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STATISTICAL ANALYSIS PLAN

Protocol: MO28048

EUDRACT: 2011-005328-17

Treatment: TRASTUZUMAB SC (RO45-2317)

A PHASE III PROSPECTIVE, TWO-COHORT NON-RANDOMIZED, MULTI-CENTRE, MULTINATIONAL, OPEN LABEL STUDY TO ASSESS THE SAFETY OF ASSISTED- AND SELF-ADMINISTERED SUBCUTANEOUS TRASTUZUMAB AS THERAPY IN PATIENTS WITH OPERABLE HER2-POSITIVE EARLY BREAST CANCER [SafeHer Study]

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Approvals

The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan as final. Programming of the tables and listings based upon the specifications within this document can proceed.

Covance Approval

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Contents

Abbreviations

ADA	Anti-Drug Antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ARR	Administrative Related Reactions
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CHF	Congestive Heart Failure
CT	Computerized Tomography
CTC	Common Terminology Criteria
CXR	Chest X-ray
DCIS	Ductal carcinoma in situ
DFS	Disease Free Survival
EBC	Early Breast Cancer
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Co-operative Oncology Group
eCRF	Electronic Case Report Form
EU	European Union
FDG-PET	Fluorodeoxyglucose-positron Emission Tomography
HCP	Health Care Professional
HER2	Human Epidermal Growth Factor Receptor 2
IHC	Immunohistochemistry
IHS	In Situ Hybridization
ISR	Injection Site Reaction
ITT	Intent-to-Treat
KM	Kaplan-Meier
LLOQ	Lower Limit of Quantification
LVEF	Left Ventricular Ejection Fraction
MCU	Medical Care Unit
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MUGA	Multiple Gated acquisition
NCI CTC-AE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
OS	Overall Survival
PP	Per Protocol
PK	Pharmacokinetic
rHuPH20	Recombinant Human Hyaluronidase
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SC	Subcutanious
SID	Single Injection Device
SID OUQ	Single-use Injection Device (SID) Observer Usability Questionnaire
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
SPM	Second Primary Malignancies
WBC	White Blood Count
WHO	World Health Organisation

1 Introduction

This document presents the statistical analysis plan (SAP) for F.Hoffmann-La Roche Ltd, Protocol No. MO28048: A phase III prospective, two-cohort non-randomized, multi-centre, multinational, open label study to assess the safety of assisted and self-administered subcutaneous trastuzumab as therapy in patients with operable HER2-positive early breast cancer.

This analysis plan is based on the final protocol Version 4.0, dated 11Nov2016. It provides a description of three planned interim analyses, the primary analysis and analysis at the end of survival follow-up (final analysis). All data available at the cut-off point for interim reporting for each cohort (Cohort A: assisted administration; Cohort B: self administration) will be included in the statistical analyses and summaries.

Medical Care Utilization (MCU, e.g. Time and Motion) and/or pharmacoeconomic sub-studies will be conducted in some countries and sites. Details of the sub-studies will be described in separate protocols and will not form part of this SAP.

2 Study Objectives

The primary objective of the study is to assess the overall safety and tolerability of trastuzumab SC in HER2-positive early breast cancer (EBC) patients with assisted administration using a conventional syringe and needle (vial formulation) or with assisted- and self-administration using a single use injection device (SID) in selected patients.

Secondary objectives include the evaluation of the following parameters:

- Disease Free Survival (DFS)
- Overall Survival (OS)
- Patient satisfaction with trastuzumab SC administration using the SID (patients in Cohort B who went on to self-administration of the study drug).

Exploratory objective of this study are:

- To assess the immunogenicity of trastuzumab and recombinant human hyaluronidase (rHuPH20) in a subset of patients receiving trastuzumab SC using the SID (Cohort B) at selected sites.
- To examine and characterize tolerability of the trastuzumab SC over a 6 hour time period after the start of the first administration and over a 2 hour time period after the start of subsequent trastuzumab administrations [only in patients using the SID (Cohort B)]
- Monitoring of SID usability in a subgroup of 48 patients in Cohort B.

In addition, in some countries and sites, Medical Care Utilization (MCU, e.g. Time and Motion) and/or pharmacoeconomic sub-studies will be conducted. Details of the sub-studies will be described in separate protocols and will not form part of this SAP.

2.1 Primary endpoints - Safety

Safety is the primary objective in this study and analyses will include:

- All adverse events (AEs)
- Injection Site Reactions (ISRs)
- Administration Related Reactions (ARRs)
- Grade ≥3 AEs
- Serious adverse events (SAEs)
- AEs leading to premature discontinuation of study treatment
- AEs causing interruption of trastuzumab SC
- Cardiac AEs
- Congestive Heart Failure (CHF) related SAEs
- Premature withdrawals from study and study medication

- Exposure to treatment
- Laboratory parameters
- Left Ventricular Ejection Fraction (LVEF)
- Vital signs
- Electrocardiogram (ECG)
- Weight
- Eastern Co-operative Oncology Group (ECOG) performance status

The primary analysis and the final analysis of safety endpoints will be performed for the safety population.

2.2 Secondary endpoints - Efficacy

Secondary efficacy endpoints include

- Disease Free Survival (DFS)
- Overall Survival (OS)
- Patients' satisfaction with trastuzumab using SID Satisfaction Questionnaire

DFS and OS, as further described in Section 4.4, will be assessed in both cohorts. The analysis of the above efficacy endpoints will be performed for the Intent-to-Treat (ITT) and Per-Protocol (PP) populations.

Patient satisfaction with the SID will be assessed in patients in Cohort B who went on to self-administration of the study drug only for ITT population.

2.3 Exploratory endpoints

Exploratory endpoints are:

- Assessment of the immunogenicity of trastuzumab and rHuPH20
- Examination and characterization of the tolerability of trastuzumab SC over a 6-hour time period after the start of the first administration and over a 2-hour time period after the start of subsequent trastuzumab administrations (only in patients using the SID)
- Exploratory analyses on the usability of the SID summarizing the parameters collected via SID monitoring questionnaire will be provided to the first 48 patients enrolled in Cohort B who were judged able, and were willing to self-administer remaining doses from the SID under direct supervision of the HCP.

The analysis of the above exploratory endpoint will be performed for the Safety population (Cohort B).

Information on the usability of the SID will be collected via SID Observer Usability Questionnaire which will be provided to the first patients enrolled in Cohort B who were judged able, and were willing to self-administer remaining doses from the SID under direct observation of the HCP to collect 816 dosing events.

3 Study Design

3.1 Discussion of Study Design

This is a Phase III, prospective, two-cohort, non-randomized, multi-centre, multinational, open label study in approximately 2,500 patients with HER2-positive EBC who are eligible for anti-HER2 therapy. A planned total of approximately 2,500 evaluable patients will be enrolled into the study. The trial will be conducted at approximately 520 centres in approximately 60 countries.

Eligible patients will be allocated to Cohort A or B at the investigators' discretion depending upon availability of the Cohorts for recruitment:

- Cohort A (approximately 1,800 patients): trastuzumab SC 600mg, assisted administration into the thigh over a period of approximately 5 minutes, using conventional handheld syringes with hypodermic needles;
- Cohort B (approximately 700 patients): trastuzumab SC at a fixed dose of 600mg presented in a SID. The first administration will be assisted (performed by a HCP). If well tolerated and if the patient is willing and judged competent by the HCP to do so subsequent administrations may be self-administered into the thigh over a period of approximately 5 minutes using the SID for a total of up to 18 cycles (3-weekly).

Patients will remain at the study site to be observed for a period of 6 hours after their first trastuzumab administration and 2 hours thereafter for subsequent trastuzumab administrations. Patients may be required to remain onsite for an extended period of time if considered clinically necessary by the Investigator. Patients in both cohorts will receive a fixed dose of 600 mg trastuzumab SC 3-weekly throughout the study, administered 3-weekly for a total of 18 cycles (3-weekly), unless disease recurrence, unacceptable toxicity or study withdrawal necessitates earlier treatment cessation.

The target population is patients with newly diagnosed HER2-positive (immunohistochemistry [IHC] 3+ or HER2-positive in situ hybridization [ISH]) clinical stage I (T1, N0, M0) to IIIC (any T, N3, M0) EBC who are eligible for treatment with trastuzumab SC. Patients treated without neoadjuvant or adjuvant chemotherapy, such as patients with low risk node negative tumours ≤ 1.0 cm, elderly patients (>65 years of age) or patients who refuse chemotherapy, will also be eligible to participate in the study, but their enrolment will be limited to approximately 10% of the total study population.

All potential study patients must provide signed written informed consent (approved by the relevant independent Ethics Committee [EC]) before undergoing any study-specific procedure. Results of the screening assessments must be available and patients must meet all eligibility criteria prior to enrolment into the study.

Patients will undergo a Safety Follow-up visit 4 weeks after their last dose of study treatment, with further follow-up according to the American Society of Clinical Oncology (ASCO) 2006 Guideline for Breast Cancer Follow-up[1] in the adjuvant setting (Khatcheressian et al. 2006) or investigator's routine practice. All patients will be followed-up for cancer recurrence and survival until study end at yearly or at a higher frequency based on the sites standard of care. The duration of follow-up will be at least 5 years after their last study treatment, unless one of the following occurs first: withdrawal of consent, loss to follow up or death. After disease

recurrence patients will be managed as per local practice and followed for survival only. Patients will be assessed for safety and efficacy, as detailed in Table 1, Study Schedule (Section 3.3). In addition select sites will collect samples for trastuzumab drug concentrations and immunogenicity testing to determine whether antibodies against trastuzumab or rHuPH20 develop in patients receiving trastuzumab SC using the SID. Since the evaluation of anti-trastuzumab assay results requires corresponding serum trastuzumab concentrations, the anti-trastuzumab analyses will be coupled with PK assessments.

As per the SafeHER Study Protocol, Cohort B patients will remain on site to be observed for 6 hours after the start of their first Trastuzumab SC administration and for 2 hours after the start of each subsequent Trastuzumab SC administration. Patients may be required to remain on site for an extended period of time if considered clinically necessary by the investigator (e.g., because of emergence of AEs). During this time, detailed information of AEs and associated treatment will be recorded and analyzed relative to the last preceding administration of trastuzumab. Therefore, in Cohort B, in addition to onset and resolution dates and times of AEs, detailed information about pre-medications prior to trastuzumab administration will be collected.

Patients in either study arm who cannot tolerate trastuzumab SC will come off study and be further treated at the investigator's discretion.

Three interim safety analyses will be reported when approximately 500, 1,000, and 2,500 patients have received at least one trastuzumab SC injection. The primary analysis of safety endpoints and a preliminary analysis of efficacy (DFS, OS) will take place when all patients have received 18 cycles of trastuzumab SC and have completed the post-treatment Safety Follow-up assessments. The final analysis of DFS and OS and updated summaries for safety parameters will be performed when the last patient has been followed up for at least 5 years after her/his last study treatment, or earlier, if one of the following is documented for all treated patients: withdrawal of consent, loss to follow up or death. This is expected to take place approximately 8 years after the enrolment of the first patient, based on an expected 18-month recruitment period per cohort, 12 months of study treatment and 5 years of follow- up after the last study treatment.

3.2 Study Treatment

Patients in both cohorts will receive a fixed dose of 600 mg trastuzumab SC throughout the study, administered 3-weekly for a total of 18 cycles, unless disease recurrence, unacceptable toxicity or patient withdrawal necessitates earlier treatment cessation. The trastuzumab SC is a fixed dose of 600 mg of trastuzumab formulated with rHuPH20, 2,000 U/ml (to give a fixed dose of 10,000 U).

Eligible patients will be allocated to Cohort A or B at the investigators' discretion depending upon availability of the Cohorts for recruitment:

- **Cohort A**: Trastuzumab SC 600mg will be injected subcutaneously by an HCP, into the thigh over a period of approximately 5 minutes, using a handheld syringe with a gauge 25 or 27 hypodermic needle.
- **Cohort B**: Trastuzumab SC 600mg will be injected subcutaneously into the thigh, over a period of approximately 5 minutes using the SID. The first injection will be administered by a trained HCP, and then following administrations may be self-

administered if the patient is judged by the HCP to be capable and willing to self-administer the dose from the SID.

Trastuzumab SC treatment may be initiated

- after completion of neoadjuvant or adjuvant chemotherapy (sequentially)
- in combination with neoadjuvant or adjuvant paclitaxel or docetaxel chemotherapy (concurrently)
- or without adjuvant chemotherapy
- or in combination with neoadjuvant chemotherapy followed by trastuzumab therapy for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter.

For patients receiving trastuzumab SC with adjuvant chemotherapy, trastuzumab SC must be administered first, followed by the administration of chemotherapy. Hormonal therapy and radiotherapy (if applicable) may be given concomitantly with trastuzumab SC, as per local guidelines.

Administration of trastuzumab SC may be delayed to assess or treat adverse events.

If the patient misses a dose of trastuzumab SC, then the usual fixed dose (600mg) should be given as soon as possible, with subsequent doses given every 3 weeks. No dose adjustment is needed in case of delayed administration of trastuzumab SC as a fixed (600mg) dose of trastuzumab is given for all SC cycles in this study.

Dose reductions are not permitted for toxicity. Patients who experience injection-related symptoms may be pre-medicated with paracetamol and antihistamines for subsequent infusions/injections.

In the event of a SID failure which results in incomplete administration (injection of a portion of the full dose) to the patient, the missed portion of the trastuzumab SC dose may be manually administered from a vial. An instruction leaflet will be provided that will explain how to assess the amount needed to inject from a vial in the event of a SID failure. Subsequent doses should be administered using the SID. Device failures must also be reported to the Sponsor as a Medical Device Complaint (see Protocol v4 Section 5.4.4). The device must then be returned via courier to Roche for assessment. In case of multiple (>1) device failures during the treatment of a patient, the patient will revert to manual SC administrations of trastuzumab (using a conventional hand-held SC syringe) for all remaining cycles, in order to complete 18 cycles in total as part of the study.

3.3 Study Schedule

Unscheduled visit assessments other than the scheduled visits specified in the table below may be performed.

Table 3.3 Schedule of Assessments

Study week (TreatmentCycle #)	Screening	Study treatment 3-weekly (18cycles)				Safety Follow-up visit [q] [r]	Follow-up visits [k] [r]
	day -28 to 1	Week 1 to 22 Cycles 1 to 8[r]	Week 25 Cycle 9[r]	Week 28 to 49 Cycles 10 to 17[r]	Week 52 Cycle 18[r]	4 weeks after last study treatment	(minimum 5 years after last study treatment)
Explain study and obtain signed Informed Consent [a]	x						
Demographic profile [b] and medical history	x						
HER2 Determination	x						
Review inclusion/exclusion criteria	x						
Physical Exam [c]	x	Approximately 3-monthly (every 4 cycles) [p]				x	x [k]
Weight, height [d]	x		x [d]				x [d]
Vital Signs [e]	x	Approximately 3-monthly (every 4 cycles) [e]				x	
ECOG performance status	x	Approximately 3-monthly (every 4 cycles) [p]				x	
Cardiac monitoring - 12-lead ECG -LVEF[f] -Signs/symptoms	 x x [f] x	Approximately 3-monthly (every 4 cycles) [p]				x[s]	Cardiac assessments at 6, 12 and 24 months, and 3, 4 and 5 years following treatment cessation
Pregnancy test[g]	x	as clinically indicated					
Blood samples for immunogenicity and PK testing [h]	x[h]		x[h]				x (6-month after last

Study week (TreatmentCycle #)	Screening	Study treatment 3-weekly (18cycles)				Safety Follow-up visit [q] [r]	Follow-up visits [k] [r]
	day -28 to 1	Week 1 to 22 Cycles 1 to 8[r]	Week 25 Cycle 9[r]	Week 28 to 49 Cycles 10 to 17[r]	Week 52 Cycle 18[r]	4 weeks after last study treatment	(minimum 5 years after last study treatment)
							study treatment)
Haematology and biochemistry [i]	x[t]		x		x	x	
Imaging scan to exclude residual/recurrent disease [j]	x						
Routine Breast-cancer follow-up [k]		Assessments as per institutional practice or ASCO adjuvant follow-up guidelines 2006 to be reported 6-monthly [k]					
AEs and SAEs [l]	x	x	x	x	x	x	x
Concomitant medication [m]	x	x	x	x	x	x	x [m]
Trastuzumab SC [n]		x	x	x	x		
Exploratory Observation Time [v]		x	x	x	x		
SID Observer Usability Questionnaire [w]		x	x	x	x		
Treatment compliance		x	x	x	x		
SID Satisfaction Questionnaire [o]		After Cycle 4 [o]				x	
Survival		x [u]	x	x	x	x	x (at 12, 24 months and at 3, 4 and 5 years after last treatment)

First dose of study drug = study cycle 1, Day 1

Notes

[a] Written Informed Consent must be obtained before any study-specific assessments or procedures are performed.

[b] Demographic data include date of birth, gender, and self-reported ethnic origin.

[c] General physical exam may include neurological exam, as clinically indicated.

[d] Weight is measured for all patients at screening. For patients in Cohort B, weight is also measured on the day of immunogenicity testing. Height is only measured at screening.

[e] Vital signs include blood pressure and heart rate measurement at screening and at the Safety Follow-up visit, as well as pre- and immediately post-trastuzumab SC administration at cycles 1, 5, 9, 13, and 18.

[f] LVEF has to be assessed within 14 days prior to the first study treatment for prior anthracycline use or 28 days prior to the first study treatment for TCH and anthracycline free regimens, and 3-monthly thereafter by ECHO, MUGA, or MRI. The same imaging technique needs to be used per patient throughout the study. A further LVEF assessment will be performed if patients are symptomatic at an LVEF between 45-49% and a drop $\geq$ 10% as clinically indicated, but within 3 weeks. LVEF at the safety follow-up visit (4 weeks after the end of treatment) is not mandatory but will be performed if clinically indicated.

[g] Applicable to women of childbearing potential; a serum pregnancy test needs to be completed within 7 days prior to the first dose of study treatment or within 14 days with a confirmatory urine pregnancy test within 7 days prior to the first study treatment. Subsequent pregnancy testing should be completed as clinically indicated for the duration of study treatment and until at least 7 months after the last dose of study treatment. Any positive urine pregnancy test needs to be confirmed by serum pregnancy test.

[h] Subset of Cohort B, selected sites only: Blood samples (4 ml for PK and anti-trastuzumab analysis and 2 ml for rHuPH20 antibody analysis) should be taken at baseline (after eligibility is confirmed, i.e. just before the first study treatment), pre-Cycle 9 dose and 6 months after the last dose of study treatment.

[i] Haematology: haemoglobin, WBC and differential, absolute neutrophil count (ANC), platelet count. Biochemistry: creatinine, urea (BUN), SGPT (ALT), SGOT (AST), total bilirubin, alkaline phosphatase, albumin, sodium, potassium and calcium. Additional haematology and biochemistry tests may be performed as per institutional practice, but these data will not be collected. On day 1 of Cycles 9 (week 25) and 18 (week 52), samples will be taken pre-dose and the results will be reviewed prior to dosing.

[j] Screening radiologic examinations to exclude metastatic disease should include a bilateral mammogram or breast MRI, and chest X-ray (CXR). These imaging tests do not need to be repeated if completed within 6 months prior to the first study treatment. In addition, bone scan, liver imaging, and brain CT scan should be performed if clinically indicated.

[k] American Society of Clinical Oncology (ASCO) 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting (Khatcheressian et al. 2006). In brief:

History/physical examination - every 3 to 6 months for the first 3 years after primary therapy; every 6 to 12 months for years 4 and 5; then annually.

Mammography - first post-treatment mammogram 1 year after the initial mammogram that leads to diagnosis, but no earlier than 6 months after definitive radiation therapy. Subsequent mammograms should be obtained as indicated for surveillance of abnormalities.

Pelvic examination - regular gynecologic follow-up is recommended for all women. Patients who receive tamoxifen should be advised to report any vaginal bleeding to their physicians.

The following are not recommended for routine surveillance: Routine blood tests (full blood counts and liver function tests), imaging studies (chest x-ray, bone scans, liver ultrasound, CT scans, FDG-PET scans, and breast MRI), tumour marker assessments (CA 15-3, CA 27.29, and CEA).

[l] After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected. All treatment-emergent AEs occurring until 4 weeks after the last administration of trastuzumab SC will be recorded in the eCRF, irrespective of the type of event and drug-event relationship. From 4 weeks after the last study drug administration until the end of the follow-up period, related AEs, related/unrelated SAEs and cardiac AEs should be reported.

[m] All concomitant medication will be recorded between the Screening and the Safety Follow-up visits. Thereafter, only breast cancer treatments (e.g., endocrine therapy) anti-cancer treatments given to treat a recurrence, and medications related to the treatment of SAEs will be recorded.

[n] Trastuzumab SC is administered subcutaneously in the upper thigh at a fixed dose of 600 mg, 3-weekly for a total of 18 cycles.

[o] After the 4th cycle and at their final study visit (at least 1 day after the last trastuzumab SC injection), patients in Cohort B, who have successfully completed a minimum of 2 self-administrations of the study drug, will be asked to assess their satisfaction with the administration of trastuzumab SC using the SID by completing the 5-item SID Satisfaction Questionnaire.

[p] Approximately 3-monthly (every 4 cycles) refers to pre-dosing at: Week 13/Cycle 5, Week 25/Cycle 9, Week 37/Cycle 13, and Week 52/Cycle 18.

[q] Patients will undergo a Safety Follow-up visit 4 weeks after their last dose of study treatment.

[r] Visit windows of ±3 days allowed for all visits (Cycles 1 to 18), ±5 days at Safety Follow-up visit, and ±15 days allowed for Follow-up visits.

[s] An LVEF is only required at the Safety Follow-up visit if clinically indicated.

[t] Screening laboratory values should be used to confirm eligibility.

[u] For patients initiated on trastuzumab SC in neoadjuvant setting, surgery should be scheduled after dosing at Cycle 8. Pathologist post-surgery tumor assessment should be recorded.

[v] Cohort B only, observation time (6 hours post start of the first administration trastuzumab and 2 hours after the start of subsequent administrations) will include in addition to onset and resolution dates and times of adverse events, the collection of detailed information about pre-medications prior to trastuzumab administration and in addition to the date, the onset and resolution time of treatment of AEs occurring during the observation time is investigated.

[w] For SID monitoring purposes, the first 48 patients enrolled in Cohort B will have their SID use monitored and recorded on the SID monitoring questionnaire by the trained HCP or investigator intended to collect information about aspects of use related to usability of the device.

3.4 Concomitant Medication

All concomitant medications and prior treatments for breast cancer are to be reported in the eCRF starting at the Screening visit. These include:

- Date and extent of primary surgery;
- Any loco-regional radiation therapy (extent or volume and total dose);
- Any hormonal therapy and/or surgical and radiation-induced ovarian ablation and drug-induced ovarian suppression (type, drug name, dose and schedule, anticipated duration of therapy);
- Bisphosphonate therapy.

All concomitant medications are to be reported until the Safety Follow-up visit. Thereafter, only the following medications must be reported:

- Breast cancer treatments (e.g., hormonal therapy);
- Anti-cancer treatments given to treat a recurrence;
- Medications related to the treatment of serious AEs.

3.4.1 Permitted Therapy

Trastuzumab SC treatment may be initiated after completion of neoadjuvant or adjuvant chemotherapy (sequentially), in combination with neoadjuvant or adjuvant paclitaxel or docetaxel chemotherapy (concurrently), or without adjuvant chemotherapy; or in combination with neoadjuvant chemotherapy followed by trastuzumab therapy, for locally advanced (including inflammatory disease or tumours >2 cm in diameter). The choice of adjuvant chemotherapy will be at the investigator's discretion and according to standard of care for EBC.

Any medication which is necessary for the management of side effects of trastuzumab may be used at the discretion of the investigator. Paracetamol (acetaminophen), antihistamines and other supportive medication may be used according to local clinical practice, for the treatment of reactions associated with trastuzumab SC administration, including pyrexia.

Adjuvant tamoxifen (with or without a gonadotropin releasing hormone agonist) or an aromatase inhibitor may be administered to patients with hormone receptor (oestrogen and/or progesterone receptor) positive disease according to local practice. Adjuvant hormonal therapy and adjuvant radiotherapy (if indicated) may be given concomitantly with trastuzumab SC.

Patients may have started bisphosphonate therapy for a licensed indication before entering the study and if so, this may continue. Bisphosphonate therapy (oral and IV only) can also be initiated during the study for the treatment of documented osteoporosis. If started during the trial, the patient must be assessed for evidence of progression first. The use of bisphosphonates for prevention of bone metastases is not allowed unless they become licensed for this indication during the study.

Other permitted concomitant therapies include:

- Supportive care, including transfusions, which should be prescribed according to local guidelines and the Investigator's clinical judgment.
- Anti-emetic regimens may be used at the discretion of the investigator.
- Growth factors (i.e., G- or GM-CSF) may be used as clinically indicated according to institutional guidelines.
- Maintenance therapy for patients with chronic conditions, such as hypothyroidism, hypertension, diabetes, etc.
- Radiotherapy

Subcutaneous injections (e.g. insulin, heparin) are allowed as long as they are administered at a different injection site from that of the study drug (i.e. other than the thigh).

3.4.2 Prohibited Therapy

The following treatments are not permitted during trastuzumab SC treatment:

- Concurrent treatment with other systemic HER2-directed immunotherapy
- Concurrent investigational agents of any type.
- Concurrent treatment with anthracyclines in the adjuvant setting.

3.5 Study Analysis Populations

There will be 4 analysis populations defined for the study analyses.

3.5.1 Safety Population

The Safety Population will include all enrolled patients who received at least one dose of study medication. There will be two safety populations, one for each cohort (Safety Population for Cohort A, Safety Population for Cohort B)

Cohorts are assigned at the start of the study and will not be reassigned even if the patient switches from SID to SC vial. However, information on SC vial administration in Cohort B will be collected and analysed as described in Section 4.10.2.

3.5.2 Intent to treat (ITT) Population

The ITT population will include all patients enrolled in the study, i.e. all patients that signed informed consent and did not fail screening.

3.5.3 Per-Protocol (PP) Population

The PP population will include all ITT patients who have received at least one dose of study medication and did not have any major protocol deviations that led to exclusion from the PP population.

Major protocol deviations which may lead to exclusion from the PP population are defined in Section 4.12.

A separate document "Per Protocol Analysis set Specification" will be developed to detail which Major deviations will be programmed and which will be selected in the PV trackers. For more details, please see section 4.12.

3.5.4 PK Evaluable Population

The PK evaluable population will include all ITT patients in Cohort B with at least one valid serum trastuzumab concentration result at either of the Baseline, Pre-Cycle 9 Dose or 6 months after last study treatment sampling time points.

Hereby a result is deemed to be valid when it is non-missing, e.g. either a real number or indicated by a reference range, e.g. < LLOQ (lower limit of quantification) or similar. A result is deemed to be not valid, when it is missing, e.g. blank or recorded as "Not Done", "Not Applicable" or similar.

3.5.5 Subgroups

The following subgroups are defined:

- Medication Subgroup: Patients with 'Concurrent Chemotherapy' (i.e. all patients with any chemotherapy that overlaps with the Herceptin administration dates) or 'Patients Treated with Sequential or no Chemotherapy' (all other patients)
- Patients receiving no Chemotherapy
- Patients receiving Concurrent Taxane
- Patients receiving Concurrent Anthracycline
- Patients receiving Concurrent Radiotherapy
- Neoadjuvant Patients (i.e. all patients receiving breast cancer surgery after their first dose of study drug)
- Weight (i.e. <45kg, 0-10%, 0-25%, >25%-<=50%, >50%-<=75%, >75%-<=100% of the weight of all subjects in safety population)
- Patients Aged 75 years and Older (i.e. all patients at least 75 years old)
- Region (Western European, Eastern European, Africa, Asia Pacific, Americas)
- Low Risk Population based on tumor size less or equal to 1.0 cm and no lymph node involvement.

In addition, 'Patients Aged 75 years and Older' may also be presented by 'Medication Subgroup'.

The following 5 regions will be used in all analyses by region:

- Western European including France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom and Turkey
- Eastern European including Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Hungary, Lithuania, Poland, Romania, Russian Federation, Serbia, Slovakia, Slovenia and Ukraine
- Africa including Algeria, South Africa and Egypt
- Asia Pacific including Australia, Hong Kong, Indonesia, Republic of Korea, Malaysia, New Zealand, Pakistan, Philippines, Saudi Arabia, Singapore, Taiwan, Thailand and United Arab Emirates
- Americas including Argentina, Brazil, Canada, Chile, Colombia, El Salvador, Ecuador, Guatemala, Mexico, Panama, Peru, Uruguay and Venezuela

3.6 Withdrawn Patients

Reasons for withdrawal from the study may include the following:

- Withdrawal of consent by the patient
- Treatment failure
- Protocol violation
- Lack of compliance with study and/or study procedures (e.g. dosing instructions, study visits).

Every effort will be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study will be documented on the appropriate eCRF.

Enrolled patients who are prematurely discontinued from the study will not be replaced, irrespective of the reason for withdrawal.

3.7 Randomisation

This is an open label non-randomized study. Assignment of patients to cohorts is at the discretion of the investigator.

3.8 Blinding

This is an open label study. There is no blinding of study treatment.

3.9 Sample Size

A sample size of approximately 2,500 patients is planned for this study, approximately 1,800 patients in Cohort A and approximately 700 patients in Cohort B. There is no formal

statistical hypothesis testing, but all safety (primary) endpoints results will be descriptively explained and 95% confidence intervals added where relevant.

For the purpose of the estimation of sample size, the incidence/proportion of congestive heart failure (CHF)-related SAEs was chosen as a safety endpoint of primary interest.

The table below includes 95% Clopper-Pearson confidence intervals for CHF-related SAE incidence range between 1% and 10%.

Table 3.9 Clopper-Pearson 95% Confidence Intervals for the Observed CHF-Related SAE Incidence

Cohort A: **Total number of patients: 1,800**	
Number of patients with CHF-related SAEs (incidence rate)	***95% Clopper Pearson Confidence Interval***
18 (1%)	0.1% - 1.6%
36 (2%)	1.4% - 2.8%
72 (4%)	**3.1% - 5.0%**
108 (6%)	5.0% - 7.2%
144 (8%)	6.8% - 9.4%
180 (10%)	8.7% - 11.5%
Cohort B: **Total number of patients: 700**	
7 (1%)	0.04% – 2.1%
14 (2%)	1.1% - 3.3%
28 (4%)	**2.7% - 5.7%**
42 (6%)	4.4% - 8.0%
56 (8%)	6.1% - 10.3%
70 (10%)	7.9% - 12.5%

CI=Confidence Interval; CHF=congestive heart failure; SAE= serious adverse event

Therefore, based on an observed CHF-related SAE incidence rate of 4% (Romond et al. 2005; Ewer and O'Shaughnessy 2007) and a sample size of 1,800 patients in Cohort A, the upper limit of the 95% confidence interval (CI) for the incidence rate will be 5.0%. For Cohort B, the same CHF-related SAE incidence rate and a sample size of 700 patients will give an upper limit of the 95% CI of 5.7%.

The estimation of the sample size was produced by a SAS program and nQuery Version 6.

The split of the two cohorts in the current study was based on the availability of the SID which was planned to be due by the end of 2012. The planned patient size was then further supported by the sample size calculation for the target event of CHF-related SAEs. Based on an observed CHF-related SAE incidence rate of 4% (Romond et al. 2005; Ewer and O'Shaughnessy 2007) and a sample size of 700 patients for Cohort B, the upper limit of the 95% confidence interval [CI] for the incidence rate will be 5.7%. CHF-related SAE events N=28 (4%) CI 2.7% - 5.7%.

In Cohort B only, exploratory analyses on the usability of the SID summarizing the parameters collected via SID monitoring questionnaire (Protocol v4 - Appendix 7) will be provided to the first 48 patients enrolled who were judged able and were willing to self-administer remaining doses from the SID under direct observation of the HCP. A sample size of 48 patients using the SID for 17 cycles to self-administer a dose without assistance equates to sample of n = 816 dosing events. If 0 events occur in this sample of trials, it can be stated with 99% confident it will be <1% in the true population. The Adjusted Wald Approximate lower-limit of one-sided confidence interval for binomial distributed proportions statistical model has been used.

4 Statistical Methodology

4.1 Planned Analyses

Demographic and baseline characteristics, all safety variables (primary endpoints) and exploratory endpoints will be summarized for the safety population. In addition baseline characteristics and demography will be summarized using the ITT and PP populations. Summaries of the secondary endpoints will be presented for the ITT and PP populations. Subgroup analysis will be done for selected safety and efficacy summaries including Adverse Events, Baseline Characteristics, Active Medical History, Breast Cancer Diagnosis, Overall Survival and Disease Free Survival.

Summary statistics will be presented for continuous variables; by way of number of observations (n), mean, standard deviation, median, minimum and maximum and by way of group frequencies and percentages for categories of categorical variables. Unless specified otherwise, percentages will be calculated using the total number of patients in the relevant cohort and applicable population.

Cohorts A and B will be analyzed separately and overall. Unscheduled visit assessments will be listed only, if not differently stated. In particular, unscheduled visit assessments will be considered in the analysis of laboratory findings and LVEF values as described in Section 4.5.2 and Section 4.5.3 respectively.

Notes:

Baseline is defined as the last value recorded prior to first dose of study drug.

Please find additional analysis performed during the primary analysis descripted in a File Note (22Apr2015).

4.2 Interim Analysis

Three interim safety analyses are planned, when approximately 500, 1,000 and 2,500 patients have received at least one trastuzumab SC injection. Details regarding the interim safety reporting will be provided in the Steering Committee Charter.

4.3 Demographic and Cancer History

All baseline and demographic characteristics will be summarized for the safety, ITT and PP populations for each cohort. Included will be race, ethnicity, gender, age (descriptive statistics and the number and percentage of patients <75 years, ≥ 75 years), height, weight (descriptive statistics and the number and percentage of patients by weight categories), region (in categories as defined in Section 3.5.5), female reproductive status, human epidermal growth factor receptor 2 (HER2) test results, active and relevant medical history, breast cancer diagnosis, previous cancer treatment, neoadjuvant treatment and adjuvant treatment. Pregnancy test results (serum and confirmatory urine test) will be summarized for women of child-bearing potential for the safety population. Serum pregnancy test will be also presented in a data listing at the time of final analysis.

Subgroup analyses by Medication Subgroup, for Patients receiving no Chemotherapy, by Weight, for Patients receiving Concurrent Taxane, for Patients aged >=75 years, for Patients receiving Concurrent Anthracyclines, for Neoadjuvant Patients and for Patients receiving Concurrent Radiotherapy will be done for Demographics, Baseline Characteristics, Active Medical History and Breast Cancer Diagnosis.

A table with Breast Cancer Diagnosis, Demographics and Baseline Characteristics on PP population will be also produced at the time of final analysis.

Notes:

- Age will be calculated as the integer ((Date of Consent – Date of Birth) / 365.25). Only year of birth is collected. Day and month will be replaced with the 1st of the month and year (January) respectively. Age will be presented/summarized as a whole number. Derived age will be used in all summaries.
- Weight categories <45kg, 0-10% 0-25%, >25%-<=50%, >50%-<=75% and >75%-<=100% (percentages are derived from the overall safety population) will be used as the cut off points for the weight categories.
- Medical history will be coded according to the latest version of Medical Dictionary for Regulatory Activities (MedDRA).
- Active medical histories are defined as histories ongoing at study entry.
- Relevant medical histories are all medical histories recorded in the eCRF.

4.4 Efficacy Analysis

All efficacy parameters will be analyzed, summarized and presented for each cohort.

No formal hypothesis testing is planned.

4.4.1 Disease Free Survival

Disease Free Survival (DFS) is defined as time from first treatment with trastuzumab to local, regional or distant recurrence, contra-lateral invasive breast cancer (including contralateral or ipsilateral ductal carcinoma in situ) or death due to any cause (whichever occurs first). Patients who have neither had a recurrence nor died will be censored on the date of their last visit or last known date they were alive. Time will be calculated in months as follows:

DFS = (date of event – date of first treatment + 1) / 30.5

For the analysis of the ITT population date of informed consent will be used in place of date of treatment for patients without treatment with trastuzumab.

In addition to death, the following recurrence events will be considered for the analysis of DFS (time to first event):

- Ipsilateral breast
- Soft tissue
- Ipsilateral internal mammary
- Ipsilateral axillary lymph nodes

- Extranodal soft tissue of the ipsilateral axilla
- Skin
- Subcutaneous Tissue
- Lymph nodes
- Bone
- Bone marrow
- Lung
- Liver
- CNS
- Other
- Contralateral invasive breast cancer

For DFS analyses, patients will be considered as having an event if:

- at least, one of above event has a non missing date,

  Or

- the CRF variable "Has the disease recurrence occurred" equals to "Yes" even if there is no event date. In that case, the imputation rule below will be applied.

To handle the missing and partial date with disease recurrence, *The imputation for the missing date will be done based on the "(Last Breast Cancer follow-up assessment date + one day more)" with Last Recurrent Disease Diagnosed response "No" irrespective of the assessment method*.

Thus the **Date of Event** will be considered as 'Last Breast Cancer follow-up assessment date + one day more' since we have Disease Diagnosed response assessment 'No' till Last Breast Cancer follow-up assessment date.

The estimate of the survivor function will be displayed graphically using a Kaplan-Meier (KM) curve and listed along with the associated 95% confidence intervals. Disease free survival rates at 6, 12, 18, and 24 months, and 3, 4 and 5 years will be estimated and presented along with the corresponding two-sided 95% confidence interval. The final analysis will take place when the last patient has been followed up for at least 5 years or after their last study treatment, or earlier if one of the following is documented for all treated patients; withdrawal of consent, loss to follow up or death.

The above analysis will also be performed in the PP population.

A sensitivity analysis using an extended definition including also the second primary malignancies (SPM) (as identified from the AEs by medical review) will be produced at the time of final analysis. Additional Figures of the Kaplan-Meier Plot and Tables will be produced in ITT and PP.

SPM events are all TEAE whose System Organ Class is NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS).

A frequency table of the type of event presenting the number and percentage of patients in each category (local recurrence, regional recurrence, distant recurrence, contra-lateral breast cancer,death and second primary malignancy) will also be presented at the time of final analysis.

The categories of type of events are defined and ordered as following:

1) Local recurrence: Ipsilateral breast, Soft tissue
2) Regional recurrence: Ipsilateral internal mammary, Ipsilateral axillary lymph nodes, Extranodal soft tissue of the ipsilateral axilla
3) Distant recurrences: Skin, Subcutaneous Tissue, Lymph nodes, Bone, Bone marrow, Lung, Liver, CNS, Other
4) Contralateral Breast Cancer
5) Second Primary Malignancies*
6) Death
7) Missing#

Patients could have several simultaneous first types of event. It that cases they are counted in all categories.

*Same table will be produced for the sensitivity analysis including SPM events..

Missing category will correspond to patients without any event date but with the CRF variable "Has the disease recurrence occurred" equals to "Yes" (and so it will be an imputed date).
A table with Disease Free Survival by Timing of Chemotherapy (Concurrent Chemotherapy, No Chemotherapy, Sequential Chemotherapy) will be additionally presented at the final analysis for ITT and PP.

A table with Disease Free Survival by Low Risk population subgroup will be presented for ITT and PP.

Listing for DFS and disease recurrence without SPM and with SPM will be presented at the time of final analysis.

4.4.2 Overall Survival

Overall Survival (OS) is defined as the time from date of first treatment with trastuzumab SC until date of death, regardless of cause of death. Patients who have not died will be censored on their last known date they were alive. Time will be calculated in months as follows:

OS = (date of event – date of first treatment + 1) / 30.5

Note: For the analysis of the ITT population date of informed consent will be used in place of date of treatment for patients without treatment with trastuzumab.

The estimate of the survivor function will be displayed graphically using a KM curve and listed along with the associated 95% confidence intervals. OS rates will be presented as described above for DFS.

The analysis will also be performed in the PP population.

A table with Overall Survival by Low Risk population subgroup will be presented for ITT and PP.

4.4.3 Patient Satisfaction

Patient satisfaction with the SID will be evaluated in patients in Cohort B who choose to self-administer using the SID and have completed a minimum of 2 self administrations. Patients will be given an evaluation questionnaire at their last visit of their 4th cycle at least a day after their last self-administration and at Safety Follow-up.

Patient satisfaction question responses (Strongly disagree, Disagree, Unsure, Agree, Strongly agree) will be summarized by presenting number and percentage of patients for each cohort and overall.

Patient satisfaction will be graphically illustrated by a bar chart showing the percentage of patients that strongly disagree (1), disagree (2), are unsure (3), agree (4) and strongly agree (5) at each time point. For each of the five questions a separate graphic will be produced.

4.5 Safety Analysis

The safety endpoints will be summarized for each cohort by their respective safety populations and overall.

All AEs and laboratory variables will be assessed according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTC-AE) version 4.0 grading system.

4.5.1 Adverse events

Prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention will be reported (e.g., SAEs related to invasive procedures such as biopsies). After initiation of study drug, all AEs/SAEs, (except unrelated and non serious and non-cardiac AEs in the follow-up period), regardless of relationship to study drug, will be reported until study closure. Any injection site reactions are considered to be related AEs/SAEs and should be reported accordingly.

Only treatment emergent AEs (starting on the day of or after the first administration of trastuzumab SC) will be included in summary tables. AE summaries will be presented separately for the treatment period and follow-up period. Treatment period and follow-up period are defined as detailed in Appendix 6.3.1.

Non-treatment emergent events (starting prior to first administration of trastuzumab SC) will be listed only. Where an AE start date is partially or fully missing, and it is unclear as to whether the AE is treatment emergent, it will be assumed to be treatment emergent.

AEs and SAEs, in total as well as by region, in the treatment period will be summarized separately by presenting the number and percentage of patients having any event, events leading to discontinuation of study drug, events leading to interruption of study drug, medical device complaint/events, cardiac events, CHF-related SAEs (as assessed by the investigator

per eCRF-tickbox) and events by CTC grade, relationship and outcome. Similarly, AEs and SAEs in total will be summarized for the follow-up period and the whole study.

Summary tables by system organ class (SOC) and preferred term (PT) of the number and percentage of patients having events including number of events within the treatment period will be presented for:

- All AEs
- All AEs by Medication Subgroup
- All AEs for Patients receiving no Chemotherapy
- All AEs for Patients receiving no Chemotherapy by Weight
- All AEs by Weight
- All AEs for Patients receiving Concurrent Taxane
- All AEs for Patients Aged 75 years or Older
- All AEs for Patients Aged 75 years or Older by Medication Subgroup
- All AEs for Patients receiving Concurrent Anthracycline
- All AEs for Neoadjuvant Patients
- All AEs for Patients receiving Concurrent Radiotherapy
- All AEs by Race
- All SAEs
- All SAEs by Medication Subgroup
- All SAEs for Patients receiving No Chemotherapy
- All SAEs by Weight
- All SAEs for Patients receiving Concurrent Taxane
- All SAEs for Patients Aged 75 years or Older
- All SAEs for Patients Aged 75 years or Older by Medication Subgroup
- All SAEs for Patients receiving Concurrent Anthracycline
- All SAEs for Neoadjuvant Patients
- All SAEs for Patients receiving Concurrent Radiotherapy
- All SAEs by Race
- Related AEs
- Related SAEs
- AEs Grade 3 or more
- AEs Grade 3 or more by Medication Subgroup
- AEs Grade 3 or more for Patients receiving no Chemotherapy

- AEs Grade 3 or more by Weight
- AEs Grade 3 or more for Patients receiving Concurrent Taxane
- AEs Grade 3 or more for Patients Aged 75 years or Older
- AEs Grade 3 or more for Patients Aged 75 years or Older by Medication Subgroup
- AEs Grade 3 or more for Patients receiving Concurrent Anthracycline
- AEs Grade 3 or more for NeoAdjuvant Patients
- AEs Grade 3 or more for Patients receiving Concurrent Radiotherapy
- AEs Grade 3 or more by Race
- AEs Leading to Study Drug Discontinuation
- AEs Leading to Study Drug Discontinuation by Weight
- AEs Leading to Study Drug Discontinuation by Race
- AEs Leading to Study Drug Interruption
- AEs by CTC Grade and Relationship
- AEs by Maximum CTC Grade
- SAEs by Maximum CTC Grade
- Cardiac AEs
- Cardiac AEs by Medication Subgroup
- Cardiac AEs for Patients receiving no Chemotherapy
- Cardiac AEs by Weight
- Cardiac AEs by Race
- Congestive Heart Failure Related SAEs
- Injection Site Reactions
- Administration Related Reactions
- Administration Related Reactions by Medication Subgroup
- Administration Related Reactions for Patients receiving no Chemotherapy
- Administration Related Reactions by Weight
- Administration Related Reactions for Patients receiving Concurrent Taxane
- Administration Related Reactions for Patients Aged 75 years or Older
- Administration Related Reactions for Patients Aged 75 years or Older by Medication Subgroup
- Administration Related Reactions for Patients receiving Concurrent Anthracyclines
- Administration Related Reactions for Neoadjuvant Patients

- Administration Related Reactions for Patients receiving Concurrent Radiotherapy
- Administration Related Reactions Grade 3 or more
- Administration Related Reactions by Race
- Adverse Events starting Post-dose on Day of Trastuzumab Administration
- Adverse Events Starting Post-Dose on Day of Trastuzumab Administration by CTC Grade and Cycle
- Serious Adverse Events Starting Post-Dose on Day of Trastuzumab Administration by Cycle
- Adverse Events Grade 3 or More Starting Post-Dose on Day of Trastuzumab Administration by Cycle

Injection Site Reactions and Administration Related Reactions are defined in Appendix 1. Cardiac AEs are defined as a System Organ Class of "Cardiac Disorders" or a high level term of "Cardiac Function Diagnostic Procedures", "Cardiac Imaging Procedures", "ECG Investigations" or "Heart and Pulse Investigations". Significant Cardiac Adverse Events are defined as all cardiac events serious, Grade 3 or higher, NYHA class III or higher, or leading to discontinuation of study medication. Congestive heart Failure will be identified by eCRF tickbox. Cardiac dysfunction is defined as all events attributed to the Cardiac Failure Standardised MedDRA Queries (SMQ) equals to broad. Infections are defined as all events attributed to the SOC'Infections and Infestations'.

Medication Subgroup is defined in Section 3.5.4.

Most frequent adverse events, i.e. those with a frequency >=5% in any cohort, will be summarized by preferred term (PT).

In addition, 95% Clopper-Pearson confidence intervals associated with the incidence of AEs Grade 3 or more, AEs leading to study drug discontinuation, AEs leading to study drug interruption, Cardiac AEs, and all SAEs will be presented for the treatment period.

Summary tables by system organ class (SOC) and preferred term (PT) of the number and percentage of patients having events including number of events in the follow-up period will be based on reportable Adverse Events only and presented for:

- All AEs
- All AEs by Race
- All SAEs
- All SAEs by Race
- All SAEs by Weight
- Related AEs
- Related SAEs
- AEs Grade 3 or more

- AEs Grade 3 or more by Race
- Cardiac AEs
- Cardiac AEs by Race
- Significant Cardiac AEs
- Congestive Heart Failure Related SAEs

Summary tables by system organ class (SOC) and preferred term (PT) of the number and percentage of patients having events including number of events in the whole study period (all AEs in treatment period and reportable AEs in follow-up period) will be presented for:

- All AEs
- All SAEs
- Related AEs
- Related SAEs
- Related SAEs by Weight
- AEs Grade 3 or more
- Cardiac AEs
- Cardiac AEs and maximum CTC grade
- Significant Cardiac AEs
- Congestive Heart Failure Related SAEs
- Second Primary Malignancies AEs
- Administration Related Reactions
- Administration Related Reactions by Age Group
- Administration Related Reactions by Region
- Administration Related Reactions by Race
- Administration Related Reactions by CTC Grade
- Administration Related Reactions by CTC Grade and Age Group
- Administration Related Reactions by CTC Grade and Region
- Administration Related Reactions by CTC Grade and Race

A patient with more than one occurrence of the same adverse event in a particular system organ class/preferred term will be counted only once in the total of those experiencing adverse events in that particular system organ class/preferred term.

If a patient experiences the same adverse event at more than one CTC grade level, or with more than one relationship to study drug, the most severe rating or the stronger causal relationship to study drug will be given precedence. Any missing CTC grade, causality, or outcome will not be imputed but classed as unknown.

Related refers to those events with a reasonable suspected causal relationship to the study drug, or with an unknown relationship as per investigator assessment.

Events starting in the treatment period and continuing into the follow-up period will be counted in the treatment period only unless the severity of the event worsens or the event changes from unrelated to related.

Time to onset (days) to first episode of cardiac AE will be summarized using the Kaplan Meier (KM) approach. Treatment Emergent Cardiac Adverse Event free survival rates at 6, 12, 18, and 24 months, and 3, 4 and 5 years will be estimated and presented along with the corresponding two-sided 95% confidence interval. The survivor function will be displayed graphically using a Kaplan-Meier curve. This will be repeated for Treatment Emergent Cardiac Adverse Events by Medication Subgroup as well as for Patients receiving no Chemotherapy.

Time to onset will be calculated as follows:

(start date of AE – date of first treatment) + 1

Patients who have a cardiac AE with missing or partial start dates will be classified as having an event and will not be censored. Patients who have not experienced a cardiac AE will be censored on the date of their last visit.

Event free survival rates of injection site reactions and administration related reactions will be summarized separately as described above for cardiac events, but no subgroup analysis will be done.

A summary of deaths will be presented, tabulating the number and percentage of patients by primary cause of death, and relationship to study drug for the treatment period, follow-up and whole study periods separately.

Further analyses on adverse events starting shortly after study drug intake are described in Section 4.6.3.

The adverse event listings of the primary analysis and final analysis are displayed in section 5.4.

The following listings of adverse events will be updated at the time of **final analysis:**

- AE
- Non Reportable AE
- Admistration Related AE
- Related AE
- SAE
- Grade 5 AE
- Cardiac AE
- Congestive Heart Failure Related SAE
- Deaths
- Cardiac Dysfunction SAE

- Second Primary Malignancies
- Grades 3 or 4 Cardiac AE
- Grades 3 or 4 Infections
- Significant Cardiac AE
- Glossary of Reported Terms and Preferred Terms for Adverse Events

Notes:

- Reportable AE are all related or serious or cardiac AE.
- Non reportable AE are all AE that occur during the follow-up period and which are not serious and not related and not cardiac
- Adverse events will be coded according to the latest version of MedDRA
- In case of patially missing start/stop dates, please refer to section 4.13.

Adverse event outputs are based on all TEAEs in the treatment period and reportable AE in the follow-up period.

4.5.2 Laboratory findings

Samples are scheduled at screening, and on day 1 (pre-dose) of cycles 9 and 18 of study treatment and at the safety follow-up visit 4 weeks after last study treatment.

Results from the following laboratory parameters will be converted to standard international units and summarized for each cohort and overall:

Hematology:

Hemoglobin, platelet count, white blood cell (WBC) count, neutrophils, basophils, eosinophils, lymphocytes and monocytes

Biochemistry:

Calcium, urea, creatinine, sodium, potassium, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP)

Changes in hematology and biochemistry laboratory values from Baseline to each visit will be summarized.

The graphical presentation of the mean value of selected laboratory parameters, WBC, ANC, platelets, haemoglobin, total bilirubin, AST, ALT, ALP, will be displayed.

Shift tables for the hematology and biochemistry laboratory parameters comparing NCI-CTC grade at baseline versus worst grade during the trastuzumab treatment period for each cohort and overall will be presented. NCI-CTC grade will be derived according to Table 4.5.2.1.

Table 4.5.2.1 CTC Grade Derivation

Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin (g/L)	>=LLN	<LLN - 100, >0 - 20 incr*	<100 - 80, >20 - 40 incr*	<80, >40 incr*	

Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Platelets (10^9/L)	>=LLN	<LLN – 75	<75 - 50	<50 – 25	<25
White Blood Cell (10^9/L)	>=LLN - 100	<LLN – 3	<3 - 2	<2 - 1, >100	<1
Neutrophils (10^9/L)	>=LLN - ULN	<LLN - 1.5	<1.5 - 1	<1 - 0.5	<0.5
Lymphocytes (10^9/L)	>=LLN - 4	<LLN - 0.8	<0.8 - 0.5, >4 - 20	<0.5 - 0.2, >20	<0.2
Calcium (mmol/L)	>=LLN - ULN	>ULN - 1.5, <LLN – 1	>1.5 - 1.6, < 1 - 0.9	> 1.6 - 1.8, <0.9 - 0.8	>1.8, <0.8
Creatinine (umol/L)	<=ULN	>ULN - 1.5xULN and >1 – 1.5x baseline	>1.5xULN - 3xULN and >1.5 – 3x baseline	>3xULN - 6xULN and >3x baseline	>6xULN
Sodium (mmol/L)	>=LLN - ULN	>ULN - 150, <LLN – 130	>150 - 155	>155 - 160, <130 – 120	>160, <120
Potassium (mmol/L)	>=LLN - ULN	<LLN - 3, >ULN - 5.5	>5.5 - 6	<3 - 2.5, >6 – 7	<2.5, >7
Albumin (g/L)	>=LLN	<LLN – 30	<30 - 20	<20	
Total Bilirubin (umol/L)	<=ULN	>ULN - 1.5xULN	> 1.5xULN - 3xULN	>3xULN - 10xULN	>10xULN
Aspartate Aminotransferase (U/L)	<=ULN	>ULN - 3xULN	>3xULN - 5xULN	>5xULN - 20xULN	>20xULN
Alanine Aminotransferase (U/L)	<=ULN	>ULN - 3xULN	>3xULN - 5xULN	>5xULN - 20xULN	>20xULN
Alkaline Phosphatase (U/L)	<=ULN	>ULN - 2.5xULN	>2.5xULN - 5xULN	>5xULN - 20xULN	>20xULN

Increase (incr) denotes a rise of the value above ULN or above baseline if baseline is above ULN.

A listing will be created for patients with marked abnormalities only. A marked abnormality test result is defined as a value outside of the marked abnormality result with a clinically relevant change from baseline as per Table 4.5.2.2 following Roche International Standard for the Handling and Reporting of Laboratory Data COG 3007 (2).

Table 4.5.2.2 Marked Abnormality Derivation

Parameter	SI Unit	Significant Decimals	Marked Abnormality Range	Direction of Change	Clinically Relevant Change from Baseline
Hemoglobin	g/L	0	110-200	Increase Decrease	≥ 15 % ≥ 15 %
Platelets	10^9/L	0	100 – 550	Increase Decrease	≥ 50 % ≥ 30 %
White Blood Cells	10^9/L	1	3.0 – 18.0	Increase Decrease	≥ 30 % ≥ 30 %
Neutrophils	10^9/L	2	1.50 – 9.25	Increase Decrease	≥ 20 % ≥ 20 %
Basophils	10^9/L	2	0 – 0.40	Increase	≥ 100 %
Eosinophils	10^9/L	2	0 – 0.90	Increase	≥ 100 %
Lymphocytes	10^9/L	2	0.70 – 7.60	Increase Decrease	≥ 30 % ≥ 30 %
Monocytes	10^9/L	2	0 – 1.70	Increase	≥ 100 %
Calcium	mmol/L	2	2.00 – 2.90	Increase Decrease	≥ 10 % ≥ 10 %

Parameter	SI Unit	Significant Decimals	Marked Abnormality Range	Direction of Change	Clinically Relevant Change from Baseline
UREA	mmol/L	1	0 – 14.3	Increase	≥ 50 %
Creatinine	umol/L	0	0 – 154	Increase	≥ 50 %
Sodium	mmol/L	0	130 – 150	Increase Decrease	≥ 7 % ≥ 7 %
Potassium	mmol/L	1	2.9 – 5.8	Increase Decrease	≥ 20 % ≥ 20 %
Albumin	g/L	1	≥ 30	Decrease	≥ 20 %
Total Bilirubin	umol/L	0	0 – 34	Increase	≥ 75 %
Aspartate Aminotransferase	U/L	0	0 – 80	Increase	≥ 50 %
Alanine Aminotransferase	U/L	0	0 – 110	Increase	≥ 50 %
Alkaline Phosphatase	U/L	0	0 – 220	Increase	≥ 50 %

Notes:

- Repeated laboratory results within a visit will replace the original value. Unscheduled results will be considered for the identification of the worst grade values and of marked abnormalities.

4.5.3 LVEF

LVEF observations are recorded at Screening (within 14 days for prior anthracycline use or within 28 days prior to the first trastuzumab SC administration for anthracycline-free regimens) and on Day 1 (pre-dose) of cycles 5, 9, 13 and 18, the safety follow-up visit (if clinically indicated), and at follow-up cardiac assessments at 6, 12 and 24 months and 3, 4 and 5 years following last treatment. The algorithm for classification of follow-up assessments is reported in Appendix 6.3.2.

Clinically indicatedLVEF measurements are defined as:

- An LVEF result between 45 – 49%;
- A symptomatic drop of ≥ 10% versus baseline. Baseline is defined as the last value recorded prior to first dose of study drug. An event is considered symptomatic if it's associated with new cardiac signs and symptoms or worsening cardiac signs and symptoms or signs and symptoms of CHF.
- A significant drop in LVEF that causes the permanent stop of study drug.
- AEs codified with a Low Level Term equal to "LEFT VENTRICULAR EJECTION FRACTION DECREASED" or "EJECTION FRACTION DECREASED" are considered as significant drop in LVEF events.

LVEF will be summarized over time using descriptive statistics for each cohort and overall. LVEF will also be summarised by number and percentage of patients within the following categories by cycle and by worst (lowest) on treatment value and worst post baseline value:

- Increase or no change from baseline
- Decrease of <10 points from baseline
- Decrease of >=10 points from baseline
- 45<= LVEF <50
- LVEF <50 and decrease of >=10 points from baseline
- LVEF <45 and decrease of >=10 points from baseline

This summary table will be repeated by weight.

Mean LVEF values will be presented graphically with line graphs over time by cohort.

Time to onset (days) to first clinically indicated LVEF measurement will be summarized using the KM approach. Clinically indicated LVEF free survival will be summarized using a Kaplan-Meier plot, and in terms of minimum and maximum time to onset (in months) and survival rates at 6, 12, 18, and 24 months, and 3, 4 and 5 years, along with corresponding 95% confidence intervals.

Time to onset will be calculated as follows:

(start date of first clinically indicated LVEF measurement – date of first treatment) + 1.

Patients who have a clinically indicated LVEF measurement with missing or partial date will be classified as having an event and will not be censored. Kindly refer to section 4.13.3 for missing or partial date imputation. Patients who have no clinically indicated LVEF measurement be censored on the date of their last visit.

LVEF assessments during unscheduled visits will be included in the analyses regarding worst values (on-treatment, post-baseline and follow-up worst values). They will also be taken into account for the analyses of time to onset to first clinically indicated LVEF measurement.

LVEF data will be also presented in a data listing at the time of final analysis.

For LVEF listing of Patients with Significant Drop, the subgroup of patients with significant drop is define as following:

- Any patient with any post-baseline LVEF value below 50, that is a decrease compared to baseline LVEF of 10 percentage points or higher

4.5.4 Vital signs

Vital signs (systolic and diastolic blood pressure, pulse and temperature) are recorded at screening, on Day 1 (pre and post dose) of cycles 1, 5, 9, 13 and 18, and at the safety follow-up visit. Systolic and diastolic blood pressure and pulse will be summarized over time using descriptive statistics for each cohort and overall.

4.5.5 ECG

ECG findings (normal, abnormal) are recorded and a 12-lead ECG examination performed at screening and on Day 1 (pre-dose) of cycles 5, 9, 13 and 18, and as part of the follow-up cardiac assessments at 6, 12 and 24 months, and at 3, 4, and 5 years following last treatment. ECG findings and 12 lead ECG results will be summarized over time using descriptive

statistics for each cohort and overall. The algorithm for classification of follow-up assessments is reported in Appendix 6.3.2.

ECG data will be also presented in summary table and data listing at the time of final analysis.

4.5.6 Weight

Weight (kg) is measured for all patients at screening, Cycle 9 and the follow-up visit. Weight will be summarized over time using descriptive statistics for each cohort and overall.

Weight (kg) data will be also presented in summary output and data listing at the time of final analysis.

4.5.7 ECOG Performance Status

ECOG performance status (Grade 0 - Grade 5) will be recorded at screening, on Day 1 of cycles 5, 9, 13 and 18, and at the safety follow-up visit. ECOG performance status (Grade 0 - Grade 5) will be summarized by over time by presenting the number and percentage of patients in each grade by cohort and overall.

Percentage of patients in each grade will also be presented graphically in a bar chart over time by cohort.

4.5.8 Duration of Follow-up

Duration of follow-up in months (from date of first administration of trastuzumab SC to date of last available assessment) will be analyzed using the Reverse Kaplan-Meier method: A patient will be censored if the patient died (date of censoring = date of death). A patient will be considered as having an event if the patient did not die (date of event = last date known to be alive). The Kaplan-Meier estimates of the median time to event and the corresponding two-sided 95% confidence interval will be presented along with the estimates for the 25th and 75th percentiles and the associated ranges (minimum, maximum).
A table with Duration of Follow-up by Timing of Chemotherapy (Concurrent Chemotherapy, No Chemotherapy, Sequential Chemotherapy) will be additionally presented at the final analysis.

4.5.9 Physical Exam

A general physical examination will be performed at screening. Follow-up physical examinations will also be performed on Day 1 of cycles 5, 9, 13 and 18. Furthermore a physical examination according to the American Society of Clinical Oncology (ASCO) 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting will be performed every 6 months or per institutional standard practices.

Physical examination results will be listed only. The data for physical examination will be presented at the time of final analysis.

4.6 Exploratory analysis

4.6.1 Immunogenicity

For patients in Cohort B, in addition to efficacy and safety assessments, selected sites will also perform immunogenicity testing to determine whether antibodies against trastuzumab or rHuPH20 develop in patients receiving trastuzumab SC using the SID. Serum samples (for anti-trastuzumab antibody analysis) and plasma samples (for anti-rHuPH20 antibody analysis) will be drawn at Baseline (after eligibility is confirmed, i.e. just before the first study treatment), on-treatment (Pre-Cycle 9 Dose, Week 25) and 6 months after the end of treatment.

All analyses of immunogenicity (anti-drug antibody (ADA) and neutralizing antibody (Nab)) will be based on the safety population in Cohort B. However, percentages will always be calculated with respect to the total number of patients in this population with a non-missing immunogenicity result at the respective time point.

Immunogenicity results (ADA: positive, negative, titer; NAb: positive, negative) will be summarized at Baseline, Pre-Cycle 9 Dose and at Follow-up by presenting the number and percentage of patients with ADAs to trastuzumab SC and antibodies to rHuPH20 as well as the number of patients with ADA to either moiety.

The number of patients with at least one result (at baseline and post-baseline) for ADA to trastuzumab SC with baseline result only and the number of patients evaluable for ADA to trastuzumab (i.e. with at least one post-baseline result) will be presented. The number of patients with positive ADA status at baseline will be evaluated by calculating the Prevalence (%) as the number of patients with a positive ADA result at baseline compared to those patients with a baseline result.

The number of patient with a treatment-emergent ADA response will be evaluated by calculating the incidence of treatment-emergent ADA response compared to evaluable patients, i.e. with at least one post-baseline result.

In addition, the number of patients with treatment-unaffected ADA response as well as the number of patients with post-baseline neutralizing antibody positive results. The above analyses will be repeated for the rHuPH20 antibody results.

Patients with any positive confirmatory assay result for anti-trastuzumab or anti-rHuPH20 antibodies will be listed. In order to investigate possible correlation with specific AEs, separate listings will be produced for patients with any injection site reaction and for patients with any administration related reaction. Additionally, all patients with positive confirmatory assay results both for anti-trastuzumab and anti-rHUPH20 will be presented in a separate listing.

The analysis of immunogenicity for both trastuzumab and rHuPH20 described above will also be performed using the following updated definitions at the time of final analysis.

- Treatment-emergent ADA is a post-baseline evaluable patient with an ADA response categorized as either treatment-induced or treatment-enhanced.
- Post-baseline evaluable is a patient with an ADA result from at least one post-baseline sample.

- Treatment-induced is a patient that is either ADA-negative or missing an ADA result at baseline and has at least one ADA-positive result post-baseline.
- Treatment-enhanced is a patient that is ADA-positive at baseline who has one or more ADA-positive titer results post-baseline that are atleast 4 times greater than the baseline titer result.
- Treatment-unaffected is a patient that is ADA-positive at baseline and where all post-baseline titer results are less than 4 times greater than the baseline titer result.

4.6.2 Drug concentration measurement

Serum trastuzumab concentrations will be collected in a subset of Cohort B subjects to aid in interpretation of immunogenicity data (the presence and titer of anti-trastuzumab antibodies). Sampling time points will match those used for immunogenicity testing in these patients, as described in Section 4.6.1. Trastuzumab concentration data will be listed and summarized in the PK evaluable population.

Serum trastuzumab concentrations for the overall population will be summarized using descriptive statistics (n, mean, standard deviation, geometric mean, %CV, median, minimum, and maximum) at Baseline and Pre-Cycle 9 dose, and 6 months after the last study treatment. In addition serum trastuzumab concentrations will be summarized by anti-trastuzumab antibody status (negative, positive) at each visit.

For the calculation of summary statistics any values that are below the limit of quantification (BLQ) will be assigned to 0. If the calculated mean value is less than the lower limit of quantification (LLOQ), then the summary statistics will be left blank, with 'BLQ' presented only for the mean value. However, since a high proportion of BLQ values may affect the SD, if more than 50% of values are imputed, then no summary statistics will be calculated and 'BLQ' will be presented only for the mean value. Within the summary statistics, any minimum or median that are calculated to be LLOQ will be presented as 'BLQ' within the summary presentation. In listings values that are BLQ will be displayed as <XXX, where XXX represents the numerical value of LLOQ.

PK data will be provided in a dataset containing variables including patient identifier, cohort, immunogenicity and PK data, indicator flags for a variety of AEs.

4.6.3 Tolerability of trastuzumab SC

Examination and characterization of tolerability of trastuzumab SC over a 6-hour time period after the start of the first administration and over a 2-hour period after the start of subsequent trastuzumab administrations (only in patients using the SID) will be performed.

For all patients in Cohort B, exploratory study analyses for clinical AEs that occur during observation will be evaluated, analyzed and presented and further analyses will be performed on AEs starting post-dose on the same day as study drug administration. In general (if not stated otherwise below), all analyses will be performed by cycle. Additionally for Cohort A and overall, analyses of AEs starting post-dose on the same day as study drug administration, will be performed.

An AE is defined to have started during observation, if at least one of the following statements is true:

1) The AE has a full start date/time indicating the AE clearly started during the first 6 hours after start of first trastuzumab administration or during the first 2 hours after start of following trastuzumab administrations.
2) The AE does have a full date indicating the AE started on same day as administration of trastuzumab but does not have a full start time and the question whether the AE started during observation was answered with Yes.

If the conditions above are not satisfied, it will be assumed that the AE did not start during observation. Missing or partial dates will be excluded from this analysis as all of these have been queried so that it is very unlikely that an AE starting on a distinguished day as administration of trastuzumab was not recorded as such.

AEs, ISRs and ARRs that started during observation will be summarized presenting the number and percentage of patients having an event, by relationship to study drug medication, CTC grade, concomitant medication given (yes/no) and outcome. This analysis will be repeated for all post-dose AEs, ISRs and ARRs that started on a day of trastuzumab administration – here, the summary of concomitant medication given (yes/no) will include all concomitant medications which started on the same day as the adverse event, irrespective of whether pre-dose or post-dose.

For AEs, ISRs and ARRs that started during observation, summary statistics will be presented for time to onset defined as the time from last preceding administration of study drug to start time of AE as well as for time to resolution defined as the time from start of AE to end of AE. These analyses will be performed both event-based and patient-based: The patient-based analysis will use the longest time-to-onset and longest time to resolution per patient and cycle.

Time to onset (hours) = (AE start date/time – start date/time of last preceding administration of trastuzumab)

Time to resolution (days) = (AE end date/time – AE start date/time)

All analyses of time to onset will be performed twice: once calculating time to onset for AEs with non-missing times only and once performing a worst case analysis calculating time to onset for all AE's starting during observation which uses maximum time span for AEs with missing times, e.g. 6 hours for first cycle, 2 hours for subsequent cycles.

For AEs, SAEs, ISRs and ARRs as well as AEs of CTC Grade >=3 and ARRs of CTC Grade >=2 all starting during observation, summary tables by system organ class (SOC) and preferred term (PT) of the number and percentage of patients having an event including number of events will be presented by cycle. The summary Table by SOC and PT for AEs starting during observation will be also repeated by CTC grade.

Summary Tables by SOC and PT will also be produced for all AEs, all ISRs and ARRs starting after observation but on the same day as study drug administration and will also be repeated by CTC grade. These analyses will only be performed overall, i.e. pooling all cycles.

For AEs, SAEs, and AEs of CTC Grade >=3 starting post-dose on the same day as study drug administration summary Tables by SOC and PT will be presented. For AEs starting post-dose

on the same day as study drug administration a summary Table will be also presented by SOC, PT and CTC grade.

In addition, the incidence of AEs, ISRs and ARRs as well as ARRs of CTC grade >=2 will be graphically illustrated by cycle split by time period (during observation, on day 1 but after observation, from day 2 onwards) utilizing bar charts. Hereby, AEs with completely missing date will be assigned to Day 2 onwards of the first cycle and AEs with partial date will be assigned to the earliest possible date given the partial information.

Notes:

- Time to resolution will only be calculated for AEs with an outcome of recovered/resolved or with an outcome of recovered/resolved with sequelae. Partial stop dates/times will be implemented as the last possible date/time. For entirely missing stop dates, the date of last contact will be used. In the patient-based analysis, a patient will only be included if all AEs for this patient have an outcome of recovered/resolved or recovered/resolved with sequelae. If a corresponding study drug administration can be identified, partial AE start dates/times will be implemented as date/time of the administration of study drug, otherwise there will be no imputation.
- For all definitions and calculations, should an AE start on the day of study drug administration and the administration time is missing, then this AE will be treated in the same way as if AE start time was missing.

For patients, who consented to Protocol Version 3, and have trastuzumab administered via the SID the question is asked in the eCRF whether the patient was observed for at least 6 hours after their first trastuzumab administration and 2 hours thereafter for subsequent trastuzumab administrations.

This information is collected in the eCRF tick-box which asks "was the patient observed for at least 6 hours after their first trastuzumab administration and 2 hours thereafter for each subsequent administration?"

To evaluate the amount of adherence to the observation time, the number and percentage of patients who were not being observed for the full 6 hours after their first administration (cycle 1) or 2 hours thereafter for subsequent administrations (cycle 2 onwards) for at least one cycle will be presented. The first cycle at which patients were not observed will be described presenting the number and percentages of patients who were not being observed by first cycle. Total number of cycles at which observation was not adhered to will be summarized via descriptive statistics. A listings with comments for non adherence to observation time will be produced.

4.6.4 SID Observer Usability

SID observer usability question responses will be summarized via descriptive statistics by presenting number and percentage of patients.

Notes:

- Evaluable patients will be identified as those having an answer to at least one item.

4.7 Disposition of Patients

The number of patients enrolled, number and percentage in each analysis population, completed treatment (Yes, No), completed follow-up (Yes, No) and the reasons for discontinuation of treatment and follow-up will be presented by cohort and overall.

The number and percentage of screen failures and by reason for failure will be presented for Treatment Period and Follow-up.

Subgroup analyses for Treatment Period by Medication Subgroup, for Patients receiving no Chemotherapy, by Weight, for Patients receiving Concurrent Taxane, for Patients aged >75 years, for Patients receiving Concurrent Anthracyclines and for Neoadjuvant Patients will also be analyzed and presented as described above.

The enrollment per country and age groups will be additionally presented at the final analysis.

4.8 Concomitant Medication

Summaries of prior and concomitant medications will be presented for the safety population. Prior medications are those that stopped before exposure to study drug; concomitant medications are all those taken during the study, including those started before but ongoing at first dose of study drug.

Incidence of prior medications and concomitant medications will be presented separately by therapeutic area and preferred drug name, by cohort and overall. The table for concomitant medications will also be presented for the Follow- Up period.

Where a medication end date is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant.

In case of missing or patially missing start/stop dates, please refer to section 4.13.

In addition, summary tables will be created for all concomitant medications given in response to an AE starting during observation time by cycle. This analysis will be repeated for all concomitant medications starting on same day as study drug administration (irrespective of whether pre-dose or post-dose) by cycle.

Medications are coded using the latest version of the World Health Organization (WHO) Drug dictionary.

Prior and concomitant medications will be listed separately. Additional listings will be created for all concomitant medications given in response to AE starting during the observation time as well as for AE starting on same day as study drug administration.

4.9 Chemotherapy, Hormone Therapy and Radiotherapy

Summaries of concurrent chemotherapy, hormone therapy and radiotherapy as well as previous chemotherapy will be presented for the safety populations. Incidence of concurrent chemotherapy and hormone therapy will be presented separately by medication name or procedure by cohort and overall. Previous and post last dose chemotherapy will be described

also. Similarly the number and percentage of patients undergoing radiotherapy will be presented by cohort and overall. The eCRF tick-box was unclean at the time of primary analysis. Thus the low risk population will be derived based on the tumor size less or equal to 1.0 cm and no lymph node involvement. These will be further summarized showing the number of patients in the low risk population and the reason these were included in the low risk population summary according to risk/benefit ratio (tumor burden, tumor size, endocrine responsiveness, other health or patient related condition, patient refusal to accept a validated chemotherapy, other).

4.10 Exposure

4.10.1 Study Drug Exposure

The total number of cycles received will be summarized both by descriptive statistics and by presenting the number and percentage of patients in each category. The number and percentage of patients by total number of cycles self-administered will also be presented for Cohort B.

Study drug administration details will be summarized by descriptive statistics and will include the duration of exposure (days), percentage of missed doses, percentage of cycles delayed, average number of days delayed and percentage of doses interrupted.

Duration of exposure will be derived as follows:

(Date of last administration – Date of first administration) + 1

4.10.2 Study Drug Administration Form in Cohort B

For Patients in Cohort B, for whom the SC SID administration results in an incomplete administration at any cycle, the missed portion of the trastuzumab SC dose may be manually administered from a Vial. In case of multiple device failures at different treatment cycles, the patient is to be reverted to SC Vial administrations of trastuzumab (using a conventional hand-held SC syringe) for all remaining cycles, in order to complete 18 cycles in total as part of the study.

The number of incomplete SC SID administrations (partial or no administration) and percentage (based on all SC SID administrations), will be presented by administration personal (self administered, HCP administered, overall) and amount of administration (partial or no medication). The reason for incomplete administration will be summarised by presenting the number and percentage (based on all events of incomplete administration) of reasons. In addition, the number of patients in Cohort B with at least on incomplete SID administration will be presented by administration personal and amount of administration.

The number of SC Vial administrations in Cohort B and percentage (based on number of cycles), will be presented by administration personal and reason of administration (supplementary after incomplete SC SID administration or non-supplementary without any prior SC SID administration).

The number and percentage of patients and their exact number of incomplete SC SID administrations, partial SID administrations and SID administrations with no study medication being administered at all will be presented.

The number and percentage of patients and their exact number of SC Vial administrations, supplementary SC Vial administrations and non-supplementary SC Vial administrations will

be presented. Details of SC Vial administrations including volume administered, dose received, amount of dose received (full dose, less than full dose) and reason for not fully administered dose will be summarised for all SC Vial administrations.

Notes:

- In case that a SID does not start at all, the dose can be completed by another SID or by a handheld syringe from a vial. According to the eCRF guideline (SafeHer_SID Failure scenarios with eCRF and IWRS instructions_v3_final_30Mar2015.pptx, Scenario 2 and Scenario 3), these two cases will be identified from the text comment to the eCRF field: "If 'NO medication at all' or 'Partially', please provide all reasons why the injection was not fully administered". If the verbatim is "supplementary vial", dose will be identified as administered by a handheld syringe from a vial; whereas if the verbatim contains "supplementary SID" (it might be "supplementary SID, self" or "supplementary SID, HCP") dose will be identified as administered by a SID.
- In cases of multiple (>1) device failures at different treatment cycles, the patient will revert to manual SC administrations of trastuzumab (by a handheld syringe from a vial) for all remaining cycles. These occurrences will be identified as the doses in which the text comment to the eCRF field: "If 'NO medication at all' or 'Partially', please provide all reasons why the injection was not fully administered" contains the verbatim "Repeated SID failures" (SafeHer_SID Failure scenarios with eCRF and IWRS instructions_v3_final_30Mar2015.pptx, Scenario 4).

4.11 Adjustment for Covariates

Not applicable.

4.11.1 Centre effects

This is a multi-center, international trial. Patients from all centres will be pooled.

Adverse Events will be summarized by region, but no formal comparison will be performed.

4.12 Protocol Violations or Deviations

4.12.1 Violation criteria

The following major deviations criteria may result in a patient being excluded from the PP population:

a) Under the Section Inclusion Criteria (Appendix 2)

   1) Eastern Cooperative Oncology Group (ECOG) performance status greater than equal to 2 or no sign of ECOG less than 2 (Inclusion Criteria 3).

   2) No valid confirmation of breast cancer diagnosis Evidence of residual, locally recurrent or metastatic disease or No radiological evidence of absence of residual, locally recurrent or metastatic disease per protocol requirements (Inclusion Criteria 4).

3) No valid confirmation of HER2 positivity or IHC<3 and Negative ISH testing (Inclusion Criteria 5).

b) Under the Section Exclusion Criteria (Appendix 2)

1) Enrolment of a patient with previous treatment with anti-HER2 agent. (Exclusion Criteria 1).
2) Enrolment of a patient with a current malignant disease (other than Breast cancer) that requires active treatment during the study or Enrolment of a patient with previous history of Invasive Breast Cancer (Exclusion Criteria 2).
3) Previous treatment of DCIS in the ipsilateral breast where invasive cancer subsequently develops with any systemic (chemotherapy, hormonal therapy or immunotherapy) or radiation therapy (Exclusion Criteria 3).
4) Enrolment of a patient with any evidence of metastatic disease (Exclusion Criteria 4)
5) Enrolment of a patient without assessing the eligibility-defining laboratory parameters per protocol requirements and retrospective results reveal that patient's safety may be jeopardized (Exclusion Criteria 5).
6) Enrolment of a patient with lab value that is significantly (evaluated on a case by case basis) deviated from the protocol-defined values without justification of the risk-benefit ratio and retrospective results reveal that patient's safety may be jeopardized (Exclusion Criteria 6).
7) Enrolment of a patient with significant lab abnormality, ≥ grade 3 CTCAE.v4 (Exclusion Criteria 7).
8) Other concurrent serious diseases that may interfere with planned treatment including severe pulmonary conditions/illness (Exclusion Criteria 9).
9) Prior maximum cumulative dose of doxorubicin >360 mg/m2 or maximum cumulative dose of epirubicin >720 mg/m2 or equivalent (Exclusion Criteria 10).
10) Enrolment of a patient with a known hypersensitivity to trastuzumab or Enrolment of a patient with a known hypersensitivity to adhesives (Cohort B only) (Exclusion Criteria 11)
11) Enrolment of a patient with History of severe allergic or immunological reactions, e.g. difficult to control asthma (Exclusion Criteria 12)
12) Concurrent enrolment in another clinical trial using an investigational anti-cancer treatment, including hormonal therapy, bisphosphonate therapy and immunotherapy, within 28 days prior to the first dose of study treatment (Exclusion Criteria 15)
13) Enrolment of a patient with more than 12 weeks between the end of the last chemotherapy cycle and the first dose of study treatment, in case these treatments are initiated sequentially (Exclusion Criteria 17)

c) Under the Section During Study Conduct (Appendix 2)

1) Patients enrolled and did not receive any dose of the study drug (Study Drug Admin).

2) The use of protocol-defined prohibited therapy like Concurrent treatment with other systemic HER2-directed immunotherapy or Concurrent investigational agents of any type or Concurrent treatment of anthracyclines with trastuzumab in the adjuvant setting (Prohibited Meds).
3) Assessment:
   Follow-Up visits (including Breast Ca FU, Survival, weight) other than LVEF assessment
   a) Missing more than 2 consecutive Follow-Up visits
   b) 5-year follow-up visit not performed without a valid reason or performed more than 3 months too early (*additional visit will be requested within the time window for assessment of AEs and the Clinical Assessment for Recurrence/Progressive Disease;) Note: If the last LVEF assessment was performed > 9 months ago, then an LVEF assessment is required to be performed at the additional visit.
4) Continuation of study drug administration despite the existence of a protocol defined reason for study drug discontinuation (Withdrawl).
5) Non compliance with study drug treatment (Study Drug Treatment)
   a) Unjustifiable treatment interrupting with the study drug
   b) In patients with early breast cancer eligible for neoadjuvant treatment, trastuzumab SC should only be used concurrently with low-dose anthracycline regimens (maximum cumulative doses: doxorubicin 180 mg/m2 or epirubicin 360 mg/m2).
   c) If patients have been treated concurrently with low-dose anthracyclines and trastuzumab in the neoadjuvant setting, no additional cytotoxic chemotherapy should be given after surgery.
   d) Surgery should be planned after dosing at Cycle 8 without interruption of trastuzumab treatment.

The process of selecting and excluding the subjects from PPS will be based on the derivation of the above deviations criterias. If the derivation is not possible, we will use the PDMS tracker (new) and PD legacy tracker (old) which are combined to identify and exclude the subjects from PPS .

A separate document "Per Protocol Analysis set Specification" will be developed to detail which Major violations will be programmed and which ones will be selected in the tracker.

4.12.2 Protocol deviations

Protocol violations will be presented for patients with at least one violation and for the different violation descriptions by cohort and overall.

4.13 Missing Values – Missing Visits

Generally, there will be no imputation of missing values except for adverse event, concomitant medication and LVEF . Missing start times for adverse events during observation

will be imputed by the maximum (6 hours for Cycle 1 and 2 hours for all cycles afterwards) in a sensitivity analysis.

For missing or partially missing start/stop dates of AE, the following rules will be applied:

Table 4.13.1: Substituting rules for (partially) missing AE start/stop dates

Missing start or stop date	**Substituted start date**	**Substituted stop date (recovery date if AE outcome is "Resolved without sequelae" or "Resolved with sequelae" or if AE is not ongoing)**
.. /mmm/yyyy (= missing day)	If same year and same month of the first intake date, then **First intake date + 1** Else First day of the month	If same month and year than last visit date, then: **Last visit date** Else Last day of the month
../…/yyyy (= missing day and month)	If same year of the first intake date, then **First intake date + 1** Else First day of the year	If same year than last visit date, then: **Last visit date** Else Last day of the year
.. /… /…. (= completely missing date)	**First intake date + 1**	**Last visit date**

In case of missing or partially missing dates for concomitant medication, the following rules will be applied:

Table 4.13.2: Substituting rules for concomitant medication with (partially) missing dates

Missing start or stop date	**Substituted start date**	**Substituted stop date**
../mmm/yyyy (= missing day)	**01/mmm/yyyy**	**the last day of the month (28-29-30-31/mmm/yyyy)**
../…/yyyy (= missing day and month)	**01/JAN/yyyy**	**the last day of the year : 31/DEC/yyyy.**
../.../…. (= completely missing date)	**Informed consent date of the patient - 1**	**- No substitution** (i.e., treatment considered as still ongoing)

In case of missing or partially missing dates for LVEF events, the following rules will be applied:

Table 4.13.3: Substituting rules for LVEF with (partially) missing

Missing LVEF date	Substituted date
.. /mmm/yyyy (= missing day)	If date of visit is not missing, and same month and same year of date of visit, then date of visit Otherwise 01/mmm/yyyy
../…/yyyy (= missing day and month)	If date of visit is not missing, and same year of date of visit, then date of visit else 01/Jan/yyyy
.. /… /…. (= completely missing date)	If date of visit is not missing, then date of visit Else First administration date + 1

4.14 Deviations from SAP

Any deviations from the statistical plan will be described and justified in the final clinical study report, whether written post interim or final analysis.

Section 4.14.1 to section 4.14.6 are referring to the time of the primary analysis and section 4.14.7 is referring to the time of the final analysis.

4.14.1 Additional exploratory Objectives

Following a protocol amendment, additional exploratory objectives were added to the SAP.

As per the SafeHER Study Protocol, patients will remain on site to be observed for 6 hours after the start of their first Trastuzumab SC administration and for 2 hours after the start of each subsequent Trastuzumab SC administration. Patients may be required to remain on site for an extended period of time if considered clinically necessary by the investigator (e.g., because of emergence of AEs). During this time, detailed information of AEs and associated treatment will be recorded and analyzed relative to the last preceding administration of trastuzumab. Therefore, in Cohort B, in addition to onset and resolution dates and times of AEs, detailed information about pre-medications prior to trastuzumab administration will be collected.

In Cohort B only, exploratory analyses on the usability of the SID summarizing the parameters collected via SID Observer Usability Questionnaire (SID UOQ) will be provided to the first patients enrolled who were judged able, and were willing to self-administer

remaining doses from the SID under direct observation of the HCP to achieve a sample size of 816 dosing events in total.

Serum trastuzumab concentrations will be collected and analyzed in a subset of Cohort B subjects to aid in interpretation of immunogenicity data (the presence and titer of anti-trastuzumab antibodies). Sampling time points will match those used for immunogenicity testing in these patients.

4.14.2 Additional primary safety endpoints

Following a protocol amendment, injection site reactions as well administration related reactions were added as primary endpoints.

4.14.3 Analysis set update

The PK Evaluable Population was defined. This analysis set will be used for all PK analysis.

In the ITT population definition, the term "enrolled" was further clarified.

4.14.4 Subgroup analysis

Following requirements from steering committee, subgroup analysis were updated as specified in Section 3.5.5.

4.14.5 Time to event analysis

Due to low incidence of events, Kaplan Meier estimates for the 25th and 75th percentiles are unlikely to be reached and therefore survival rates for overall survival and disease free survival are calculated instead.

4.14.6 Summary of Low Risk Population

A summary of the low risk population was added including the reason why patients were added to the low risk population.

4.14.7 Additional updates for the final analysis

The following additional outputs were added or updated for the final analysis

- Disposition of Patients will be additionally presented for Follow-up
- Demographics, Baseline Characteristics and Breast Cancer Diagnosis on PP population
- Incidence of concomitant medications will be presented by therapeutic area and preferred drug name, by cohort and overall for the Follow- up period.
- A sensitivity analysis (SPM) using an extended definition including also the 2nd primary malignancies (as identified from the AEs by medical review) will be produced at the time of final analysis for Disease Free Survival (DFS) for ITT an PP population (KM plots and tables). Disease Free Survival and Disaese Recurrence listing including SPM will be generated.

- Low risk population summary (The low risk population will be derived based on the tumor size less or equal to 1.0 cm and no lymph node involvement for the final analysis).
- AEs and SAEs in total will be summarized for the follow-up period and the whole study.
- Congestive Heart Failure Related SAEs, Cardiac Dysfunction SAE, Infections grade 3-4.
- All SAEs by Weight, Significant Cardiac AEs and Congestive Heart Failure Related SAEs for Follow-up
- Related SAEs by Weight, Congestive Heart Failure Related SAEs, Significant Cardiac AEs, Cardiac AEs and maximum CTC grade and Second Primary Malignancies Adverse Events for the Whole Study
- Administration Related Reactions by System Organ Class and Preferred Term (12 Tables) for the Whole Study
- The enrollment per country and age groups
- Disease Free Survival by Timing of Chemotherapy (Concurrent Chemotherapy, No Chemotherapy, Sequential Chemotherapy) analysis for ITT and PP.
- Duration of Follow-up by Timing of Chemotherapy (Concurrent Chemotherapy, No Chemotherapy, Sequential Chemotherapy)
- Disease Free Survival by Low Risk population Subgroup analysis for ITT and PP.
- Overall Survival by Low Risk population Subgroup analysis for ITT and PP.
- Summary output and Listings for ECG findings
- Listings for physical exam and serum pregnancy test.
- Summary output and listing for weight.
- Outputs with new immunogenicity definitions
- Post last dose Chemotherapy

4.15 Changes in Conduct or Planned Analyses from the Protocol

There are no changes in the conduct of the study or planned analyses as described in the protocol.

4.16 Algorithms/SAS Codes

- **Tables that need descriptive statistics – continuous variables:**

```
PROC UNIVARIATE DATA=DSET NOPRINT;
    VAR VAR1 VAR2 VAR3 ... VARN;
    BY BYVAR; (optional)
    OUTPUT OUT=OUTNAME
    N=N MEAN=MEAN MIN=MIN MAX=MAX MEDIAN=MEDIAN  STD=STD;
```

RUN;

- **Tables that need frequency counts:**
PROC FREQ DATA=DSET NOPRINT;
BY BYVAR; (optional)
*TABLES VAR1*VAR2;*
OUTPUT OUT=OUTNAME;
RUN;

- **Tables that need 95% Clopper Pearson CIs for binomial proportions:**
PROC FREQ DATA=DSET;
BY BYVAR; (optional)
TABLES VAR1 / BINOMIAL EXACT|CLOPPERPEARSON ALPHA=0.05;
RUN;

- **Tables that need life table with estimates of survival, with CIs:**
PROC LIFETEST DATA=DSET OUTSURV=LIFE METHOD=KM;
*TIME time to response*censor (0 or 1);*
ID patient;
STRATA treatment;
RUN;

5 Tables and Listings

5.1 Table Format

All output will be produced using SAS version 9.2 or a later version.

In the top left portion of each table/listing, a *table/listing number* followed by the *title* of the table/listing will be presented. After the title line, optional *sub-title* or *population* information can be presented. Horizontal lines will appear before and after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page.

The *sponsor name*, *protocol number,* programmers User ID, status of the table/listing (i.e. draft or final) and *SAS program name* will appear bottom left in a string and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of table/listing will appear bottom left under the sponsor name. The source listing number will appear bottom left.

A *landscape layout* is proposed for both table and listing presentations.

The *left* and *right margins* of all tables and listings will be a minimum of 2.1 cm from the left and 1.9cm from the right. The *top and bottom margins* will be a minimum 2.92cm. *Header and footer* will be both 1.27 cm.

There is no special requirement of *font type* and *size*, but an *8-point* font size for tables and *7*or *8-point* for listings is proposed using *Courier New* font. A maximum SAS line size=141 and page size=45 for *8-point* font size, and line size=161 and page size=54 for *7-point* will be used so as to fit on both UK and US paper sizes.

In a listing, in the case that a patient's record has been continued to the next page, an appropriate identification (e.g., the patient ID number) must be presented at the beginning of that page.

5.2 Conventions

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data. Wherever possible the data will be decimal aligned.

Unless otherwise specified frequency tabulations will be presented by number and percentage, where the percentage is presented in brackets to 1 decimal place.

All tables will have their source listing referenced in a footnote. Listings should be sorted by patient and have the source data received by data management referenced in a footnote. All tables and listings will be converted into Microsoft Word documents and collated into two complete documents.

5.3 Tables

An # indicates table will be presented for the final analysis.

5.3.1 Demographic and Baseline

Table Number	Table Title
14.1.1	Screening Failures (All Screened Patients)
14.1.2.1	Patient Disposition – Treatment Period (ITT)
14.1.2.1.1	Patient Disposition – Treatment Period by Medication Subgroup (ITT)
14.1.2.1.2	Patient Disposition – Treatment Period for Patients receiving no Chemotherapy (ITT)
14.1.2.1.3	Patient Disposition – Treatment Period by Weight (ITT)
14.1.2.1.4	Patient Disposition – Treatment Period for Patients receiving Concurrent Taxane (ITT)
14.1.2.1.5	Patient Disposition – Treatment Period for Patients Aged 75 years or Older (ITT)
14.1.2.1.6	Patient Disposition – Treatment Period for Patients receiving Concurrent Anthracyclines (ITT)
14.1.2.1.7	Patient Disposition – Treatment Period for Neoadjuvant Patients (ITT)
14.1.2.2#	Patient Disposition – Follow-up (ITT)
14.1.2.3#	Enrollment per Country and Age Groups
14.1.3#	Protocol Deviations (ITT)
14.1.4.1	Demographics (Safety)
14.1.4.1.1	Demographics by Medication Subgroup (Safety)
14.1.4.1.2	Demographics for Patients receiving no Chemotherapy (Safety)
14.1.4.1.3	Demographics by Weight (Safety)
14.1.4.1.4	Demographics for Patients receiving Concurrent Taxane (Safety)
14.1.4.1.5	Demographics for Patients Aged 75 years or Older (Safety)
14.1.4.1.6	Demographics for Patients receiving Concurrent Anthracyclines (Safety)
14.1.4.1.7	Demographics for Neoadjuvant Patients (Safety)
14.1.4.1.8	Demographics for Patients receiving Concurrent Radiotherapy (Safety)
14.1.4.2#	Demographics (PP)
14.1.5.1	Baseline Characteristics (Safety)
14.1.5.1.1	Baseline Characteristics by Medication Subgroup (Safety)
14.1.5.1.2	Baseline Characteristics for Patients receiving no Chemotherapy (Safety)
14.1.5.1.3	Baseline Characteristics by Weight (Safety)
14.1.5.1.4	Baseline Characteristics for Patients receiving Concurrent Taxane (Safety)
14.1.5.1.5	Baseline Characteristics for Patients aged 75 years or Older (Safety)

Table Number	Table Title
14.1.8.2	Previous Cancer Treatment (ITT)
14.1.8.2.1#	Previous Cancer Treatment (PP)
14.1.9.1	Neoadjuvant Treatment (Safety)
14.1.9.2	Neoadjuvant Treatment (ITT)
14.1.10.1	Adjuvant Treatment (Safety)
14.1.10.2	Adjuvant Treatment (ITT)
14.1.11	Pregnancy Test at Baseline (Safety)

5.3.2 Medications and Exposure (Safety Population)

Table Number	Table Title
14.1.12.1	Prior Medications
14.1.12.2	Concomitant Medications
14.1.12.2.1	Concomitant Medications Given for AE Starting During Observation by Cycle
14.1.12.2.2	Concomitant Medications Given for AE Starting on Day of Trastuzumab Administration by Cycle
14.1.12.3.1	Previous Chemotherapy
14.1.12.3.2	Concurrent Chemotherapy
14.1.12.3.3#	Post last dose Chemotherapy
14.1.12.4	Concurrent Hormonal Therapy
14.1.12.5	Radiotherapy
14.1.12.6#	Concomitant Medications – Follow Up
14.1.13.1	Study Drug Exposure – Number of Cycles
14.1.13.2	Study Drug Exposure – Duration, Missed Doses, Delays and Interruptions
14.1.13.3	Study Drug Exposure – Drug Administration in Cohort B
14.1.13.4	Study Drug Exposure – Number of Incomplete SID Administrations in Cohort B
14.1.13.5	Study Drug Exposure – Number of Vial Administration in Cohort B
14.1.13.6	Study Drug Exposure – Details of Vial Administration in Cohort B
14.1.14#	Low Risk Population Summary
14.1.15	Adherence to observation

5.3.3 Efficacy

Table Number	Table Title
14.2.1.1#	Disease Free Survival (ITT)
14.2.1.1.1#	Disease Free Survival by Timing of Chemotherapy (ITT)
14.2.1.2#	Disease Free Survival (PP)

Table Number	Table Title
14.2.1.3#	Disease Free Survival – Sensitivity (SPM) (PP)
14.2.1.4#	Disease Free Survival by Timing of Chemotherapy (PP)
14.2.1.5#	Disease Free Survival – Sensitivity (SPM) (ITT)
14.2.2.1#	Disease Free Survival - Type of Event (ITT)
14.2.2.1.1#	Disease Free Survival - Type of Event by Medication Subgroup (ITT)
14.2.2.1.2#	Disease Free Survival - Type of Event for Patients receiving no Chemotherapy (ITT)
14.2.2.1.3#	Disease Free Survival by Low Risk Population Subgroup (ITT)
14.2.2.1.4#	Disease Free Survival - Type of Event Sensitivity (SPM) (ITT)
14.2.2.2#	Disease Free Survival - Type of Event (PP)
14.2.2.2.1#	Disease Free Survival by Low Risk Population Subgroup (PP)
14.2.2.2.2#	Disease Free Survival - Type of Event Sensitivity (SPM) (PP)
14.2.3.1#	Overall Survival (ITT)
14.2.3.1.1#	Overall Survival by Low Risk Population Subgroup (ITT)
14.2.3.2#	Overall Survival (PP)
14.2.3.2.1#	Overall Survival by Low Risk Population Subgroup (PP)
14.2.4.1	Patient Satisfaction (SID) Questionnaire (ITT)

5.3.4 Safety

5.3.4.1 Adverse events (Safety Population)

Table Number	Table Title
14.3.1.1	Summary of Adverse Events – Treatment Period
14.3.1.1.1	Summary of Adverse Events – Treatment Period by Region
14.3.1.1.2	Summary of Adverse Events starting post-dose on Day of Trastuzumab Administration by Cycle
14.3.1.1.3	Summary of Administration Related Reactions starting post-dose on Day of Trastuzumab Administration by Cycle
14.3.1.1.4	Summary of Injection Site Reactions starting post-dose on Day of Trastuzumab Administration by Cycle
14.3.1.1.5#	Summary of Adverse Events – Follow-up
14.3.1.1.6#	Summary of Adverse Events – Whole Study
14.3.1.2	Summary of Serious Adverse Events – Treatment Period
14.3.1.2.1	Summary of Serious Adverse Events – Treatment Period by Region
14.3.1.2.2#	Summary of Serious Adverse Events – Follow-up
14.3.1.2.3#	Summary of Serious Adverse Events – Whole Study
14.3.1.3	Summary of Related Adverse Events – Treatment Period

Table Number	Table Title
14.3.1.4	Summary of Related Serious Adverse Events – Treatment Period
14.3.1.5	Most Frequent Adverse Events by Preferred Term (>=5% Events in Any Cohort) – Treatment Period
14.3.1.6.1	Adverse Events by System Organ Class and Preferred Term – Treatment Period
14.3.1.6.1.1	Adverse Events by System Organ Class and Preferred Term – Treatment Period by Medication Subgroup
14.3.1.6.1.2	Adverse Events by System Organ Class and Preferred Term – Treatment Period for Patients receiving no Chemotherapy
14.3.1.6.1.2.1	Adverse Events by System Organ Class and Preferred Term – Treatment Period for Patients receiving no Chemotherapy by Weight
14.3.1.6.1.3	Adverse Events by System Organ Class and Preferred Term – Treatment Period by Weight
14.3.1.6.1.4	Adverse Events by System Organ Class and Preferred Term – Treatment Period for Patients receiving Concurrent Taxane
14.3.1.6.1.5	Adverse Events by System Organ Class and Preferred Term – Treatment Period for Patients Aged 75 years or Older
14.3.1.6.1.5.1	Adverse Events by System Organ Class and Preferred Term – Treatment Period for Patients Aged 75 years or Older by Medication Subgroup
14.3.1.6.1.6	Adverse Events by System Organ Class and Preferred Term – Treatment Period for Patients receiving Concurrent Anthracyclines
14.3.1.6.1.7	Adverse Events by System Organ Class and Preferred Term – Treatment Period for Neoadjuvant Patients
14.3.1.6.1.8	Adverse Events by System Organ Class and Preferred Term – Treatment Period for Patients receiving Concurrent Radiotherapy
14.3.1.6.1.9	Adverse Events by System Organ Class and Preferred Term – Treatment Period by Race
14.3.1.6.2.1[#]	Adverse Events by System Organ Class and Preferred Term – Follow-up
14.3.1.6.2.2[#]	Adverse Events by System Organ Class and Preferred Term – Follow-up by Race
14.3.1.6.3[#]	Adverse Events by System Organ Class and Preferred Term – Whole study
14.3.1.7.1	Serious Adverse Events by System Organ Class and Preferred Term – Treatment Period
14.3.1.7.1.1	Serious Adverse Events by System Organ Class and Preferred Term – Treatment Period by Medication Subgroup
14.3.1.7.1.2	Serious Adverse Events by System Organ Class and Preferred Term – Treatment Period for Patients receiving no Chemotherapy

Table Number	Table Title
14.3.1.7.1.3	Serious Adverse Events by System Organ Class and Preferred Term – Treatment Period by Weight
14.3.1.7.1.4	Serious Adverse Events by System Organ Class and Preferred Term – Treatment Period for Patients receiving Concurrent Taxane
14.3.1.7.1.5	Serious Adverse Events by System Organ Class and Preferred Term – Treatment Period for Patients Aged 75 years or Older
14.3.1.7.1.5.1	Serious Adverse Events by System Organ Class and Preferred Term – Treatment Period for Patients Aged 75 years or Older by Medication Subgroup
14.3.1.7.1.6	Serious Adverse Events by System Organ Class and Preferred Term – Treatment Period for Patients receiving Concurrent Anthracyclines
14.3.1.7.1.7	Serious Adverse Events by System Organ Class and Preferred Term – Treatment Period for Neo-adjuvant Patients
14.3.1.7.1.8	Serious Adverse Events by System Organ Class and Preferred Term – Treatment Period for Patients receiving Concurrent Radiotherapy
14.3.1.7.1.9	Serious Adverse Events by System Organ Class and Preferred Term – Treatment by Race
14.3.1.7.2[#]	Serious Adverse Events by System Organ Class and Preferred Term – Follow-up
14.3.1.7.2.1[#]	Serious Adverse Events by System Organ Class and Preferred Term – Follow-up by Weight
14.3.1.7.2.2[#]	Serious Adverse Events by System Organ Class and Preferred Term – Follow-up by Race
14.3.1.7.3[#]	Serious Adverse Events by System Organ Class and Preferred Term – Whole study
14.3.1.8.1	Related Adverse Events by System Organ Class and Preferred Term – Treatment Period
14.3.1.8.2[#]	Related Adverse Events by System Organ Class and Preferred Term – Follow-up
14.3.1.8.3[#]	Related Adverse Events by System Organ Class and Preferred Term – Whole Study
14.3.1.9.1	Related Serious Adverse Events by System Organ Class and Preferred Term - Treatment Period
14.3.1.9.2[#]	Related Serious Adverse Events by System Organ Class and Preferred Term - Follow-up
14.3.1.9.3[#]	Related Serious Adverse Events by System Organ Class and Preferred Term – Whole Study
14.3.1.9.4[#]	Related Serious Adverse Events by System Organ Class and Preferred Term – Whole Study by Weight

Table Number	Table Title
14.3.1.10.1	Adverse Events Grade 3 or more by System Organ Class and Preferred Term – Treatment Period
14.3.1.10.1.1	Adverse Events Grade 3 or more by System Organ Class and Preferred Term – Treatment Period by Medication Subgroup
14.3.1.10.1.2	Adverse Events Grade 3 or more by System Organ Class and Preferred Term – Treatment Period for Patients receiving no Chemotherapy
14.3.1.10.1.3	Adverse Events Grade 3 or more by System Organ Class and Preferred Term – Treatment Period by Weight
14.3.1.10.1.4	Adverse Events Grade 3 or more by System Organ Class and Preferred Term – Treatment Period for Patients receiving Concurrent Taxane
14.3.1.10.1.5	Adverse Events Grade 3 or more by System Organ Class and Preferred Term – Treatment Period for Patients Aged 75 years or Older
14.3.1.10.1.5.1	Adverse Events Grade 3 or more by System Organ Class and Preferred Term – Treatment Period for Patients Aged 75 years or Older by Medication Subgroup
14.3.1.10.1.6	Adverse Events Grade 3 or more by System Organ Class and Preferred Term – Treatment Period for Patients receiving Concurrent Anthracyclines
14.3.1.10.1.7	Adverse Events Grade 3 or more by System Organ Class and Preferred Term – Treatment Period for Neoadjuvant Patients
14.3.1.10.1.8	Adverse Events Grade 3 or more by System Organ Class and Preferred Term – Treatment Period for Patients receiving Concurrent Radiotherapy
14.3.1.10.1.9	Adverse Events Grade 3 or more by System Organ Class and Preferred Term – Treatment Period by Race
14.3.1.10.2[#]	Adverse Events Grade 3 or more by System Organ Class and Preferred Term – Follow-up
14.3.1.10.2.1[#]	Adverse Events Grade 3 or more by System Organ Class and Preferred Term – Follow-up by Race
14.3.1.10.3[#]	Adverse Events Grade 3 or more by System Organ Class and Preferred Term – Whole Study
14.3.1.11.1.1	Adverse Events starting Post-dose on Day of Trastuzumab Administration by System Organ Class and Preferred Term by Cycle
14.3.1.11.1.2	Adverse Events Starting Post-Dose on Day of Trastuzumab Administration by System Organ Class and Preferred Term by CTC Grade and Cycle
14.3.1.11.2.1	Serious Adverse Events Starting Post-Dose on Day of Trastuzumab Administration by System Organ Class and Preferred Term by Cycle

Table Number	Table Title
14.3.1.11.3.1	Adverse Events Grade 3 or More Starting Post-Dose on Day of Trastuzumab Administration by System Organ Class and Preferred Term by Cycle
14.3.1.12.1	Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term - Treatment Period
14.3.1.12.1.1	Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term - Treatment Period by Weight
14.3.1.12.1.2	Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term - Treatment Period by Race
14.3.1.13.1	Adverse Events Leading to Study Drug Interruption by System Organ Class and Preferred Term - Treatment Period
14.3.1.14.1	Adverse Events by System Organ Class and Preferred Term Classified According to CTC Grade and Relationship - Treatment Period
14.3.1.14.2	Adverse Events by System Organ Class, Preferred Term and Maximum CTC Grade - Treatment Period
14.3.1.14.3#	Cardiac Adverse Events by System Organ Class and Preferred Term and maximum CTC grade – Whole Study
14.3.1.15	Serious Adverse Events by System Organ Class, Preferred Term and Maximum CTC Grade - Treatment Period
14.3.1.16.1	Cardiac Adverse Events by System Organ Class and Preferred Term - Treatment Period
14.3.1.16.1.1	Cardiac Adverse Events by System Organ Class and Preferred Term - Treatment Period by Medication Subgroup
14.3.1.16.1.2	Cardiac Adverse Events by System Organ Class and Preferred Term - Treatment Period for Patients receiving no Chemotherapy
14.3.1.16.1.3	Cardiac Adverse Events by System Organ Class and Preferred Term - Treatment Period by Weight
14.3.1.16.1.4	Cardiac Adverse Events by System Organ Class and Preferred Term - Treatment Period by Race
14.3.1.16.2#	Cardiac Adverse Events by System Organ Class and Preferred Term – Follow-up
14.3.1.16.2.1#	Cardiac Adverse Events by System Organ Class and Preferred Term – Follow-up by Race
14.3.1.16.3#	Cardiac Adverse Events by System Organ Class and Preferred Term – Whole Study
14.3.1.16.4.1#	Significant Cardiac Adverse Events by System Organ Class and Preferred Term - Follow-up
14.3.1.16.4.2#	Significant Cardiac Adverse Events by System Organ Class and Preferred Term - Whole Study

Table Number	Table Title
14.3.1.17.1	Injection Site Reactions by System Organ Class and Preferred Term - Treatment Period
14.3.1.18.1	Administration Related Reactions by System Organ Class and Preferred Term - Treatment Period
14.3.1.18.1.1	Administration Related Reactions by System Organ Class and Preferred Term – Treatment Period by Medication Subgroup
14.3.1.18.1.2	Administration Related Reactions by System Organ Class and Preferred Term – Treatment Period for Patients receiving no Chemotherapy
14.3.1.18.1.3	Administration Related Reactions by System Organ Class and Preferred Term – Treatment Period by Weight
14.3.1.18.1.4	Administration Related Reactions by System Organ Class and Preferred Term – Treatment Period for Patients receiving Concurrent Taxane
14.3.1.18.1.5	Administration Related Reactions by System Organ Class and Preferred Term – Treatment Period for Patients Aged 75 years or Older
14.3.1.18.1.5.1	Administration Related Reactions by System Organ Class and Preferred Term – Treatment Period for Patients Aged 75 years or Older by Medication Subgroup
14.3.1.18.1.6	Administration Related Reactions by System Organ Class and Preferred Term – Treatment Period for Patients receiving Concurrent Anthracyclines
14.3.1.18.1.7	Administration Related Reactions by System Organ Class and Preferred Term – Treatment Period for Neoadjuvant Patients
14.3.1.18.1.8	Administration Related Reactions by System Organ Class and Preferred Term – Treatment Period for Patients receiving Concurrent Radiotherapy
14.3.1.18.1.9	Administration Related Reactions by System Organ Class and Preferred Term – Treatment Period by Race
14.3.1.19	Administration Related Reactions Grade 3 or more by System Organ Class and Preferred Term - Treatment Period
14.3.1.20.1#	Congestive Heart Failure Related Serious Adverse Events by System Organ Class and Preferred Term – Treatment Period
14.3.1.20.2#	Congestive Heart Failure Related Serious Adverse Events by System Organ Class and Preferred Term – Follow-up
14.3.1.20.3#	Congestive Heart Failure Related Serious Adverse Events by System Organ Class and Preferred Term – Whole Study

Table Number	Table Title
14.3.1.21#	Second Primary Malignancies Adverse Events by System Organ Class and Preferred Term - Whole Study
14.3.2.1#	Treatment Emergent Cardiac Adverse Events – Event Free Rates
14.3.2.1.1#	Treatment Emergent Cardiac Adverse Events – Event Free Rates by Medication Subgroup
14.3.2.1.2#	Treatment Emergent Cardiac Adverse Events – Event Free Rates for Patients receiving no Chemotherapy
14.3.2.2	Injection Site Reactions – Event Free Rates
14.3.2.3	Administration Related Reactions – Event Free Rates
14.3.3.1	Deaths – Treatment Period
14.3.3.2#	Deaths – Follow-up
14.3.3.3#	Deaths – Whole Study
14.3.5.9.5.1#	Administration Related Reactions by System Organ Class and Preferred Term - Whole Study (Safety)
14.3.5.9.5.1.1#	Administration Related Reactions by System Organ Class and Preferred Term - Whole Study by Age Group (<=50 vs. >50 years) (Safety)
14.3.5.9.5.1.2#	Administration Related Reactions by System Organ Class and Preferred Term - Whole Study by Age Group (<=65 vs. >65 years) (Safety)
14.3.5.9.5.1.3#	Administration Related Reactions by System Organ Class and Preferred Term - Whole Study by Age Group (<=75 vs. >75 years) (Safety)
14.3.5.9.5.1.4#	Administration Related Reactions by System Organ Class and Preferred Term - Whole Study by Region (Safety)
14.3.5.9.5.1.5#	Administration Related Reactions by System Organ Class and Preferred Term - Whole Study by Race (Safety)
14.3.5.9.5.2#	Administration Related Reactions by System Organ Class and Preferred Term by CTC Grade - Whole Study (Safety)
14.3.5.9.5.2.1#	Administration Related Reactions by System Organ Class and Preferred Term by CTC Grade - Whole Study by Age Group (<=50 vs. >50 years) (Safety)
14.3.5.9.5.2.2#	Administration Related Reactions by System Organ Class and Preferred Term by CTC Grade - Whole Study by Age Group (<=65 vs. >65 years) (Safety)
14.3.5.9.5.2.3#	Administration Related Reactions by System Organ Class and Preferred Term by CTC Grade - Whole Study by Age Group (<=75 vs. >75 years) (Safety)
14.3.5.9.5.2.4#	Administration Related Reactions by System Organ Class and Preferred Term by CTC Grade - Whole Study by Region (Safety)

Table Number	Table Title
14.3.5.9.5.2.5#	Administration Related Reactions by System Organ Class and Preferred Term by CTC Grade - Whole Study by Race (Safety)

5.3.4.2 Laboratory results (Safety Population)

Table Number	Table Title
14.3.4.1	Laboratory Results – Hematology
14.3.4.2	Laboratory Results Change from Baseline – Hematology
14.3.4.3	Shift Table of NCI CTC Grades – Hematology
14.3.4.4	Laboratory Results – Biochemistry
14.3.4.5	Laboratory Results Change from Baseline – Biochemistry
14.3.4.6	Shift Table of NCI CTC Grades – Biochemistry

5.3.4.3 Other safety (Safety Population)

Table Number	Table Title
14.3.5.1.1	Vital Signs – Systolic Blood Pressure (mmHg)
14.3.5.1.2	Vital Signs – Diastolic Blood Pressure (mmHg)
14.3.5.1.3	Vital Signs – Pulse (bpm)
14.3.5.2#	Weight (kg)
14.3.5.3#	ECG – Overall Interpretation
14.3.5.4.1#	Left Ventricular Ejection Fraction (%)
14.3.5.4.2#	Left Ventricular Ejection Fraction (%) – Changes
14.3.5.4.2.1#	Left Ventricular Ejection Fraction (%)– Changes by Weight
14.3.5.4.3#	Left Ventricular Ejection Fraction (%) – Rates of Clinical Indication
14.3.5.5	ECOG Performance Status
14.3.5.6#	Duration of Follow-up
14.3.5.6.1#	Duration of Follow-up by Timing of Chemotherapy

Cohort B only:

14.3.5.7.1#	Summary of Anti-Trastuzumab Antibodies Over Time (New Definitions)
14.3.5.7.2	Summary of Anti-Trastuzumab Antibodies
14.3.5.7.2.1#	Baseline Prevalence and Post-Baseline Incidence of Anti-Trastuzumab Antibodies (New Definitions)
14.3.5.7.3#	Summary of Anti-rHuPH20 Antibodies Over Time (New Definitions)
14.3.5.7.4	Summary of Anti-rHuPH20 Antibodies
14.3.5.7.4.1#	Baseline Prevalence and Post-Baseline Incidence of Anti-rHuPH20 Antibodies (New Definitions)
14.3.5.8.1#	Summary of Observed Serum Trastuzumab Concentration by Anti-Trastuzumab Antibody Status at each Visit (New Definitions) (PK)
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Listing Number	Listing Title
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Figure Number	Figure Title
	(Safety)
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14.2.7	SID Patient Satisfaction (Safety)
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Tables, listings, and figures will follow the format of: MO28048 SafeHer TLFs Final 20Feb2020.doc.

5.6 Appendices

Appendix 1 Raw SAS Statistical Output

5.7 References

1. American Society of Clinical Oncology (ASCO) 2006 Guideline for Breast Cancer Follow-up Khatcheressian et al. 2006.
2. Roche SOP, International Standard for the Handling and Reporting of Laboratory Data (COG 3007), Version 4, dated 04 July 2007
3. Romond et al. 2005; Ewer and O'Shaughnessy 2007

6 Appendices

6.1 Appendix 1

6.1.1 List of High Level Terms for Injection Site Reactions

ADMINISTRATION SITE REACTIONS NEC
APPLICATION AND INSTILLATION SITE REACTIONS
INJECTION SITE REACTIONS

6.1.2 List of Preferred Terms for Administration Related Reactions

ACUTE RESPIRATORY FAILURE
ALLERGIC OEDEMA
ANAPHYLACTIC REACTION
ANAPHYLACTIC SHOCK
ANAPHYLACTIC TRANSFUSION REACTION
ANAPHYLACTOID REACTION
ANAPHYLACTOID SHOCK
ANGIOEDEMA
ASTHMA
BLOOD PRESSURE DECREASED
BLOOD PRESSURE DIASTOLIC DECREASED
BLOOD PRESSURE SYSTOLIC DECREASED
BRONCHIAL OEDEMA
BRONCHOSPASM
CARDIAC ARREST
CARDIO-RESPIRATORY ARREST
CARDIO-RESPIRATORY DISTRESS
CARDIOVASCULAR INSUFFICIENCY
CHEST DISCOMFORT
CHOKING
CHOKING SENSATION
CIRCULATORY COLLAPSE
CIRCUMORAL OEDEMA
COUGH
CYANOSIS
DIASTOLIC HYPOTENSION
DRUG HYPERSENSITIVITY
DYSPNOEA
ERYTHEMA
EYE OEDEMA
EYE PRURITUS
EYE SWELLING
EYELID OEDEMA
FACE OEDEMA
FIRST USE SYNDROME
FLUSHING

GENERALISED ERYTHEMA
HYPERSENSITIVITY
HYPERVENTILATION
HYPOTENSION
INFUSION RELATED REACTION
INJECTION SITE HYPERSENSITIVITY
INJECTION SITE URTICARIA
KOUNIS SYNDROME
LARYNGEAL DYSPNOEA
LARYNGEAL OEDEMA
LARYNGOSPASM
LARYNGOTRACHEAL OEDEMA
LIP OEDEMA
LIP SWELLING
NASAL OBSTRUCTION
OCULAR HYPERAEMIA
OEDEMA
OEDEMA MOUTH
OROPHARYNGEAL SPASM
OROPHARYNGEAL SWELLING
PERIORBITAL OEDEMA
PRURITUS
PRURITUS ALLERGIC
PRURITUS GENERALISED
RASH
RASH ERYTHEMATOUS
RASH GENERALISED
RASH PRURITIC
RESPIRATORY ARREST
RESPIRATORY DISTRESS
RESPIRATORY FAILURE
REVERSIBLE AIRWAYS OBSTRUCTION
SENSATION OF FOREIGN BODY
SHOCK
SKIN SWELLING
SNEEZING
STRIDOR
SWELLING
SWELLING FACE
SWOLLEN TONGUE
TACHYPNOEA
THROAT TIGHTNESS
TONGUE OEDEMA
TRACHEAL OBSTRUCTION
TRACHEAL OEDEMA
TYPE I HYPERSENSITIVITY
UPPER AIRWAY OBSTRUCTION

URTICARIA
URTICARIA PAPULAR
WHEEZING

6.2 Appendix 2

6.2.1 List of protocol violations due to non compliance with inclusion criteria

Code	Description	Major or Minor
Inclusion criterion 1	**Signed Informed Consent.** Patient enrolment without a signed informed consent form	Major. If signed retrospectively, Minor
Inclusion criterion 2	**Female or male aged 18 years or above** Enrolment of a patient younger than 18 years	 Major
Inclusion criterion 3	**Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1** Not assessing ECOG status at screening Enrolment of a patient with ECOG performance status ≥ 2	 Major. If there is no sign that ECOG was <2, Minor Major
Inclusion criterion 4	**Histologically confirmed early invasive HER2-positive carcinoma of the breast with no evidence of residual, locally recurrent or metastatic disease and defined as clinical stage I (T1, N0, M0) to IIIC (any T, N3, M0) that is eligible for adjuvant treatment with trastuzumab** No valid confirmation of breast cancer diagnosis Evidence of residual, locally recurrent or metastatic disease No radiological evidence of absence of residual, locally recurrent or metastatic disease per protocol requirements	 Major
Inclusion criterion 5	**HER2-positive EBC, defined as IHC 3+, or a positive in situ hybridization (ISH testing) by validated and approved methods within a certified laboratory** No valid confirmation of HER2 positivity IHC<3 and Negative ISH testing	 Major
Inclusion criterion 6	**Screening left ventricular ejection fraction (LVEF) ≥ 50% as measured by echocardiography, Multi Gated Acquisition (MUGA) scan or Magnetic Resonance Imaging (MRI) per local practice** No LVEF assessment at screening LVEF < 50% at screening LVEF assessment not within 14 days prior to first study drug treatment for patients treated previously with anthracycline LVEF assessment not within 28 days prior to first study drug treatment for patients not treated previously with anthracycline	 If LVEF at screening is missed and the first LVEF is <50% then it is Major Major Major Minor
Inclusion criterion 7	**Agreement to use an adequate, non-hormonal means of contraception by women of childbearing potential (defined as pre-menopausal and not surgically sterilized or < 1 year after the onset of menopause) and by male participants with partners of childbearing potential only.**	

	Examples of adequate contraceptive measures are an intra-uterine device, a barrier method (condoms, diaphragm) in conjunction with spermicidal jelly, or total abstinence. Oral, injectable, or implant hormonal contraceptives are not acceptable for females participating in the study. Enrolment of a patient without obtaining his/her agreement on the use of adequate contraception.	Major
Inclusion criterion 8	**Intact skin at site of SC injection on the thigh.** Enrolment of a patient with damaged skin in both thighs which makes it impossible to administer the study drug in the thigh.	Major

6.2.2 List of protocol violations due to non compliance with exclusion criteria

Code	Description	Major or Minor
Exclusion criterion 1	**Previous neoadjuvant or adjuvant breast cancer treatment with an approved or investigational anti-HER2 agent** Enrolment of a patient with previous treatment with anti-HER2 agent.	Major
Exclusion criterion 2	**History of other malignancy which could affect compliance with the protocol or interpretation of results (including previous invasive ipsilateral or contralateral breast cancer). Patients with curatively treated carcinoma in situ of the cervix or basal cell carcinoma, and patients with other curatively-treated malignancies who have been disease-free for at least 5 years, are eligible.** Enrolment of a patient with a current malignant disease (other than Breast cancer) that requires active treatment during the study. Enrolment of a patient with previous history of Invasive Breast Cancer	Major Major
Exclusion criterion 3	**Past history of ductal carcinoma in situ (DCIS) within the last 5 years that has been treated with any systemic therapy OR with radiation therapy to the ipsilateral breast where invasive cancer subsequently develops. Patients who had their DCIS treated with surgery only are allowed to enter the study.** Previous treatment of DCIS in the ipsilateral breast where invasive cancer subsequently develops with any systemic (chemotherapy, hormonal therapy or immunotherapy) or radiation therapy.	Major
Exclusion criterion 4	**Metastatic disease** Enrolment of a patient with any evidence of metastatic disease	Major
Exclusion criteria 5, 6, 7	**Hematological, Biochemical and Organ Function** Enrolment of a patient without assessing the eligibility-defining laboratory parameters per protocol requirements. Enrolment of a patient with lab value that is significantly (evaluated on a case by case basis) deviated from the protocol-defined values without justification of the risk-benefit	Minor. If retrospective results reveal that patient´s safety may be jeopardized then it is Major Minor. If retrospective results reveal that patient´s safety may be

	ratio Enrolment of a patient with significant lab abnormality, ≥ grade 3 CTCAE.v4	jeopardized then it is Major Major
Exclusion criterion 8	**Serious cardiac illness** Enrolment of a patient with any of the following: History of documented heart failure or systolic dysfunction (LVEF < 50%) High-risk uncontrolled arrhythmias such as atrial tachycardia with a heart rate > 100/min at rest, significant ventricular arrhythmia (ventricular tachycardia) or higher-grade atrioventricular (AV) block (second degree AV-block Type 2 [Mobitz 2] or third degree AV-block) Angina pectoris requiring anti-anginal medication Clinically significant valvular heart disease Evidence of transmural infarction on electrocardiogram (ECG) Poorly controlled or uncontrolled hypertension (blood pressure constantly over 140/90 mm/hg, despite treatment), or history of hypertensive crisis or hypertensive encephalopathy	Assessed on a case by case basis
Exclusion criterion 9	**Other concurrent serious diseases that may interfere with planned treatment including severe pulmonary conditions/illness** Enrolment of a patient with concurrent serious illness unless the risk-benefit ratio is justified	Major
Exclusion criterion 10	**Prior maximum cumulative dose of doxorubicin >360 mg/m^2 or maximum cumulative dose of epirubicin >720 mg/m^2 or equivalent** Enrolment of a patient with a documented prior cumulative dose of anthracycline that exceeds the limits allowed per protocol.	Major
Exclusion criterion 11	**Known hypersensitivity to trastuzumab, murine proteins, or excipients, or a general hypersensitivity to adhesives (Cohort B only) .** Enrolment of a patient with a known hypersensitivity to trastuzumab Enrolment of a patient with a known hypersensitivity to adhesives (Cohort B only)	Major Major
Exclusion criterion 12	**History of severe allergic or immunological reactions, e.g. difficult to control asthma.** Enrolment of a patient with history of severe allergic or immunologic reactions unless the risk-benefit ratio is justified	Major
Exclusion criterion 13	**Pregnancy or lactation** Enrolment of a known pregnant or lactation female Enrolment a patient of child bearing potential without performing pregnancy test as per protocol requirements	Major Major If the test is done prior to first dose and is negative then it is Minor
Exclusion criterion 14	**Unable or unwilling to comply with the requirements of the protocol, as assessed by the investigator** Enrolment of a patient without prior agreement on complying with protocol requirement	Major. If signed retrospectively, Minor
Exclusion criterion	**Concurrent enrolment in another clinical trial using an investigational anti-cancer treatment, including**	

15	**hormonal therapy, bisphosphonate therapy and immunotherapy, within 28 days prior to the first dose of study treatment** Less than 28 days from the last administration of an investigational drug in a prior clinical trial and the first study treatment in the current study	Major
Exclusion criterion 16	**Major surgical procedure or significant traumatic injury within 14 days prior to the first dose of study treatment or anticipated need for major surgery during the course of study treatment except for breast cancer surgery for patient receiving study drug in the neoadjuvant setting. Patients must be free of any clinically significant sequelae of prior surgery before they can receive their first dose of study treatment.** Enrolment of a patient with significant post-traumatic or post-surgery sequelae that can jeopardize the patient safety	Major
Exclusion criterion 17	**More than 12 weeks between the end of the last chemotherapy cycle and the first dose of study treatment, in case these treatments are initiated sequentially. This criterion does not apply to patients who are starting trastuzumab SC without previous or concurrent chemotherapy or concurrently with chemotherapy.** This should be considered as Major Violation if the long period (more 12 weeks) between last dose of chemotherapy and first dose of study drug was not justified by the investigator	Major Minor. If the time lapse from last chemotherapy to start of Transtuzumab is over 15 weeks then it is Major
Exclusion criterion 18	**Current peripheral neuropathy of grade 3 or greater per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.** Enrolment of a patient with current peripheral neuropathy of grade 3 or greater per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.	Major

6.2.3 List of protocol violations during study conduct

Code	Description	Major or Minor	Withdraw patient?
Study Drug Admin	**Patients enrolled and did not receive any dose of the study drug.**	Major	Discuss on a case by case basis
Study Drug Toxicity	**Non compliance with protocol defined instructions for Management of Trastuzumab-related Toxicity.**		
	Not delaying trastuzumab SC therapy despite the presence of nonhaematological, grade 3 or 4 (excluding cardiac) toxicity and toxicity resolved within a maximum of 5 weeks calculated from last administration	Major	Discuss on a case by case basis
	No permanent discontinuation of trastuzumab SC therapy despite the presence of non-haematological, grade 3 or 4 (excluding cardiac) toxicity and toxicity NOT resolved to grade <2 or disappeared within a maximum of 5 weeks calculated from last administration	Major	As above
	No permanent discontinuation of trastuzumab SC therapy despite the recurrence of nonhaematological grade 3 or 4 (excluding cardiac) toxicity upon rechallenge.	Major	As above
	Not delaying trastuzumab SC therapy despite the presence of haematological toxicity (Neutropenia < 1.5 x 10^9/L) and toxicity is considered resolved until neutrophils ≥ 1.5 x 10^9/L.	Major	As above
	Not delaying of trastuzumab SC therapy despite the presence of cardiac toxicity: (significant asymptomatic drop in LVEF (≥ 10 percentage points from baseline and to a LVEF < 50%).	Major	As above
	No permanent discontinuation of trastuzumab SC therapy despite the presence of cardiac toxicity: symptomatic congestive heart failure.	Major	As above
	Dose reduction of the study drug injections of the study drug in a location other than the patient's thigh(s).	Major	As above
	Any other administration of the study drug other than subcutaneous (SC).	Major	As above
Prohibited Meds	**The use of protocol-defined prohibited therapy including** Concurrent treatment with other systemic HER2-directed immunotherapy	Major	Discuss on a case by case basis
	Concurrent investigational agents of any type.	Major	
	Concurrent treatment of anthracyclines with trastuzumab in the adjuvant setting	Major	As above
Study Drug	**Administration of Study Drug** Administration of study drug in sites other than the thigh.	Major	Discuss on

Admin	Any other administration of the study drug other than subcutaneous (SC).	Major	a case by case basis
LVEF	**Non compliance with protocol-defined algorithm for continuation and discontinuation of trastuzumab SC based on LVEF assessment in asymptomatic patients (protocol Appendix 4)** Not delaying trastuzumab SC therapy despite a LVEF of ≤ 44% Not delaying trastuzumab SC therapy despite a LVEF 45 – 49% with a drop in the LVEF value by ≥ 10 points compared to baseline No permanent discontinuation of trastuzumab SC therapy following a repeat assessment of LVEF done 3 weeks after holding of trastuzumab SC therapy and the result of the repeat assessment was a LVEF value of ≤ 44% or 45 – 49% with a drop in the LVEF value by ≥ 10 points compared to baseline.	Major Major Major	Discuss on a case by case basis As above
SID	**Use of the device** All deviations with regard to the use of the device should be reported to CIL MM who shall discuss the reported deviation with Roche IML and other relevant team members. The grading of those deviations will be done on a case-bycase basis.	As appro-priate	Discuss on a case by case basis
Assessments	**Non compliance with protocol-defined schedule of assessments** No LVEF assessment as required per protocol schedule of assessments during treatment phase. No LVEF assessment as required per protocol schedule of assessments during follow-up phase. If LVEF assessment is performed as required per protocol schedule of assessment during the follow-up phase but delayed more than 15 days: **<u>1 year post-study treatment:</u>** - A delay of up to 4 months from the defined schedule of LVEF assessments - A delay of more than 4 months from the defined schedule of LVEF assessments **<u>2 to 5 years post-study treatment:</u>** - A delay of up to 8 months from the defined schedule of LVEF assessments	Major Major Minor Major Minor	

	- A delay of more than 8 months from the defined schedule of LVEF assessments	Major	
	Delayed Safety Follow-up visit for more than 3 months.	Major	Discuss on a case by case basis
	<u>Follow-Up visits (including Breast Ca FU, Survival, weight) other than LVEF assessment</u>		
	Follow-up visit missed or delayed more than 15 days[1]	Minor	Retain patient
	Missing more than 2 consecutive Follow-Up visits	Major	Retain patient
	5-year Follow-up visit 5-year follow-up visit not performed without a valid reason or performed more than 3 months too early (*additional visit will be requested within the time window for assessment of AEs and the Clinical Assessment for Recurrence/Progressive Disease;)	Major	Assessed on case by case basis.
	** Note: If the last LVEF assessment was performed > 9 months ago, then an LVEF assessment is required to be performed at the additional visit.*		
	5-year follow-up visit performed < 1 month too early	No action taken	Retain patient
	5-year follow-up visit performed >= 1 month too early	will be queried for confirma-tion	Retain patient
	5- year FU Visit performed too late	no action required	Retain patient
	Visit performed up to 1 month late –		
	Visit performed greater than 1 month late	will be queried for confirma-tion	Retain patient
	No PD needs to be reported for ANY visit performed too late		

[1] This category refers to follow-up visits other than the last 5-y FU visit

Withdraw-al	**Treatment discontinuation and withdrawal from the study** Continuation of study drug administration despite the existence of a protocol defined reason for study drug discontinuation.	Major	Discuss on a case by case basis
SAEs	**Non compliance with protocol-defined instructions for Reporting of SAE** Deviation from the protocol required timelines for SAE reporting.	Major if the SAE is reported over 3 days from the protocol defined time point during treatment periods. Otherwise minor.	Discuss on a case by case basis
Study Drug Treatment	**Non compliance with study drug treatment** Unjustifiable treatment interrupting with the study drug	Major	Discuss on a case by case basis
	Administering study drug for less than 8 cycles in the neoadjuvant setting for patient receiving study drug in the neoadjuvant setting.	Minor	
	In patients with early breast cancer eligible for neoadjuvant treatment, trastuzumab SC should only be used concurrently with low-dose anthracycline regimens (maximum cumulative doses: doxorubicin 180 mg/m^2 or epirubicin 360 mg/m^2).	Major	As above
	If patients have been treated concurrently with low-dose anthracyclines and trastuzumab in the neoadjuvant setting, no additional cytotoxic chemotherapy should be given after surgery.	Major	As above
	Surgery should be planned after dosing at Cycle 8 without interruption of trastuzumab treatment.	Major	As above
Observa-tion time	**Non compliance with observation time after drug administration (Cohort B)** • No observation took place at all, first dose • No observation took place at all, subsequent doses • Observation for a period less than protocol requirement (less than 50% of the required time, example: 2 hours instead of 6 hours for first dose) Observation for a period less than protocol requirement (less than 100% but more than 50% of the required time, example: 1.5 hours instead of 2 hours for subsequent doses)	Minor	No

6.3 Appendix 3

6.3.1 Definition of Treatment period and Follow-up period

Treatment period and Follow-up period are defined as:

- Treatment Period: Starting from the first dose of Herceptin SC study treatment and ending at (and including) 33 days after the last dose of Herceptin SC study treatment.
- Follow-Up Period: Starting from 34 days after the last dose of Herceptin SC study treatment until the end of study.

6.3.2 Classification of Follow-up assessments

The 6, 12, 24 months and 3, 4 and 5 years follow-up assessments will generally be identified by the time elapsed from the last dose, evaluating all assessments recorded (i.e. both during follow-up and unscheduled visits):

- The FUP assessment at 6 months will be the assessment the patient undergoes in the time window [date of safety follow-up visit + 1 day; 6 months + 91 days] which is closest to 6 months. In case that a safety follow-up visit has not been performed, the time window will start at 29 days after last dose. In case that there are 2 assessments closest (i.e. at the same distance prior to and after 6 months), the later will be taken.
- The FUP assessment at 12 months will be the assessment the patient undergoes in the time window [6 months + 92 days; 12 months + 182 days] which is closest to 12 months. In case that there are 2 assessments closest (i.e. at the same distance prior to and after 12 months), the later will be taken.
- The FUP assessment at 24 months will be the assessment the patient undergoes in the time window [12 months + 183 days; 24 months + 182 days] which is closest to 24 months. In case that there are 2 assessments closest (i.e. at the same distance prior to and after 24 months), the later will be taken.
- The FUP assessment at 3 years will be the assessment the patient undergoes in the time window [24 months + 183 days; 36 months + 182 days] which is closest to 36 months. In case that there are 2 assessments closest (i.e. at the same distance prior to and after 36 months), the later will be taken.
- The FUP assessment at 4 years will be the assessment the patient undergoes in the time window [36 months + 183 days; 48 months + 182 days] which is closest to 48 months. In case that there are 2 assessments closest (i.e. at the same distance prior to and after 48 months), the later will be taken.
- The FUP assessment at 5 years will be the assessment the patient undergoes in the time window [48 months + 183 days; 60 months + 182 days] which is closest to 60 months. In case that there are 2 assessments closest (i.e. at the same distance prior to and after 60 months), the later visit will be taken.

The convention 1 month=30.5 days will be applied.