpress the human epidermal growth factor receptor 2 (HER2).

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. Unpublished market research results revealed that the anti-HER2 targeted treatment most frequently used is trastuzumab, either alone or in combination. In first-line treatment, taxanes (paclitaxel or docetaxel) are frequently combined with trastuzumab, whereas in second- and third-line treatments, even though combinations are more diversified, vinorelbine and capecitabine are the leading agents to be combined with trastuzumab.

Other treatment options for patients with HER2-positive mBC include trastuzumab-emtansine (T-DM1), lapatinib, and pertuzumab, the latter being given in combination with trastuzumab. The treatment of HER2-positive mBC will continue to evolve as new agents become available.

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 is part of a global umbrella study, UMBTDM1, and will allow descriptive analyses to identify associations between patient risk factors, 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. The data captured will allow both descriptive and inferential comparative analyses to be made to evaluate associations between patient risk factors, treatments and outcomes. Safety and effectiveness data will be collected in local (Daughter) studies and transferred to a global database for a pooled analysis.

Research Question and Objectives

Safety Objectives

The safety objectives for this study are as follows:

- To observe and describe the safety of different anti-cancer treatment regimens through the reporting of serious adverse events (SAEs) 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 document and describe the treatment of population of special interest by estimating the incidence and prevalence (during the observation period) of cardiac events related to left ventricular dysfunction, pregnancy and pregnancy outcomes
- To document the incidence (during the observation period) of AEs of interest related to the use of Roche products and their combination partners.

Effectiveness Objectives

The primary effectiveness objective for this study is as follows:

- In patients with unresectable locally advanced (LA) or metastatic HER2 positive breast cancer (mBC),
    1. To estimate and describe progression-free survival (PFS)
    2. To describe treatment regimens and their sequencing

The secondary effectiveness objectives for this study are as follows:

- To observe and describe overall survival (OS)
- To observe duration of response (DoR) per anti-cancer treatment regimen (including but not limited to the following sub-populations):
    - Pertuzumab treated patients in 1st line mBC after trastuzumab adjuvant treatment
    - Pertuzumab treated patients in 1st line mBC after pertuzumab neo-adjuvant treatment
    - Trastuzumab emtansine treated patients in 2nd line after 1st line pertuzumab treatment
    - Trastuzumab emtansine treated patients with (controlled and active) CNS metastasis
    - Patients treated without chemotherapy
- To observe and describe objective response rate (ORR) per anti-cancer treatment regimen (including but not limited to the following sub-populations):
    - Pertuzumab treated patients in 1st line mBC after trastuzumab adjuvant treatment
    - Pertuzumab treated patients in 1st line mBC after pertuzumab neo-adjuvant treatment
    - Trastuzumab emtansine treated patients in 2nd line after 1st line pertuzumab treatment
    - Trastuzumab emtansine treated patients with (controlled and active) CNS metastasis
    - Patients treated without chemotherapy

Other Objectives

- To observe the HER2 testing results and degree of overexpression
    - To observe frequency of HER2 re-testing of metastasis
    - To observe switch rate in HER2-positivity (if there is a change in HER2 status between the primary tumor and the re-tested metastasis
    - To observe type of HER2-testing (immune histochemistry and/or fluorescence in situ hybridization (FISH)
- To observe and describe country/regional differences in anti-cancer treatment regimens
- To observe and describe patients' demographics and breast cancer histories for each anti-cancer treatment regimen
- To evaluate quality of life (QoL) using patient-reported outcomes (PROs), only if used in routine clinical practice.

Health Economic Assessment Objectives

- To examine the healthcare costs and resource utilization associated with various anti-cancer treatment regimens including the cost of treating associated adverse events (AEs)

Study Design

Description of Study

This disease registry is a prospective, multicentre non-interventional study designed to observe anti-cancer treatment regimens and clinical outcomes in patients with human epidermal growth factor receptor 2 (HER2)-positive unresectable LA/mBC. Diagnosis of unresectable LA or mBC

can be up to 6 months old prior to registry enrolment 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. Once a patient is enrolled in the study, she/he will be followed until death, withdrawal of consent or study termination, whichever occurs first.

No treatment regimen is mandated by this protocol.

This is a disease registry in which clinical decisions concerning the optimum management strategy for a particular patient are be 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.

This study is part of the global umbrella UMBTDM1.

Start Date of Study:

The study start date will be the date of the first data collection: the date from which information on the first study subject is recorded in the study database or, in the case of secondary use of data, the date from which data extraction starts.

End of Study

The end of the study will be the date from which the last information of the last subject is recorded in the study database.

Length of Study:

This study will last approximately 8 years.

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 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.

There are no exclusion criteria for entry into this study.

Variables

Only variables, obtained according to routine clinical practice can and should be documented in this study.

Safety Variables

Where available, the following safety parameters will be documented:

- Comparative safety of various HER2-targeted treatment regimens and their combinations. This will be measured by summarizing and comparing SAEs
- Safety of Roche oncology products in a real-world setting.
- Summary of non-serious AEs leading to discontinuation or dose modification of an anti-cancer therapy
- Estimation of the incidence and prevalence (during the observation period) of AEs of interest related to the use of Roche products and their combination partners, including cardiac events related to left ventricular dysfunction, pregnancy and pregnancy outcomes

Primary Effectiveness Variables

The effectiveness variables for this study are as follows:

- Progression free survival, per anti-cancer treatment regimens.
- Unique treatment regimen frequency, distribution, and sequencing in patients with HER2-positive unresectable LA/mBC.

Secondary Effectiveness Variables

The secondary effectiveness variables for this study are as follows and documented when available:

- Overall survival
- Duration of response, per anti-cancer treatment regimens.
- Objective response rate, per anti-cancer treatment regimens.
- The number of treatment regimens received by patients

Other Variables of Interest

Where available, the following parameters will be documented:

- To observe the HER2 testing results and degree of overexpression
- Measure of association between patient characteristics and prescription of particular anti-cancer treatment regimens
- Measure of association between patient characteristics and particular anti-cancer treatment regimens effectiveness
- To evaluate quality of life (QoL) using patient-reported outcomes (PROs), only if used in routine clinical practice
- Resource utilization including associated procedures, hospitalizations, emergency room attendances and outpatient visits

Data Sources

This local disease registry is named: UMBTDM1: SAMANTHA. Source data for patient data and healthcare resource utilization 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.

PROs will be collected via a self-completed questionnaire during routine clinic visits via paper questionnaires.

Study Size

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 recruit approximately *635* patients in 3 years from the time this protocol is approved by the participating European countries Institutional Review Board/Ethics Committee. As this study is part of the global umbrella, UMBTDM1, patients from this study will be pooled and analysed together with the totality of patients in the umbrella.

Studied Medicinal Product All medicinal products used to treat metastatic breast cancer are considered studied in this local disease registry.**Statistical Considerations**

The study will be analysed according to the separate Statistical Analysis Plan. Effectiveness, PRO and other measures will be analyzed using methods that will be dependent upon local endpoints and sampling design. These data will also be analyzed in subgroups according to study design, patient population and other relevant factors.

Analysis Methods

– The full analysis set will comprise all enrolled patients; this will be the primary analysis population for safety and effectiveness parameters. Other analysis populations may be defined based on more restrictive criteria, such as patients receiving a particular anti-cancer treatment (including but not limited to the following sub-population):

- Pertuzumab treated patients in 1st line mBC after trastuzumab adjuvant treatment
- Pertuzumab treated patients in 1st line mBC after pertuzumab neo-adjuvant treatment
- Trastuzumab emtansine treated patients in 2nd line after 1st line pertuzumab treatment
- Trastuzumab emtansine treated patients with (controlled and active) CNS metastasis
- Patients treated without chemotherapy

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.

Safety Outcome Measures

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 following safety parameters will be evaluated:

- Comparative safety of various HER2-targeted treatment regimens and their combinations.
- Safety of Roche oncology products in a real-world setting.
- AEs leading to discontinuation or dose modification of an anti-cancer therapy
- Estimation of the incidence and prevalence (during the observation period) of cardiac events related to left ventricular dysfunction, pregnancy and pregnancy outcomes

Primary and Secondary Effectiveness Analysis

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 summarized 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.

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.

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 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-/country-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.

Other Analyses

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). If PROs are not part of national routine clinical practice, and addition of PRO is considered as an intervention, it is not considered a protocol deviation to omit 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 (Brady 1997)

Health Economic Outcome Measures

Healthcare costs and resource utilization (e.g. hospitalizations, emergency room attendances and outpatient visits) associated with various anti-cancer treatment regimens including the cost of treating associated AEs

Interim Analyses

For this study, annual interim analyses will be performed for safety reporting and presentation of safety results, and 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 annually until study end. Effectiveness analyses may be performed provided that the number of enrolled patient allows such analysis.

Sample Size Justification

This study has a planned sample size of approximately *635*. Patients will be enrolled in approximately *64* sites in Region Europe. Enrollment will be opened for 3 years. The primary effectiveness objective of the study is to observe treatment regimens and their sequencing and to describe treatment outcomes (PFS) 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.

4. PROTOCOL AMENDMENTS AND UPDATES

Any protocol amendments will be prepared by the Marketing Holder or designee.

Protocol amendments will be submitted to the Institutional Review Board (IRB)/Ethics Committee (EC) and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes that involve logistical or administrative aspects only (e.g., change in Study Monitor or contact information).

Substantial protocol amendments/updates so far: see table below

Amendment/ Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	{25-May-2016}	{NA	{Initial protocol version}	{Reason}
2	{09-Sep-2016}	{ SECTION 7.7.5: Determination of Sample Size SECTION 7.4.2.6: Performance Status Table 1-4 References APPENDIX 3: Data Collected During the Observational Study Appendix 3 has been updated }	{Relevant sections updated with the new patient ans site number}	{ Protocol MO39146 has been amended to include additional patients and sites which came as a consequence of Italy joining the study.}
{3}	{Date}	{ SECTION 7.5.1, 7.5.2 SECTION 7.7.5: Determination of Sample Size Table 1-4 SECTION 7.6.1 SECTION 7.8.1 SECTION 9.1.3.5.: Reporting Requirements for Adverse Events originating from Patient Reported Outcomes Appendix 6: Questionnaires added Minor typo mistakes.}	{ Relevant sections updated with the new patient and site number and PRO management }	{ Protocol MO39146 has been amended to include additional patients and sites which came as a consequence of Romania joining the study.}

5. RATIONALE AND BACKGROUND

5.1 BACKGROUND ON 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). Metastatic breast cancer (mBC) is incurable, with the primary goal of treatment being to extend life and palliate symptoms while preserving quality of life (QoL). Annually, almost 100,000 breast cancer-related deaths occur in patients whose tumors overexpress the human epidermal growth factor receptor 2 (HER2).

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 dimerization and cell signaling through the phosphatidylinositol 3-kinase/AKT pathway for promotion of tumor 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 tumors (Slamon et al. 1987).

5.2 BACKGROUND ON 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. However, a recent market research study showed that during the course of HER2-positive breast cancer disease, the anti-HER2 targeted treatment most frequently used is trastuzumab, either alone or in combination (unpublished data held on file with Roche). In first-line treatment, taxanes (paclitaxel or docetaxel) are frequently combined with trastuzumab, whereas in second- and third-line treatments, even though combinations are more diversified, vinorelbine and capecitabine are the leading agents to be combined with trastuzumab.

Other newer treatment options for patients with HER2-positive mBC include trastuzumab-emtansine (T-DM1) and pertuzumab, the latter being given in combination with trastuzumab. The treatment of HER2-positive mBC will continue to evolve as new agents become available.

5.3 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 risk factors, 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.

6. RESEARCH QUESTION AND OBJECTIVES

6.1 RESEARCH QUESTION

This observational disease registry is a prospective, multinational, 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 in Europe.

6.2 OBJECTIVES

Safety Objectives

The safety objectives for this study are as follows:

- To observe and describe the safety of different anti-cancer treatment regimens through the reporting of serious adverse events (SAEs) 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 document and describe the treatment of population of special interest by estimating the incidence and prevalence (during the observation period) of cardiac events related to left ventricular dysfunction, pregnancy and pregnancy outcomes

- To document the incidence (during the observation period) of specific AEs related to the use of Roche products and their combination partners.

Effectiveness Objectives

The primary effectiveness objective for this study is as follows:

- In patients with unresectable locally advanced (LA) or metastatic HER2 positive breast cancer (mBC),
  1. To estimate and describe progression-free survival (PFS)
  2. To describe treatment regimens and their sequencing

The secondary effectiveness objectives for this study are as follows:

- To observe and describe overall survival (OS)
- To observe duration of response (DoR) per anti-cancer treatment regimen (including but not limited to the following):
  - Pertuzumab treated patients in 1st line mBC after trastuzumab adjuvant treatment
  - Pertuzumab treated patients in 1st line mBC after pertuzumab neo-adjuvant treatment
  - Trastuzumab emtansine treated patients in 2nd line after 1st line pertuzumab treatment
  - Trastuzumab emtansine treated patients with (controlled and active) CNS metastasis
  - Patients treated without chemotherapy

- To observe and describe objective response rate (ORR) per anti-cancer treatment regimen (including but not limited to the following):
  - Pertuzumab treated patients in 1st line mBC after trastuzumab adjuvant treatment
  - Pertuzumab treated patients in 1st line mBC after pertuzumab neo-adjuvant treatment
  - Trastuzumab emtansine treated patients in 2nd line after 1st line pertuzumab treatment
  - Trastuzumab emtansine treated patients with (controlled and active) CNS metastasis
  - Patients treated without chemotherapy

Other Objectives

- To observe the HER2 testing results and degree of overexpression
  - To observe frequency of HER2 re-testing of metastasis

- To observe switch rate in HER2-positivity (if there is a change in HER2 status between the primary tumor and the re-tested metastasis
- To observe type of HER2-testing (immune histochemistry and/or fluorescence in situ hybridization (FIitSH)

- To observe and describe country/regional differences in anti-cancer treatment regimens
- To observe and describe patients' demographics and breast cancer histories for each anti-cancer treatment regimen
- To evaluate quality of life (QoL) using patient-reported outcomes (PROs), only if used in routine clinical practice.

Health Economic Assessment Objectives

- To examine the healthcare costs and resource utilization associated with various anti-cancer treatment regimens including the cost of treating associated adverse events (AEs)

7. RESEARCH METHODS

7.1 STUDY DESIGN

This disease registry is a prospective, multicentre non-interventional study designed to observe anti-cancer treatment regimens and clinical outcomes in patients with human epidermal growth factor receptor 2 (HER2)-positive unresectable LA/mBC. Diagnosis of unresectable LA or mBC can be up to 6 months old prior to registry enrolment. Approximately *635* patients are planned to be enrolled in approximately *64* sites in Europe. Enrollment will be opened for 3 years. Enrolled patients will be prospectively followed for at least 5 years after study enrolment to evaluate their anti-cancer treatments, allowing a total follow-up per patient of up to 8 years. 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".

The frequency of subsequent visits will be determined by the treating physician, and routine clinical 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), clinically relevant AEs and survival status will be collected.

Patient source data and healthcare resource utilization data will be taken from the patient's medical records and reported by means of a web-based electronic data collection (EDC) system. Patient Reported Outcome (PROs) data will be collected by a self-completed paper questionnaire during routine clinical visits at approximately 3-month intervals throughout study participation.

The study is designed with only one "on study" observational period and no follow-up period or visit frequency is imposed. Patients will be considered "on study" until death, withdrawal of consent, loss to follow-up, or end of study September 1st 2024, whichever comes first.

This study will be analysed according to a 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 log document should be maintained in strict confidence by the Investigator and will not be submitted to the Sponsor.

7.1.1 Overview of Study Design

Because investigators will follow local, national or on-label guidelines, no specified assessments are to be captured, with the exception of specific adverse events that must be transmitted to the Sponsor.

To guide investigators, a data collection overview of routine clinical assessments is provided in Appendix 2.

7.1.2 Rationale for Disease Registry 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 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. Safety and effectiveness data will be collected in local (Daughter) studies and transferred to a global database for a pooled analysis.

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.

7.1.3 Number of Patients Observed in the Disease Registry

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 disease registry will enroll approximately *635* patients over 3 years from the time this protocol is approved by the country Institutional Review Board (IRB)/Ethics Committee (EC).

7.1.4 Centers

The study will be performed at approximately *64* centers in approximately *5* countries in Europe. An appropriate number of sites will be opened to ensure that the recruitment target is reached within 3 years.

Additional countries and centers may be added or substituted if underperforming.

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.

7.2 POPULATION

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.

Exclusion Criteria

There are no exclusion criteria for entry into this study.

7.2.1 Rationale for 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.

To minimize patient selection bias, the Investigator (or sub-Investigator) should invite all eligible consecutive patients. 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. Written informed consent where local regulations allow or require it will be obtained prior to first data entry in the CRF.

Due to the nature of this NIS, subgroup analyses will be defined once collected data are matured enough to define specific subgroups. Patients will be grouped according to treatment regimens received. Some analyses may exclude investigational regimens or regimens that do not include HER2-targeted treatment.

7.3 VARIABLES

7.3.1 Safety Variables

- Where available, the following safety parameters will be documented and examined per subgroups, if relevant: Comparative safety of various HER2-targeted treatment regimens and their combinations. This will be measured by summarizing and comparing SAEs
- Safety of Roche oncology products in a real-world setting.
- Summary statistics of AEs leading to discontinuation or dose modification of an anti-cancer therapy
- Estimation of the incidence and prevalence (during the observation period) of AEs of interest related to the use of Roche products and their combination partners, including cardiac events related to left ventricular dysfunction, pregnancy and pregnancy outcomes

For further descriptions about the AEs that will be collected, please refer to Section 7.4.2.4.

7.3.2 Primary Effectiveness Variable

The effectiveness variables for this study are 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.

- Number and proportion of patients receiving each unique treatment, where treatment can be a combination of anti-cancer therapies.
- Treatment sequences
- First-line anti-cancer treatment versus subsequent-line therapy, where first-line is defined therapies received after initial diagnosis of HER2 positive unresectable LA/mBC and before a patient experiences their first disease progression event

7.3.2.1 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 following 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)

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 anti-hormonal therapy will be considered as one regimen.

7.3.3 Secondary Effectiveness Variables

- OS: defined as the date from initiation of treatment to the date of death from any cause.
- 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.
- 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-/country-specific medical practice.

- Patient characteristics associated with receipt of particular anti-cancer treatment regimens
- The number of treatment regimens received by patients

7.3.4 Other Variables of Interest

Where available, the following parameters will be documented:

- Measure of association between patient characteristics and prescription of particular anti-cancer treatment regimens
- Measure of association between patient characteristics and particular anti-cancer treatment regimens effectiveness

7.3.4.1 Quality of Life Measures

PRO measures that capture quality of life (QoL) data will be used in this study where it is routine clinical practice.

7.3.4.2 Health Economic Outcome Measures

Healthcare costs and resource utilization (e.g. hospitalizations, emergency room attendances and outpatient visits) associated with various anti-cancer treatment regimens including the cost of treating associated AEs

7.4 DATA COLLECTION

7.4.1 Data sources

This local disease registry is named: SAMANTHA. Patients' charts and other medical records will be the source of routine clinical data that will be recorded in the CRFs. Therefore, only data available and already existing in patient's files will be recorded in CRFs.

PROs will be collected via a self-completed questionnaire during routine clinic visits and reported by an EDC system, if performed as routine, or not considered an intervention.

The degree of detail and completeness of data collected is dependent on what is recorded in the patient charts. For clinical monitoring reasons, physicians are encouraged to provide sufficient details in the patient's record to allow proper CRF data entry (see Section 7.8). Data will be collected approximately every 3 months from patient charts, clinic notes, and diagnostic tests and labs.

7.4.2 Data Collected During the Observation Period

During the observational period, patients will receive anti-cancer therapy and routine laboratory tests will be performed. Available results from the range of assessments described below will be documented on the CRF (non-exhaustive list). Most data will be documented around the time when the treating physician meets the patient.

In the routine care setting, patients are seen regularly by their treating physicians either for treatment or for regular assessment after treatment, such as monitoring the left ventricular ejection fraction. Thus, no study-specific visits or evaluations are required by this protocol. It is up to the treating physician to perform and document the assessments as performed in the real clinical setting.

Please see Appendix 3 for the data collection overview.

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

- Medical history (Section 7.4.2.1)
- Breast cancer history (e.g. surgical procedures, sites of metastases, disease status; Section 7.4.2.1)
- Anti-cancer treatments (Section 7.3.2.1, Section 7.4.2.3 and Section 7.5.4), including any changes and reasons for them
- Concomitant medications (Section 7.4.2.3 and Section 7.5.4)
- Performance status (Section 7.4.2.6)
- Patient-reported QoL outcomes (Section 7.3.4.1 and Section 7.4.2.7)
- PROs (Section 7.4.2.7 and Section 7.6.3)
- Healthcare resource utilization within 6 months prior to enrolment (Section 7.7.3.4)
- Specific AE as per Section 7.4.2.4
- Pregnancies and pregnancy outcomes (Section 7.4.2.5)
- SAEs (see Section 9.1.1) and AEs (Section 7.4.2.4) leading to discontinuation or dose modification of an anti-cancer therapy (Section 9.1)

After the study completion/early termination visit, ongoing SAEs and ongoing treatment-related AEs should be followed as outlined in Section 9.1.4.1

7.4.2.1 Patient Medical History

Medical history will be collected as per routine clinical practice and, if available, recorded in the eCRF pages. The below is a non-exhaustive list of what could be captured:

- 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 hybridization 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 pharmacological anti-cancer therapies, such as targeted therapies), reasons that led to treatment discontinuation or modification, and other clinically relevant information

- Breast cancer history after diagnosis of unresectable LA/mBC:

  - Sites of metastases

  - Disease status as assessed by the Investigator

  - Patient status, including left ventricular ejection fraction (LVEF), safety laboratory results, etc.

  - 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)

7.4.2.2 Demographics

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

7.4.2.3 Anti-Cancer and Concomitant Medications

Data on all anti-cancer and concomitant medications will be collected and recorded in the CRF. 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

7.4.2.4 Collection of Safety Information

All routine clinical data, such as LVEF assessments, tumor assessments, routine blood work, etc. will be transcribed from patient charts, clinical notes, and diagnostic and laboratory test results and transcribed into the CRF (see Section 7.1 and Appendix 3)

The following specific AEs, serious and non-serious, will be recorded in the CRF during the 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) (See Appendix 5).

All serious adverse events (SAE)

All AEs that leads to either discontinuation or dose modification of any anti-cancer treatment must be reported on the appropriate page of the CRF. 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 only when observed concomitantly to the use of Roche products or their combination partner:

- 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 adverse events please refer to section 9.1.3.

7.4.2.5 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.

For the reporting of pregnancy please refer to section 9.1.3.

7.4.2.6 Performance Status

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

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

7.4.2.7 Quality of Life and Patient-Reported Outcomes

PROs will be collected (only if used in routine clinical practice, or considered as non-interventional) at study enrolment and periodically throughout study participation, if considered a part of routine clinical practice. This includes 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 QoL 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 (Brady 1997)

7.4.2.8 Health Economic Outcome Measurements

Health economic outcome measurements (see Section 7.3.4.2 for details) will be collected at study entry for the 6-month period prior to enrolment and prospectively during the observation period.

7.4.3 Data Collected at Study Completion

For subjects who complete the observation period, the study completion visit should be documented and the study completion page should be completed in the CRF.

7.5 PATIENT, STUDY, AND SITE DISCONTINUATION

7.5.1 Patient Discontinuation

Patients have the right at any time and for any reason to withdraw their consent that their data are collected and used for the study. Reasons for discontinuation of treatment with the medicinal product or withdrawal from the study may include, but are not limited to, the following:

Patient withdrawal of consent at any time

Patient is lost to follow-up.

When a patient faces end of life and decides to enter the hospice for end of life cares, the patient shouldn't be considered as discontinued from the registry, although the patient does not receive any anti-cancer treatment anymore. Instead data from patient's charts and note will continue to be transferred into the CRF until registry discontinuation.

The date of patient discontinuation and final status (i.e. withdrawal of consent, physician's decision, loss to follow up or death) for a patient who discontinues from the registry should be recorded in the eCRF.

7.5.2 Withdrawal from Registry

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

7.5.3 Registry and Site Discontinuation

The Marketing Authorization Holder has the right to terminate this registry at any time.

7.5.4 Discontinuation from Anti-Cancer Treatment

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

The decision for discontinuation from treatment lies with the treating physician in agreement with the patient's decision and is not regulated by this protocol.

7.6 DATA MANAGEMENT

7.6.1 Data Quality Assurance

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 anonymized and entered into the CRF via a secure web-based EDC system.

The study initiator or designated contract research organization (CRO), as appropriate, will be responsible for data management of this study, including quality checking. Data entered manually will be captured via EDC using CRFs. Sites will be responsible for data entry into the EDC system. *PROs will be collected on paper and will be entered in Case Report Forms by site staff, as determined by the Study Sponsor.*

In the event of discrepant data, the study initiator or a designated CRO will request data clarification from the sites, which the sites will resolve electronically within the EDC system. CRFs and correction documentation will be maintained in the EDC system audit trail. System backups for data stored by the study initiator and records retention for the study data will be consistent with the study initiator's standard procedures.

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.

Paper PRO questionnaires will be collected on paper and will be entered into EDC system by site staff.

The study initiator maintains high data quality standards and utilizes 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.

7.6.2 Electronic Case Report Forms

CRFs are to be completed using a study initiator's designated electronic data capture (EDC) system. Sites will receive training and have access to a manual for appropriate CRF completion. CRFs will be submitted electronically to the study initiator and should be handled in accordance with instructions from the study initiator. All CRFs should be completed by designated trained site staff. CRFs should be reviewed and electronically signed and dated by the physician or a designee.

At the end of the study, the physician will receive the data related to subjects from his or her site in an electronically readable format (e.g., on a compact disc). Data must be kept with the study records. Acknowledgement of receipt of the data is required.

7.6.3 Patient-Reported Outcome Data

In this study, PRO data will be elicited from the patients to more fully characterize the clinical profile of anti-cancer treatments. The PRO instruments should be validated in the local language and authorized for use. The validated and approved PRO instrument will be distributed by the physician's staff and completed in their entirety by the patient at specified timepoints during the study. Patients will use paper forms for all PROs. The data from the questionnaires will be entered into the EDC system by site staff.

Once the study is complete, the PRO (paper or electronic) 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.

7.6.4 Source Data Documentation

Site Operations Representative will perform ongoing SDV as defined in the Trial Monitoring Plan to confirm that critical protocol data (i.e., source data) entered in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which subject data are recorded and documented for the first time. Before study initiation, the types of source documents that contain study-relevant information will be clearly defined in the Trial Monitoring Plan. The Trial monitoring plan defines which kind of source data – if available from clinical routine - can be used for documentation into CRF. No additional source data creation beyond routine is allowed.

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

Source documents that are required to verify the validity and completeness of data entered in the CRF must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.6.

To facilitate SDV, the physicians and institutions must provide the Marketing Authorization Holder direct access to applicable source documents and reports for trial-related monitoring, Marketing Authorization Holder audits, and IRB/EC review. The participating sites must also allow inspection by applicable health authorities.

7.6.5 Use of Site Computerized Systems

When clinical observations are entered directly into a participating site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6.6 Retention of Records

Records and documents pertaining to the conduct of this study as Informed Consent Forms, must be retained by the physician for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the study initiator. Written notification should be provided to the study initiator prior to transferring any records to another party or moving them to another location.

7.7 STATISTICAL CONSIDERATIONS

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

7.7.1 General Considerations

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, AEs leading to discontinuation or dose modification of an anti-cancer therapy, specific AEs 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. Patient characteristics associated with particular anti-cancer treatment

regimens as well as the number of treatment regimens received by patients will be collected and examined to control for potential confounding when comparing treatment regimens.

The primary effectiveness 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.

7.7.2 Analysis Populations

Effectiveness analyses will be based on all enrolled patients. Safety analyses will be carried out for all patients independently of the anti-cancer therapies they received.

7.7.3 Analysis Methods

The following is an outline of the statistical methodology that will be used to report and analyze 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 effectiveness 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 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 summarized 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.

7.7.3.1 Safety Analysis

Where available, the following safety parameters will be documented:

- Comparative safety of various HER2-targeted treatment regimens and their combinations. This will be measured by comparing SAEs
- Incidence of treatment discontinuations due to SAEs or AEs
- Incidence of pregnancies during the observation period, as well as the incidence of abortions and pregnancy outcomes
- Safety profile based on AEs related to Roche oncology products in a real-world setting.
- Incidence of cardiac dysfunctions per line of treatment and type of anti-cancer therapy.

AEs will be coded and categorized, using the latest edition of Medical Dictionary for Regulatory Activities (MedDRA), by system organ class (SOC). Coded AEs will be tabulated by treatment group, SOC and preferred term for individual events within each body system. AEs will also be tabulated by severity and relationship to medication. AEs will be summarized separately. AEs associated with laboratory abnormalities will be listed.

7.7.3.2 Primary Effectiveness Analysis

The primary effectiveness 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 summarized. 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 summarized. Temporal changes in treatment patterns will be summarized across 6-month intervals.

7.7.3.3 Secondary Effectiveness Analysis

Where available, the following effectiveness parameters will be documented:

- Patient characteristics associated with receipt of particular anti-cancer treatment regimens
- OS for the overall population
- 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-/country-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. The treatment includes, but is not limited to the following:
- Pertuzumab treated patients in 1st line mBC after trastuzumab adjuvant treatment
- Pertuzumab treated patients in 1st line mBC after pertuzumab neo-adjuvant treatment
- Trastuzumab emtansine treated patients in 2nd line after 1st line pertuzumab treatment
- Trastuzumab emtansine treated patients with (controlled and active) CNS metastasis
- Patients treated without chemotherapy
- The number of treatment regimens received by patients

7.7.3.4 Other Analyses

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 7.3.4.1 and Section 7.4.2.7).

Healthcare Utilization and Cost Analysis

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

- Utilization or adherence to predefined clinical guidelines regarding treatment regimen decisions
- Healthcare resource utilization and direct medical costs associated with the treatment of AEs, including associated procedures, hospitalizations, emergency room attendances and outpatient visits

7.7.3.5 HER2 testing

- To observe frequency of HER2 re-testing of metastases
- To observe switch rate in HER2-positivity (if there is a change in HER2 status between the primary tumor and the re-tested metastases
- To observe type of HER2-testing (immune histochemistry and/or fluorescence in situ hybridization (FISH)

7.7.4 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 annually until study end. Effectiveness analyses may be performed provided that the number of enrolled patient allows such analysis. Data from other disease registries may be pooled to support the effectiveness and safety analyses.

7.7.5 Determination of Sample Size

This study will enrol approximately *635* 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. As no formal comparisons will be performed in this study, the patient number does not reflect statistical power. In the nature of being a NIS, our objective is to observe treatment patterns and outcomes. Thus, the number of patients is based on eligible patients in the participating countries.

The primary effectiveness objective of the study is to observe treatment regimens and their sequencing and to describe treatment outcomes (PFS) 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 effectiveness – 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).

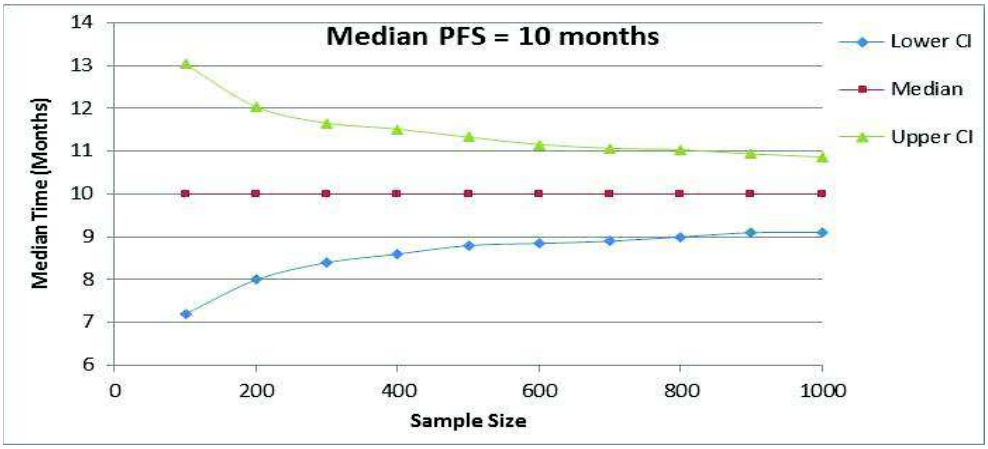
The median PFS time used in the simulations was approximately 10 months. The results show that *with 635 patients the expected 95% confidence interval (CI) for the median will extend from 8.89 to 11.15 months (a width of 2.26 months).* The precision of this estimate is deemed sufficient to draw valid conclusions around this measure of effectiveness. Table 1 and Figure 1. show the expected estimates of the 95% CIs for the median PFS using different sample sizes.

Table 1. 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)
100	7.23	13.04	6.01
200	8.02	12.04	4.02
300	8.41	11.66	3.25
400	8.59	11.52	2.93
465	8.66	11.34	2.68
500	8.80	11.33	2.53
600	8.85	11.16	2.31
635	**8.89**	**11.15**	**2.26**
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 400 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 400 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.

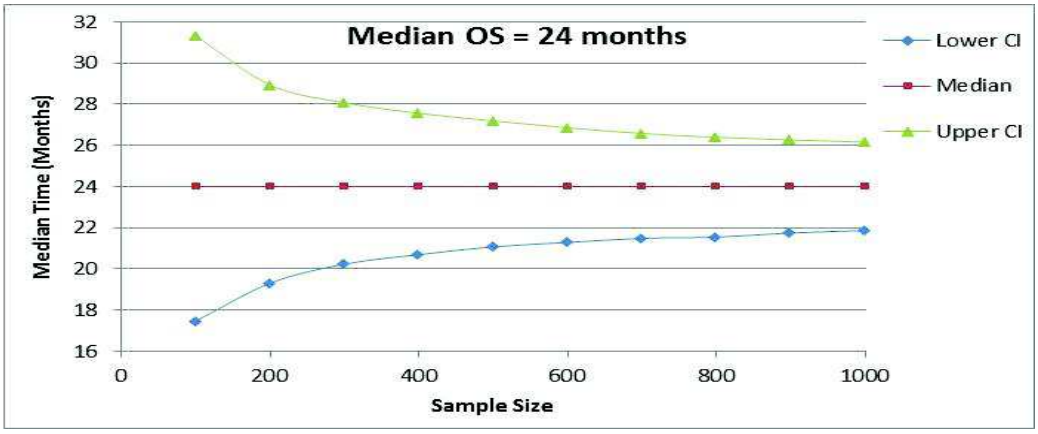
An additional simulation study was performed to evaluate the precision of median OS time for sample sizes from 100 to 1000. The median OS time used in this simulation was 24 months. *With 635 patients, the expected CI for median OS will extend from 21.39 to 26.69 months (a width of 6.44 months).* Table 2 and Figure 2 show the expected estimates of the 95% CIs for the median OS using different sample sizes.

Table 2. 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)
100	17.48	31.31	13.83
200	19.32	28.93	9.61
300	20.24	28.07	7.83
400	20.70	27.56	6.86
465	20.84	27.28	6.44
500	21.08	27.19	6.11
600	21.29	26.86	5.57
635	**21.39**	**26.69**	**5.30**
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.

Confidence intervals for the median times (PFS and OS) were constructed using the method described by Klein and Moeschberger (1997) with a log-log transformation.

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 635 patients the 95% Clopper–Pearson CI around that incidence will extend from 0.39% to 2.13%. For events occurring in 10% of patients, the CI will extend from 7.78% to 12.6%*. 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 3 shows the estimated 95% CIs for different event rates.

Table 3. 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
465	95% CI, %	0.0 – 1.0	0.3 – 2.4	0.9 – 3.7	3.2 – 7.4	7.4 - 13.1
600	95% CI, %	0.0–0.8	0.37–2.2	1.0–3.5	3.4–7.1	7.7–12.7
635	**95% CI, %**	**0.0 – 0.76**	**0.39 – 2.13**	**1.06 – 3.42**	**3.45 – 7.0**	**7.78 – 12.6**
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 4 shows the probability of detecting occurrences for different event rates with different sample sizes.

Table 4. 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 observing at least one event	0.18	0.87	0.98	1.0	1.0
400	Probability of observing at least one event	0.33	0.98	1.0	1.0	1.0
465	Probability of observing at least one event	0.37	0.99	0.99	1.0	1.0
600	Probability of observing at least one event	0.45	1.0	1.0	1.0	1.0
635	**Probability of observing at least one event**	**0.47**	**1,0**	**1.0**	**1.0**	**1.0**
800	Probability of observing at least one event	0.55	1.0	1.0	1.0	1.0
1000	Probability of observing 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.

7.8 STUDY DOCUMENTATION AND MONITORING

7.8.1 Study Documentation

The physician must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval/notification. In addition, at the end of the study, the physician will receive the patient data, which include an audit trail containing a complete record of all changes to data.

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 CRFs (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 CRFs must not be obliterated or destroyed and must be retained as detailed in the policy for retention of records (see Section 7.6.6).

The Marketing Authorization Holder shall ensure that the dataset and statistical programs used for generating the data included in the final report are kept in electronic format and are available for auditing and inspection.

7.8.2 Site Audits and Inspections

Site visits will be conducted by the study initiator or an authorized representative for audit of study data, subjects' medical records, and CRFs.

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

7.8.3 Administrative Structure

All contact details and the list of all Investigators will be kept in a standalone document, and will be available upon request.

The study may also have a local advisory committee.

The study uses an adapted CRF and it's conducted by a CRO on behalf of the Sponsor.

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

7.9 LIMITATIONS OF THE RESEARCH METHOD

As any other disease registry, patient selection bias may be an issue. To minimize patient selection bias, the Investigator (or sub-Investigator) should invite all eligible consecutive patients.

7.10 OTHER ASPECTS

Not applicable

8. PROTECTION OF HUMAN SUBJECTS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for GPP published by the International Society of Pharmacoepidemiology (ISPE) and the laws and regulations of the country in which the research is conducted.

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

The study initiator's sample Informed Consent Form will be provided to each site.

The Consent Forms must be signed and dated by the subject or the subject's legally authorized representative before start of documentation of his or her data in the CRF. The case history or clinical records for each subject shall document the informed

consent process and that written informed consent was obtained prior to first documentation of this subject's data in the CRF.

By signing the form, the subject confirms that he/she has been informed about the study and agrees to pseudonymous data collection, pooling of data with similar scientific data (if applicable), and the possibility of monitoring activities. It is the responsibility of the physician to obtain written informed consent from each subject participating in the study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The physician must also explain that the subject is completely free to refuse to enter the study or to withdraw from it at any time, for any reason and without losing the benefit of any medical care to which the subject is entitled or is presently receiving.

A copy of each signed Consent Form must be provided to the subject or the subject's legally authorized representative. All signed and dated Consent Forms must remain in each subject'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

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Site Operations Representative in consultation with the Scientific Responsible and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

8.4 CONFIDENTIALITY

The study initiator maintains confidentiality standards by coding each subject enrolled in the study through assignment of a unique subject identification number. This means that subject names are not included in datasets that are transmitted to any study initiator's location. 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 be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

The anonymized data, as entered into the EDC system, will be visible to the CRO and the Study Initiator, but only center 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.

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 national and local health authorities, Marketing Authorization Holder monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

9. MANAGEMENT OF ADVERSE EVENTS

Disease registries are recognized as a source of adverse event reporting, and while it is not a requirement to collect all AEs as part of a disease registry, any AEs which are collected in the course of the registry should be forwarded to the Marketing Authorization Holder **as solicited reports**.

In addition, the following should also be reported if occurring during exposure to a marketed medicinal product:

- pregnancy
- abnormal laboratory findings with or without associated AEs (see Appendix 5.3.5)
- overdose, abuse, misuse, medication error, occupational exposure with or without associated AEs
- reports of lack of efficacy
- drug interactions

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 9.1.1.

9.1 ADVERSE EVENTS

According to the International Conference of Harmonisation (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- 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.

Any AE that leads to either discontinuation or dose modification of an anti-cancer treatment must be reported on the appropriate page of the CRF. Dose modification due to AEs refers to any change in the prescribed quantity of drug and/or the dosing interval, including the withholding or delaying of doses.

9.1.1 Assessment of Serious Adverse Events (Immediately Reportable to the Marketing Authorization Holder) 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 5)
- 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 5); 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.

SAEs related to Roche products are required to be immediately reported by the physician to the Sponsor (i.e., no more than 24 hours after learning of the event; see Section 9.1.3).

Non-Serious Adverse Events

For this disease registry, non-serious AEs must be collected as per protocol section 7.4.2.4.

9.1.2 Methods and Timing for Capturing and Assessing Safety Parameters

The physician is responsible for ensuring that all AEs collected as per protocol (see Section 9.1 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 Appendix 5.

For each AE recorded in the AE section of the CRF, the physician will make an assessment of seriousness, severity, and causality (see Appendix 5).

9.1.2.1 Adverse Event Reporting Period

All AEs collected in this registry are subject to the collecting and reporting requirements outlined in this protocol. Whether reported by the patient or noted by the site's personnel, AEs should be recorded in the patient's medical record and transcribed to the AE section of the CRF. Particular attention should be given to AEs described in section 7.4.2.4, which **must be collected** for the registry to meet its objectives.

Once the patient is enrolled in the study, AEs will be collected until the end of the 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 Roche medicinal product they should be notified to the competent authority in the Member State where the reactions occurred or to the Marketing Authorization Holderof the suspected medicinal product, but not to both (to avoid duplicate reporting).

9.1.2.2 Procedures for Recording Adverse Events

It is recommended that physicians use correct medical terminology/concepts when recording AEs in the patients' record and 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 5for 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 7.6). 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 Marketing Authorization Holder

- Pre-existing Medical Conditions
- Hospitalization or Prolonged Hospitalization
- Overdoses, Misuses, Abuses, Off-Label Use, Occupational Exposure, or Medication Error (including potentially exposed in case of medication error or intercepted medication error) or Quality Defects
- Quality Defects and Falsified Medicinal Products

9.1.3 Reporting Requirements from Physician to Marketing Authorization Holder

9.1.3.1 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

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 9.1.3.3. Pregnancy should not be recorded on the Adverse Event eCRF but by submitting a paper Pregnancy Reporting Form (see section 9.1.3.4).

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

9.1.3.2 Reporting Requirements for Non-Serious Adverse Events

For all non-serious AEs, 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 Safety to allow appropriate reporting to relevant competent authorities.

In the event that the EDC system is temporarily unavailable, please refer to Section 9.1.3.3.

9.1.3.3 If EDC System is Temporarily Unavailable or not Used

In the event that the EDC system is temporarily, 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.

9.1.3.4 Reporting Requirements for Pregnancies

Female patients of childbearing potential will be instructed to immediately inform the physician if they become pregnant during the observation period. 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. 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 also be reported to Roche Drug Safety.

9.1.3.5 Reporting Requirements for Adverse Events originating from Patient Reported Outcomes

Although physicians are not expected to review the PRO data, if physician/study personnel become aware of a potential adverse event during review of the PRO questionnaire data, he/she will determine whether the criteria for an adverse event have been met and, if so, these must be reported using the Adverse Event (e)CRF.

9.1.4 Follow-Up of Patients after Adverse Events

9.1.4.1 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.

During the study period, resolution of AEs (with dates) should be documented in the AE section of the CRF and in the patient's medical record to facilitate SDV.

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

9.1.4.2 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. .AE follow-up should be documented in the AE section of the CRF.

9.2 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.

10. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the study initiator is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The study initiator will comply with all requirements for publication of study results.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the physician must agree to submit all manuscripts or abstracts to the study initiator prior to submission for publication or presentation. This allows the study initiator to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the physician.

In accordance with standard editorial and ethical practice, study initiator will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating physician will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements. Any formal publication of the study in which contribution of the study initiator personnel exceeded that of conventional monitoring will be considered as a joint publication by the physician and the appropriate study initiator's 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 study initiator, except where agreed otherwise.

Annual interim analyses will be performed for safety reporting, and presentation of safety results and the different treatment regimens and their sequencing. These annual reporting events will start 1 year after first patient first visit and will continue annually until study end. Effectiveness analyses may be performed provided that the number of enrolled patient allows such analysis.

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Appendix 1
List of Stand-Alone Documents Not Included in the Protocol

List of contact details of responsible parties and all physicians

Appendix 2
Data Collection Overview

Table 7. 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 8.2)	Demographic data (Section 7.4.2.2)	
	Patient past medical history, including surgeries, cardiovascular risk factors, comorbid medical conditions and their treatments, and other relevant medical history (7.4.2.1)	Changes in medical history (Section 7.4.2.1)
	Breast cancer specific history (from initial diagnosis) including details regarding early breast cancer (Section 7.4.2.1)	Changes in breast cancer history (e.g. interval surgeries, site of metastases, disease status; Section 7.4.2.1)
	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 7.3.2.1 and Section 7.4.2.3)	Anti-Cancer treatments (radiation, chemotherapy, hormonal, and/or other anti-cancer therapy such as targeted therapy) along with reasons for changes (Section 7.3.2.1 and Section 7.4.2.3)
	Characteristics of the investigational site, e.g. type of healthcare provider, type and size of hospital (Section 7.1.4)	
	Concomitant medications (Section 7.4.2.3)	Concomitant medications (Section 7.4.2.3)
	Disease and performance status (Section 7.4.2.6)	Disease and performance status (Section 7.4.2.6)
	Patient-reported QoL (Section 7.4.2.7)	Patient-reported QoL (Section 7.4.2.7)
	PROs (Section 7.6.3)	PROs
	Healthcare resource utilization (Section 7.7.3.4)	Healthcare resource utilization (Section 7.7.3.4)
	Pregnancy status (Section 7.4.2.5)	Pregnancy status and pregnancy outcome
		SAEs (Section 9.1.1), AEs leading to discontinuation or modification of an anti-cancer therapy, specific AEs (section 7.4.2.4)
Abbreviations: AE = adverse event; BC = breast cancer; PRO = patient-reported outcome; SAE = serious adverse event; ADR = adverse drug reaction.		

Appendix 3
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[b,c,d]		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]
Patient performance status (eg. ECOG)[h]		X	X
Quality of life assessments[e]		X	X[b,e]
Safety events[g]			Continuous
Pregnancy and pregnancy outcome		X	X
Healthcare resource utilization[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. HER2 status repeated during later lines of treatment should also be captured in the CRF.

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 and except in countries where this is prohibited in observational studies) will be collected on-site: EQ-5D. FACT-B

f Healthcare resource utilization will be collected at the time of disease progression (where it is routine clinical practice

g Including all SAEs, AEs leading to treatment discontinuation or modification, and specific AEs. SAEs must be reported to Sponsor within 24 hours of learning of the events.

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

Appendix 4
ENCePP Checklist for Study Protocols (Revision 2)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the Investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorization holders when submitting the protocol of a non-interventional post-authorization safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorization safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good Pharmacovigilance Practices (GVP).

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☐	☐	☐	
1.1.2 End of data collection[1]	☐	☐	☐	
1.1.3 Study progress report(s)	☐	☐	☐	
1.1.4 Interim progress report(s)	☐	☐	☐	
1.1.5 Registration in the EU PAS register	☐	☐	☐	

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[1] Date from which the analytical dataset is completely available.

Appendix 4
Schedule of Pharmacodynamic and Pharmacokinetic Assessments (cont.)

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1.6 Final report of study results.	☐	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☐	☐	☐	
2.1.2 The objective(s) of the study?	☐	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☐	☐	☐	
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☐	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomized controlled trial, new or alternative design)	☐	☐	☐	
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☐	☐	
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☐	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☐	☐	☐	
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☐	☐	☐	
4.2.2 Age and gender?	☐	☐	☐	
4.2.3 Country of origin?	☐	☐	☐	
4.2.4 Disease/indication?	☐	☐	☐	
4.2.5 Comorbidity?	☐	☐	☐	

Appendix 4
Schedule of Pharmacodynamic and Pharmacokinetic Assessments (cont.)

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.2.6 Seasonality?	☐	☐	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☐	☐	☐	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☐	☐	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☐	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☐	☐	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☐	

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☐	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☐	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☐	☐	☐	
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☐	☐	☐	
8.1.3 Covariates?	☐	☐	☐	
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☐	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☐	
8.2.3 Covariates? (e.g. age, gender, clinical and drug use history, comorbidity, co-medications, life style, etc.)	☐	☐	☐	
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☐	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☐	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☐	☐	☐	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☐	
10.2 Is the choice of statistical techniques described?	☐	☐	☐	
10.3 Are descriptive analyses included?	☐	☐	☐	

Appendix 4
Schedule of Pharmacodynamic and Pharmacokinetic Assessments (cont.)

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.4 Are stratified analyses included?	☐	☐	☐	
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☐	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☐	☐	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☐	☐	
11.3 Are methods of quality assurance described?	☐	☐	☐	
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☐	☐	
11.5 Is there a system in place for independent review of study results?	☐	☐	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☐	☐	☐	
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☐	
12.3 Does the protocol address other limitations?	☐	☐	☐	

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☐	☐	☐	

Appendix 4
Schedule of Pharmacodynamic and Pharmacokinetic Assessments (cont.)

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☐	
13.3 Have data protection requirements been described?	☐	☐	☐	

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☐	☐	☐	

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☐	☐	☐	
15.2 Are plans described for disseminating study results externally, including publication?	☐	☐	☐	

Comments:

Name of the main author of the protocol: _____

Date: / /
Signature: _____

Appendix 5
Adverse Events

Appendix 5.1 Assessment of Severity of Adverse Events
Appendix 5.2 Assessment of Causality of Adverse Events
Appendix 5.3 Procedures for Recording Adverse Events

Appendix 5.1 Assessment of Severity of Adverse Events

The AE severity grading scale for the NCI CTCAE (v 4.0) 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 (v 4.0), 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 9.1.3.1 for reporting instructions), per the definition of SAE in Section 9.1.1.

[d] Grade 4 and 5 events must be reported as SAEs (see Section 9.1.3.1 for reporting instructions), per the definition of SAE in Section 9.1.1.

Appendix 3.2 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 5.3 Procedures for recording Adverse Events

Appendix 5.3.1 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 reaction or anaphylactic reaction).

Appendix 5.3.2 Diagnosis versus Signs and Symptoms

For AEs, other than infusion-related or injection reactions (see Appendix 5.3.1) 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.

Appendix5.3.3 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 5.3.4 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 9.1.3.1 for 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 5.3.5 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
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the physician's judgment

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 × 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 5.3.4 for details on recording persistent AEs).

Appendix 5.3.6 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
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the physician's judgment

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 5.3.4 for details on recording persistent AEs).

Appendix 5.3.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($> 3 \times$ the baseline value) in combination with either an elevated total bilirubin ($> 2 \times$ 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 $> 3 \times$ the baseline value in combination with total bilirubin $> 2 \times$ the ULN (of which $\geq 35\%$ is direct bilirubin), except in patients with documented Gilbert's syndrome. For patients with Gilbert's syndrome, elevation of direct bilirubin >2 × ULN should be used instead.
- Treatment-emergent ALT or AST $> 3 \times$ the baseline value 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 5.3.5) and reported to the Marketing Authorization Holder immediately (i.e., no more than 24 hours after learning of the event).

Appendix 5.3.8 Deaths

For this protocol, mortality is a secondary effectiveness objective (Section 6.2).

- Deaths that are attributed by the physician solely to progression of breast cancer should be recorded only on the Study Completion/Early Discontinuation CRF. They will not be considered an SAE for the purposes of this study and are thus exempt from expedited reporting.
- All other deaths that occur during the observational period, regardless of relationship to therapy, must be recorded on the AE CRF and immediately reported to the Marketing Authorization Holder as a SAE (see Section 9.1.1).

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 5.3.9 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 5.3.10 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 9.1.1), 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 was solely related to progression of the underlying breast cancer

Appendix 5.3.11 Overdoses, Misuses, Abuses, Off-Label Use, Occupational Exposure, or Medication Error or Quality Defects

Any overdose, misuse, abuse, off-label use, occupational exposure, medication error, 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, 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 9.1.3.1).

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 5.3.12 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 9.1.3.1).

Appendix 6
Questionnaires

Appendix 6.1 FACT-B
Appendix 6.2 EQ-5D-5L

Appendix 6.1 FACT-B

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4

GP7	I am forced to spend time in bed.....	0	1	2	3	4

SOCIAL/FAMILY WELL-BEING

		Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends.....	0	1	2	3	4
GS2	I get emotional support from my family.....	0	1	2	3	4
GS3	I get support from my friends.....	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness.....	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support).....	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please r☐k this box and go to the next section*					
GS7	I am satisfied with my sex life	0	1	2	3	4

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

MOBILITY

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

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

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

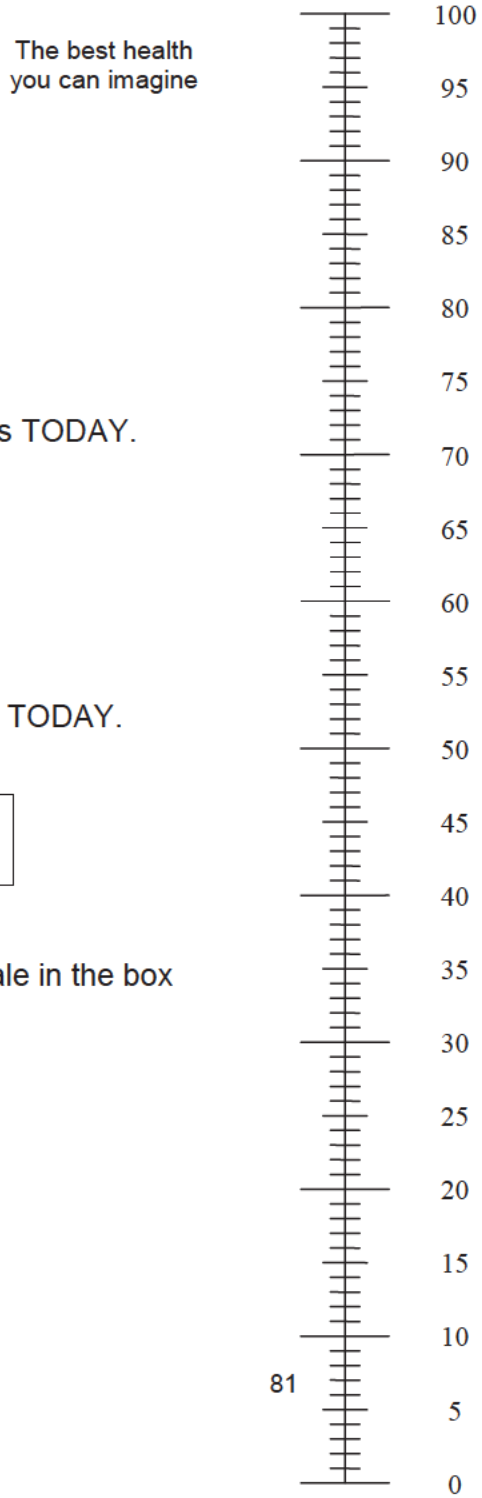
I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑



- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.

YOUR HEALTH TODAY = ☐

- Now, please write the number you marked on the scale in the box below.

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4

GF4	I have accepted my illness.....	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun.....	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
B1	I have been short of breath	0	1	2	3	4
B2	I am self-conscious about the way I dress	0	1	2	3	4
B3	One or both of my arms are swollen or tender	0	1	2	3	4
B4	I feel sexually attractive	0	1	2	3	4
B5	I am bothered by hair loss	0	1	2	3	4
B6	I worry that other members of my family might someday get the same illness I have	0	1	2	3	4
B7	I worry about the effect of stress on my illness	0	1	2	3	4
B8	I am bothered by a change in weight	0	1	2	3	4
B9	I am able to feel like a woman	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4