NI PASS PROTOCOL (PRIMARY DATA COLLECTION)

TITLE:	**A PROSPECTIVE, NON-INTERVENTIONAL STUDY ASSESSING THE DIAGNOSTIC, THERAPEUTIC PROCEEDINGS AND SAFETY OF ANTI-HER2 TREATMENT IN ELDERLY PATIENTS (≥70 YEARS OLD) WITH HER2 POSITIVE BREAST CANCER IN ROUTINE CLINICAL PRACTICE IN POLAND - MULTICENTER, OBSERVATIONAL STUDY (HEROLD)**
PROTOCOL NUMBER:	ML40006
VERSION NUMBER:	1.0
AUTHOR:	[redacted], MD [redacted] [redacted]
EU PASS REGISTER NUMBER:	{ To be determined }
ACTIVE SUBSTANCES:	L01XC03: trastuzumab L01XC13: pertuzumab
STUDIED MEDICINAL PRODUCTS:	Herceptin SC, Herceptin IV, Perjeta IV
PRODUCT REFERENCE NUMBERS:	Trastuzumab subcutaneous: EU/1/00/145/002 Trastuzumab intravenous: EU/1/00/145/001 Pertuzumab intravenous: EU/1/13/813/001
JOINT PASS:	No
RESEARCH QUESTION AND OBJECTIVES:	According to the National Cancer Registry in Poland in 2013 women aged 65+ accounted for 37.4% of the whole group, whereas deaths in this age group accounted for 55.9% of all deaths caused by breast cancer. This group of women is particularly challenging to treat because of the associated comorbidities and general health. **Primary Safety Objectives** The safety objectives pertain only to those patients who qualify for anti-HER2 therapy and are

	prescribed anti-HER2 treatment (Herceptin SC or Herceptin IV with or without Perjeta IV) – a subgroup. These objectives are as follows: • To assess frequency of discontinuation of anti-HER2 treatment (Herceptin SC or Herceptin IV with or without Perjeta IV) caused by adverse events • To evaluate safety of anti-HER2 treatment (Herceptin SC or Herceptin IV with or without Perjeta IV) and summarize frequency of adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESIs) • To evaluate frequency of anti-HER2 treatment interruptions, discontinuations and reintroductions • To assess the completion of the assumed treatment plan (Herceptin SC or Herceptin IV with or without Perjeta IV). Treatment plan will be assumed as completed when patient completes 18 cycles or one year of treatment (for eBC patients or LABC patients qualified for local regional treatment – surgery or radical radiotherapy) or when patient continues treatment until progression, death or until the end of the observation in the study (for mBC patients). **Effectiveness Objectives** The secondary objectives for this study are as follows: • Summarize epidemiological information among all included patients: age, BMI, BSA, cigarette smoking, comorbidities (hypertension, diabetes, coronary artery disease, heart failure, thromboembolic disease, medically relevant arrhythmias, thyroid disease, chronic kidney disease, osteoporosis, dementia, coexisting cancer, COPD, rheumatoid arthritis, liver disease, and depression) and others • Summarize all diagnostic proceedings performed before qualification for anti-HER2 therapy (including: ER/PgR, HER2 status by IHC/ISH) • Summarize all information about any anticancer therapies administered before qualification or disqualification for anti-HER2 therapy (including: surgery, systemic therapy or radiotherapy) • Summarize information concerning qualification process for anti-HER2 therapy and the reasons for disqualification

	•Summarize all information about anticancer therapies administered concurrently with anti-HER2 therapy (hormonal or chemotherapy) •Summarize information about timing and types of surgery and radiotherapy in eBC patients that at the start of the study received neoadjuvant anti-HER2 therapy with Herceptin SC. **Other Objectives (anti-HER2 treated subgroup only)** •Disease recurrence (local, regional or distant), a contralateral invasive breast cancer, a second primary cancer, or death from any cause for eBC patients or LABC patients qualified for local regional treatment – surgery or radical radiotherapy •First disease progression or death from any reason for mBC patients (whatever occurs first during treatment period in the study).
COUNTRY OF STUDY POPULATION:	Poland
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany
MAH CONTACT PERSON:	[redacted]
DATE FINAL:	

Based on NI-PASS protocol template (PDC) Version 3.0 released on 15-Nov-2016

PROTOCOL FINALIZATION SIGNATURE PAGE

TITLE:	**A PROSPECTIVE, NON-INTERVENTIONAL STUDY ASSESSING THE DIAGNOSTIC, THERAPEUTIC PROCEEDINGS AND SAFETY OF ANTI-HER2 TREATMENT IN ELDERLY PATIENTS (≥70 YEARS OLD) WITH HER2 POSITIVE BREAST CANCER IN ROUTINE CLINICAL PRACTICE IN POLAND - MULTICENTER, OBSERVATIONAL STUDY (HEROLD)**
PROTOCOL NUMBER:	ML40006
VERSION NUMBER:	1.0
EU PASS REGISTER NUMBER:	To be determined
STUDIED MEDICINAL PRODUCTS:	Herceptin SC, Herceptin IV, Perjeta IV
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany
DATE FINAL:	20.04.2018

This protocol was finalized on the date shown above.

[redacted] (Scientific Responsible)

Date

[redacted]

Date

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

PROTOCOL ACCEPTANCE FORM

TITLE:	**A PROSPECTIVE, NON-INTERVENTIONAL STUDY ASSESSING THE DIAGNOSTIC, THERAPEUTIC PROCEEDINGS AND SAFETY OF ANTI-HER2 TREATMENT IN ELDERLY PATIENTS (≥70 YEARS OLD) WITH HER2 POSITIVE BREAST CANCER IN ROUTINE CLINICAL PRACTICE IN POLAND - MULTICENTER, OBSERVATIONAL STUDY (HEROLD)**
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I agree to conduct the non-interventional study in accordance with the current protocol.

_____
Treating Physician's Name (print)

_____ _____
Treating Physician's Signature Date

Please return a copy of this form directly to your Site Operations Representative (the Monitor from [redacted] - CRO) or MAH Representative. Please retain the signed original for your study files.

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
(e)CRF	Electronic Case Report Form
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AESI	Adverse events of special interest
ALAT	Alanine transaminase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARIS/IRT	Adverse Reaction Information System/ Inbound Receipt & Triage
ASAT	Aspartate transaminase
AST	Aspartate aminotransferase
BMI	Body mass index
BSA	Body surface area
CB	Core biopsy
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
CRO	Contract research organization
CSO	Central Statistical Office
CT	Computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease free survival
eBC	Early breast cancer
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EMA	European Medicines Agency
ER	Estrogen receptor
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiological Practice
GVP	EU Guideline on Good Pharmacovigilance Practices
HER	Human epidermal growth factor receptor
HLT	High level term
ICH	International Conference of Harmonisation
ICSR	Individual Case Safety Report
IHC	ImmunoHistoChemistry
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ISH	In situ hybridization
ISPE	International Society of Pharmacoepidemiology
IV	Intravenous
LABC	Locally advanced breast cancer
LPLA	Last patient, last assessment
LPLV	Last patient, last visit
LSR/LSU	Local Safety Responsible / Local Safety Unit
LVEF	Left ventricular ejection fraction
MAH	Marketing authorization holder
mBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NA	Not applicable
NCI	National Cancer Institute
NHF	National Health Fund

Abbreviation	Definition
NIS	Non-interventional study
NYHA	New York Heart Association
OS	Overall survival
PFS	Progression-free survival
PgR	Progesterone receptor
PRO	Patient Reported Outcomes
QTT	Quarterly Tracking Tool
RA	Regulatory authorities
RBC	Red blood cells
RECIST	Response Evaluation Criteria In Solid Tumors
RTG/X-ray	Projectional radiography
RTL	Responsible Team Lead
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SDV	Source data verification
SIOG	The Society of Geriatric Oncology
SMT	Study management team
SOC	System Organ Class
SPC	Summary of Product Characteristics
ULN	Upper limit of normal
USG	Ultrasonography
WBC	White blood cells
WHO	World Health Organization

2. RESPONSIBLE PARTIES

Protocol Development Responsible

[redacted], Roche Poland, Domaniewska St. 39B, 02-672 Warsaw, e-mail: [redacted], Tel. [redacted]

Scientific Responsible

[redacted], Roche Poland, Domaniewska St. 39B, 02-672 Warsaw, e-mail: [redacted], Tel. [redacted]

3. SYNOPSIS

TITLE:	**A PROSPECTIVE, NON-INTERVENTIONAL STUDY ASSESSING THE DIAGNOSTIC, THERAPEUTIC PROCEEDINGS AND SAFETY OF ANTI-HER2 TREATMENT IN ELDERLY PATIENTS (≥70 YEARS OLD) WITH HER2 POSITIVE BREAST CANCER IN ROUTINE CLINICAL PRACTICE IN POLAND - MULTICENTER, OBSERVATIONAL STUDY (HerOld)**
PROTOCOL NUMBER:	ML40006
VERSION NUMBER:	1.0
DATE OF SYNOPSIS:	08.06.2017
EU PASS REGISTER NUMBER	To be determined
STUDIED MEDICINAL PRODUCTS	Herceptin SC, Herceptin IV, Perjeta IV
SCIENTIFIC RESPONSIBLE/MAIN AUTHOR:	[redacted] [redacted] Roche Polska Domaniewska St. 39B 02-672 Warsaw, [redacted], MD [redacted] [redacted]
PHASE	IV, non-interventional study
INDICATION:	Early, locally advanced or metastatic HER2 positive breast cancer
MARKETING AUTHORIZATION HOLDER	Roche Registration GmbH Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany

Rationale and Background

Breast cancer is the most common malignant tumor in women, with a global prevalence of more than 1 million patients. The annual mortality rate is approximately 450,000 deaths (American Cancer Society). Due to the growing average life expectancy of women in Poland, population of elderly females is increasing significantly. According to the Central Statistical Office (CSO) forecast, the number of women over the age of 65

years will increase from 3.65 million in 2015 to 4.94 million in 2030. Currently there is a relative lack of data from studies specifically designed for elderly population, which would be able to address the question of safety, tolerance and efficiency of therapeutic choices of HER family agents. Additionally, patients are often reluctant to enroll in clinical trials because of misconceptions and inadequate efforts in explaining the benefits of such participation by geriatricians. For these reasons, there is a need for comprehensive assessment of the course of anti-HER2 targeted therapies (Herceptin SC or Herceptin IV with or without Perjeta IV) in the population of older women that focuses on safety and tolerance of the treatment. The most vital aspect of such study is broadening of knowledge about adverse events affecting this population as well as frequency of discontinuations of anti-HER2 treatment caused by adverse events. At the same time there is a need for appraisal of what part of the population of patients with HER2 positive breast cancer at the age of 70 years or above is not qualified for chemotherapy and targeted therapies and what are reasons of disqualification from anti-HER2 therapy.
For information on the condition under observation and on Herceptin SC or Herceptin IV with or without Perjeta IV please refer to the most recent version of the SPC.

Research Question and Objectives

Due to the extending length of the average life expectancy for women in Poland, population of elderly female is increasing significantly. According to the Central Statistical Office (CSO) forecast the number of women over the age of 65 years will increase from 3.65 million in 2015 to 4.94 million in 2030. The risk of developing and dying from breast cancer increases with age. According to the National Cancer Registry in Poland in 2013 women aged 65+ accounted for 37.4% of the whole group, whereas deaths in this age group accounted for 55.9% of all deaths caused by breast cancer. This group of women is particularly challenging to treat because of the associated comorbidities and general health. Age alone is often considered as a factor in the decision process of the type of adjuvant treatment or even disqualifying from chemotherapy and / or molecular targeted therapy. Population of elderly patients has not been taken into consideration in many clinical trials. Furthermore, the number of enrolled patients did not match the number of elderly patients in the actual population. Example could be HERA, a prospective Phase III study assessing the efficacy of adjuvant treatment with Herceptin, where only 16.2% of randomized patients were over 60 years old. For this reason, there is a need for comprehensive assessment of the course of anti-HER2 targeted therapies (Herceptin SC or Herceptin IV with or without Perjeta IV) in the population of older women. At the same time there is a need to try to answer the question of what part of the population of patients with HER2 positive breast cancer at the age of 70 years or above is not qualified for chemotherapy and targeted therapies and identifying the reason of disqualification for anti-HER2 therapy.

Data concerning secondary study objectives will be analyzed among all included patients while primary safety objectives focus on the population subgroup defined as those patients who qualify for anti-HER2 therapy and are prescribed anti-HER2 treatment (Herceptin SC or Herceptin IV with or without Perjeta IV).

Objectives

Primary Objectives - Safety

The safety objectives of this study pertain to a subgroup consisting of patients treated with anti-HER2 treatment (Herceptin SC or Herceptin IV with or without Perjeta IV) and are as follows:

- To assess frequency of discontinuation of anti-HER2 treatment (Herceptin SC or Herceptin IV with or without Perjeta IV) caused by adverse events
- To evaluate safety of anti-HER2 treatment (Herceptin SC or Herceptin IV with or without Perjeta IV) and summarize frequency of adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESIs)
- To evaluate frequency of anti-HER2 treatment interruptions, discontinuations and reintroductions
- To assess the completion of the assumed treatment plan (Herceptin SC or Herceptin IV with or without Perjeta IV). Treatment plan will be assumed as completed when patient completes 18 cycles or one year of treatment (for eBC patients or LABC patients qualified for local regional treatment – surgery or radical radiotherapy) or when patient continues treatment until progression, death or end of the observation in the study (for mBC patients).

Secondary Objectives - Effectiveness

The effectiveness objectives for this study are as follows:

- Summarize epidemiological information among all included patients: age, BMI, BSA, cigarette smoking, comorbidities (hypertension, diabetes, coronary artery disease, heart failure, thromboembolic disease, medically relevant arrhythmias, thyroid disease, chronic kidney disease, osteoporosis, dementia, coexisting cancer, COPD, rheumatoid arthritis, liver disease, and depression)
- Summarize all diagnostic proceedings performed before qualification for anti-HER2 therapy (including: ER/PgR, HER2 status by IHC/ISH)
- Summarize all information about any anticancer therapies administered before qualification or disqualification for anti-HER2 therapy (including: surgery, systemic therapy or radiotherapy)
- Summarize information concerning qualification process for anti-HER2 therapy and the reasons for disqualification
- Summarize all information about anticancer therapies administered concurrently with anti-HER2 therapy (hormonal or chemotherapy)
- Summarize information about timing and types of surgery and radiotherapy in eBC patients that at the start of the study received neoadjuvant anti-HER2 therapy with Herceptin SC.

Other Objectives (anti-HER2 treated subgroup only)

- Disease recurrence (local, regional or distant), a contralateral invasive breast cancer, a second primary cancer or death from any cause for eBC patients or LABC patients qualified for local regional treatment – surgery or radical radiotherapy
- First disease progression or death from any reason for mBC patients (whatever occurs first during treatment period in the study).

Study Design

This single cohort, observational, local, multicenter, prospective, primary data collection, non-interventional, Post Authorization Safety Study (NI-PASS) will assess the safety and tolerance of treatment with anti-HER2 therapy in routine clinical practice. Secondary goal of the study is to collect information about epidemiological characteristics, diagnostic and therapeutic proceedings in elderly women (≥70 years old) with HER2-positive early, locally advanced or metastatic breast cancer, according to medical standard of care and reimbursement indications in Poland, following actual National Health Fund (NHF) - Drug Program "Treatment of Breast Cancer" and current version of SPC.

Information about reasons why patients were disqualified from anti-HER2 therapy will also be collected. Additionally, information concerning concomitant chemotherapy and/or hormonal therapy will also be gathered.

The following patients will be enrolled into the study: all 70 years or older patients diagnosed with early, locally advanced or metastatic HER2 positive breast cancer who agree to participate in the observational, non-interventional study conducted in local research centers, regardless of the planned therapeutic proceedings. Recruitment for the study will take place after confirmation of HER2 positive breast cancer and prior to qualification for the treatment.

Data will be collected from elderly women (≥70 years old) with HER2-positive early, locally advanced or metastatic breast cancer, treated with anti-HER2 therapies and from patients who are not prescribed (disqualified from) anti-HER2 therapy.

Duration of observation for each patient is from the time of inclusion to the study until maximum 2 years after the last patient enrolled or the date of death (if death occurs first). Data on patients not qualifying for National Health Fund (NHF) - Drug Program "Treatment of Breast Cancer" will be collected only on a screening visit and visit 1 and no further observation will take place.

For certain analyses, a subgroup of this population is defined as those patients who qualify for, and receive, anti-HER2 therapy (Herceptin SC or Herceptin IV with or without Perjeta IV) according to records in actual NHF Drug Program "Treatment of Breast Cancer".

Based on information from patients and their medical history, Physicians will collect the following data during visits:

- TNM classification of tumor at the time of diagnosis and stage at the time of recruitment
- microscopic diagnostic: verification of the diagnosis of breast cancer - execution of core biopsy (CB) or other possible methods of verification
- IHC/ISH panel (ER/PgR, HER2 status)
- pTNM classification
- WHO/ECOG performance status
- Age, height, weight, BMI, BSA, smoking
- Comorbidities: hypertension, diabetes, coronary artery disease, heart failure, thromboembolic disease, medically relevant arrhythmias, thyroid disease, chronic kidney disease, osteoporosis, dementia, coexisting cancer, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, liver disease, depression and others
- LVEF (left ventricular ejection fraction) - according to the records in actual NHF Drug Program "Treatment of Breast Cancer"
- Assessment of cardiotoxicity and occurrence of congestive heart failure (using CTCAE 4.0 criteria), and for CHF, in addition, assessment based on NYHA criteria

- Type of the previous surgery, radiotherapy, hormonal therapy or/and chemotherapy (including chemotherapy containing anthracyclines) as well as hormonal therapy and chemotherapy concurrent with anti-HER2 treatment
- In patients that start participation in the study receiving neoadjuvant therapy with Herceptin SC information about surgical operations and radiotherapy as well as subsequent change of anti-HER2 treatment will be collected
- Laboratory results and diagnostics required by NHF Drug Program "Treatment of Breast Cancer"
- Data on anti-HER2 treatment dosage and treatment interruptions, discontinuations and reintroductions
- Disease status assessment – disease recurrence, contralateral invasive breast cancer, second primary cancer, unacceptable toxicities or death from any cause
- Occurrence of adverse events - serious and non-serious adverse events (SAEs) and AEs of special interest (AESI)
- Concomitant medications.

If the patient continues treatment with anti-HER2 therapy (Herceptin with Perjeta IV) for more than 2 years (mBC patients according to the actual NHF Drug Program) after the inclusion to the observational study, an information will be included in the study documentation that the patient is continuing treatment without progression, unacceptable toxicities and is no longer in observation in the study.

The study will not require that patients undergo any additional medical interventions, tests, or procedures.

Description of Study

This is a single cohort, observational, local, multicenter, prospective primary data collection, non-interventional Post Authorization Safety Study (NI-PASS). Data from Polish patients diagnosed with HER2-positive breast cancer that are being qualified and treated in NHF Drug Program "Treatment of the Breast Cancer" will be prospectively collected during three years period (one year of recruitment and up to two years of observation). For patients that failed qualification to NHF Drug Program "Treatment of the Breast Cancer", reasons for disqualification will be collected and no further observation in the study will take place.

Target Population

Elderly women (70 years old or above) diagnosed with HER2-positive breast cancer confirmed by validated immunohistochemistry (IHC) or in situ hybridization (ISH) methods.

The study will enroll only HER2-positive breast cancer patients who are eligible for anti-HER2 therapy as well as patients who were disqualified for anti-HER2 treatment.

Eligible patients scheduled for neoadjuvant, adjuvant or metastatic treatment with Herceptin subcutaneous or intravenous formulation with or without Perjeta IV in real-world settings, according to actual NHF Drug Program "Treatment of Breast Cancer" in Poland and current SPC.

Patients must meet all of the following criteria for study entry:

- Elderly postmenopausal female patients: ≥70 years of age
- Histologically confirmed HER2 positive breast cancer (all breast cancer stages, all patients)
- ER or PgR receptor status assessed in all patients

- Patients currently qualified for any anticancer treatment (including: surgery, systemic therapy – prior to the first administration of anti-HER2 treatment in NHF Drug Program "Treatment of Breast Cancer" or radiotherapy)
- All patients eligible or disqualified for anti-HER2 treatment (Herceptin SC or Herceptin IV with or without Perjeta IV) in accordance with actual reimbursement inclusion criteria in Poland (actual NHF Drug Program "Treatment of Breast Cancer") and current SPC
- Signed, written informed consent to data collection

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

- Patient is participating in any other clinical trial at the moment of enrollment

Studied Medicinal Product

Patients will be treated with anti-HER2 therapy (Herceptin SC or Herceptin IV with or without Perjeta IV) in accordance with established standards, Summary of Product Characteristics and reimbursement criteria in Poland (actual NHF Drug Program "Treatment of Breast Cancer"), while the decision on treatment will be independent of the inclusion of the patient for this non-interventional, observational study. The studied medicinal products are Herceptin IV, Herceptin SC and Perjeta IV.

Variables

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

Primary Safety Variables (anti-HER2 treated subgroup only)

- Discontinuations of anti-HER2 treatment
- Adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESIs)
- Dosage of anti-HER2 therapy (number of administered cycles as well as occurrence of interruptions, discontinuations, or reintroductions)
- The treatment plan completion – as patients will normally receive 18 administrations per year, in early or locally advanced breast cancer (neoadjuvant and adjuvant settings) treatment will be considered as complete after 18 administrations or one year of treatment, otherwise plan will be assumed as not completed. For mBC patients, treatment will be assumed as complete if it continues until progression, death or end of the observation in the study.
- Left ventricular ejection fraction assessed in routine clinical practice according to actual NHF Drug Program "Treatment of Breast Cancer"

Occurrence of unacceptable toxicities during anti-HER2 treatment

- Assessment of cardiotoxicity and occurrence of congestive heart failure (based on CTCAE 4.0 criteria) and, in addition, assessment of Congestive Heart Failure (CHF) based on NYHA criteria

Safety information will be collected through the course of the study:

- All SAEs, regardless of whether they are related to Herceptin or Perjeta IV treatment
- All AEs regardless of whether they are related to Herceptin or Perjeta IV treatment
- All AESIs regardless of whether they are related to Herceptin or Perjeta IV treatment.

Secondary Effectiveness Variables

- Age, body mass index (BMI), body surface area (BSA), and cigarette smoking
- Comorbidities (hypertension, diabetes, coronary artery disease, heart failure, thromboembolic disease, medically relevant arrhythmias, thyroid disease, chronic kidney disease, osteoporosis, dementia, coexisting cancer, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, liver disease, and depression) and other
- Performance (WHO/ECOG) status
- Histological diagnostic for breast cancer by core biopsy or other verification method
- Progesterone receptor (PgR) status before administration of HER2 therapy
- Estrogen receptor (ER) status before administration of HER2 therapy
- Previous anticancer therapies (surgery, systemic therapy, or radiotherapy) administered before anti-HER2 therapy
- Disqualification of patients from anti-HER2 therapy
- Reasons of disqualification from anti-HER2 therapy (existing comorbidities, prior use of anti-HER2 therapy excluding from drug program (Herceptin, Perjeta IV), presence of adverse events – for example concurrent to prior chemotherapy/systemic therapy or caused by such therapy (such as use of anthracyclines and cardiotoxicity), sociologic issues, economic issues, patient refusal to be treated, others)
- Type of surgery, radiotherapy, hormonal therapy, or chemotherapy (including chemotherapy containing anthracyclines) planned and performed during the observational study
- Concomitant medications.

Other Variables of Interest (anti-HER2 treated subgroup only)

- Disease recurrence (local, regional or distant), a contralateral invasive breast cancer, a second primary cancer, or death from any cause for eBC patients or LABC patients qualified for local regional treatment – surgery or radical radiotherapy
- First disease progression or death from any reason for mBC patients.

Data Sources

Patients' data will be collected prospectively during routine visits and subsequently recorded in CRFs. The degree of detail and completeness of data collected is dependent on local clinical practice. Data from patient source documentation should be entered into the CRF as soon as they become available.

This is a non-interventional study and no additional patient's data, assessments, laboratory tests or visits except those collected/ performed as a routine clinical practice will be required for the purpose of this study.

Data will be collected from up to 8 oncologic centers in Poland.

Study Size/Determination of Sample Size

In this study we plan to enroll 150 of HER2 positive breast cancer patients across up to 8 sites.

Based on the calculations from NHF Drug Program "Treatment of the Breast Cancer" report and information received from Polish [redacted] International Society of Geriatric Oncology (SIOG) we assumed that we will enroll 100 patients treated with anti-HER2 therapy for a subgroup analysis from among all 150 HER2 positive breast cancer patients recruited to the study).

Data Analysis

A formal statistical analysis plan with all detailed analyses and a presentation of study data will be approved by the study team prior to data analysis.

As no formal hypothesis will be tested in this non-interventional study, all analyses will be descriptive in nature.

Descriptive statistics will include at least number of subjects, mean, standard deviation, minimum, and maximum for quantitative variables; and frequency and percentage for categorical variables. Additionally, 95% confidence interval will be provided.

When relevant, statistical analyses for patients receiving anti-HER2 medication will be carried out by treatment arms of NHF Drug Program "Treatment of the Breast Cancer" as well as stage (early or locally advanced and metastatic breast cancer) . Statistical analysis will be carried out by the treatment arm only for the descriptive analysis, no intent to statistically compare Herceptin IV to SC formulation.

Primary Safety Analysis

The safety analyses will be performed by treatment arm using all the data collected from subjects belonging to a subgroup. Adverse events registered in all patients prior to the first administration of Herceptin SC or Herceptin IV with or without Perjeta IV will not be analyzed and only presented as listing.

Safety variables include adverse events, which will be coded using the current version (at the time of database lock) of Medical Dictionary for Regulatory Activities.

- Percentage and number of discontinuations will be summarized by reason
- Listings of SAEs, AEs leading to discontinuation, and fatal SAEs will also be provided
- A summary table presenting the number and percentage of patients with AEs, serious AEs, AEs of special interest (serious and non-serious) and AEs leading to discontinuation (serious and non-serious) will be provided
- A table presenting number and percentage of adverse events by severity (NCI CTCAE grade: mild, moderate, severe, life-threatening, death) will be provided
- The summary table will provide information about the relationship (Not related, Possibly related, Related) of the AE to the treatment
- The number and percentage of patients with at least one AE will be tabulated by system organ class (SOC), high level term (HLT), and preferred term (PT)
- A frequency analyses of AEs, SAEs and AESIs will be performed in the context of categorized age, cigarette smoking and comorbidities
- A listing of adverse events related to unacceptable toxicities will be produced
- Left ventricular ejection fraction will be presented as median, lower and upper quartile, minimum and maximum at baseline as well as during subsequent visits
- Number and percentage of patients that experienced at least 10 percentage points drop of LVEF from the baseline and to a value of below 50% will be tabulated
- Cardiotoxicity, at least possibly related to the therapies used, defined as:
    - An asymptomatic decline in LVEF requiring treatment or leading to discontinuation of study treatment
    - The occurrence of symptomatic heart failure (CHF)

This will be summarized as overall number and percentage of patients experiencing such cardiotoxicity and tabulated by treatment

- Cardiotoxic AEs (an asymptomatic decline in LVEF requiring treatment or leading to discontinuation of study treatment or occurrence of congestive heart failure), at least possibly related to the therapy, will be analyzed in the context of previously reported comorbidities
- A summary table presenting number and frequency of dose interruptions, discontinuations and reintroductions
- A summary table presenting data on completion/realization of anti-HER2 treatment plan as well as number of cycles of anti-HER2 therapy.

Secondary Effectiveness Analysis

The following effectiveness analyses will be performed using the data from all patients included in the study:

- The quantitative epidemiological characteristics as age, body mass index and cigarette smoking will be summarized
- The number (%) of patients will be calculated for each comorbidity (hypertension, diabetes, coronary artery disease, heart failure, thromboembolic disease, medically relevant arrhythmias, thyroid disease, chronic kidney disease, osteoporosis, dementia, coexisting cancer, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, liver disease, and depression) and other
- A statistical summary relative to all included patients will be provided for the progesterone receptor (PgR) status, Estrogen receptor (ER) status, collected at Screening before the start of anti-HER2 therapy
- The number (%) of patients will be computed at Screening for all included patients by previous anticancer therapy (surgery, systemic therapy, or radiotherapy) administered before anti-HER2 therapy
- At Screening the number and percentage of disqualified patients for anti-HER2 therapy will be calculated for all included patients. The frequency (number and percentage) of patients will also be computed at Screening by reason of disqualification to anti-HER2 therapy for all included patients.

Following statistical summaries will be broken down by treatment, where subgroup is taken into account.

- Number and percentage of patients will be tabulated by type of surgery, radiotherapy, hormonal therapy, or chemotherapy performed during anti-HER2 treatment
- The lack of a therapy completion, caused by insufficient number of drug administration (for early or locally advanced stage cancer) or socioeconomic issues (for all patients undergoing anti-HER2 treatment) will be analyzed by period (Observation and Follow-Up) and treatment
- Concomitant medication will be analyzed separately for all patients (data collected during screening visit) and for a subgroup (patients receiving anti-HER2 medications).

Other Analyses

Statistical analyses will be performed using data from subgroup receiving anti-HER2 therapy (Herceptin SC or Herceptin IV with or without Perjeta IV) and presented as tabulation of numbers and percentages of:

- Disease recurrence (local, regional or distant), a contralateral invasive breast cancer, a second primary cancer, or death from any cause for eBC patients or LABC patients qualified for local regional treatment – surgery or radical radiotherapy.
- First disease progression or death from any reason for mBC patients.

Milestones

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 patient is recorded in the study database. The planned start date is April 2018.

End of Study

The end of the study will be the date from which the last information of the last patient is recorded in the study database (eCRF). The planned end of study date is April 2021.

Length of Study

This study will last 3 years and consists of 3 periods:

- one year of recruitment starting from first patient enrolled (first data collection)
- treatment period:
  - maximum one year of anti-HER2 treatment starting from last patient enrolled among eBC patients or LABC patients qualified for local regional treatment – surgery or radical radiology
  - maximum 2 years of anti-HER2 treatment starting from last patient enrolled among mBC patients. If applicable treatment will be continued (according to actual NHF Drug Program)
- maximum one year of follow-up for each eBC patient or LABC patient qualified for local regional treatment – surgery or radical radiotherapy; as well as for mBC patients who stopped receiving anti-HER2 treatment due to reasons other than disease progression. Follow-up will start from the last cycle administered. Total time of follow-up for each patient will not be longer than one year.

4. PROTOCOL AMENDMENTS AND UPDATES

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

Protocol amendments will be submitted only for notification to the Institutional Review Board (IRB)/Ethics Committee (EC) and for approval to regulatory authorities in accordance with local legislation requirements for PASS and PAES. Approval must be obtained from regulatory authorities (as locally required) before implementation of any changes, except for changes that involve logistical or administrative aspects only (e.g., change in Site Operations Representative or contact information).

Substantial protocol amendments/updates so far: none.

5. MILESTONES

Study milestones are given in the following table.

Milestone	Planned Date
Registration of protocol in the EU PAS register	Jun 2018
Start of data collection	Jul 2018
End of data collection	Jul 2021
Study progress report 1	Jul 2019
Study progress report 2	Jul 2020
Study progress report 3	Jul 2021
Interim reports	Not applicable
Final report of study results	Jun 2022
Registration of the results in the EU PAS register	Jun 2022

6. RATIONALE AND BACKGROUND

6.1 STUDY RATIONALE

The present study is designed as prospective non-interventional study assessing safety and tolerance of anti-HER2 treatment as well as diagnostic and therapeutic proceedings in elderly, postmenopausal women (≥70 years old) with HER2 positive breast cancer in routine clinical practice in Poland. It is a multicenter observational study.

Approximately 150 patients will be enrolled across up to 8 sites. Patients will be treated with anti-HER2 therapy (Herceptin SC or Herceptin IV with or without Perjeta IV) in accordance with established standards, Summary of Product Characteristics and reimbursement criteria in Poland (actual NHF Drug Program "Treatment of Breast Cancer"), while the decision on treatment will be independent of the inclusion of patient for this non-interventional, observational study. The studied medicinal products are Herceptin IV, Herceptin SC and Perjeta IV. This study aims to collect information about safety and tolerance of anti-HER2 treatment as well as epidemiological characteristics, diagnostic and therapeutic proceedings in elderly, postmenopausal patients (≥70 years old) with HER2-positive early, locally advanced or metastatic breast cancer, according to local standards and practice. Information about reasons for patient disqualification for anti-HER2 therapy will also be collected. Data concerning study objectives will be analyzed among all included patients (cohort) and additionally in a subgroup population defined as those patients who qualify for anti-HER2 therapy and anti-HER2 treatment will be applied (Herceptin SC or Herceptin IV with or without Perjeta IV) according to records in actual NHF Drug Program "Treatment of Breast Cancer".

6.2 STUDY BACKGROUND

Breast cancer is the most common malignant tumor in women, with a global prevalence of more than 1 million patients. The annual mortality rate is approximately 450,000 deaths (American Cancer Society). Due to the growing average life expectancy of women in Poland, population of elderly females is increasing significantly. According to the Central Statistical Office (CSO) forecast, the number of women over the age of 65 years will increase from 3.65 million in 2015 to 4.94 million in 2030. One of the biggest risk factors for the development of breast cancer is age. The median age of breast cancer diagnosis is about 60 years, and over 40% of all breast cancers are diagnosed in women aged 65 years or older (Turner et al. 2013). According to the Polish National Cancer Registry in 2013 women aged 65+ accounted for 37.4% of the whole group, whereas deaths in this age group accounted for 55.9% of all deaths caused by breast cancer. Therefore the proportion of older woman with breast cancer will grow considerably in the future. This group of women is particularly challenging to treat because of the associated comorbidities and general health. Data relating to the treatment of breast cancer in women over 65 years old, however, are very limited and there is a pressing need for developing of appropriate treatment recommendations. Age alone is often considered as a factor in the decision about the type of adjuvant treatment or even disqualification from chemotherapy and/or molecular targeted therapy.

Population of elderly patients has not been taken into consideration in many clinical trials. Furthermore, the number of enrolled patients did not match the number of elderly patients in the actual population. One such example could be HERA, a prospective Phase III study assessing the efficacy of adjuvant treatment with Herceptin, where only 16.2% of randomized patients were over 60 years old. The same situation occurred in CLEOPATRA study, the randomized, double-blind, placebo-controlled Clinical Evaluation of pertuzumab and trastuzumab, which assessed the efficiency and safety of combination of pertuzumab and trastuzumab with docetaxel as a first-line treatment for patients with HER2 positive metastatic breast cancer - there were only 127 (15.7%) patients from this age group among 808 patients enrolled.

Preliminary results on safety of IIIb PERUSE trial were presented. This study assessed the safety of first-line pertuzumab plus trastuzumab associated to investigator's chosen taxane in routine clinical practice. The safety profile of the study is consistent with previous clinical experience of CLEOPATRA trial and no unexpected safety data were observed. It is currently in course of enrollment as a multicenter international single-arm, clinical practice study, commissioned by EMA to evaluate the safety of the combination in the real life practice. Baseline characteristics show that median age of the randomized patients was 55 years old and only 26% of them were over 65 years old. The lack of data in elderly patients with breast cancer results from the trend to exclude older patients from randomized phase III trials, especially those focusing on newly developed treatments. On the other hand, because of a low overall survival in the population older than 65 years there is a need for new agents with novel mechanism of action, with a non-overlapping toxicity, which can be combined with established treatment for breast cancer. Evidence suggests that dysregulation of ligands and receptors of the HER family is important in the pathogenesis of cancer. Approximately 18-24% of patients overexpress HER2. This overexpression in breast cancer, has been correlated with poorer disease-free survival and overall survival compared with tumors that do not overexpress HER2 (Pauletti et al. 2000).

Trastuzumab is a humanized monoclonal antibody binding with high affinity and specificity to extracellular domain, sub-domain IV of receptor HER2. Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signaling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. As a result, trastuzumab has been shown, in both in vitro assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2. Additionally, trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC). In vitro, trastuzumab-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

Trastuzumab is indicated for the treatment of patients with HER2 positive breast cancer both in adjuvant and metastatic setting. The addition of trastuzumab to standard chemotherapy increases time to progressive disease or the length of progression-free survival (PFS) and improves survival when administered with chemotherapy to women with HER2 positive breast cancer (Romond et al. 2005). Trastuzumab is well tolerated both as a single agent and in combination with standard chemotherapy (Salmon et.al

2001). The most significant adverse event (AE) observed in patients who received trastuzumab was cardiac dysfunction, presenting as asymptomatic decrease of LVEF. Risk factors for cardiac failure in the setting of trastuzumab treatment include co-administration with anthracycline-based chemotherapy, increasing age and use the anti-hypertensive medications (Tan-Chiu et al. 2005).

Pertuzumab (Perjeta) is a fully humanized monoclonal antibody based on the human immunoglobulin (Ig)G1 framework sequences and consisting of two heavy chains (449 residues) and two light chains (214 residues). Pertuzumab is directed against the extracellular domain of HER2. It binds to an epitope within, what is known as sub-domain 2 of HER2 (Franklin et al 2004), and acts by blocking the dimerization of HER2 with other family members, including HER1, HER3 and HER4. Due to its complementary modes of action with trastuzumab, it plays a significant role in treatment of HER2-overexpressing diseases. Pertuzumab in combination with Herceptin and docetaxel is indicated for the treatment of patients with HER-2 positive breast cancer in the first line metastatic setting and is also approved by FDA for use prior to surgery in patients with high-risk, HER2-positive early stage breast cancer as a part of complete treatment. The most significant adverse events (AE) observed in patients who received pertuzumab is subclinical and clinical cardiac failure manifesting as decreased LVEF and congestive heart failure (CHF).

Currently there is a relative lack of data from studies specifically designed for the elderly population, which would be able to address the question of safety, tolerance and efficiency of therapeutic choices of HER family agents. Patients are often reluctant to enroll in clinical trials because of misconceptions and inadequate efforts in explaining the benefits of such participation by geriatricians. For these reasons, there is a need for comprehensive assessment of the course of anti-HER2 targeted therapies (Herceptin SC or Herceptin IV with or without Perjeta IV) in the population of older women that focuses on safety and tolerance of the treatment. The most vital aspect of such a study is broadening the knowledge about adverse events affecting this population as well as frequency of discontinuations of anti-HER2 treatment caused by adverse events. At the same time there is a need for appraisal of what part of the population of patients with HER2 positive breast cancer at the age of 70 years or above is not qualified for chemotherapy and targeted therapies and what are the reasons of disqualification from anti-HER2 therapy.

For information on the condition under observation and on Herceptin SC or Herceptin IV with or without Perjeta IV please refer to the most recent version of the SPC.

7. RESEARCH QUESTION AND OBJECTIVES

7.1 RESEARCH QUESTION

The main goal of this study is to assess frequency of discontinuations of anti-HER2 therapy due to occurrence of adverse events as well as safety and tolerance of such therapy in population of elderly, postmenopausal, patients (≥70 years old) with HER2-positive early, locally advanced or metastatic breast cancer. Additionally, information about epidemiological characteristics, diagnostic and therapeutic proceedings according to local standards and practice in this population will be collected.

Another important goal is to answer the question of what part of the population of postmenopausal patients with HER2 positive breast cancer at the age of 70 years or above is not qualified for chemotherapy and targeted therapies and identifying the reason of disqualification from anti-HER2 therapy.

7.2 OBJECTIVES

Primary Objectives - Safety

The safety objectives of this study pertain to the subgroup - defined as those patients who qualify for anti-HER2 therapy and are prescribed anti-HER2 treatment (Herceptin SC or Herceptin IV with or without Perjeta IV). There are the following safety objectives:

- To assess frequency of discontinuation of anti-HER2 treatment (Herceptin SC or Herceptin IV with or without Perjeta IV) caused by adverse events
- To evaluate safety of anti-HER2 treatment (Herceptin SC or Herceptin IV with or without Perjeta IV) and summarize frequency of adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESIs)
- To evaluate frequency of anti-HER2 treatment interruptions, discontinuations and reintroductions
- To assess the completion of the assumed treatment plan (Herceptin SC or Herceptin IV with or without Perjeta IV). Treatment plan will be assumed as completed when patient completes 18 cycles or one year of treatment (for eBC patients or LABC patients qualified for local regional treatment – surgery or radical radiotherapy) or when patient continues treatment until progression, death or end of the observation in the study (for mBC patients).

Secondary Objectives - Effectiveness

The effectiveness objectives for this study are as follows:

- Summarize epidemiological information among all included patients: age, BMI, BSA, cigarette smoking, comorbidities (hypertension, diabetes, coronary artery disease, heart failure, thromboembolic disease, medically relevant arrhythmias, thyroid disease, chronic kidney disease, osteoporosis, dementia, coexisting cancer, COPD, rheumatoid arthritis, liver disease, and depression) and other
- Summarize all diagnostic proceedings performed before qualification for anti-HER2 therapy (including: ER/PgR, HER2 status by IHC/ISH)
- Summarize all information about any anticancer therapies administered before qualification or disqualification for anti-HER2 therapy (including: surgery, systemic therapy or radiotherapy)
- Summarize information concerning qualification process for anti-HER2 therapy and the reasons for disqualification
- Summarize all information about anticancer therapies administered concurrently with anti-HER2 therapy (hormonal or chemotherapy)
- Summarize information about timing and types of surgery and radiotherapy in eBC patients that at the start of the study received neoadjuvant anti-HER2 therapy with Herceptin SC.

Other Objectives (anti-HER2 treated subgroup only)

- Disease recurrence (local, regional or distant), a contralateral invasive breast cancer, a second primary cancer or death from any cause for eBC patients or LABC patients qualified for local regional treatment – surgery or radical radiotherapy
- First disease progression or death from any reason for mBC patients (whatever occurs first during treatment period in the study).

8. RESEARCH METHODS

8.1 STUDY DESIGN

This single cohort, observational, local, multicenter, prospective primary data collection non-interventional PASS study will assess the safety and tolerance of treatment with anti-HER2 therapy in routine clinical practice. Secondary goal of the study is to collect information about epidemiological characteristics, diagnostic and therapeutic proceedings in elderly women (≥70 years old) with HER2-positive early, locally advanced or metastatic breast cancer, according to medical standard of care and reimbursement indications in Poland, following actual National Health Fund (NHF) - Drug Program "Treatment of Breast Cancer" and current SPC.

Information about reasons why patient were disqualified from anti-HER2 therapy will also be collected. Additionally, information concerning concomitant chemotherapy and/or hormonal therapy will also be gathered.

The following patients will be enrolled into the study: all 70 years or older patients diagnosed with early, locally advanced or metastatic HER2 positive breast cancer who agree to participate in the observational, non-interventional study conducted in local research centers, regardless of the planned therapeutic proceedings. Recruitment for the study will take place after confirmation of HER2 positive breast cancer and prior to qualification for the treatment.

Data will be collected from elderly women (≥70 years old) with HER2-positive early, locally advanced or metastatic breast cancer, treated with anti-HER2 therapies and also from patients who are disqualified from National Health Fund (NHF) - Drug Program "Treatment of Breast Cancer".

Duration of observation for each patient who qualified for anti-HER2 therapies is from the time of inclusion to the study until maximum 2 years after the last patient enrolled or the date of death (if death occurs first). Data on patients not qualifying for National Health Fund (NHF) - Drug Program "Treatment of Breast Cancer" will be collected only on a screening visit and visit 1 and no further observation will take place.

For certain analyses, a subgroup of this population is defined as those patients who qualify for, and receive, anti-HER2 therapy (Herceptin SC or Herceptin IV with or without Perjeta IV) according to records in actual NHF Drug Program "Treatment of Breast Cancer" and current version of SPC.

Based on information from patients and their medical history, Physicians will collect the following data during visits:

- TNM classification of tumor at the time of diagnosis and stage at the time of recruitment.
- microscopic diagnostic: verification of the diagnosis of breast cancer - execution of core biopsy (CB) or other possible methods of verification
- IHC/ISH panel (ER/PgR, HER2 status)
- pTNM classification
- WHO/ECOG performance status

- Age, height, weight, BMI, BSA, smoking
- Comorbidities: hypertension, diabetes, coronary artery disease, heart failure, thromboembolic disease, medically relevant arrhythmias, thyroid disease, chronic kidney disease, osteoporosis, dementia, coexisting cancer, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, liver disease, depression and others
- LVEF (left ventricular ejection fraction) - according to the records in actual NHF Drug Program "Treatment of Breast Cancer"
- Assessment of cardiotoxicity and occurrence of congestive heart failure (using CTCAE 4.0 criteria), and for CHF, in addition, assessment based on NYHA criteria
- Type of the previous surgery, radiotherapy, hormonal therapy or/and chemotherapy (including chemotherapy containing anthracyclines) as well as hormonal therapy and chemotherapy concurrent with anti-HER2 treatment
- In patients that start participation in the study receiving neoadjuvant therapy with Herceptin SC information about surgical operations and radiotherapy as well as subsequent change of anti-HER2 treatment will be collected
- Laboratory results and diagnostics required by NHF Drug Program "Treatment of Breast Cancer"
- Data on anti-HER2 treatment dosage and treatment interruptions, discontinuations and reintroductions
- Disease status assessment – disease recurrence, contralateral invasive breast cancer, second primary cancer, unacceptable toxicities or death from any cause
- Occurrence of adverse events - serious and non-serious adverse events (SAEs) and AEs of special interest (AESI)
- Concomitant medications.

If the patient continues treatment with anti-HER2 therapy (Herceptin with Perjeta IV) for more than 2 years (mBC patients according to the actual NHF Drug Program) after the inclusion to the observational study, information that the patient is continuing treatment without progression and serious adverse events and is no longer in observation will be included in the study documentation. The study will only collect data available from routine clinical practice and not require any additional patient's diagnostic methods, tests or procedures.

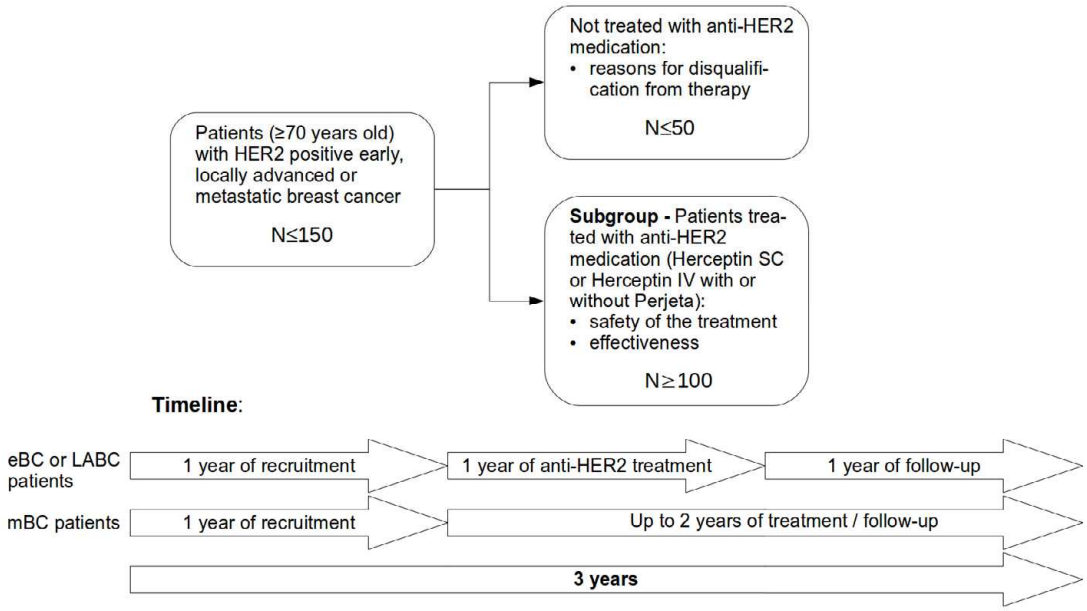

Figure 1. Overall study scheme

Start Date of Study:

The study start date will be the date of the first data collection that is the date when data of the first study patient is recorded in the study database. The planned start date is April 2018.

End of Study:

The end of the study will be the date on which the last information of the last patient is recorded in the study database. The planned end of study date is April 2021.

Length of Study:

This study will last 3 years and consists of 3 periods:

- one year of recruitment starting from first patient enrolled
- treatment period:
    - maximum one year of anti-HER2 treatment starting from last patient enrolled among eBC patients or LABC patients qualified for local regional treatment – surgery or radical radiology
    - maximum 2 years of anti-HER2 treatment starting from last patient enrolled among mBC patients. If applicable treatment will be continued (according to actual NHF Drug Program)
- maximum one year of follow-up for each eBC patient or LABC patient qualified for local regional treatment – surgery or radical radiotherapy, as well as for mBC patients who stopped receiving anti-HER2 treatment due to reasons other than disease progression. Follow-up will start from the last cycle administered. Total time of follow-up for each patient will not be longer than one year.

Overall scheme of the study is presented in Figure 1. A data collection overview is provided in Appendix 2.

8.1.1 Rationale for Study Design

This study is specifically designed for elderly population and as such will be able to address the question of long-term safety and tolerances of anti-HER2 agents among this group of patients. Additionally, it is designed to establish diagnostic proceedings and epidemiological characteristic of elderly women with HER2-positive breast cancer in a "real world" setting of daily clinical practice. Standard safety assessments, including assessment of type, and severity (graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)) will be used.

Targeting anti-HER2 therapy, trastuzumab and pertuzumab is a standard therapy for HER2-overexpressing breast cancer. But there are less data available related to anti-HER-2 therapy in elderly patients because they have been consistently underrepresented in clinical trials. Recommendations are mainly based on retrospective studies, subgroup analyses within larger randomized trials and expert opinion. Treatment decisions should consider the performance status of the patient reflected by ECOG score (Eastern Cooperative Oncology Group), co-morbidities, in addition to chronological age with the aim to balance risks and potential benefits from treatments. There is a need to discuss assessment tools to aid clinicians to select elderly patients who are 'fit' for chemotherapy. In 2007 The Society of Geriatric Oncology (SIOG) created a task force to provide evidence-based recommendations for the management of breast cancer in elderly patients (Wildiers et al, 2007). Recommendations were updated in 2010 (Biganzoli et al, 2012). The committee recommended assessing multiple factors of a patient including life expectancy, risks and benefits of treatment, patient preference, potential treatment barriers, in addition to chronological age (Biganzoli et al, 2012). The St. Gallen International Expert Consensus also states that the decision for systemic treatment, qualification process for anti-HER2 therapy as well as the reasons for disqualification in elderly breast cancer patients should not be based solely on age (Coates et al, 2015). In fact, a study looking at the impact of patient age on clinical decision-making in oncology showed that oncologists consistently scored age-related factors such as co-morbidity and frailty as more important than age itself (Rule *et al*, 2012). The major toxicity associated with trastuzumab is the risk of cardiotoxicity, especially in older patients who are also more likely to have pre-existing cardiac disease. An independent review of the NSABP B31 and NCCTG N9831 trials showed that age >50 was one of the independent predictors for cardiac events, defined as heart failure, myocardial infarction or primary arrhythmias that resulted in death, or decline of at least 10 percentage points (absolute) from baseline of LVEF and a decline to <50% (Russell *et al*, 2010). However, this result was not seen in the HERA trial that showed no difference in cardiac events in patients over and under 60 years old (de Azambuja *et al*, 2014). A cohort study of elderly patients (aged 66 and over) looked at the rate of

cardiotoxicity in patients who received trastuzumab and chemotherapy (anthracycline and/or taxane) compared with chemotherapy alone (Chavez-MacGregor *et al*, 2013). The study showed a 10% increase in congestive heart failure in the group treated with trastuzumab and chemotherapy compared with the chemotherapy alone group (Chavez-MacGregor *et al*, 2013). Among trastuzumab-treated patients, older age (age >80 years old) was one of the factors that increased the risk of congestive heart failure (Chavez-MacGregor *et al*, 2013). Another retrospective study of elderly women aged 67–94 compared different combinations of trastuzumab and chemotherapy (±trastuzumab±anthracycline/non-anthracycline chemotherapy; Chen *et al*, 2012). Results showed that the addition of an anthracycline to trastuzumab was associated with the highest rate of cardiotoxicity (Chen *et al*, 2012).

Good efficiency and manageable safety profile of trastuzumab and pertuzumab have been demonstrated in clinical trials. Safety will be carefully evaluated, and the type of data collected and the frequency with which patients are monitored will ensure the safety of the patients at all times, as well as fulfilling regulatory requirements of NHF drug program ”Treatment of Breast Cancer” in Poland.

This study specifically focusing on older, postmenopausal patients may help to clarify the absolute benefits and risks of systemic anti–HER2 therapy in this age group.

8.2 SETTING

8.2.1 Centers

This study will be conducted at approximately up to 8 sites in Poland. Additional centers may be added or substituted if underperforming.

8.2.2 Study Population

Despite improved disease free survival (DFS) and overall survival (OS) with Herceptin and Perjeta – containing systemic therapy – there remains a risk for recurrence and breast cancer related death in HER2 positive breast cancer, especially in the higher-risk subpopulation. One of the biggest risk factors for the development of breast cancer is age. Management of breast cancer in the elderly is complex, firstly, because this population is heterogeneous. Secondly, limited data are available, mainly because the elderly population is poorly represented, especially in randomized controlled trials. Level 1 evidence data from randomized controlled trials in specific elderly populations (medically fit and medically frail patients) are urgently needed. This study is designed to enroll postmenopausal patients, 70 years old or above, to collect information on safety and tolerance of anti-HER2 therapy and about epidemiological characteristics, diagnostic and therapeutic proceedings in elderly, postmenopausal patients with HER2-positive early, locally advanced or metastatic breast cancer, according to local standards and practice. Information about reasons for patient disqualification for anti-HER2 therapy will be also collected, without interference in local clinical practice.

The target population for this study will be:

- Elderly postmenopausal women (70 years old or above) diagnosed with HER2-positive breast cancer confirmed by validated immunohistochemistry (IHC) or in situ hybridization (ISH) methods
- The study will enroll patients who are eligible for anti-HER2 therapy as well as patients who were disqualified from anti-HER2 treatment
- Eligible patients scheduled for neoadjuvant, adjuvant or metastatic treatment with Herceptin subcutaneous or intravenous formulation with or without Perjeta IV in real-world settings, according to NHF drug program "Treatment of Breast Cancer" in Poland. Baseline visit and follow up will be planned according to local standards and NHF drug program "Treatment of Breast Cancer" requirements in Poland.

Patients must meet the following criteria for study entry:

- Elderly female postmenopausal patients: ≥70 years of age
- Postmenopausal - defined as at least 60 years of age, having undergone bilateral oophorectomy, medically confirmed ovarian failure or younger than 60 years of age and having had cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and having serum levels of estradiol and follicle stimulating hormone within the laboratory's reference range for postmenopausal females[1]
- Histologically or cytologically confirmed and documented adenocarcinoma of the breast (all breast cancer stages, all patients)
- HER2-positive (defined as either IHC3+ or in situ hybridization (ISH) positive) as assessed by local laboratory on primary tumor and/or metastatic site if primary tumor is not available (ISH positivity is defined as ratio of 2.0 or for the number of HER2 gene copies to the number of signals for CEP17, or for single probe test, a HER2 gene count greater than 4
- ER or PgR receptor status assessed in all patients
- Patients currently qualified for any anticancer treatment (including: surgery, systemic therapy – prior to the first administration of anti-HER2 treatment in NHF Drug Program "Treatment of Breast Cancer" or radiotherapy)
- Patients eligible for or disqualified from anti-HER2 treatment (Herceptin SC or Herceptin IV with or without Perjeta IV) in accordance with actual reimbursement inclusion criteria in Poland (NHF drug program "Treatment of Breast Cancer") and current SPC

[1] https://www.fda.gov/downloads/Drugs/.../UCM135338

- Signed, written informed consent to data collection

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

- Patient is participating in any other clinical trial at the moment of enrollment

Occurrence of disease recurrence (local, regional or distant), a contralateral invasive breast cancer, a second primary cancer, or death from any cause among eBC (or LABC) patients and occurrence of first disease progression or death from any reason among mBC patients cannot happen prior to study enrollment.

8.2.3 Concomitant Medication and Treatment

Concomitant medication prescribed for concomitant diseases and treatment for breast cancer at the beginning of the study or introduced during the observation period will be documented in the CRF from the start of therapy with Herceptin subcutaneous or intravenous formulation with or without Perjeta IV until discontinuation of the treatment, if applicable. Concomitant therapy includes any medication (e.g. prescription drugs, over-the counter drugs, herbal/homeopathic remedies, nutritional supplements and others) used by the patient prior to study enrollment up to the 28 days post-treatment follow-up. Physicians should enter data on concomitant medications received by patient prior to the study enrollment independent of the time period, provided they consider them important to patient's health status at the time of recruitment.

8.2.4 Dosage, Administration, and Compliance

Dosing and treatment duration of any studied medicinal products collected as parts of this non-interventional study are at the discretion of the physician in accordance with local clinical practice and local labeling. Patients will be treated with anti-HER2 therapy (Herceptin SC or Herceptin IV with or without Perjeta IV) in accordance with established standards, Summary of Product Characteristics and reimbursement criteria in Poland, while the decision on treatment will be independent from the inclusion of patient in this non-interventional, observational study. The studied medicinal products are Herceptin IV, Herceptin SC and Perjeta IV.

8.3 VARIABLES

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

8.3.1 Primary Safety Variables

The primary variables, collected for patients receiving anti-HER2 therapy (subgroup) will be:

- Discontinuations of anti-HER2 treatment

- Adverse events (AEs), serious adverse events (SAEs) and AEs of special interest (AESIs)
- Dosage of anti-HER2 therapy (number of administered cycles as well as occurrence of interruptions, discontinuations, or reintroductions)
- The treatment plan completion – as patients will normally receive 18 administrations per year, in early or locally advanced breast cancer (neoadjuvant and adjuvant settings) treatment will be considered as complete after 18 administrations or one year of treatment, otherwise plan will be assumed as not completed. For mBC patients, treatment will be assumed as complete if it continues until progression, death or end of the observation in the study.
- Left ventricular ejection fraction assessed in routine clinical practice according to actual NHF Drug Program "Treatment of Breast Cancer"

- Occurrence of unacceptable toxicities during anti-HER2 treatment
  - Assessment of cardiotoxicity and occurrence of congestive heart failure (based on CTCAE 4.0 criteria), and for CHF, in addition, assessment based on NYHA criteria.

Safety information will be collected through the course of the study:

- All SAEs, regardless of whether they are related to Herceptin or Perjeta IV treatment
- All AEs regardless of whether they are related to Herceptin or Perjeta IV treatment
- All AESIs regardless of whether they are related to Herceptin or Perjeta IV treatment.

8.3.2 Secondary Effectiveness Variables

- Age, body mass index (BMI), body surface area (BSA), and cigarette smoking
- Comorbidities (hypertension, diabetes, coronary artery disease, heart failure, thromboembolic disease, medically relevant arrhythmias, thyroid disease, chronic kidney disease, osteoporosis, dementia, coexisting cancer, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, liver disease, and depression) and other
- Performance (WHO/ECOG) status
- Histological diagnostic for breast cancer by core biopsy or other verification method
- Progesterone receptor (PgR) status before administration of HER2 therapy
- Estrogen receptor (ER) status before administration of HER2 therapy
- Previous anticancer therapies (surgery, systemic therapy, or radiotherapy) administered before anti-HER2 therapy

- Disqualification of patients from anti-HER2 therapy
- Reasons of disqualification from anti-HER2 therapy (existing comorbidities, prior use of anti-HER2 therapy excluding from drug program (Herceptin, Perjeta IV), presence of adverse events – for example concurrent to prior chemotherapy/systemic therapy or caused by such therapy (such as use of anthracyclines and cardiotoxicity), sociologic issues, economic issues, patient refusal to be treated, others)
- Type of surgery, radiotherapy, hormonal therapy, or chemotherapy (including chemotherapy containing anthracyclines) planned and performed during the observational study
- Concomitant medications.

8.3.3 Other Variables of Interest

Following variables of interest will be considered in the study (anti-HER2 treated subgroup only):

- Disease recurrence (local, regional or distant), a contralateral invasive breast cancer, a second primary cancer, or death from any cause for eBC patients or LABC patients qualified for local regional treatment – surgery or radical radiotherapy
- First disease progression or death from any reason for mBC patients.

8.4 DATA SOURCES

Patients' medical records will be the source of all data that will be recorded in the CRFs. Therefore, only data available and already existing in patient's files will be recorded.
The degree of detail and completeness of data collected will be dependent on local routine clinical practice. Data from patient source documentation should be entered on the CRF as soon as they become available. This is a non-interventional study and no additional patient's data, assessments, laboratory tests or visits except those collected/ performed as a routine clinical practice will be required for purpose of this study.
Study monitors will perform ongoing source data verification to confirm that critical protocol data entered into the eCRFs by authorized site personnel are accurate, complete and verifiable from source documents.
Data will be collected from up to 8 oncologic centers in Poland.

8.4.1 Collection of Data on the CRF

Patients' data will be recorded on CRFs. The degree of detail and completeness of data collected is dependent on local clinical practice. Data from patient notes should be entered on the CRF as soon as they become available.

8.4.2 Data Collected during the Observation Period

During therapy with Herceptin SC or Herceptin IV with or without Perjeta IV, laboratory assessments are routinely performed in accordance with current guidelines and local standard of care. When performed during the observational period, available results from the range of assessments described below will be documented on the CRF. Most data will be documented during the treatment period when the respective assessments are usually performed according to standard of care. The proposed assessments and suggested timings for assessments in the protocol/observational plan are not mandatory. It is up to the treating physician to perform and document the assessments as performed in the real clinical setting.

Types of information to be collected:

1) Baseline information:

- Epidemiological characteristics (Age, Race/Ethnicity, Height, Weight, Body mass index (BMI), Body Surface Area (BSA), Cigarette smoking)
- Diagnosis confirmation:
  - Histological confirmation of breast cancer diagnosis
  - TNM staging
  - Histologic grade
  - Hormone receptor status (ER, PR)
  - HER2 receptor overexpression confirmation by IHC or ISH.
- Comorbidities (hypertension, diabetes, coronary artery disease, heart failure, thromboembolic disease, medically relevant arrhythmias, thyroid disease, chronic kidney disease, osteoporosis, dementia, coexisting cancer, COPD, rheumatoid arthritis, liver disease, depression) and other
- Concomitant medication
- ECOG performance status
- Any anticancer treatment before anti-HER2 therapy started (including: surgery, systemic therapy or radiotherapy).

2) Laboratory assessments (Schedule and applicability of laboratory assessment will follow rules specified in National Health Fond (NHF) - Drug Program “Treatment of Breast Cancer”*:*

- Hematology including: hemoglobin, platelet count, RBC, WBC, neutrophils
- Creatinine
- Alanine transaminase (ALAT)
- Aspartate transaminase (ASAT)
- Total bilirubin
- Alkaline phosphatase (ALP)
- Sodium
- Potassium
- Calcium
- USG /CT pelvis and abdomen
- X-Ray /CT chest

- Bone scintigraphy
- ECG
- Echo
- Cardiologic consultation
- Mammogram or breast and lymph node USG (or CT/MRI method selected based on possibility of evaluation of tumor size)
- CT/MRI Brain.

3) Qualification to anti-HER2 therapy (collects data on inclusion of patients into one of the following arms of National Health Fund (NHF) - Drug Program "Treatment of Breast Cancer"):

- adjuvant therapy with trastuzumab IV
- adjuvant therapy with trastuzumab SC
- neoadjuvant therapy with trastuzumab SC
- trastuzumab IV therapy for mBC
- trastuzumab SC therapy for mBC
- trastuzumab + pertuzumab therapy for mBC.

For patients that do not qualify for drug program, information on reasons of disqualification will be collected (only on screening or 1st visit).

4) Anti-HER2 treatment dosage and treatment interruptions, discontinuations and reintroductions.

5) Type of surgery, radiotherapy, hormonal therapy, or chemotherapy (including chemotherapy containing anthracyclines) planned and performed during the observational study.

6) Left Ventricular Ejection Fraction (LVEF)
7) Cardiotoxicity and congestive heart failure assessment (based on CTCAE 4.0 criteria), and for CHF, in addition, assessment based on NYHA criteria

8) Adverse events (serious and non-serious) and adverse events of special interest (AESIs)

9) Disease status assessment:

- Disease recurrence (local, regional or distant), a contralateral invasive breast cancer, a second primary cancer, unacceptable toxicities or death from any cause for eBC patients or LABC patients qualified for local regional treatment – surgery or radical radiotherapy,
- First disease progression, unacceptable toxicities or death from any reason for mBC patients (whatever occurs first during treatment period in the study).

10) Treatment plan completion - treatment plan will be assumed as completed when patient completes 18 cycles or one year of treatment (for eBC patients or LABC patients qualified for local regional treatment – surgery or radical radiotherapy) or when patient continues treatment until progression, death or end of the observation in the study (for mBC patients).

In the routine care setting, patients are seen regularly by their treating physicians either for treatment or for regular assessment after treatment. Thus, no study-specific visits or evaluations are required by this protocol.
Please see Appendix 2 for the data collection overview (as per standard of care).

8.4.3 Data Collected at Study Completion/Early Termination Visit

For patients who complete the observation period or early termination treatment with Herceptin SC or Herceptin IV with or without Perjeta IV, the study completion visit /early termination visit should be documented.
Please see Appendix 2 for the data collection overview at the study completion visit.

8.4.4 Safety Data Collection

Clinical AEs, serious and non-serious, as well as safety data other than AEs as described in Section 8.3 will be recorded in the CRF during the total observation period. For clinical AEs, serious and non-serious, 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 v 4.0], for CHF, in addition, using NYHA criteria) and relationship to therapy (i.e., related or unrelated) will be recorded as described in Appendix 3.

8.5 STUDY SIZE

As no formal hypothesis will be tested in this non-interventional study all analyses will be descriptive in nature. Therefore, sample size was not estimated; instead, number of 150 patients was selected based on calculations from NHF Drug Program "Treatment of the Breast Cancer" report and information received from Polish [redacted] International Society of Geriatric Oncology (SIOG).
In this study we plan to enroll 150 postmenopausal HER2 positive breast cancer patients across up to eight sites, and we assume that 100 patients from among that group will be qualified to NHF Drug Program "Treatment of the Breast Cancer", receive anti-HER2 medication and will be observed for a period of up to two years (early, locally advanced and metastatic breast cancer patients). Data collected from patients receiving anti-HER2 treatment will be used for a subgroup analysis
For that subgroup 95% CI (Clopper-Pearson confidence intervals) will be provided.

Table 1 95% Confidence Intervals for the percentage of discontinuations due to adverse events, based on 100 patients qualified to NHF Drug Program "Treatment of the Breast Cancer"

Number (%) of discontinuations due to AE	95% Confidence Interval
5 (5.0%)	1.6% - 11.3%
10 (10.0%)	4.9% - 17.6%
15 (15.0%)	8.6% - 23.5%
20 (20.0%)	12.7% - 29.2%
25 (25.0%)	16.9% - 34.7%
30 (30.0%)	21.2% - 40.0%
35 (35.0%)	25.7% - 45.2%
40 (40.0%)	30.3% - 50.3%
45 (45.0%)	35.0% - 55.3%
50 (50.0%)	39.8% - 60.2%
55 (55.0%)	44.7% - 65.0%
60 (60.0%)	49.7% - 69.7%
65 (65.0%)	54.8% - 74.3%
70 (70.0%)	60.0% - 78.8%
75 (75.0%)	65.3% - 83.1%
80 (80.0%)	70.8% - 87.3%
85 (85.0%)	76.5% - 91.4%
90 (90.0%)	82.4% - 95.1%
95 (95.0%)	88.7% - 98.4%

As no formal hypothesis will be tested in this non-interventional study, all analyses will be descriptive in nature.

8.6 DATA MANAGEMENT

8.6.1 Data Quality Assurance

A contract research organization (CRO) will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using CRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

[redacted] will produce a Data Quality Review Plan that describes the quality checking to be performed on the data.

The MAH will perform oversight of the data management of this study, including approval of the CRO data management plans (including Data Quality Review Plan) and guidance. Data will be periodically transferred electronically from the CRO to the MAH,

and the CRO's standard procedures will be used to handle and process the electronic transfer of these data.
CRFs and correction documentation will be maintained in the EDC system audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the marketing authorization holder and CRO standard procedures. The CRO will comply with the MAH's procedures regarding archiving and record management.

8.6.2 Electronic Case Report Forms

CRFs are to be completed using a MAH 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 MAH and should be handled in accordance with instructions from the MAH.
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 patients 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.

8.6.3 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 patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical study.
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.
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 8.8.3.
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 EC review. The participating sites must also allow inspection by applicable health authorities.

8.7 DATA ANALYSIS

8.7.1 Rationale for Patient Population and Analysis Groups

Despite the high prevalence of breast cancer among older woman and a significant associated morbidity and mortality, researches have only recently focused on treatment questions in this group of patients. Most clinical trials and almost all randomized trials have included relatively few women aged over 65. Extrapolation of results of many clinical trials to the geriatric population must be done with caution because of differences in tumor biology and problems common among older patients including comorbidity, impaired functional status and lack of social support. Elderly patients are often reluctant to enroll in clinical trials because of misconceptions and inadequate efforts in explaining by geriatricians, which is why this study is specifically designed for elderly population. The following patients will be enrolled into the study: all 70 years old or above diagnosed with early, locally advanced or metastatic HER2 positive breast cancer postmenopausal patients who qualify for anti-HER2 treatment (Herceptin SC or Herceptin IV with or without Perjeta IV) according to records in actual NHF Drug Program “Treatment of Breast Cancer”. Patients who were disqualified from anti-HER2 treatment will also be enrolled in order to collect information about reasons for disqualification. Patients receiving anti-HER2 therapy will form a subgroup for purpose of secondary effectiveness, safety and other analyses.

The following is an outline of the statistical methodology to be used in analysis of the data collected in the study. A detailed statistical analysis plan will be approved prior to finalization of the study database that may include additional analyses not mentioned in the following sections.

As no formal hypothesis will be tested in this non-interventional study, all analyses will be descriptive in nature. Descriptive statistics will include at least number of subjects, mean, standard deviation, minimum, and maximum for quantitative variables; and frequency and percentage for categorical variables.

Statistical analyses for patients receiving anti-HER2 medication will be carried out by treatment arms of NHF Drug Program as well as stage (early or locally advanced and metastatic breast cancer). Statistical analysis will be carried out by the treatment arm only for the descriptive analysis, and are not intended to statistically compare Herceptin IV to SC formulation.

8.7.2 Safety Analyses

Safety Analysis Population: subgroup defined as all enrolled patients receiving Herceptin SC or Herceptin IV with or without Perjeta IV. Adverse events registered in all patients prior to the first administration of Herceptin SC or Herceptin IV with or without Perjeta IV will not be analyzed and only presented as listing.

The analysis of safety outcomes/variables is based on the incidence and severity of all AEs, SAEs, AESIs with NCI CTCAE version 4.0.
The incidence of AEs and SAEs will be summarized according to the SOC and within each SOC, by MedDRA preferred term (version of MedDRA current at the time of database lock will be used).
Events rates per 100 patient years (of treatment exposure) will be determined by treatment and corresponding 95% confidence intervals will be provided.
The safety analyses will be performed by treatment arm using all data collected from subjects belonging to subgroup.

Safety variables include adverse events, which will be coded using the Medical Dictionary for Regulatory Activities and following descriptive analyzes will be performed:

- Percentage and number of discontinuations will be tabulated by reason
- Listings of SAEs and AEs leading to discontinuation as well as fatal SAEs will also be provided
- A summary table presenting the number and percentage of patients with AEs, serious AEs, AEs of special interest (serious and non-serious) and AEs leading to discontinuation (serious and non-serious) will be provided
- A table presenting number and percentage of adverse events by severity (NCI CTCAE grade: mild, moderate, severe, life-threatening, death) will be provided
- The summary table will provide information about the relationship (not related, possibly related, related) of the AE to the treatment
- The number (%) of patients with at least one AE will be tabulated by system organ class (SOC), high level term (HLT), and preferred term (PT)
- A frequency analyses of AEs, SAEs and AESIs will be performed in the context of categorized age, cigarette smoking and comorbidities
- A listing of adverse events related to unacceptable toxicities will be produced
- Left ventricular ejection fraction will be presented as median, lower and upper quartile, minimum and maximum at baseline as well as during subsequent visits
- Number and percentage of patients that experienced at least 10 percentage points drop of LVEF from the baseline or reduction of LVEF below 50% will be tabulated
- Cardiotoxicity, at least possibly related to the therapies used, defined as:
    - An asymptomatic decline in LVEF requiring treatment or leading to discontinuation of study treatment
    - The occurrence of congestive heart failure
- Cardiovascular AEs (an asymptomatic decline in LVEF requiring treatment or leading to discontinuation of study treatment or occurrence of congestive heart failure), at least possibly related to the therapy, will be analyzed in the context of previously reported comorbidities

This will be summarized as overall number and percentage of patients experiencing such cardiotoxicity as well as tabulated by treatment

- A summary table presenting number and frequency of dose interruptions, discontinuations and reintroductions
- A summary table presenting data on completion/realization of anti-HER2 treatment plan as well as number of cycles of anti-HER2 therapy.

8.7.3 Effectiveness Analyses

The effectiveness analyses will be performed using data from all patients included in the study:

- The quantitative epidemiological characteristics such as age, body mass index, and cigarette smoking will be summarized
- Patient performance as expressed by WHO/ECOG status will be summarized as number and percentage of patients with each value of ECOG
- The number (%) of patients will be calculated for each comorbidity (hypertension, diabetes, coronary artery disease, heart failure, thromboembolic disease, medically relevant arrhythmias, thyroid disease, chronic kidney disease, osteoporosis, dementia, coexisting cancer, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, liver disease, and depression) and other
- A statistical summary relative to all patients will be provided for the progesterone receptor (PgR) status and estrogen receptor (ER) status as well as results of histological diagnostics to establish HER2 status (either immunohistochemistry - IHC or in-situ hybridization - ISH) from data collected at Screening before the start of anti-HER2 therapy
- The tabulation of the number (%) of patients at Screening will be computed for all included patients by previous anticancer therapy (surgery, systemic therapy, or radiotherapy) administered before anti-HER2 therapy
- Total dosage of anthracyclines will be summarized as mean and standard deviation as well as median, lower and higher quartile, minimum and maximum
- At Screening the number and percentage of disqualified patients for anti-HER2 therapy will be calculated for all included patients. The frequency (number and percentage) of patients will be also computed at Screening by reason of disqualification to anti-HER2 therapy for all included patients.

Additional effectiveness analyzes will be performed using data from subgroup receiving anti-HER2 therapy (Herceptin SC or Herceptin IV with or without Perjeta IV) and presented as tabulation by treatment as number and percentage of:

- During each period - type of surgery, radiotherapy, hormonal therapy, or chemotherapy concurrent with anti-HER2 treatment

- The lack of a therapy completion, caused by insufficient number of drug administrations (for early or locally advanced stage cancer) or socioeconomic issues (for all patients undergoing anti-HER2 treatment) will be analyzed by period (Observation and Follow-Up) and treatment
- Concomitant medication will be analyzed separately for all patients (data collected during screening visit) and for a subgroup (patients receiving anti-HER2 medications). Each concomitant medication will be coded with appropriate Anatomical-Therapeutic-Chemical (ATC) code. The number and percentage of patients receiving each medicalization will be provided. Additionally, tabulations will be provided for five levels of ATC classification.

Corresponding confidence intervals will be provided for all statistical estimates.

8.7.4 Other Analyses

Statistical analyses will be performed using data from subgroup receiving anti-HER2 therapy (Herceptin SC or Herceptin IV with or without Perjeta IV). Statistical summaries will be broken down by treatment:

- Disease recurrence (local, regional or distant), a contralateral invasive breast cancer, a second primary cancer, or death from any cause for eBC patients or LABC patients qualified for local regional treatment – surgery or radical radiotherapy will be summarized (as number and percentage).
- First disease progression or death from any reason for mBC patients will be similarly tabulated.

8.7.5 Final Analyses and Timing of Analyses

Final analyses will be performed after last patient in the subgroup completes final visit or terminates participation early and database locking procedure will be complete.

8.8 QUALITY CONTROL

8.8.1 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 EC notification and governmental approval. 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.

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

8.8.2 Site Audits and Inspections

Site visits will be conducted by the MAH or an authorized representative for audit of study data, patients' medical records, and CRFs.
The physician will also permit national and local health authorities to inspect facilities and records relevant to this study.

8.8.3 Retention of Records

Records and documents pertaining to the conduct of this study, including CRFs and 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 marketing authorization holder. Written notification should be provided to the marketing authorization holder prior to transferring any records to another party or moving them to another location.
All supporting functional parties will comply with the MAH procedures regarding archiving and record management.

8.8.4 Administrative Structure

Roche Poland is acting as MAH representative in this study. All MAH obligations indicated in the Protocol will be conducted by MAH representative. [redacted] Company is responsible for Data Management and Statistics. [redacted] is responsible for monitoring activities. Medical Manager or National Coordinator will be in charge of any protocol questions that arise during the course of the study.

8.9 LIMITATIONS OF THE RESEARCH METHOD

Taking into account study design and its goals the following limitations apply:

- Small number of elderly patients are diagnosed with HER2 positive breast cancer which is exacerbated by underdiagnosis (e.g. ER/PgR and HER2 receptor status)
- Number of HER2 positive elderly patients qualified for anti-HER2 therapy is further reduced due to contraindications
- Lack of consent of the patients to take part in the observational study
- The difficulties in contracts approval with the hospitals due to unclear NHF attitude toward conducting non-interventional observation during Herceptin treatment within a drug program
- Launch of Herceptin biosimilars will influence the usage of original anti-HER2 therapy.

To address these limitations following steps will be undertaken:

- Sites selected to participate in the study have considerable experience in clinical and observational studies as well as high recruitment potential and employ adequate diagnostic methods

- As a consequence of site selection, participating physicians are educated in NHF Drug Program (with particular emphasis on program's inclusion criteria)
- Due to physicians' experience risk of patients not giving consent is estimated as low
- Chosen sites are aware of differences between original and biosimilar drugs and MAH representatives will keep physicians abreast of information regarding biosimilars; nevertheless this issue has high probability of occurring and possible impact on the progress of this study.

9. PROTECTION OF HUMAN SUBJECTS

9.1 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.

9.1.1 Discontinuation from Treatment with Studied Medicinal Product

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.
The early termination visit should be completed for patients who discontinue treatment with Herceptin SC or Herceptin IV with or without Perjeta IV earlier than planned according to NHF Drug Program "Treatment of the Breast Cancer" and labeling (SPC). The primary reason for early treatment discontinuation should be documented on the appropriate CRF page. Every effort should be made to obtain information on patients who discontinue treatment.

9.1.2 Withdrawal from Study

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

9.1.3 Study and Site Discontinuation

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

- Patient enrollment is unsatisfactory

The MAH will notify the physician, the EC and health authorities if the study is placed on hold, or if the marketing authorization holder decides to discontinue the study.
The MAH has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the Guidelines for Good Pharmacoepidemiological Practices (GPP) or any other pertinent local law or guideline.

9.2 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 in Poland.
The study will comply with national and European Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorization safety studies.
Considering the non-interventional NI-PASS design of the study, submission for approval to the regulatory authority will be performed. The relevant EC will be notified about this NI-PASS.

9.3 INFORMED CONSENT

The Marketing Authorization Holder's sample Informed Consent Form will be provided to each site. If applicable, it will be provided in a certified translation in the local language. The Marketing Authorization Holder must review and approve any proposed deviations from the Marketing Authorization Holder's sample Informed Consent Forms proposed by the site (collectively, the "Consent Forms") before implementation if required.
The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative prior to documenting any of his or her data in the CRF. The case history or clinical records for each patient shall document the informed consent process and the fact that written informed consent was obtained prior to the first documentation of this patient's data in the CRF.
By signing the form, the patient confirms that he/she has been informed about the study and agrees to an anonymous 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 patient 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 patient 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 patient is entitled or is presently receiving.
A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by Site Operations Representative at any time.

9.4 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 for notification to the EC by the Country/Site Operations Representative in consultation with the Scientific Responsible and reviewed by the EC before the study is initiated. In addition, any patient recruitment materials must be approved by the EC if applicable according to the local legislation. In addition to the requirements for collecting and reporting all AEs, adverse events of

special interest (AESI), and SAEs to the marketing authorization holder, physicians must comply with requirements for AE reporting to the local health authority and EC if applicable according to the local legislation.

9.5 CONFIDENTIALITY

The Marketing Authorization Holder maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in datasets that are transmitted to any marketing authorization holder location.

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.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, marketing authorization holder monitors, representatives, and collaborators, and the EC for each study site, as appropriate.

By signing the protocol, the participating physician commits to complying with all related applicable local laws and regulations, as well as any applicable EU regulations, such as the EU Data Privacy Act.

9.6 FINANCIAL DISCLOSURE

Physicians will provide the marketing authorization holder with sufficient, accurate financial information in accordance with local regulations to allow the marketing authorization holder to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Physicians are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (last data collection).

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

The following flow chart represents the general principles of safety reporting flow in the study (direct transfer).

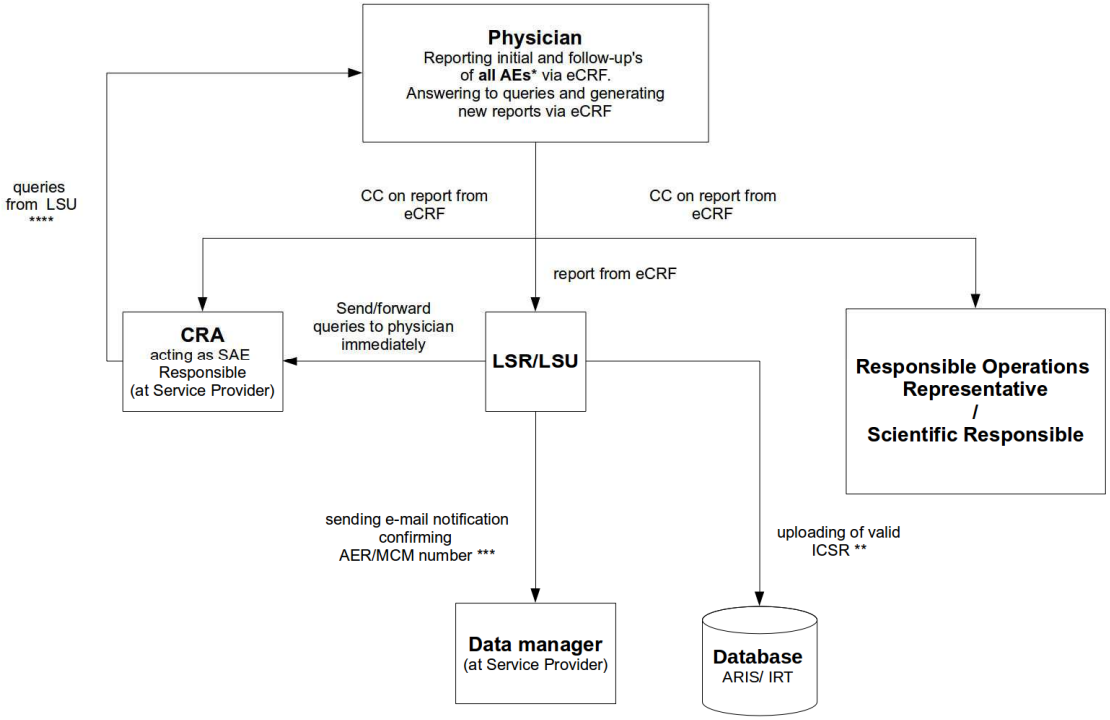

Figure 2. Safety flow in NIS HEROLD

All AEs must be entered in eCRF.

***** All AEs including:

- serious AEs, AEs of special interest (being reported in eCRF and via eCRF to LSR/LSU within 24h of learning the event),
- non-serious AEs and reports of Special Situations as indicated in Protocol (being reported in eCRF and via eCRF to LSR/LSU within 30 calendar days of learning the event),
- pregnancies - NA (population is consist of female patients over 70 years old)

****** Reports are directly transmitted from eCRF to LSR/LSU with all 4 valid elements present.

Valid elements are: physician's name, product, event term, patient's identification (e.g., patient's number, year of birth, gender).

******* Notification is being sent after ICSR is processed locally by LSU at ARIS/IRT (at the same day). Timelines for LSU to process reports are:

- one business day for SAE, AESI
- five calendar days for non-serious AE, Special Situations

**** Queries are being sent/ forwarded to physician within one business day from the date of receipt.

When EDC system is temporarily unavailable, paper version of ICSR is used (indirect transfer) – process, role and responsibilities are described in Safety Management Plan that was mutually agreed between Roche and Service Provider.

10.1 SAFETY REPORTING REQUIREMENTS FOR STUDIED MEDICINAL PRODUCTS

10.1.1 Safety Parameters and Definitions

The reporting requirements in this section apply to all studied medicinal products (observational products of interest, as specifically stated in the study objectives). For safety reporting requirements for non-studied medicinal products, see Section 10.2.
Safety assessments will consist of monitoring and recording SAEs and non-serious AEs (including AEs of special interest), performing safety laboratory assessments, measuring vital signs and conducting other tests that are deemed critical to the safety evaluation of the study as per standard medical practice.

10.1.1.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Appendix 3
- 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
- Herceptin and Perjeta may be associated with the risk of cardiac dysfunction. Risk factors for HER2 agents-associated cardiotoxicity include age and declining LVEF while on Herceptin and Perjeta treatment. According to the labeling (SPC of Herceptin and Perjeta) all patients during therapy with Herceptin SC or Herceptin IV with or without Perjeta IV must have completed an assessment of LVEF with a minimal baseline value of 50% as determined by either echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA)
-

- According to Herceptin and Perjeta labeling (SPC) administration of monoclonal antibodies like pertuzumab and trastuzumab may cause infusion-associated symptoms such as: fever, chills, hypotension, skin rashes, allergic reactions, headache, nausea, vomiting, dyspnea, wheezing, bronchospasm, asthma, tachycardia, reduced oxygen saturation, anaphylaxis, respiratory distress, urticaria, angioedema. Infusion – associated reactions typically occur during or shortly after infusions of monoclonal antibodies but may also show a delayed onset. In general, antibody infusion-associated AEs/SAEs are more frequent and severe during the first infusion, and decrease in number and severity over time and the majority of AEs fully resolve
- Certain pulmonary events, such as dyspnea, bronchospasm or asthma can occur as part of an infusion reaction. These are common with the first infusion, and their occurrence decreases with subsequent infusions.

10.1.1.2 Assessment of Serious Adverse Events (Immediately Reportable to the Marketing Authorization Holder), Non-serious Adverse Events of Special Interest (AESI) 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 3)
- 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 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)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study medicine*

* Due to an age of the population in this study (≥70 years old postmenopausal women), this point is not applicable.

The terms “severe” and “serious” are <u>not</u> 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 3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the CRF (for detailed instructions, see Appendix 3).

Non-Serious Adverse Events of Special Interest

AEs of special interest for this study include the following:

- Cases of potential drug-induced liver injury, i.e. a treatment-emergent ALT or AST > 3 x baseline value in combination with either a total bilirubin > 2 x ULN (of which 35% is direct bilirubin) or clinical jaundice., as defined by Hy's law (see Appendix 3)
- 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.
- Congestive heart failure (CHF)
- An asymptomatic decline in LVEF requiring treatment or leading to discontinuation of study treatment.

Non-Serious Adverse Events other than Adverse Events of Special Interest

All non-serious AEs (in addition to AEs of special interest) must be collected for this study as per protocol section Safety Data Collection (8.4.4).

Exemption of Specific Adverse Events from Collection

Events that are consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on both clinical and laboratory findings. In rare cases the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression using objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

Clinical symptoms of progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of disease, or does not fit the expected pattern of progression of disease. If there is any uncertainty about an adverse event being due only to breast cancer progression, it should be reported as an AE or SAE, as applicable.

Following the above rationale, the following Adverse Events will not be collected for this study:

- disease progression resulting from natural course of disease and not related with a use of Roche drug.

Although these adverse events are not being actively solicited, the physician/consumers are reminded of the possibility 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.

10.1.2 Methods and Timing for Capturing and Assessing Safety Parameters

The physician is responsible for ensuring that all AEs collected as per protocol (see Section 10.1.1.1 for definition) are recorded in the AE section of the CRF and reported to the marketing authorization holder in accordance with instructions provided in this section and in Section 10.1.3.

For each AE recorded in the AE section of the CRF, the physician will make an assessment of seriousness (see Section 10.1.1.2), severity (see Appendix 3), and causality (see Appendix 3).

10.1.2.1 Adverse Event Reporting Period

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

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

10.1.2.2 Procedures for Recording Adverse Events

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

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

See Appendix 3 for further specific instruction regarding:

- Infusion-Related or Injection-related 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 10.3). All deaths that occur during the protocol-specified AE reporting period, regardless of relationship to study medicine, must be recorded in the AE section of the CRF and immediately reported to the marketing authorization holder
- Pre-existing Medical Conditions
- Lack of Therapeutic Efficacy
- Hospitalization or Prolonged Hospitalization
- Overdoses, Misuses, Abuses, Off-Label Use, Occupational Exposure, or Medication Error
- Drug Interactions
- Quality Defects and Falsified Medicinal Products

10.1.3 Reporting Requirements from Physician to Marketing Authorization Holder

10.1.3.1 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
- Non-serious AEs of special interest

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 and non-serious AEs of special interest, 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 10.1.3.3.

10.1.3.2 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 case that the EDC system is temporarily unavailable, please refer to Section 10.1.3.3.

10.1.3.3 If EDC System is Temporarily Unavailable

In the case that the EDC system is temporarily unavailable, a completed paper reporting form and fax coversheet should be faxed/scanned to Roche Drug Safety or its designee immediately (i.e., no more than 24 hours after learning of the event) or within 30 days for non-serious AEs if not AEs of special interest, 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.

10.1.3.4 Reporting Requirements for Pregnancies/Breastfeeding

This section is not applicable due to the age of the population in this study (≥70 year old postmenopausal women).

10.1.3.5 Reporting Requirements for Adverse Events originating from Patient Reported Outcomes

This section is not applicable due to study design not anticipating any PRO data and questionnaires.

10.1.4 Follow-Up of Patients after Adverse Events

10.1.4.1 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.

10.1.4.2 Marketing Authorization Holder Follow-Up

For all AEs, the marketing authorization holder or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

10.2 SAFETY REPORTING REQUIREMENTS FOR NON-STUDIED MEDICINAL PRODUCTS

Although adverse event information is not being actively solicited for non-studied medicinal products, the physician/patients 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.
In addition, the following should also be reported if occurring during exposure to a marketed medicinal product, even in the absence of adverse events:

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

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

11. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the MAH is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The MAH 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 marketing authorization holder prior to submission for publication or presentation. This allows the MAH 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, the MAH will generally support publication of multicenter studies 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 MAH personnel exceeded that of conventional monitoring will be considered as a joint publication by the physician and the appropriate MAH 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 marketing authorization holder, except where agreed otherwise.

The results of safety and effectiveness as well as other analyses – if deemed feasible – are planned to be either presented during a scientific conference or published in a scientific journal within six months from the date of study report finalization.

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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 (as per Standard of Care)

Data Collection (available data will be collected; no additional diagnostic or monitoring procedures shall be applied to the patients outside of routine clinical practice)	Screening (the screening and the first observation visit can coincide)	Data Collected during Observational Period		Data Collected at Study Completion/ Early Termination Visit[2]	Data Collected during Follow-Up[3]
		First visit	Subsequent visits (every 3 weeks)[1]		
Informed consent [a]	x				
Epidemiological characteristics[4]:	x				
Diagnosis confirmation[5]	x				
Comorbidities[6]	x				
Concomitant medication	x	x	x	x	
ECOG performance status	x	x	x	x	x
Any anticancer treatment before anti-HER2 therapy started[7]	x				
Treatment with: Herceptin SC (600mg q3w), Herceptin IV (loading dose 8mg/kg and maintenance dose 6mg/kg or loading dose 4mg/kg and maintenance dose 2mg/kg) Perjeta IV (loading dose 840 mg and maintenance dose 420mg q3w)		x	x		
Chemotherapy or hormonal therapy concomitant to anti-HER2 therapy		x	x[13]		
LVEF (%)[9,15]		x	x	x	x[14]
Hematology[8,9]		x	x	x	
Creatinine[9] Alanine transaminase (ALAT) [9] Aspartate transaminase (ASAT) [9] Total bilirubin[8]		x	x	x	

Data Collection (available data will be collected; no additional diagnostic or monitoring procedures shall be applied to the patients outside of routine clinical practice)	Screening (the screening and the first observation visit can coincide)	Data Collected during Observational Period		Data Collected at Study Completion/ Early Termination Visit[2]	Data Collected during Follow-Up[3]
		First visit	Subsequent visits (every 3 weeks)[1]		
ALP[9] Sodium[9] Potassium[9] Calcium[9]		x	x	x	
USG /CT pelvis and abdomen[9]		x	x		
X-Ray /CT chest[9]		x	x		
Bone scintigraphy[9]		x	x		
ECG[9]		x	x	x	
Echo[9]		x	x	x	x[14]
Mammogram or breast and lymph node USG (or CT/MRI method selected based on possibility of evaluation of tumor size)[9]		x	x		
CT/MRI Brain[9]		x			
Qualification to anti-HER2 therapy[10]		x			
Disease status assessment[11]			x	x	x
Treatment plan completion[12]				x	
AEs/SAEs/AESI	x	x	x	x	x

[a] Written informed consent must be obtained before any data collection.

Data overview legend:

1)Visits during observational period will take place every three weeks after first visit, independently from the number of anti-HER2 drug administrations.

2)Study Completion/ Early Termination Visit may coincide with last administration of anti-HER2 medication unless patients are treated with Herceptin SC for mBC in which case study completion should take place 4-6 weeks after last dose of Herceptin and include ECG and echocardiography results.

3) Follow up visits will take place 3 and 9 months after conclusion of anti-HER2 therapy. In mBC patients receiving anti-HER2 medication for a period longer than one year follow-up visits will take place only if the total time of observation (that is treatment and follow-up) in the study is no longer than two years.

4) Epidemiological characteristics: Age, Race/Ethnicity, Height, Weight, Body mass index (BMI), Body Surface Area (BSA), Cigarette smoking.

5) Diagnosis confirmation: Histological confirmation of breast cancer diagnosis, TNM staging, Histologic grade, Hormone receptor status (ER, PgR), HER2 receptor overexpression confirmation by IHC or ISH.

6) Comorbidities: hypertension, diabetes, coronary artery disease, heart failure, thromboembolic disease, medically relevant arrhythmias, thyroid disease, chronic kidney disease, osteoporosis, dementia, coexisting cancer, COPD, rheumatoid arthritis, liver disease, depression, other.

7) Anticancer treatment before anti-HER2 therapy started includes: surgery, systemic therapy or radiotherapy.

8) Hematology includes: hemoglobin, hematocrit, platelet count, RBC, WBC, neutrophils.

9) Depending on rules and schedule specified in National Health Fund (NHF) - Drug Program “Treatment of Breast Cancer”.

10) Qualification to anti-HER2 therapy will collect data on inclusion of patients into one of the following arms of National Health Fund (NHF) - Drug Program “Treatment of Breast Cancer”:

- adjuvant therapy with trastuzumab IV
- adjuvant therapy with trastuzumab SC
- neoadjuvant therapy with trastuzumab SC
- trastuzumab IV therapy for mBC
- trastuzumab SC therapy for mBC
- trastuzumab + pertuzumab therapy for mBC.

For patients that do not qualify for drug program, information on reasons of disqualification will be collected.

11) Disease status assessment:

- disease recurrence (local, regional or distant), a contralateral invasive breast cancer, a second primary cancer, unacceptable toxicities or death from any cause for eBC patients or LABC patients qualified for local regional treatment – surgery or radical radiotherapy,
- first disease progression, unacceptable toxicities or death from any reason for mBC patients (whatever occurs first during treatment period in the study).

12) Treatment plan completion: - treatment plan will be assumed as completed when patient complete 18 cycles or one year of treatment (for eBC patients or LABC patients qualified for local regional treatment – surgery or radical radiotherapy) or when patient continue treatment until progression, death or end of the observation in the study (for mBC patients).

13) In patients that start participation in the study receiving neoadjuvant therapy with Herceptin SC information about surgical operations and radiotherapy as well as subsequent change of anti-HER2 treatment will be collected.

14) If clinically indicated

15) If decrease of LVEF is observed, physicians will be asked to assess cardiotoxicity and occurrence of congestive heart failure (based on CTCAE 4.0 criteria), and for CHF, in addition, assessment based on NYHA criteria

Appendix 3
Methods for Assessing and Recording Adverse Events

3.1 Assessment of Severity of Adverse Events
3.2 Assessment of Causality of Adverse Events
3.3 Procedures for Recording Adverse Events

Appendix 3.1 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 (v4.0), 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 10.1.3.1 for reporting instructions), per the definition of SAE in Section 10.1.1.2.

[d] Grade 4 and 5 events must be reported as SAEs (see Section 10.1.3.1 for reporting instructions), per the definition of SAE in Section 10.1.1.2.

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 3.3 Procedures for recording Adverse Events

Appendix 3.3.1 Infusion-Related or Injection-Related 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 injection-related reaction).

Appendix 3.3.2 Diagnosis versus Signs and Symptoms

For AEs, other than infusion-related or injection-related (see Section 3.3.1), a diagnosis (if known) should be recorded in the AE section of the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded in the AE section of the CRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

Appendix 3.3.3 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 3.3.4 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. 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 10.1.3.1 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 3.3.5 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 $\times$ 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 3.3.4 for details on recording persistent AEs).

Appendix 3.3.6 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 3.3.4 for details on recording persistent AEs).

Appendix 3.3.7 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)
- 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 3.3.5) and reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event) either as an SAE or a non-serious AE of special interest (see Section 10.1.3.1).

Appendix 3.3.8 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 10.1.2.1), regardless of relationship to study medicine, must be recorded in the AE section of the eCRF and immediately reported to the marketing authorization holder (see Section 10.1.3.1).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the AE section of the CRF. Generally, only one such event should be reported. The term **"sudden death"** should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the AE section of the CRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

Appendix 3.3.9 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 3.3.10 Lack of Therapeutic Efficacy

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as effectiveness assessment data only. In most cases, the expected pattern of progression will be based on Response Evaluation Criteria In Solid Tumors (RECIST). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. Data concerning disease progression will be collected in the CRF and will be provided with information whether it is caused by natural course of disease, not related with Roche studied medicines OR it is a disease progression related with Roche studied medicines. Disease progression related with Roche studied medicines will be reported as an AE.

If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE. This exception from reporting includes events of disease progression with a fatal outcome which are clearly attributable to disease progression.

Appendix 3.3.11 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 10.1.1.2), except as outlined below.

The following hospitalization scenarios are not considered to be SAEs:

Hospitalization for respite care

Hospitalization for a preexisting condition provided that all of the following criteria are met:

- The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
- The patient has not suffered an AE.

Hospitalization due solely to progression of the underlying cancer

Appendix 3.3.12 Overdoses, Misuses, Abuses, Off-Label Use, Occupational Exposure, or Medication Error

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

Reports with or without an AE should be forwarded to the marketing authorization holder as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event, see 10.1.3.1).

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 3.3.13 Quality Defects and Falsified Medicinal Products

Reports of suspected or confirmed falsified medicinal product or quality defect of a medicinal product, with or without an associated AE, should be forwarded to the marketing authorization holder as per non-serious timelines. If the associated AE fulfills

the seriousness criteria, the event should be reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event, see 10.1.3.1).

Appendix 3.3.14 Drug Interactions

Reports of suspected or confirmed drug interactions, including drug/drug, drug/food, drug/device and drug/alcohol, should be forwarded to the marketing authorization holder as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event, see 10.1.3.1).

Appendix 3.3.15 Safety data other than Adverse Events

Safety data other than AEs (see section 8.3 Variables) should be recorded in an appropriate section of the CRF and reviewed on an ongoing basis.