Official Title: A PHASE III PROSPECTIVE, TWO-COHORT NON-RANDOMIZED, MULTICENTER, 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]

NCT Number: NCT01566721

Document Date: Protocol Version 4: 11-November-2016

PROTOCOL

TITLE:	**A PHASE III PROSPECTIVE, TWO-COHORT NON-RANDOMIZED, MULTICENTER, 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]**
PROTOCOL NUMBER:	MO28048
VERSION NUMBER:	4
EUDRACT NUMBER:	2011-005328-17
IND NUMBER:	Not applicable
TEST PRODUCT:	Trastuzumab SC (RO 45-2317)
MEDICAL MONITOR:	[redacted] Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 30 November 2011
DATES AMENDED:	Version 2: 19 November 2012 Version 3: 18 March 2013 Version 4: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	11-Nov-2016 20:30:25

PROTOCOL AMENDMENT, VERSION 4:
RATIONALE

Changes to the protocol, along with a rationale for each change, are summarized below:

- The protocol title page was updated to align with current Sponsor practices. The Medical Monitor and the primary and secondary contacts for the study were updated.
- The guidelines for additional follow-up of patients beyond the Safety Follow-up visit (performed 4 weeks after the last dose of study treatment) were revised to include "or investigator's routine practice" for consistency in Section 3.1, Section 4.5.1.3, Section 4.5.1.8, Section 4.5.2.2, and Section 5.1.1 and the Schedule of Assessments in Appendix 1.
- The concomitant medications monitored after the Safety Follow-up visit were clarified in Section 3.4.2, Section 4.4, Section 4.5.2.4, and the Schedule of Assessments in Appendix 1 to include breast cancer treatments (e.g., endocrine therapy), anti-cancer treatments given to treat breast cancer recurrence, and medications related to the treatment of serious adverse events (SAEs) for consistency and clarity.
- As noted in the Note to File (dated 30 September 2016), an inconsistency was noted in the following sections of Protocol MO28040, Version 3: Section 4.5.2.4, Section 5.3.1, and Appendix 1, Footnote (l). Changes were made to maintain consistency between Section 4.5.2.4 and Section 5.3.1.
- The term "Study Completion/Early Discontinuation eCRF" was updated to "Death eCRF page" in Section 5.3.5.7 to maintain consistency between the protocol and the eCRF.
- The Herceptin (RO 45-2317, Trastuzumab) Investigator's Brochure was clarified as the primary reference safety information for determining the expectedness of adverse events in Section 5.7.

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

PROTOCOL AMENDMENT, VERSION 4:
SUMMARY OF CHANGES

GLOBAL CHANGES

The Medical Monitor has been changed to [redacted], Ph.D.

PROTOCOL SYNOPSIS

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

SECTION 1.2.2.3.2: Study BO22227 (HannaH)

Study BO22227 ~~was~~*is* a Phase III, randomized, open-label, multicenter trial involving 596 female patients with HER2-positive early breast cancer in which the pharmacokinetics, efficacy, and safety of trastuzumab SC were compared with IV trastuzumab. Co-primary endpoints are serum C_{trough} pre-surgery and pathological complete response (pCR).

SECTION 2.3: EXPLORATORY OBJECTIVES

~~Two a~~*A*dditional, exploratory objectives will be investigated in a subset of patients (**Cohort B**) at selected study sites:

SECTION 3.1: DESCRIPTION OF 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 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. 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 progression, patients will be managed as per local practice and followed for survival only.

SECTION 3.4.2: Safety Outcome Measures

The safety outcome measures for this study are as follows:

- All concomitant medication will be recorded between the Screening and the Safety Follow-up visits. Thereafter, ~~only medication applicable for long-term reporting will be recorded including~~ breast cancer treatments (e.g., endocrine therapy), anti-cancer treatments given to treat a recurrence, and medications related to the treatment of SAEs ~~that are applicable for long-term reporting (e.g., treatment of heart failure)~~ *will be recorded*.

SECTION 4.4: CONCOMITANT THERAPY

All concomitant medications are to be reported until the Safety Follow-up visit. Thereafter, only ~~medication applicable for long-term reporting~~*the following medications* must be reported~~, including~~:

- Breast cancer treatments (e.g., hormonal therapy)
- Anti-cancer treatments given to treat a recurrence

- Medications related to the treatment of serious AEs~~that are applicable for long term reporting (e.g., treatment of heart failure).~~

SECTION 4.5.1.3: Physical Examinations

A general physical exam (including a general neurological exam, as clinically indicated) will be performed at screening, approximately 3-monthly during trastuzumab SC treatment (at Week 13/Cycle 5, Week 25/Cycle 9, Week 37/Cycle 13, and Week 52/Cycle 18), at the post-treatment Safety Follow-up visit, and subsequently according to the ASCO 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting (Khatcheressian et al. 2006) *or investigator's routine practice.* Physical examinations will be performed according to local practice; however, particular attention should be given to the cardiovascular system.

SECTION 4.5.1.8: Breast Cancer Evaluations and Follow-Up

Patients will be assessed for residual disease (as per institutional practice) not more than 4 weeks before the first dose of study drug. Screening radiologic examinations to exclude metastatic disease should include a bilateral mammogram or breast MRI, and chest X-ray (CXR) or breast ultrasound. Should a previously taken chest CT or PET scan be available, then these results can also be used for eligibility assessment. These imaging tests do not need to be repeated if completed within 12 months prior to the first study treatment. In addition, bone scan and liver imaging should be performed if clinically indicated. During study treatment and the post-treatment follow-up period, patients will be followed for disease recurrence according to ~~the investigator's routine practice or~~ the American Society of Clinical Oncology (ASCO) 2006 Guideline for Breast Cancer Follow-up (Khatcheressian et al. 2006) *or investigator's routine practice* (see Appendix 1, Schedule of Assessments).

SECTION 4.5.2.4: Post-treatment Follow-up Visits (minimum 5 years)

All patients will be followed-up for cancer recurrence and survival till study end (i.e., until all patients have had a minimum 5-year follow-up) yearly or at higher frequency based on the site standard of care. The duration of follow-up will be at least 5 years after the last study treatment or until withdrawal from the study, lost to follow-up, or death, whichever occurs first. During this post-treatment follow-up period, patients will undergo the following assessments:

- Breast cancer follow-up according to the ASCO 2006 Guideline for Breast Cancer Follow-up (Khatcheressian et al. 2006) and reporting every 6 months or as per institutional standard practices (see Section 4.5.1.8 for details)
- Blood samples for immunogenicity and PK analyses will be collected from a subset of **Cohort B** patients (at selected sites only) 6 months after their last study treatment.
- Patients' weight must also recorded 6 months after their last study treatment if participating to immunogenicity and PK testing.
- Pregnancy test as clinically indicated up to ~~6~~*7* months after last study treatment

- AE follow-up: *After initiation of study drug,* all AEs/SAEs (except unrelated non-cardiac AEs in the follow-up period), regardless of relationship to study drug, will be reported until study closure. The investigator does not need to actively monitor subjects for AEs once the trial has ended. However, if becoming aware of any serious adverse events and non-serious adverse events of special interest occurring to a subject, the investigator should report those to the sponsor (see Section 5.6).
- Concomitant medications: Only ~~medication applicable for long-term reporting must~~*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 ~~reported~~*recorded*; refer to Section 4.4 for details.
- Cardiac safety assessments will be performed at 6, 12, and 24 months and at yearly intervals until 5 years after treatment cessation (see Section 5.1.1.2 for details);
- Survival: After disease progression, patients will be managed as per local practice and followed for survival only.

After study treatment completion (or early discontinuation), AEs should be followed as outlined in Section 5.5 and Section 5.6.

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

SECTION 5.1.1: General Safety Assessments

Patients will be assessed by prior medical history, vital signs (including blood pressure, heart rate, temperature), weight and height (screening only), physical examination, adverse events, and concomitant medications. A complete medical history (including demographic profile and prior treatments for cancer) will be documented at screening. A general physical exam (including general neurological exam, as clinically indicated) will be performed at screening, approximately 3-monthly (every 4 cycles) during trastuzumab SC treatment, at the post-treatment Safety Follow-up visit, and subsequently according to the ASCO 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting (Khatcheressian et al. 2006) *or investigator's routine practice* during the 5-year follow-up period (see Appendix 1, Schedule of Assessments). During physical examination, particular attention should be given to the cardiovascular system. Apart from physical exams, SC injection sites will be checked at every visit, and blood pressure will be measured before and after trastuzumab SC administration every 4 cycles, as specified in Appendix 1, Schedule of Assessments.

SECTION 5.3.1: Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention should be reported

(e.g., serious adverse events related to invasive procedures such as biopsies). All other adverse events will be recorded as medical history.

After initiation of study drug, all AEs/SAEs *(except unrelated non-cardiac AEs in the follow-up period)*, regardless of relationship to study drug, will be reported until study closure. The investigator does not need to actively monitor subjects for AEs once the trial has ended. However, if becoming aware of any serious adverse events and non-serious adverse events of special interest occurring to a subject, the investigator should report those to the Sponsor (see Section 5.6).

Any injection-site reactions are considered to be related AEs/SAEs and should be reported accordingly.

Symptomatic congestive heart failure must be reported irrespective of causal relationship during the full course of the study, even if the patient starts a new anticancer regimen.

SECTION 5.3.5.7: Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur prior to study closure that are attributed by the investigator solely to progression of EBC should be recorded only on the ~~Study Completion/Early Discontinuation~~ *Death* eCRF *page*. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

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

During study survival follow-up, deaths attributed to progression of EBC should be recorded only on the ~~Survival eCRF or Study Completion/Early Discontinuation~~ *Death* eCRF *page*.

SECTION 5.4.1: Emergency Medical Contacts
Medical Monitor (Roche Medical Responsible) Contact Information

Primary Contact

Medical Monitor: [redacted] M.D.

~~Address: F. Hoffmann-La Roche Ltd.~~

~~[redacted]~~

~~4070 Basel, Switzerland~~

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Secondary Contact

Medical Monitor: Dr. [redacted] M.D.~~, PhD~~

~~Address:~~ [redacted]

~~[redacted] Belgium~~

Telephone No.: [redacted] *+650 225-1000*

~~Mobile~~*Office* Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Centre Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Centre Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information & List of Investigators").

SECTION 5.4.3.1: Pregnancies in Female Patients

For women of childbearing potential (defined as premenopausal, less than 1 year after the onset of menopause or not surgically sterilized), appropriate contraceptive measures are mandatory during study treatment (see Section 4.5.1.7.3). Based on pharmacokinetic considerations, contraceptive measures are recommended for at least 7 months following the last dose of trastuzumab.

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within ~~6~~*7* months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator within 24 hours after learning of the pregnancy and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue the study drug and counsel the patient, discussing the

risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

In the event that the EDC system is unavailable, a Pregnancy Report worksheet and Pregnancy Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee within 24 hours after learning of the pregnancy, using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). As soon as the EDC system is operating, the Pregnancy Report eCRF will be completed.

SECTION 5.4.3.2: Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within ~~6~~*7* months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator within 24 hours after learning of the pregnancy and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

SECTION 5.5.1: Investigator Follow-Up

The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all SAEs until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

The Investigator must report new significant follow-up information for these events to the Sponsor within 24 hours after becoming aware of the information. New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event (including outcome of a reported pregnancy, as applicable)

In an individual patient, AE follow-up will continue as follows:

Related *or cardiac* AEs and SAEs will be followed until one of the following occurs:

- Resolved or improved to baseline state
- Relationship is reassessed as unrelated
- Investigator confirms that no further improvement can be expected
- Start of a new anti-cancer regimen
- Death

Unrelated *non-cardiac* AEs ~~severe or life threatening~~ *(Grade 3 or Grade 4)* and SAEs *(any grade)* will be followed until one of the following occurs:

- Resolved or improved to baseline state
- Severity improved to Grade 2
- Investigator confirms that no further improvement can be expected
- Start of new anti-cancer regimen
- Death

Unrelated *non-cardiac* AEs (Grade 1 or Grade 2) will be followed until 4 weeks after the last dose of study drug in an individual patient.

The final outcome of each adverse event must be recorded on the eCRF.

Follow-up of Abnormal Laboratory Test Values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range or baseline state and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF.

SECTION 5.6: POST-STUDY ADVERSE EVENTS

At the ~~safety~~*final* follow-up visit *of the study*, the Investigator should instruct each patient to report to the Investigator any subsequent adverse events. The Sponsor should be notified if the Investigator becomes aware of any death or serious adverse event *related to study drug,* occurring at any time, after a patient has discontinued study participation, even after study closure~~, regardless of relationship to treatment of study drug~~. The investigator is not required to actively monitor patients after the study has ended.

The Sponsor should also be notified if the Investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study.

The Investigator should report these events to Roche Safety Risk Management on the Adverse Event eCRF. If the Adverse Event eCRF is no longer available, the Investigator should report these events, indefinitely, directly to Roche Safety Risk Management via telephone (see "Protocol Administrative and Contact Information & List of Investigators").

SECTION 5.7: EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, AND ETHICS COMMITTEES

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document~~(s)~~:

- Herceptin (RO 45-2317, Trastuzumab) IB
- ~~Local prescribing information for Herceptin~~
- ~~Herceptin Core Data Sheet~~

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

SECTION 6.5.1: Secondary Efficacy Variables

Secondary efficacy endpoints include disease-free survival (DFS) and overall survival (OS) and will be assessed in both cohorts.

- DFS is defined as the time from the date of first treatment to the date of local, regional, or distant recurrence; contralateral invasive breast cancer (including ~~second primary non-breast cancer or~~ contralateral or ipsilateral ductal carcinoma in situ [DCIS]); or death due to any cause.
- OS is defined as time from the date of first treatment until date of death, regardless of the cause of death.

DFS and OS will be analyzed as a time-to-event variable for the ITT population (see Section 6.5.2).

In addition, patients' satisfaction with trastuzumab SC administration using the SID will be evaluated for **Cohort B** patients who went on to self-administration only.

SECTION 6.5.2: Analyses of Efficacy Endpoints

The efficacy endpoints, DFS and OS, will be analyzed as a time-to-event variable for the ITT and PP populations and for each cohort. Estimates and corresponding 95% confidence intervals for the survivor function for the time-to-event variable will be obtained by using the KM approach. A frequency table will be also provided for the type of DFS event (e.g., local, regional, or distant recurrence; contralateral *breast cancer*; or death).

A preliminary analysis of efficacy (DFS and 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 OS and DFS will take place 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 enrollment 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

Patients' satisfaction with trastuzumab SC administration using the SID (**Cohort B** patients who went on to self-administration only) will be summarized by frequency tables and presented graphically.

APPENDIX 1: Schedule of Assessments

The Schedule of Assessments has been revised to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III PROSPECTIVE, TWO-COHORT NON-RANDOMIZED, MULTICENTER, 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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TEST PRODUCT:	Trastuzumab SC (RO 45-2317)
MEDICAL MONITOR:	[redacted], *Ph.D*
SPONSOR:	F. Hoffmann-La Roche Ltd

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

Principal Investigator's Name (print)

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III PROSPECTIVE, TWO-COHORT NON-RANDOMIZED, MULTICENTER, 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]**
PROTOCOL NUMBER:	MO28048
VERSION NUMBER:	4
EUDRACT NUMBER:	2011-005328-17
IND NUMBER:	Not applicable
TEST PRODUCT:	Trastuzumab SC (RO 45-2317)
PHASE:	Phase III
INDICATION:	HER2-positive early breast cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

Primary Objective

The primary objective of this study is to assess the overall safety and tolerability of trastuzumab subcutaneous (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

Secondary objectives include the evaluation of the following parameters:

- Efficacy (both cohorts):
  - 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 Objectives

Additional, exploratory objectives will be investigated in a subset of patients (Cohort B) at selected study sites:

- To assess the immunogenicity of trastuzumab and recombinant human hyaluronidase (rHuPH20)
- 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 substudies will be conducted. Details of the substudies will be described in separate protocols.

Study Design

This is a Phase III, prospective, two-cohort, non-randomized, multicenter, multinational, open-label study in approximately 2500 patients with HER2-positive EBC who are eligible for anti-HER2 therapy.

Eligible patients will be allocated to **Cohort A** or **B** at the investigator's discretion depending upon availability of the cohorts for recruitment:

- **Cohort A** (approximately 1,800 patients): trastuzumab SC 600 mg assisted administration into the thigh over a period of approximately 5 minutes using conventional handheld syringes with hypodermic needles for a total of 18 cycles (3-weekly);
- **Cohort B** (approximately 700 patients): trastuzumab SC at a fixed dose of 600 mg 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.

Description of Study

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 enrollment into the study.

During trastuzumab SC therapy, patients will be assessed for safety and efficacy.

In addition to efficacy and safety assessments, select sites will also perform immunogenicity testing to determine whether HAHAs against trastuzumab or rHuPH20 develop in patients receiving trastuzumab SC using the SID.

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 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting *or investigator's routine practice*. All patients will be followed-up for cancer recurrence and survival until study end. 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 progression, patients will be managed as per local practice and followed for survival only.

In some countries and sites, MCU (e.g., time and motion) and/or pharmacoeconomic substudies will be conducted. Details of the substudies will be described in separate protocols.

Number of Patients

Approximately 2500 patients will be enrolled into the study. The trial will be conducted at approximately 520 centers in approximately 60 countries.

Target Population

The study will recruit adult consenting patients with newly diagnosed HER2-positive (IHC 3+ or HER2-positive in situ hybridization [ISH]) early breast cancer who are eligible for treatment with trastuzumab (e.g., clinical Stage I [T1, N0, M0] to IIIC [any T, N3, M0]). Patients treated without neoadjuvant or adjuvant chemotherapy, such as patients with low-risk node-negative tumors $\leq$ 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 enrollment will be limited to approximately $\leq$ 10% of the total study population.

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed written informed consent approved by the reviewing independent Ethics Committee (EC)
2. Female or male aged 18 years or above
3. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
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 treatment with trastuzumab

   Note: Patients treated without neoadjuvant or adjuvant chemotherapy, such as patients with low-risk node-negative tumors ≤ 1.0 cm, elderly patients (> 65 years of age), or patients with HER2-positive EBC but denying chemotherapy, will also be eligible to participate in the study, but their enrollment will be limited to approximately ≤ 10% of the total study population.
5. HER2-positive EBC, defined as IHC 3+ or positive in situ hybridization (ISH testing) by validated and approved methods within a certified laboratory
6. Screening left ventricular ejection fraction (LVEF) ≥ 55% as measured by echocardiography, multi-gated acquisition (MUGA) scan, or Magnetic Resonance Imaging (MRI) per local practice
7. Agreement to use an adequate, nonhormonal means of contraception by women of childbearing potential (defined as premenopausal 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 intrauterine device, a barrier method (condoms or diaphragm) in conjunction with spermicidal jelly, or total abstinence. Oral, injectable, or implant hormonal contraceptives are not acceptable for females participating in the study.
8. Intact skin at site of SC injection on the thigh

Exclusion Criteria

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

Cancer-Related Criteria

1. Previous neoadjuvant or adjuvant breast cancer treatment with an approved or investigational anti-HER2 agent
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 other than breast cancer who have been disease-free for at least 5 years are eligible.

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.
4. Metastatic disease

Hematological, Biochemical, and Organ Function

5. Inadequate bone marrow function (as indicated by any of the following):
   - Total white blood cell count (WBC) $< 2500/mm^3$ ($< 2.5 \times 10^9/L$)
   - Neutrophil count $< 1500/mm^3$ ($< 1.5 \times 10^9/L$)
   - Platelets $< 100{,}000/mm^3$ ($< 100 \times 10^9/L$)
   - Hemoglobin < 10 g/dL
6. Impaired hepatic function (as indicated by any of the following):
   - Serum total bilirubin $> 1.5 \times$ upper limit of normal (ULN)
   - Alanine amino transferase (ALT) $> 2.5 \times$ ULN
   - Aspartate amino transferase (AST) $> 2.5 \times$ ULN
   - Alkaline phosphatase (ALP) $> 2.5 \times$ ULN
7. Impaired renal function, as indicated by serum creatinine $> 1.5 \times$ ULN

Other Study Drug-Related Exclusion Criteria

8. Serious cardiac illness or medical conditions including but not confined to:
   - 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 consistently over 140/90 mmHg, despite treatment) or history of hypertensive crisis or hypertensive encephalopathy
9. Other concurrent serious diseases that may interfere with planned treatment including severe pulmonary conditions/illness
10. Prior maximum cumulative dose of doxorubicin > 360 mg/m2 or maximum cumulative dose of epirubicin > 720 mg/m2 or equivalent
11. Known hypersensitivity to trastuzumab, murine proteins, or excipients, or a general hypersensitivity to adhesives (Cohort B only)
12. History of severe allergic or immunological reactions, for example, difficult to control asthma.

General Exclusion Criteria

13. Pregnancy or lactation
14. Unable or unwilling to comply with the requirements of the protocol, as assessed by the investigator
15. Concurrent enrollment 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
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.
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.
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

No exceptions or waivers will be granted for the above listed inclusion and exclusion criteria.

Length of Study

The study is estimated to last approximately 8 years, 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.

To allow for the enrolment of 1800 patients in **Cohort A** (compared to 700 in **Cohort B**), recruitment for **Cohort A** may be initiated earlier than recruitment for **Cohort B**.

End of Study

End of study is defined as the last patient last visit in the follow-up period. The study will end when all patients have been followed for approximately 5 years 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 final analysis of OS and DFS and updated summaries for safety parameters will be performed at this stage.

Safety Outcome Measures

All clinical adverse events (AEs) and serious adverse events (SAEs), as well as abnormal laboratory values, will be recorded and graded according to the NCI-CTCAE version 4.0.

Cardiac function will be evaluated by measuring LVEF (using echocardiography, Multi Gated Acquisition (MUGA) scan or Magnetic Resonance Imaging [MRI]) and ECG. Symptomatic left ventricular dysfunction (CHF) will be graded according to NCI-CTCAE, version 4.0 and the NYHA functional classification.

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 in the adjuvant setting *or investigator's routine practice*. All concomitant medication will be recorded between the Screening and the Safety Follow-up visits. Thereafter, 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*.

Efficacy Outcome Measures

DFS is defined as time from the date of first treatment to the date of local, regional, or distant recurrence; contralateral breast cancer; or death due to any cause.

OS is defined as time from the date of first treatment until date of death, regardless of the cause of death.

Patients in **Cohort B**, who went on to self-administration of the study drug will be asked to rate their overall satisfaction with trastuzumab SC administrations using the SID by completing a 5-item SID satisfaction questionnaire. The questionnaire will be completed after the 4th cycle and at the Safety Follow-up visit (or at least 1 day after the last trastuzumab SC injection), after a minimum of 2 successful self-administrations of the study drug.

Exploratory Outcome Measures

Immunogenicity of trastuzumab and rHuPH20 will be tested in a subset of patients enrolled in **Cohort B** at select sites. 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 at least 6 months after the end of treatment for testing in a central laboratory.

The exploratory MCU and/or pharmacoeconomic parameters will be described in separate substudy protocols.

In addition to the study assessments, all clinical AEs that occur during the observation period will be collected for all patients in **Cohort B** (within 6 hours after start of the first trastuzumab administration or within 2 hours (within 6 hours after start of the first trastuzumab administration or within 2 hours after start of following trastuzumab administrations). Data collected during the observation period will include: Frequency, incidence, and grade of AEs; onset and resolution times of AEs (dd:mm:yyyy:hh:mm); outcome of AEs; and details of treatments provided following AEs during the observation period.

Information on the usability of the SID will be 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 observation of the HCP. The SID Device Observation is to be completed by HCPs.

Investigational Medicinal Products

The investigational medicinal product for this study is trastuzumab SC 600 mg, supplied as a vial and SID formulations.

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.

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 tumors >2 cm in diameter

For patients receiving trastuzumab SC with concurrent 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.

All study treatment administrations will occur in a hospital setting as follows:

- **Cohort A**: Trastuzumab SC 600 mg 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 600 mg will be injected subcutaneously into the thigh over a period of approximately 5 minutes using the SID. The first administration will be assisted (performed by a HCP [physician or nurse]), and then following administrations may be self-administered into the thigh (if the patient is willing and judged competent by the HCP) over a period of approximately 5 minutes using the SID.

Non-Investigational Medicinal Products

Not applicable.

Statistical Methods

Primary Analysis

Safety endpoints are the primary objectives in this study and will include: all AEs, Grade ≥3 AEs, SAEs, AEs leading to premature discontinuation of study treatment, AEs causing interruption of trastuzumab SC, cardiac AEs, CHF-related SAEs, premature withdrawals from study and study medication, exposure to treatment, laboratory parameters, LVEF, vital signs, ECG, weight, and ECOG performance status.

The primary analyses of the safety endpoints will consist of summary results with 95% confidence intervals and descriptions. They will be performed for the safety population (SP) defined as all enrolled patients who received at least one dose of study medication. There will be two safety populations, one for each cohort (SP1 for **Cohort A** and SP2 for **Cohort B**). The safety endpoints will be summarized for each cohort and overall.

The primary analysis of the safety endpoints will take place when all patients have received 18 cycles of trastuzumab SC and have completed the Safety Follow-up assessments (4 weeks after their last dose of study treatment). The primary analysis of safety endpoints will take place when all patients have received 18 cycles of trastuzumab SC and have completed the post-treatment Safety Follow-up assessments. Updated summaries for safety parameters will be prepared 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. All safety summaries and analyses will be performed for **Cohort A** and for **Cohort B**. There is no formal statistical hypothesis comparing **Cohort A** and **Cohort B**, and there will be no adjustments for multiplicity of endpoint comparisons. The safety summaries and analyses will be summarized for each cohort and overall.

Secondary and Exploratory Analyses

Secondary efficacy endpoints include DFS, OS (both cohorts) and patients' satisfaction with trastuzumab SC administration using the SID (**Cohort B** patients who went on to self-administration only). Secondary efficacy endpoints will be analyzed for the Intent-to-Treat (ITT) population (defined as all patients enrolled in the study) and the Per-Protocol population (defined as all patients in the ITT population who have received at least one dose of study medication and did not have major protocol violations). Protocol violations necessitating exclusion from the Per-Protocol population will be described in the Statistical Analysis Plan (SAP).

A preliminary analysis of DFS and OS will be undertaken at the time of the primary safety analysis, i.e. when all patients **(Cohort A and Cohort B)** have received 18 cycles of trastuzumab SC and have completed the Safety Follow-up assessments (4 weeks after their last dose of study treatment). The final analysis of OS and DFS will take place when the last patient has been followed up for approximately 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 approximately 5 years of follow- up after the last study treatment.

Patients' satisfaction with trastuzumab SC administration using the SID (**Cohort B)** patients who went on to self-administration only) will be summarized by frequency tables and presented graphically.

Exploratory study analyses of the immunogenicity of trastuzumab and rHuPH20 will be performed in a subset of patients enrolled in **Cohort B** at select sites, based on samples collected at baseline (just before the first study treatment), on-treatment (pre-Cycle 9 dose, Week 25) and at least 6 months after the end of treatment. The percentage of patients who develop anti-trastuzumab or anti-rHuPH20 antibodies or both will be presented. Serum trastuzumab concentration data will be used in the assessment of anti-trastuzumab antibodies.

Exploratory study analyses for all clinical AEs that occur during the observation period will be evaluated, analyzed and presented and further exploratory analysis will be performed for all

patients in **Cohort B** (within 6 hours after start of the first trastuzumab administration or within 2 hours after start of following trastuzumab administrations). Details of the analysis will be documented in the Statistical Analysis Plan (SAP) and will include the following:

- Analysis of frequency, incidence and grading of AEs during the observation period
- Analysis of time from last preceding administration of study drug to onset time of AE occurrence (dd:mm:yyyy:hh:mm) during the observation period
- Analysis of time to resolution (dd:mm:yyyy:hh:mm) and outcome of AEs observed during the observation period
- Analysis of treatments provided following AEs during the observation period

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 observation of the HCP. The SID Device Observation is to be completed by HCPs.

Determination of Sample Size

A sample size of approximately 2500 patients is planned for this study with approximately 1800 patients enrolled in **Cohort A** and approximately 700 patients enrolled in **Cohort B**. There is no formal statistical hypothesis, hence all safety (primary) endpoints results will be presented by 95% confidence intervals and descriptively explained.

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. Based on an observed CHF-related SAE incidence rate of 4% and a sample size of 1800 patients in **Cohort A,** the upper limit of the 95% confidence interval 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 is produced by the SAS program and nQuery Version 6.

In Cohort B only, 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 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.

Refer to the protocol and the SAP for further details.

Interim Safety Analyses

Three interim safety analyses are planned for the study, when approximately 500, 1000, and 2500 patients have received at least one trastuzumab SC injection.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibodies
AE	Adverse event
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate aminotransferase
AUC	Area under the plasma concentration–time curve
BCIRG	Breast Cancer International Research Group
BUN	Blood urea nitrogen
CEA	Carcinoembryonic Antigen
CHF	Congestive heart failure
CI	Confidence interval
CISH	Chromogenic in situ hybridization
CL	Clearance
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
CMF	Cyclophosphamide methotraxate fluoricil
CNS	Central nervous system
CR	Complete response
CRF	Case Report Form[s]
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computerized tomography
C_{trough}	Trough plasma concentration
CV%	Coefficient of variation
CXR	Chest X-Ray
DCIS	Ductal carcinoma in situ
DFS	Disease-free survival
DISH	Dual inform in situ hybridization
EBC	Early breast cancer
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report form
EDC	Electronic data capture

EEA	European Economic Area
EFS	Event-free survival
EU	European Union
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FISH	Fluorescence in situ hybridization
GCP	Good Clinical Practice
HAHA	Human anti–human antibodies
HCP	Health Care Professional
HER2	Human epidermal growth factor receptor-2
HR	Hazard ratio
HV	Healthy volunteers
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICF	Informed Consent form
ICMJE	International Committee of Medical Journal Editors
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IMP	Investigational medicinal product
IND	Investigational New Drug
INN	International Non-proprietary Name
IRR	Infusion-related reaction
ISH	In situ hybridization
ITT	Intent-to-treat
IU	International Units
IV	Intravenous(ly)
KM	Kaplan-Meyer (analysis method)
LVEF	Left ventricular ejection fraction
LVSD	Left Ventricular Systolic Dysfunction
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Image
MUGA	Multiple gated acquisition
NCCN	National Comprehensive Cancer Network
NCCTG	North Central Cancer Treatment Group
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSABP	National Surgical Adjuvant Breast Project
NYHA	New York Heart Association

OS	Overall survival
PD	Progressive disease or Pharmacodynamic
PS	Performance Status
PK	Pharmacokinetic(s)
PPK	Population Pharmacokinetic(s)
p.o.	Per os (oral administration)
q1w	Every week
Q3W	Every 3 weeks
rHuPH20	Recombinant humanized hyaluronidase
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard Deviation
SID	Single-use injection device
SISH	Automated silver enhanced in situ hybridization
SmPC	Summary of Product Characteristics
SSR	Six-monthly SUSAR report
SUSAR	Suspected unexpected serious adverse reactions
TCH	Taxol, Carboplatin and Herceptin
$T_{1/2}$	Half-life
TNM	Primary tumor/regional lymph nodes/distant metastasis
T_{max}	Time to maximum plasma concentration
ULN	Upper limit of normal
US	United States
Vc	Volume of distribution of the central compartment
WBC	White blood count
WFI	Water for injection

1. BACKGROUND

1.1 BACKGROUND ON BREAST CANCER

1.1.1 Epidemiology

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death in women worldwide, with an estimated 1.4 million new breast cancer cases and 458,000 deaths in 2008 (Jemal et al. 2010). More than half of all cases occur in industrialized countries. It is estimated that about 361,000 women (27.3% of cancers in women) are diagnosed (Parkin et al. 2005), and around 131,900 die annually of breast cancer in Europe, with breast cancer remaining the major cause of death in women aged between 35 and 59 (Ferlay et al. 2007). In the United States, the number of newly diagnosed breast cancer cases was estimated to be 209,000 (13.7% of all cancers and 28.0% of cancers in women), and the number of breast cancer-related deaths estimated to be 40,200 (7.1% of all cancer deaths and 14.7% of cancer deaths in women) in the year 2010 (Jemal et al. 2010; Kris et al. 2010). In Europe and North America, most breast cancers are diagnosed when the cancer is still confined to the breast, with or without loco-regional lymph node spread, and can be treated with curative intent. In Europe, around 79% are potentially operable (stage T1-3/N0/+M0), 7% are locally advanced (T4/Nx/M0), and 6% are metastatic (M1) at diagnosis (Sant et al. 2003; Verma et al. 2010).

1.1.2 The Role of HER2-Receptor Status

The human epidermal growth factor receptor 2 (HER2, HER2/neu, c-erbB-2) gene, first discovered in 1984 (Schechter et al. 1984), is localized to chromosome 17q and encodes a transmembrane tyrosine kinase receptor protein that is a member of the epidermal growth factor receptor, or HER, family (Ross et al. 2009). This HER family of four receptors mediates the growth, differentiation and survival of cells (Yarden and Sliwkowski 2001; Gschwind et al. 2004). The evidence that increased expression and activity of HER2 induces cell transformation and tumorigenesis is overwhelming. In breast cancer, unlike a variety of other epithelial malignancies, HER2 gene amplification is uniformly associated with HER2 (p185neu) protein overexpression.

HER2 gene amplification and/or protein overexpression has been associated with aggressive tumor behavior, including increased cell proliferation, cell motility, tumor invasiveness, progressive regional and distant metastases, accelerated angiogenesis, and reduced apoptosis and poor prognosis (Ross et al. 2009; Slamon et al. 1987; Slamon et al. 1989; Sjögren et al. 1998; Moasser 2007; Ménard et al. 2001). A review of 107 studies involving 39,730 breast cancer patients found that in the majority (88%) of the studies, either HER2 gene amplification or HER2 (p185neu) protein overexpression predicted breast cancer outcome by either univariate or multivariate analysis (Ross et al. 2009). The frequency of HER2-positivity in these studies ranged from 9% to 74% (mean 22.2%). However, in current practice, most investigators report that the true HER2-positive rate is in the range of 15%–20% (Ross et al. 2009; Lund et al. 2010).

The major slide-based HER2 testing approaches include immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH), automated silver enhanced in situ hybridization (SISH), and dual inform in situ hybridization (DISH) (all in situ techniques).

HER2-amplified breast cancers comprise a specific disease subset with a unique molecular portrait and biologic characteristics that distinguish them from other types of breast cancers (Moasser 2007; Crowe et al. 2006). Studies have shown that women whose tumors exhibit either amplification of the HER2 gene or overexpression of its encoded protein have a more aggressive form of breast cancer that is associated with significantly shortened disease-free and overall survival (OS) compared with women whose tumors do not over express HER2 (Dawood et al. 2010).

1.1.3 Treatment of Early Breast Cancer

Surgery is the main modality of local treatment for breast cancer (with or without radiotherapy) and can control loco-regional disease in the majority of patients. However, a significant percentage of patients relapse after loco-regional treatment and develop metastases. Systemic chemotherapy (or endocrine therapy in hormone receptor-positive patients) reduces the risk of relapse and is given either prior to surgery (neoadjuvant therapy) or following surgery (adjuvant therapy). In recent decades, the use of adjuvant systemic therapies for early breast cancer (EBC) has increased extensively and has most likely contributed to the substantial decline in breast cancer mortality observed in the U.S. and in some European countries (Verma et al. 2010; Colozza et al. 2006; Autier et al. 2010).

In the last few years, there has been accelerated progress in the treatment of EBC, with the introduction of taxanes and aromatase inhibitors and, most impressively, trastuzumab to the adjuvant portfolio (Colozza et al. 2006). Cytotoxic chemotherapy, endocrine therapy, radiotherapy, and molecular targeted therapies currently represent the backbone of modern systemic breast cancer treatment. Several targeted drugs with different molecular pathways have achieved approval for metastatic breast cancer (MBC), but trastuzumab is the only such therapy that is currently approved for adjuvant or neoadjuvant treatment of EBC (Untch 2010). The use of trastuzumab in the adjuvant setting is also supported by international treatment guidelines for women with HER2-positive breast cancer (NCCN 2010; Gnant et al. 2011; Aebi et al. 2011). The introduction of trastuzumab at the end of 1990s has particularly improved the outcome for early breast cancer patients with HER2-positive disease.

1.2 BACKGROUND ON TRASTUZUMAB

1.2.1 Intravenous Trastuzumab (Herceptin®)

Trastuzumab (Herceptin®) is a humanized monoclonal antibody directed against the extracellular domain of HER2. It is indicated for the treatment of patients with HER2-positive MBC (first approved in 1998) and EBC- (approved in 2005) and

HER2-positive metastatic gastric cancer (approved in 2010). The efficacy and safety of intravenous (IV) trastuzumab have been well characterized. Since its initial approval in 1998, trastuzumab has become standard of care for patients with HER2-positive breast cancer and is widely used for its approved indications in both the adjuvant and metastatic settings (Ross et al. 2009; NCCN 2010; Gnant et al. 2011; Aebi et al. 2011).

Intravenous trastuzumab is administered to EBC patients for a total duration of one year. Adjuvant trastuzumab IV may be given as monotherapy, starting after completion of adjuvant chemotherapy, or in combination with the taxane component of adjuvant chemotherapy (followed by trastuzumab monotherapy). At the time of writing, adjuvant trastuzumab IV monotherapy is widely approved, and concurrent administration in combination with adjuvant chemotherapy is also approved or expected to be approved in many countries. Intravenous trastuzumab may be given weekly (q1w) or 3-weekly (Q3W) to patients with MBC, but in the adjuvant setting, when given as monotherapy, it is generally given Q3W.

For the regulatory status and approved indications in specific countries, please refer to the current Herceptin (RO 45-2317, Trastuzumab) Investigator's Brochure (IB) and local prescribing information.

1.2.1.1 Pharmacokinetics of Trastuzumab IV

Based on a population pharmacokinetic (PK) analysis of data primarily from the metastatic breast cancer setting (Clinical Study Report 1018264), the predicted median AUC (over a period of 3 weeks at steady-state) for the q1w and Q3W regimens were 1677 and 1793 mg • day/L, respectively, and the corresponding median C_{min} values were 64.9 and 47.3 mg/L, respectively. A two-compartment model satisfactorily described the data. The typical trastuzumab IV PK parameters were as follows: clearance (CL) of 0.026 L/day and a volume of distribution of the central compartment (Vc) of 3.17 L (which corresponds to human plasma volume, which is the Vc characteristic of IgG immunoglobulins). The equilibrium half-life is about 26 days, which is similar to that of endogenous IgG1 immunoglobulin (23 days) which constitutes the backbone of trastuzumab IV.

Refer to the Herceptin (RO 45-2317, Trastuzumab) IB for further details regarding the pharmacokinetics of trastuzumab IV.

1.2.1.2 Efficacy of Trastuzumab IV in Early Breast Cancer (Adjuvant Setting)

Six Phase III, multicenter, randomized-controlled trials investigated the efficacy and safety of adjuvant trastuzumab IV in combination with or after standard adjuvant chemotherapy in the treatment of early breast cancer:

- Herceptin Adjuvant (HERA, BO16348) trial (Piccart-Gebhart et al. 2005; Smith et al. 2007; Gianni et al. 2011)

- North Central Cancer Treatment Group trial (NCCTG) N9831 trial (Romand et al. 2005; Perez et al. 2007; Perez et al. 2009; Perez et al. 2011)
- National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-31 (Romand et al. 2005; Perez et al. 2007; Perez et al. 2009; Perez et al. 2011)
- Breast Cancer International Research Group (BCIRG-006) study (Slamon et al. 2009; Slamon et al. 2011)
- Protocol Adjuvant dans le Cancer du Sein (PACS04) trial (Spielmann et al. 2009)
- Finland Herceptin (FinHer) trial (Joensuu et al. 2009)

Together, these trials accrued more than 15,000 women with node-positive or high-risk node-negative breast cancer and used a variety of cytotoxic agents in various combinations, doses, and orders of administration. Four of these trials (HERA, N9831, B31, and BCIRG-006) are considered pivotal.

In the HERA study, trastuzumab treatment was started following completion of an approved neoadjuvant or adjuvant chemotherapeutic regimen (and radiotherapy as indicated) and continued for one or two years. In Studies B31, N9831, and BCIRG-006, trastuzumab started after completion of four cycles of doxorubicin/cyclophosphamide and was administered for one year, either concurrently with four cycles of taxane chemotherapy (B31, N9831), or concurrently with six cycles of a non-anthracycline-containing taxane-based regimen (BCIRG-006), or after completion of chemotherapy (see Table 1).

All four pivotal randomized controlled trials (HERA, N9831, B31, and BCIRG-006) demonstrated significantly improved disease-free survival (DFS), and three (HERA, B31 and BCIRG-006) demonstrated significantly improved overall survival (OS; see Table 1). The DFS benefits were observed regardless of age, nodal status, hormonal status, or tumor size in all trials (Gianni et al. 2011; Slamon et al. 2011; Perez et al. 2011). Importantly, the most recent follow-up data from the HERA trial (Gianni et al. 2011) and the combined analysis of the NCCTG N9831 and NASBP B-31 trials (Perez et al. 2011) both demonstrate consistent DFS and OS advantages of adjuvant trastuzumab over a median follow-up of 4 years. Further, the significant benefits in DFS and OS were maintained over a median follow-up of approximately 5 ½ years in the BCIRG-006 study (Slamon et al. 2011), which is the longest follow-up reported to date. The long-term clinical benefits of 1-year trastuzumab treatment clearly continue to outweigh the risks of adverse effects (Perez et al. 2011), and the regimen is considered standard of care with support from all major treatment guidelines (NCCN 2010; Gnant et al. 2011; Aebi et al. 2011).

Of the four pivotal randomized trials, the N9831 study was the only one to directly compare the concurrent and sequential use of trastuzumab. This study identified a strong trend for a 25% reduction in the risk of an outcome event when trastuzumab is started concurrently as compared to sequentially after paclitaxel (Perez et al. 2009).

Therefore, based on a positive risk/benefit ratio, the authors recommended that trastuzumab be incorporated in a concurrent fashion when administered with paclitaxel (Perez et al. 2009), which also resulted in the approval of the concurrent use of trastuzumab and chemotherapy.

For further details, refer to the current Herceptin (RO 45-2317, Trastuzumab) IB.

Table 1 Efficacy of Trastuzumab IV in the Adjuvant EBC Setting

Study	Median FU (mo)	Interventions	No. of Patients [a]	DFS	OS
SEQUENTIAL TRASTUZUMAB					
HERA (Piccart-Gebhart et al. 2005; Gianni et al. 2011) N = 5090	48	CT ± RT → OBS	1698	2-yr DFS: 81% 4-yr DFS: 72%	2-yr OS: 95% 4-yr OS: 88%
		CT ± RT → T (× 1 yr)	1703	2-yr DFS: 87% HR 0.64, p < 0.0001 4-yr DFS: 79% HR 0.76, p < 0.0001	2-yr OS: 97% HR 0.66, p = 0.012 4-yr OS: 89% HR 0.85, p = 0.11
		CT ± RT → T (× 2 yrs)	1701	NR	NR
NCCTG N9831 (Perez et al. 2009) N = 3505 (1097 sequential)	66	AC → P	1087	5-yr DFS: 72%	NR
		AC → P → T	1097 [b]	5-yr DFS: 80% HR 0.70, p = 0.0005	HR 0.86, p = 0.281
		AC → P + T → T	949	5-yr DFS: 84% HR 0.75, p = 0.019	NR
CONCURRENT TRASTUZUMAB					
NSABP B-31 (Perez et al. 2011) N = 2101	47	AC → P	1046	4-yr DFS: 72%	NR
		AC → P + T	1055	4-yr DFS: 85%	NR
B-31 + N9831 (Romond et al. 2005; Perez et al. 2007; Perez et al. 2011) N = 3351 [c]	47	AC → P	1679	3-yr DFS: 75% 4-yr DFS: 74%	3-yr OS: 92% 4-yr OS: 86%
		AC → P + T	1672	3-yr DFS: 87% 4-yr DFS: 86% HR 0.51, 95%CI: 0.44–0.59	3-yr OS: 94% 4-yr OS: 93% HR 0.59, 95%CI: 0.48–0.73

Table 1 Efficacy of Trastuzumab IV in the Adjuvant EBC Setting (cont.)

Study	Median FU (mo)	Interventions	No. of Patients [a]	DFS	OS
B-31 + N9831 (Romond et al. 2005; Perez et al. 2007; Perez et al. 2011) N = 3351 [c]	47	AC→P	1679	3-yr DFS: 75% 4-yr DFS: 74%	3-yr OS: 92% 4-yr OS: 86%
		AC→P + T	1672	3-yr DFS: 87% 4-yr DFS: 86% HR 0.51, 95%CI: 0.44–0.59	3-yr OS: 94% 4-yr OS: 93% HR 0.59, 95%CI: 0.48–0.73
BCIRG-006 (Slamon et al. 2009; Slamon et al. 2011) N = 3222	65	AC→D	1073	5-yr DFS: 75%	5-yr OS: 87%
		AC→D + T (× 1 yr)	1074	5-yr DFS: 84% HR 0.64, p < 0.001	5-yr OS: 92% HR 0.63, p < 0.001
		D + Carbo + T (× 1 yr)	1075	5-yr DFS: 81% HR 0.75, p = 0.04	5-yr OS: 91% HR 0.77, p = 0.04

AC = doxorubicin plus cyclophosphamide; Carbo = carboplatin; CEF = cyclophosphamide, epirubicin and fluorouracil; CI = confidence interval; CT = chemotherapy; D = docetaxel; DFS = disease-free survival; FU = follow-up; HR = hazard ratio; NSS = not statistically significant; OBS = observation; OS = overall survival; P = paclitaxel; RT = radiotherapy; T = trastuzumab.

[a] Number of patients denotes patients included in the efficacy analyses.

[b] Joint analysis of the NSABP B-31 and NCCTG N9831 trials.

[c] Excluded from the joint analysis by Romond et al. (Perez et al. 2007).

1.2.1.3 Safety of Trastuzumab IV

1.2.1.3.1 Cardiac Safety of Trastuzumab IV

The most clinically relevant adverse event (AE) associated with trastuzumab IV is left ventricular cardiac dysfunction (congestive heart failure or CHF). In patients with HER2-positive EBC enrolled in pivotal clinical trials described in Section 1.2.1.2, trastuzumab treatment for 1 year (administered concurrently or sequentially with chemotherapy) appeared to be associated with a decrease in LVEF, an increase in the incidence of CHF (where specified, this was severe [New York Heart Association or NYHA] Class III or IV, or Grade 3 or 4 or symptomatic CHF), and discontinuation of treatment as a result of cardiac adverse events (Garnock-Jones et al. 2010). Cardiac toxicity described as NYHA Class III/IV CHF occurred in 0%–0.9% of patients in the control arms and in 0%–3.8% of patients in the trastuzumab-containing arms of the four pivotal trials (see Table 2). However, the cardiotoxicity observed with concurrent or sequential trastuzumab treatment appeared to be mostly reversible following trastuzumab discontinuation, and no significant increase in cardiac death was reported (Garnock-Jones et al. 2010).

An overview of cardiac safety data from selected trials of trastuzumab in combination with a taxane after anthracyclines for HER2-overexpressing EBC shows rates of

symptomatic or severe CHF of $<4\%$ and asymptomatic declines in left ventricular ejection fractions of >10 percentage points in $\leq 30\%$ of patients. However, interstudy comparisons of chemotherapy-induced cardiac dysfunction are difficult because of the use of different definitions of cardiac dysfunction and different parameters for assessing cardiac safety (Ewer and O'Shaughnessy 2007). These levels were considered below safety cut-off points set by the individual studies' independent data monitoring committees (Jahanzeb et al. 2008).

The NSABP B-31 trial determined the 5-year cumulative cardiac event rate (NYHA Class III or IV CHF or cardiac death) to be 3.8% in patients randomly assigned to trastuzumab versus 0.9% in patients who received chemotherapy alone (Rastogi et al. 2007; Russell et al. 2010). In the NCCTG N9831 trial, the incidence of CHF was 0% in the chemotherapy-alone arm, 2.2% in patients who received sequential chemotherapy and trastuzumab, and 3.3% in patients who received concurrent chemotherapy and trastuzumab (Perez et al. 2008). An independent adjudication of the cardiac events occurring in Studies B-31 and N9831 determined that the incidence of symptomatic heart failure events was 2.0% in trastuzumab-treated patients compared with 0.45% in the chemotherapy-alone arm, and that and the majority (86%) of these patients recovered with appropriate treatment (Russell et al. 2010).

The long-term incidence of cardiac AEs in patients with EBC who were treated with trastuzumab IV for 1 year after completion of neoadjuvant or adjuvant chemotherapy was also evaluated in the HERA trial. Of the 1698 patients randomly assigned to observation and 1703 randomly assigned to 1 year of trastuzumab treatment, 94% had been treated with anthracyclines. The incidence of discontinuation of trastuzumab because of cardiac disorders was low (5.1%). At a median follow-up of 3.6 years, the incidence of cardiac endpoints remained low, though it was higher in the trastuzumab group than in the observation group (severe CHF, 0.8% vs. 0.0%, respectively; confirmed significant LVEF decreases, 3.6% vs. 0.6%, respectively). In the trastuzumab group, 59 of 73 patients with a cardiac endpoint reached acute recovery (Procter et al. 2010).

Table 2 Cardiac Safety of Trastuzumab IV in the Adjuvant Setting

Study	Interventions	No. of Pts [a]	LVEF↓ from BL, % of pts	Symptomatic HF, % of pts
SEQUENTIAL TRASTUZUMAB				
HERA (Piccart-Gebhart et al. 2005; Gianni et al. 2011; Procter et al. 2010) N = 5090	CT ± RT → OBS	1698	Signif: 0.5%	0.1% (NYHA Class III/IV: 0)
	CT ± RT → T × 1 yr	1703	Signif: 3%	2% (NYHA Class III/IV: 0.6%)
	CT ± RT → T × 2 yrs	1701	NR	NR

Table 2 Cardiac Safety of Trastuzumab IV in the Adjuvant Setting (cont.)

NCCTG N9831 (Perez et al. 2009) N = 3133	AC→P AC→P→T	1087 1097	NR NR	NR Gr 3/4 or SCD: 2.8%
CONCURRENT TRASTUZUMAB				
NSABP B-31 (Perez et al. 2007; Tan-Chiu et al. 2005; Romond 2005; Rastogi et al. 2007) N = 2043	AC→P AC→P + T	872 864	NR NR	NYHA Class III/IV or SCD at 5 yrs: 0.9% NYHA Class III/IV or SCD at 5 yrs: 3.8%
NCCTG N9831 (Perez et al. 2009) N = 3133	AC→P AC→P + T→T	1087 949	NR NR	NR Gr3/4 or SCD: 3.3%
BCIRG-006 (Slamon et al. 2009; Slamon et al. 2011) N = 3222	AC→D AC→D + T (× 1 yr) D + Carbo + T (× 1 yr)	1073 1074 1075	↓ > 10%: 11% ↓ > 10%:19% ↓ > 10%: 9%	Gr3/4: 0.7% Gr3/4: 2.0% Gr3/4: 0.4%

AC = doxorubicin plus cyclophosphamide; BL = baseline; CEF = cyclophosphamide, epirubicin and fluorouracil; CT = chemotherapy; D = docetaxel; FU = follow-up; Gr = Grade (NCI-CTCAE); NR = not reported; NYHA = New York Heart Association (functional class); OBS = observation; P = paclitaxel; RT = radiotherapy; SCD = sudden cardiac death; Signif = significant drop in LVEF (symptomatic or asymptomatic); T = trastuzumab; yr = year.

Note: The assessments and definitions differed among the studies; therefore the data provided are not suitable for comparisons between trials.

[a] Number of patients denotes patients included in the analyses.

1.2.1.3.2 Post-marketing Safety Summary of Trastuzumab IV

It is estimated that over 1 million patients have been treated with trastuzumab IV as of October 2011 (Roche, Data on file).

The most common (occurring in ≥ 1 out of 10 treated patients) adverse reactions are infusion-associated symptoms such as fever and chills, usually following the first infusion of trastuzumab IV. These symptoms are usually mild to moderate in severity and occur infrequently with subsequent trastuzumab IV infusions in up to 40% of patients. Other very common (≥ 1 of 10 patients) adverse reactions include febrile neutropenia, tremor, dizziness, headache, blood pressure changes (increase or decrease), irregular heartbeat, palpitation, cardiac flutter, decreased ejection fraction, dyspnea, wheezing, diarrhea, vomiting, nausea, lip swelling, abdominal pain, erythema, rash, swelling of the face, arthralgia, muscle tightness, myalgia, asthenia, chest pain, fatigue, influenza-like symptoms, infusion-related reaction, and pain.

Some adverse reactions to trastuzumab IV infusion can be serious and include dyspnea, hypotension, elevated blood pressure, wheezing, bronchospasm, tachycardia, reduced

oxygen saturation, and respiratory distress. In the post-marketing setting, very rare (< 1 of 10,000 patients) occurrences of severe infusion reactions leading to a fatal outcome have been associated with the use of trastuzumab IV.

Severe pulmonary events leading to death have been reported with the use of trastuzumab IV in the post-marketing setting (4 out of 10,000 treated patients). Signs, symptoms, and clinical findings included interstitial lung disease including pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary edema, and pulmonary insufficiency. These events may or may not occur as sequelae of infusion reactions. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs resulting in dyspnea at rest may be at greater risk of severe reactions. Other risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies such as taxanes, gemcitabine, vinorelbine, and radiation therapy.

In addition, severe hypersensitivity reactions have been infrequently reported in patients treated with trastuzumab IV (the exact incidence of these events is unknown). Signs and symptoms include anaphylaxis, urticaria, bronchospasm, angioedema, and/or hypotension. In some cases, the reactions have been fatal. Symptom onset generally occurred during an infusion, but onset after the completion of an infusion has also been reported. Reactions were most commonly reported in association with the initial infusion.

The immunogenicity of trastuzumab IV has been investigated in clinical studies that included 903 MBC patients. Human anti–human antibodies (HAHA) to trastuzumab were detected in 1 patient, who had no allergic manifestations.

More detailed information on the full safety profile of trastuzumab IV is found in the Herceptin (RO 45-2317, Trastuzumab) IB.

1.2.2 Trastuzumab SC

Trastuzumab for subcutaneous (SC) administration has been developed by F. Hoffmann La Roche Ltd to address the known limitations of IV administration (e.g., infusion-related reactions, long administration times, requirement for hospital facilities, treatment barrier for patients with poor venous access, continued use of port-a-cath systems). Subcutaneous administration of trastuzumab takes significantly less time (up to 5 minutes) compared to IV infusion (30–90 minutes), and this is expected to improve treatment convenience and compliance. These attributes are particularly important for patients treated over prolonged periods of time, such as in the adjuvant setting. Subcutaneous administration offers the potential for self-administration of trastuzumab, which is expected to further improve treatment convenience and compliance.

1.2.2.1 Recombinant human hyaluronidase (rHuPH20)

The feasibility and patient acceptability of subcutaneous administration of any drug is dependent on the volume that must be administered. A key excipient in the SC formulation is the enzyme hyaluronidase, which enables larger volumes to be administered without reduced tolerability and patient acceptability. Animal-derived hyaluronidase has been available commercially for over 60 years and is used primarily as a permeation enhancer to increase the dispersion and absorption of other co-administered drugs. Hyaluronidase transiently hydrolyses hyaluronan, a component of the subcutaneous matrix, leading to reduced viscosity of the extracellular matrix of the hypodermis and, thus, to an improved delivery of SC administered drugs to the systemic circulation. The decreased viscosity is also expected to facilitate SC administration of larger volumes of fluid.

More recently, recombinant human hyaluronidase (rHuPH20) has been developed and approved to improve dispersion and absorption of co-administered drugs. This recombinant human molecule has a higher purity and is associated with improved efficacy and tolerability compared with the animal-derived enzyme. In the US, one recombinant humanized hyaluronidase, Hylenex® (Hylenex® Prescribing Information 2005), is licensed to facilitate the absorption and dispersion of drugs when given SC at doses between 50 IU and 300 IU (Frost 2007). The rHuPH20 used in the current study is produced from a second generation of the Hylenex® process, with an improved yield and purity. It has been combined with trastuzumab to allow safe and comfortable subcutaneous injection of volumes ≥ 3 mL.

1.2.2.1.1 Nonclinical Studies with rHuPH20

After IV administration in the dose range 0.3–30 mg/kg, rHuPH20 demonstrated nonlinear PK, rapid clearance, and a half-life of around 5 minutes at the lowest dose tested. The bioavailability of rHuPH20 following SC administration was extremely low (not determinable at low doses, 6%–8% in the dose range 3–30 mg/kg). Treatment of various species with rHuPH20 (IV or SC) was generally well tolerated, and no major abnormalities were noted in any toxicology studies.

For further details on nonclinical studies with rHuPH20 refer to the Herceptin (RO 45-2317, Trastuzumab) IB.

1.2.2.1.2 Clinical Studies with rHuPH20

Mammalian hyaluronidase preparations differing in source species and manufacturing processes have been the subject of multiple investigations and regulatory approvals in Europe, the US, and Asia. It is estimated that these products have been administered to tens of millions of patients in the US. The safety and efficacy of hyaluronidase products have been widely established. The most significant safety risk identified is hypersensitivity/allergenicity, which is thought to be related to the lack of purity of the animal-derived preparations (Frost 2007; Harris 2003). Humanized recombinant

hyaluronidase preparations are associated with an improved purity and corresponding decreased safety risk.

Clinical data are available from four studies with rHuPH20.

- In an allergic sensitivity study (Study R04-0851), 100 healthy volunteers were injected intradermally with 0.1 mL (15 U) of rHuPH20 and saline control. The most common side effects were generally mild redness, bruising, swelling, discomfort, and itching. No AEs were serious, and none were judged to be related to study treatment.
- A proof-of-concept dose-escalation study (Study HZ2-06-02) with adalimumab and rHuPH20 in 15 patients with rheumatoid arthritis evaluated the effects of rHuPH20 on the PK, safety, and tolerability of adalimumab. A single co-administration of adalimumab with rHuPH20 increased adalimumab exposure by a weighted average of 13% compared to adalimumab alone. The injection was well tolerated, with only mild and moderate AEs.
- Study HZ2-07-01 was a double-blind, within-subject-controlled, two-way cross-over trial comparing the time to inject (flow rate), safety, and tolerability of a SC administered 10% (2000 mg in 20 mL) solution of immunoglobulin G (diluted Carimune® NF) with and without rHuPH20 in 30 healthy volunteers. There was a statistically nonsignificant trend towards a decrease in time to inject and an increase in flow rate in the presence of rHuPH20 relative to the control group. The most common AEs were injection-site reactions consisting of erythema, pain, edema, induration, or pruritus (communication with Halozyme Therapeutics Inc. on preliminary study results).
- Study HZ2-07-02 investigated the SC injection of different rHuPH20 concentrations in a viscous solution of IgG and adalimumab in healthy volunteers using different volumes of injection (2, 8, and 16 mL). The maximum total enzyme dose administered in this study was 96,000 U. The injections were well tolerated, with no serious adverse events (SAEs) reported. All injection-site reactions, such as erythema, pain and induration, were mild (98%) or moderate (2%) in severity. There was a trend to lower mean time to inject in subjects who received rHuPH20 compared to those who received injections without rHuPH20, as well as a trend towards an increase in the exposure to adalimumab in the presence of rHuPH20. Pain increased across all volume cohorts after injection, with no clear difference between the presence and absence of rHuPH20.

The highest total rHuPH20 dose administered in these clinical studies was 96,000 U in Study HZ2-07-02, and this was well tolerated by healthy volunteers.

For further information on the clinical trials conducted with rHuPH20, refer to the Herceptin (RO 45-2317, Trastuzumab) IB.

1.2.2.2 Nonclinical Studies with Trastuzumab SC

An overview of completed nonclinical pharmacology, PK, and toxicology studies of trastuzumab SC is provided in Table 3. Overall, these studies showed that rHuPH20 enabled more rapid absorption of trastuzumab SC, and that SC administration of trastuzumab formulated with rHuPH20 was well tolerated locally and systemically.

For further information, refer to the Herceptin (RO 45-2317, Trastuzumab) IB.

Table 3 Overview of Completed Nonclinical Pharmacology, PK, and Toxicology Studies with Trastuzumab SC (Formulated with rHuPH20)

Study Type	Objective	Species	Key findings
Pharmacology			
In vivo efficacy in mouse xenograft model	Comparison of trastuzumab SC with trastuzumab IV	Mouse	Comparable efficacy providing similar trough levels achieved
Pharmacokinetics			
PK (non GLP)	Assessment of trastuzumab SC PK in preparation for efficacy/pharmacology study (above)	Mouse	Bioavailability of trastuzumab SC estimated at 83.4%
PK/dose finding	Optimization of trastuzumab SC formulation for clinical studies	Mini-pig	More rapid absorption of trastuzumab SC formulated with rHuPH20 than without rHuPH20
PK assessment	Assessment of trastuzumab SC PK in preparation for 13 week repeat dose toxicity study	Cynomolgus monkey	Maximum serum trastuzumab levels achieved 24 hours after trastuzumab SC (PK comparable to mini-pig)

AUC = area under the curve; GLP = Good Laboratory Practices; IV = intravenous; PK = pharmacokinetic; rHUPH20 = recombinant humanized hyaluronidase; SC = subcutaneous.

Table 3 Overview of Completed Nonclinical Pharmacology, PK, and Toxicology Studies with Trastuzumab SC (Formulated with rHuPH20) (cont.)

Study Type	Objective	Species	Key findings
Toxicology			
Local tolerance	Clinical symptoms and injection site reactions following single dose trastuzumab SC	Rabbit	No signs of systemic toxicity. No macroscopic or microscopic findings attributable to treatment
13 week repeat dose toxicity	High dose toxicity, clinical symptoms, and injection site reactions	Cynomolgus monkey	Trastuzumab exposure (AUC) comparable to that achieved at highest doses in nonclinical IV safety program. No adverse findings for any of the parameters evaluated. Low immunogenicity (anti-trastuzumab antibodies found in 1 of 4 recovery animals)

AUC = area under the curve; GLP = Good Laboratory Practices; IV = intravenous; PK = pharmacokinetic; rHUPH20 = recombinant humanized hyaluronidase; SC = subcutaneous.

1.2.2.3 Clinical Studies with Trastuzumab SC

Subcutaneous trastuzumab (formulated with rHuPH20) has been studied in one completed clinical trial (BP22023, CP2) and one ongoing clinical trial (BO22227, HannaH) using conventional syringes and hypodermic needles for administration. In addition, a PK study (BO25532, CP3) now completed in healthy volunteers has demonstrated comparable exposure between SC administration with the single-use injection device (SID) versus with the conventional syringe and needle. Lastly, a patient satisfaction and health care professional (HCP) preference study (MO22982, PrefHer) comparing trastuzumab SC administration using SID and vial with trastuzumab IV administration is ongoing in parallel with the current study.

Table 4 Overview of the Clinical Development Program of Trastuzumab SC

Studies	Status	Design	Primary Objective
Trastuzumab SC (Vial)			
Phase Ib dose-finding study (BP22023, CP2)	Completed	Dose-finding/dose-confirmation study OL, PG, single-dose, MC	Select the dose of trastuzumab SC which results in comparable exposure to that achieved from an IV dose of trastuzumab
Phase III clinical study (BO22227, HannaH)	Ongoing	PK, efficacy, and safety study in the neoadjuvant/adjuvant setting OL, PG, randomized, multiple-dose, MC	Non-inferiority of pre-surgery trastuzumab C_{trough} and pCR
Phase I device qualification study (BO25532, CP3)	Ongoing	PK bridging to injection device OL, PG, randomized, single-dose, MC	Pharmacokinetic comparability of trastuzumab SC dosing via a SID or via hand-held needle and syringe used in previous clinical studies.
Additional Studies			
Phase II patient preference study (MO22982, PrefHER)	Ongoing	Patient preference and HCP satisfaction study Randomized, MC, cross-over study	To evaluate patient preference for trastuzumab SC administration using a SID or vial versus trastuzumab IV

HCP = health care professional; MC = multicenter; OL = open-label; pCR = pathological complete response; PG = parallel-group; PK = pharmacokinetic; SID = single-use injection device.

1.2.2.3.1 Study BP22023 (CP2)

Study BP22023 (Wynne et al. 2013) included two parts: trastuzumab SC dose finding in healthy male subjects and subsequent dose confirmation in female HER2-positive breast cancer patients. Twenty-four healthy male subjects and 46 female subjects with HER2-positive EBC received single doses of either trastuzumab IV or trastuzumab SC, as outlined in Table 5. The dose of rHuPH20 received depended on the volume administered, which depended on the body weight-based dose of trastuzumab. The concentration of trastuzumab in the SC formulation was 120 mg/mL. The concentration of rHuPH20 was 2000 U/mL.

Table 5 Summary of Treatment Cohorts and Adverse Events, Study BP22023

Cohort	Route of administration	Subjects	Dose (mg/kg)	AEs	
				Subjects n (%)	Events n [Gr1/Gr2/Gr3]
Part 1 (Dose finding)					
All Subjects				27 (90)	86 [61/24/1]
1	IV	6 healthy males	6	5	26 [19/6/1]
2	IV	6 HER2-positive EBC females	6	6	24 [17/7/0]
3	SC	6 healthy males	6	5	12 [9/3/0]
4	SC	6 healthy males	10	5	11 [8/3/0]
5	SC	6 healthy males	8	6	13 [8/5/0]
Part 2 (Dose confirmation)					
All subjects				39 (98)	181 [131/46/4]
A	SC	20 HER2-positive EBC females	8	19	87 [61/23/3]
B	SC	20 HER2-positive EBC females	12	20	94 [70/23/1]

EBC = early breast cancer; IV = intravenous; mod = moderate; SC = subcutaneous; sev = severe.

Safety Data from Study BP22023

The BP22023 protocol allowed healthy volunteers and patients to receive premedication (e.g., paracetamol and/or phenergan) prior to the administration of trastuzumab SC, at the discretion of the investigator, for prophylaxis of infusion-related reactions (IRRs).

In Part 1, a total of 86 AEs were observed in 27 out of 30 subjects. Of these, 71% were considered to be Grade 1 intensity, and 28% were Grade 2 intensity (Table 5). Two IRRs were observed in Cohort 1. One event was assessed as Grade 2 intensity, the other as Grade 3 intensity. Premedication to lower the risk of IRR was given to 2 subjects in Cohorts 1 and 3, respectively, and to one subject of Cohort 4. Neither of the healthy male volunteers experiencing an IRR in Cohort 1 had received any premedication before being administered trastuzumab IV. The number of subjects reporting AEs was similar in all the cohorts in Part 1, but there were fewer events reported in the SC cohorts. In Cohorts 3–5, in which male subjects received trastuzumab SC at 6, 8, and 10 mg/kg; there was no apparent dose-related increase in frequency or severity of AEs, and the SC administration was generally well tolerated.

In Part 2, a total of 181 AEs were observed in 39 out of 40 female patients. Of these, 72.5% were considered to be Grade 1 intensity, 25.5% were Grade 2 intensity, and there

were 4 (2%) Grade 3 AEs (Table 5). In Cohorts A and B, there was no apparent dose-related increase in the frequency or intensity of AEs observed, and the SC administration was generally well tolerated.

As this was the first study during which subjects received trastuzumab SC, special consideration was given to the local tolerability related to drug administration. In subjects who received trastuzumab SC, there were 18 AEs that were classified as administration site conditions. A total of 16 (89%) AEs were of mild intensity and included erythema (7), discoloration (5), injection-site swelling (2), injection-site discomfort (1), and injection-site reaction (1). There were two instances of moderate injection-site pain. There were no changes in laboratory parameters, vital signs or ECG parameters that constituted an AE.

Pharmacokinetic Data from Study BP22023

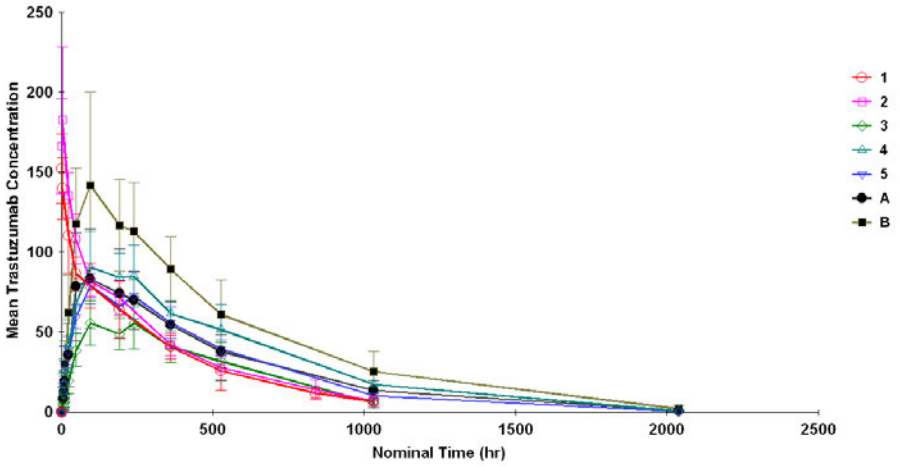
Comparable trastuzumab PK was observed in Part 1 between female patients and healthy male volunteers receiving 6 mg/kg IV, with a mean C_{max} of 185 µg/mL compared with 150 µg/mL and a mean AUC_{inf} of 1800 µg • day/mL compared with 1610 µg • day/mL in female patients and healthy male volunteers, respectively (Figure 1).

Mean maximum serum concentrations (C_{max}) of trastuzumab increased proportionally with increasing doses of trastuzumab SC, 66.8, 82.0, and 102 µg/mL for 6, 8, and 10 mg/kg trastuzumab SC, respectively. Mean $AUC_{0\text{-}inf}$ also increased over the range of SC doses administered, 1350, 1960, and 2500 day • µg/mL for 6, 8, and 10 mg/kg trastuzumab SC, respectively (Table 6).

Following preliminary PK analysis of trastuzumab serum samples in all subjects in Part 1 (Cohorts 1 to 5), 20 patients were administered a single dose of 8 mg/kg trastuzumab SC (**Cohort A**), as this was the trastuzumab SC dose level expected to achieve a comparable exposure to the approved maintenance dose of 6 mg/kg trastuzumab IV. In **Cohort B**, patients were administered a single dose of 12 mg/kg trastuzumab SC to assess PK characteristics and safety, as well as to support modelling and simulation. The absolute bioavailability based on $AUC_{0\text{-}inf}$ ranged between 83.9% and 93.2% in healthy male volunteers and 87.1% and 98.6% in female patients.

The available data suggested dose proportionality in C_{max} and $AUC_{0\text{-}inf}$ over the range of trastuzumab SC doses administered (6–12 mg/kg) both in Part 1 and Part 2.

Figure 1 Mean (±SD) Trastuzumab Concentration-Time Profile by Cohort



EBC = early breast cancer; IV = intravenous; SC = subcutaneous; SD = standard deviation.
1: 6 mg/kg IV, healthy subjects
2: 6 mg/kg IV, EBC subjects
3: 6 mg/kg SC, healthy subjects
4: 10 mg/kg SC, healthy subjects
5: 8 mg/kg SC, healthy subjects
A: 8 mg/kg SC, EBC subjects
B: 12 mg/kg SC, EBC subjects

Table 6 Mean (CV%) Trastuzumab Serum Pharmacokinetic Parameters, Following Trastuzumab IV and SC Administration, Study BP22023

Cohort	Route of Administration	Subjects (n)	Dose (mg/kg)	C_{max} (µg/mL)	t_{max} (hour) [a]	AUC_{inf} (day/µg/mL)	$t_{1/2}$ (hour)	C_{Day22} (µg/mL)
1	IV	H (6)	6	150 (9.57)	1.65 (1.6–24.0)	1610 (18.9)	254 (12.7)	25.6 (47.1)
2	IV	EBC (6)	6	185 (23.2)	3.00 (1.55–24.0)	1800 (13.9)	244 (28.4)	27.5 (27.1)
3	SC	H (6)	6	66.8 (17.1)	156.00 (95.95–216.10)	1350 (23.7)	227 (24.7)	31.6 (38.1)
5	SC	H (6)	8	82.0 (13.8)	96.00 (96.00–215.98)	1960 (12.4)	236 (18.6)	39.4 (13.9)
4	SC	H (6)	10	102 (16.8)	132.12 (96.00–216.00)	2500 (20.6)	240 (14.3)	51.4 (30.8)
A	SC	EBC (20)	8	88.4 (37.7)	97.13 (47.93–216.60)	2090 (30.6)	241 (19.9)	37.8 (27.5)
B	SC	EBC (20)	12	151 (38.7)	96.05 (24.53–241.40)	3550 (27.7)	270 (29.6)	60.8 (36.2)

AUC = area under the curve; C_{max} = maximum serum concentration; EBC = early breast cancer; H = Healthy; IV = Intravenous; SC = Subcutaneous; t_{max} = time to achieve maximum serum concentration; $t_{1/2}$ = elimination half-life.

Note: Values represent means (standard deviation), unless otherwise indicated.

[a] Median (min–max).

Plasma concentrations of rHuPH20 were assessed in all subjects who received trastuzumab SC at predose and 0.5 h, 1 h, and 24 h postdose. Plasma rHuPH20 concentrations were below the limit of quantification for all sampling points in all subjects, indicating that the use of the enzyme as a permeation enhancer for trastuzumab does not result in quantifiable systemic exposure to the enzyme.

Immunogenicity Results from Study BP22023

Blood samples were taken at screening, Days 15, 85 and follow-up (5 months postdose) to allow for testing of antibodies to either trastuzumab or rHuPH20.

Nine of 58 (15.5%) subjects who had been administered trastuzumab SC were deemed positive for antibodies to rHuPH20 after confirmatory assay analysis. Five of these subjects had a positive confirmatory assay at all timepoints including screening, one subject was positive at screening, Day 15 and follow up and negative at Day 85, one subject was positive at screening, Day 15 and Day 85 but negative at follow up, another one was positive at Day 85 but negative at follow-up; and the remaining subject was positive at Day 85 and follow-up. All samples were negative in the neutralizing antibody assay.

A total of 263 samples were assayed in 58 subjects for the occurrence of anti-trastuzumab antibodies. Eleven samples in 8 of 58 (14%) subjects receiving trastuzumab SC were positive for antibodies to trastuzumab after the confirmatory assay. All samples from the screening visits were negative for anti-trastuzumab antibodies. In 6 subjects out of the 8 above, the follow-up sample was negative after one positive sample. No anti-trastuzumab antibodies were detected in subjects receiving trastuzumab IV. Neutralizing antibody tests for trastuzumab were not performed, as the assay was not available at the time. Samples have been discarded in the interim. Likewise, results from titering assays are not available.

The presence of a positive confirmatory assay for trastuzumab or rHuPH20 was not associated with a difference in safety or trastuzumab PK profile. This also held true for the 3 patients who developed anti-drug antibodies (ADA) to both proteins.

Pharmacokinetic Modelling of Fixed Trastuzumab SC Dose Selection

In the dose-finding Study BP22023, subjects received trastuzumab SC on a body weight-adjusted basis. Preliminary trastuzumab IV and SC PK data from this study were integrated into a PK model, and simulations were then used to predict C_{trough} and AUC for various trastuzumab SC doses based on 100 simulations of 130 subjects, which provided a 5 to 95th% tile range for the 5th% tile, median, and 95% tile concentration values. The simulations were based on a normal distribution of body weight, with a mean of 68 kg and standard deviation of 11 kg. The simulations indicated that a flat and a weight-based dosing strategy would result in a comparable range of exposure with a relationship to body weight that is inverse, and a fixed dose of 600 mg would result in C_{trough} values that are at least as high as with the 3-weekly (Q3W) IV regimen (8 mg/kg loading dose followed by 6 mg/kg maintenance dose). For example, as shown in Table 7, the IV upper bound of the confidence interval (CI) of the median C_{trough} is 63 µg/mL and is comparable to the SC lower bound of the CI of the median C_{trough} predicted at 67 µg/mL.

Table 7 Predicted C_{trough} (µg/mL) at Pre-dose Cycle 8

	C_{trough} at Predose Cycle 8 (µg/mL)		
	5th% tile P5 [P5-P95]	**Median [P5-P95]**	**95th% tile P95 [P5-P95]**
Q3W IV regimen (8/6 mg/kg)	23 [16-32]	46 [37-63]	84 [67-109]
SC regimen 600 mg	38 [28-49]	79 [67-95]	143 [120-174]

P5 = 5th percentile; P95 = 95th percentile; Q3W = 3-weekly.

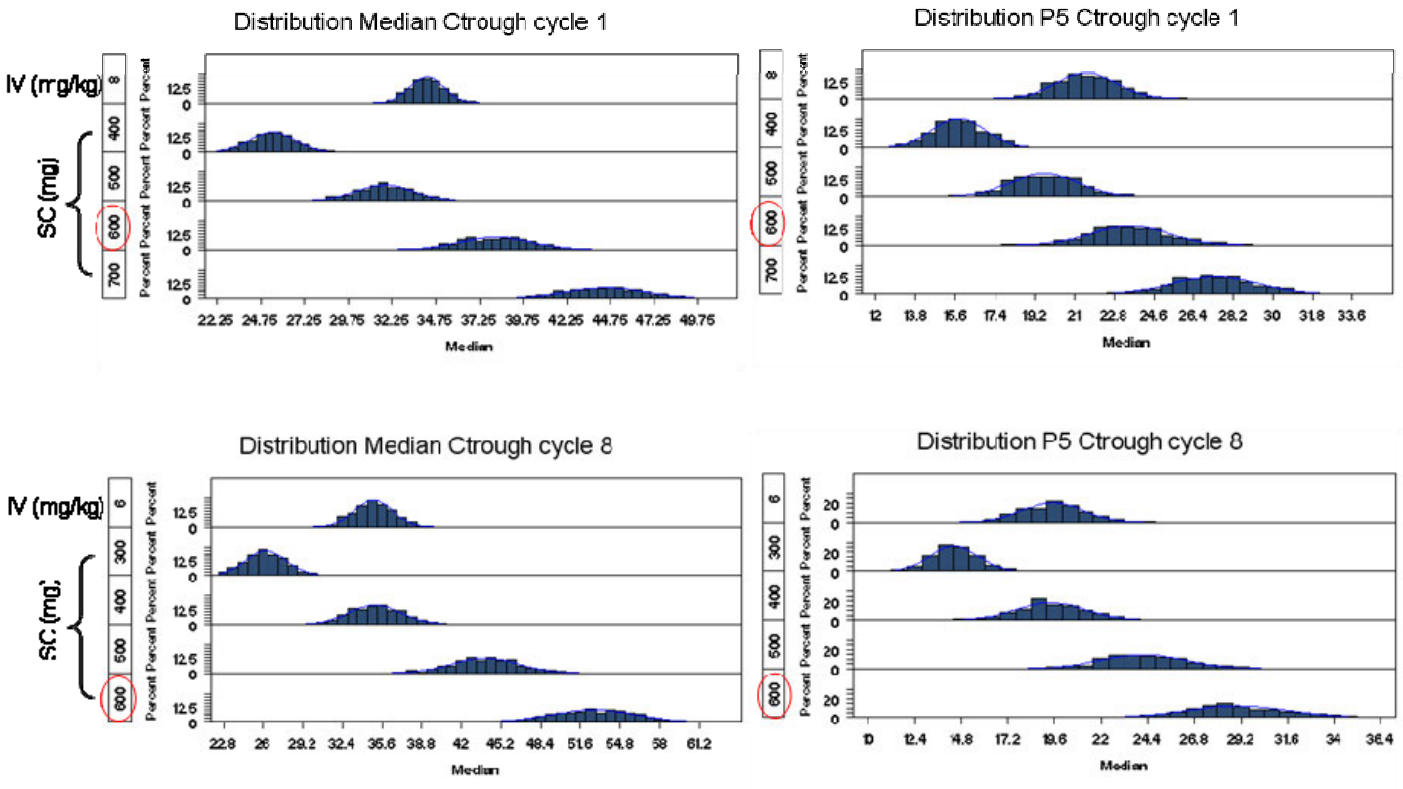
Figure 2 illustrates the distribution of predicted median C_{trough} and predicted 5th percentile of C_{trough}, respectively, at Cycles 1 and 8, comparing the IV loading and maintenance doses of 8 mg/kg and 6 mg/kg, and a fixed SC dose of 600 mg. For both

cycles, with the selected fixed dose of 600 mg, median C_{trough} values were predicted to be higher than those achieved with the IV doses.

Figure 3 illustrates the distribution of predicted median AUC_{tau} and predicted 5th percentile of AUC_{tau}, respectively, at Cycles 1 and 8, comparing the IV loading and maintenance doses of 8 mg/kg and 6 mg/kg and the fixed SC dose of 600 mg. For Cycle 8, with the selected fixed dose of 600 mg, median AUC_{tau} values were predicted to be higher than those achieved with the IV 6 mg/kg maintenance dose. For Cycle 1, median AUC_{tau} values were predicted to be lower than those achieved with the IV 8 mg/kg loading dose. It was predicted that with a 600 mg fixed dose of trastuzumab SC, a cumulative AUC comparable to the Q3W IV regimen would be reached during Cycle 3.

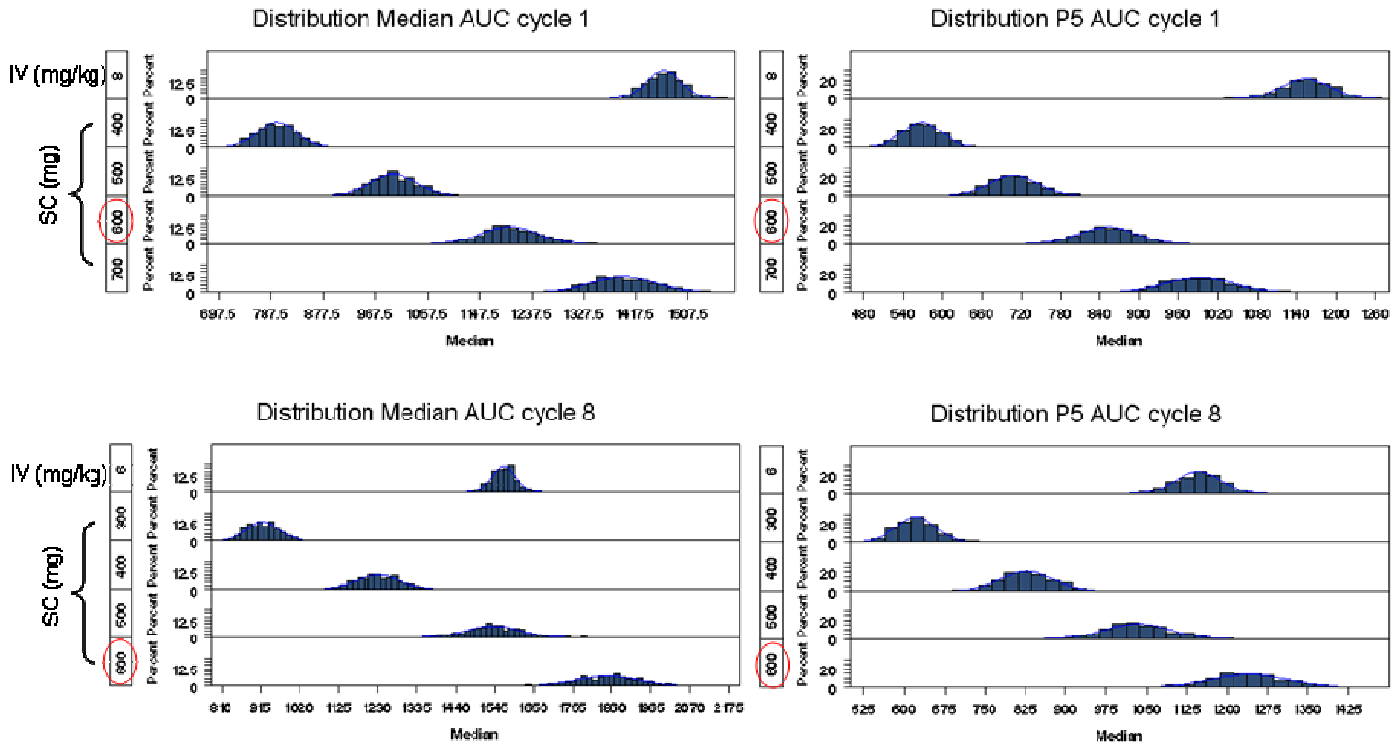
The predicted C_{max} values after SC administration (95th percentile) also did not exceed the maximum exposure previously measured for the IV regimen in the HERA trial (Clinical Study Report 1019820). Therefore, no unexpected safety issues related to trastuzumab exposure were anticipated with a 600 mg fixed dose of trastuzumab SC. Based on these data, a fixed dose of 600 mg was selected as an appropriate dose for further studies using trastuzumab SC.

Figure 2 Distribution or Simulated Median C_{trough} Levels at Cycles 1 and 8 with a Dose of 600 mg Trastuzumab SC



C_{trough} = trough plasma concentration; IV = intravenous; P5 = 5th percentile; SC = subcutaneous.

Figure 3 Distribution of Simulated Median AUC_{tau} Levels at Cycles 1 and 8 with a Dose of 600 mg Trastuzumab SC



AUC = area under the plasma concentration-time curve; IV = intravenous; P5 = 5th percentile; SC = subcutaneous.

1.2.2.3.2 Study BO22227 (HannaH)

The findings of Study BP22023 indicating that trastuzumab SC has a tendency toward fewer administration-related reactions compared to trastuzumab IV were further investigated in the Phase III clinical efficacy bridging Study BO22227 (HannaH).

Study BO22227 *is* a Phase III, randomized, open-label, multicenter trial involving 596 female patients with HER2-positive early breast cancer in which the pharmacokinetics, efficacy, and safety of trastuzumab SC were compared with IV trastuzumab. Co-primary endpoints are serum C_{trough} pre-surgery and pathological complete response (pCR).

In this study, patients with operable or locally advanced disease were randomized to eight cycles of either trastuzumab IV or trastuzumab SC given concurrently with chemotherapy. Patients randomized to trastuzumab IV received the standard 3-weekly regimen (8 mg/kg loading followed by 6 mg/kg every 3 weeks), and patients randomized to trastuzumab SC received a fixed dose of 600 mg of trastuzumab (formulated with rHuPH20 2000 IU/mL to give a fixed dose of 10,000 U) every 3 weeks by conventional SC injection using a syringe and needle. After surgery, patients received a further 10 cycles of trastuzumab IV or SC as per randomization to complete 1 year of treatment. Study BO22227 met its co-primary endpoints, which were the trastuzumab concentration in the blood (serum concentrations) and efficacy.

Results of the study indicated that trastuzumab SC demonstrated comparable efficacy to trastuzumab IV within the planned boundaries for non-inferiority with regard to the pCR and the concentration in the blood (C_{trough}). No new safety signals were identified with trastuzumab SC, and AEs were consistent with trastuzumab IV, with the most common AEs being infections and abnormal blood counts (anemia and low white blood cell count). The overall safety profile and tolerability in both arms was consistent with that expected from combination treatment with anthracycline, taxane, and trastuzumab. No new or unexpected safety findings were observed. The proportion of patients reporting an AE of any grade during neoadjuvant/adjuvant treatment and treatment-free follow-up was 93.9% (280 of 298 patients) in the trastuzumab IV arm compared with 97.3% (289 of 297 patients) in the trastuzumab SC arm. The most frequently occurring AEs were alopecia (62.8% in trastuzumab IV vs. 62.6% in trastuzumab SC), nausea (48.7% vs. 48.5%), neutropenia (46.3% vs. 44.1%), diarrhea (36.6% vs. 33.7%), asthenia (25.2% vs. 24.6), fatigue (26.5% vs. 22.6%), and vomiting (23.2% in each arm). Most AEs were Grade 1 or 2 in intensity. The incidence of Grade ≥ 3 events (severe) was 52% (155 of 298 patients) in the trastuzumab IV arm versus 51.9% (154 of 297 patients) in the trastuzumab SC arm. Full assessment of the data is publicly available (Ismael et al. 2012).

1.2.2.3.3 Study BO25532 (CP3)

Study BO25532 was a randomized, open-label, parallel, 2-arm, multicenter Phase I study to investigate the comparability of PK of trastuzumab administered subcutaneously

using either the SID or a conventional syringe with a hypodermic needle. The study also assessed the performance of the SID and evaluated the immunogenicity of trastuzumab and rHuPH20.

Enrollment was completed in September 2011, with a total of 119 healthy male subjects randomized 1:1 to receive a single 600 mg SC injection by either administration method. The primary objective of the study was met, with the results for both co-primary PK endpoints within the standard bioequivalence range of [0.8, 1.25], meeting the pre-specified criteria for comparability. Sensitivity analyses of the co-primary endpoints that included nondose normalized or non-body weight-adjusted calculations, were in line with the primary analysis.

Trastuzumab was well tolerated after single-dose administration by both methods, and there were no apparent differences related to the injection method (Wynne et al. 2012).

1.2.2.3.4 Study MO22982 (PrefHer)

This is a Phase II international, randomized, open-label, two-cohort, two-arm crossover study to evaluate patient's preference and HCP satisfaction with SC versus IV administration of trastuzumab in HER2-positive EBC following surgery and completion of chemotherapy (neoadjuvant or adjuvant). Approximately 200 patients will be randomized 1:1 in each cohort to receive either trastuzumab treatment. In Cohort 1, half of the patients will receive trastuzumab SC (600 mg fixed dose; 4 cycles) via a single use injection device (SID) followed by trastuzumab IV (8 mg/kg loading dose required only if Cycle 1 of study treatment is the initial dose of trastuzumab, otherwise 6 mg/kg Q3W; 4 cycles) or to trastuzumab IV followed by trastuzumab SC. All patients will then continue to receive the remaining trastuzumab IV to complete 18 cycles of trastuzumab administration. In Cohort 2, half of the patients will receive trastuzumab SC (600 mg fixed dose; 4 cycles) administered from a vial with a hand-held syringe followed by trastuzumab IV (8 mg/kg loading dose required only if Cycle 1 of study treatment is the initial dose of trastuzumab, otherwise 6 mg/kg Q3W; 4 cycles) or to trastuzumab IV followed by trastuzumab SC. All patients will then continue to receive the remaining trastuzumab SC to complete 18 cycles of trastuzumab administration. The primary endpoint is the proportion of subjects indicating an overall preference for either the SC or the IV route of administration. Efficacy endpoints include EFS. Immunogenicity of trastuzumab and rHuPH20 will also be evaluated.

1.2.3 Subcutaneous Single-Use Injection Device (SID)

The SID is a single-use device for the subcutaneous administration of medicinal products such as trastuzumab SC. The medicinal product to be injected is contained in an integral non-removable cartridge. The entire content of the cartridge is delivered to the patient in a single injection through a needle that retracts when the injection is complete and if prematurely removed from the body to prevent needle stick injuries in handling. The administration rate is fixed (approximately 1 mL/min, resulting in an approximate 5-minute injection time), and the dosage delivered is preset and controlled

at the product manufacturing stage (i.e., 600 mg of trastuzumab formulated with 10,000 U of rHuPH20). The medicinal product is administered through intact skin into the patient's upper thigh.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Patients with HER2-positive early breast cancer frequently require extensive treatment lasting months or years. Many require surgery, adjuvant chemotherapy (usually given IV for 4–6 months) and/or hormonal therapy, and radiotherapy (often given daily for 4–6 weeks), as well as trastuzumab. Adjuvant trastuzumab is given IV q1w or Q3W for a total of one year. This necessitates regular clinic visits, and, when started after completion of adjuvant chemotherapy and adjuvant radiotherapy if indicated, it greatly extends the period of time over which the patient is obliged to attend the hospital or clinic, which can cause inconvenience and increased costs to patients. Even when started concurrently with the taxane component of chemotherapy (Herceptin license permitting), trastuzumab monotherapy still continues for several months after completion of other systemic therapy.

Trastuzumab infusions are given over 30–90 minutes (or longer if there are infusion-related symptoms). SC administration of trastuzumab is quicker (lasting up to 5 minutes), and this alone could improve convenience for patients (and clinic staff). Furthermore, SC administration does not require IV access (which can be problematic in some patients after completion of chemotherapy). Use of a SID may also enable self-administration of trastuzumab in the future. This could potentially further improve convenience for patients and compliance with therapy.

The most clinically relevant AE associated with trastuzumab IV is left ventricular cardiac dysfunction or CHF. Cardiac toxicity, as measured by the rate of NYHA Class III/IV CHF was the most significant AE, occurring in 0%–3.8% of patients in the trastuzumab-containing arms of six randomized adjuvant trials (see Section 1.2.1.2). The current study is designed to investigate the safety and tolerability of two SC administration methods for trastuzumab in the (neo-)adjuvant setting, i.e. assisted administration using a conventional syringe (vial formulation) and self-administration using a SID. The observed incidence of CHF-related SAEs served as basis for the determining the sample size for the current trial. Patient satisfaction with self-administration using a SID is assessed as part of the secondary objectives of the study.

Trastuzumab is now a standard component of (neo)-adjuvant treatment in patients with HER2-positive EBC. The trastuzumab SC dose selected for this study is consistent with the findings of the BP22023 (CP2) trial and identical to that evaluated in the BO22227 (HannaH) study (see Section 1.2.2 for details). Efficacy is hence expected to be comparable to that that observed in trastuzumab IV trials. Safety data from the BP22023 and BO22227 studies show that trastuzumab SC is well tolerated, with no safety signals detected compared to trastuzumab IV in the BO22227 study. The benefit

to risk ratio of adjuvant trastuzumab SC in the current trial is therefore expected to be favorable. Further, the convenience of SC administration of trastuzumab will give patients greater independence, which is expected to increase compliance.

One of the exploratory objectives of the study is to collect additional safety data over a specified observation time (according to trastuzumab EU SmPc) following trastuzumab administrations in patients using the SID (**Cohort B**).

It will be assessed whether the prolonged observation time of the patients following trastuzumab SC administration (during the pre-specified time as per SmPC) is required for patients' safety. It is anticipated there may be a higher possibility of AEs following the first administration of trastuzumab; therefore, the patient will be required to remain at site for 6 hours after start of the first trastuzumab administration. For all subsequent trastuzumab applications, patients will be required to remain onsite for 2 hours after start of drug administration. However, the patient may be required to remain onsite for an extended period of time if considered clinically necessary by the investigator. 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 premedications prior to trastuzumab administration will be collected. Also, in addition to the date, the onset and resolution time of the treatment of AEs occurring during the observation time will be investigated. At the discretion of the investigator, patients will have the opportunity to self-administer trastuzumab via the SID; therefore, the SID performance under self-administration conditions will be monitored.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

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

2.2 SECONDARY OBJECTIVES

Secondary objectives include the evaluation of the following parameters:

- Efficacy (both cohorts):
  - DFS (Disease-free survival)
  - OS (Overall survival)
- Patient satisfaction with trastuzumab SC administration using the SID (patients in **Cohort B** who went on to self-administration of the study drug).

2.3 EXPLORATORY OBJECTIVES

Additional, exploratory objectives will be investigated in a subset of patients (**Cohort B**) at selected study sites:

1. To assess the immunogenicity of trastuzumab and recombinant human hyaluronidase (rHuPH20)
2. 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**])
3. 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 substudies will be conducted. Details of the substudies will be described in separate protocols.

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a Phase III, prospective, two-cohort, non-randomized, multicenter, multinational, open-label study in approximately 2500 patients with HER2-positive EBC who are eligible for anti-HER2 therapy. A planned total of approximately 2500 evaluable patients will be enrolled into the study. The trial will be conducted at approximately 520 centers in approximately 60 countries.

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 enrollment into the study.

Eligible patients will be allocated to **Cohort A** or **B** at the investigator's discretion depending upon availability of the cohorts for recruitment:

- **Cohort A** (approximately 1800 patients): trastuzumab SC 600 mg 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 600 mg 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.

To allow for the enrollment of 1800 patients in **Cohort A** (compared to 700 patients in **Cohort B**), recruitment for **Cohort A** may be initiated earlier than recruitment for **Cohort B**.

The study design is shown in Figure 4.

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. All study treatment administrations in both cohorts will occur in a hospital setting.

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 tumors >2 cm in diameter

For patients receiving trastuzumab SC with concurrent chemotherapy, trastuzumab SC must be administered first, followed by the administration of chemotherapy as per standard site procedures. The observation time starts with the start of trastuzumab SC administration.

The enrollment of patients treated without neoadjuvant or adjuvant chemotherapy, such as:

- Patients with low risk node negative tumors ≤ 1.0 cm
- Elderly patients (>65 years of age)
- or patients who refuse chemotherapy will be limited to $\leq 10\%$ of the total study population)

Hormonal therapy and radiotherapy (if applicable) may be given concomitantly with trastuzumab SC, as per local guidelines.

Patients will be assessed for safety and efficacy, as detailed in Appendix 1, Schedule of Assessments. In addition to efficacy and safety assessments, select sites will also perform immunogenicity testing to determine whether HAHAs 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.

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

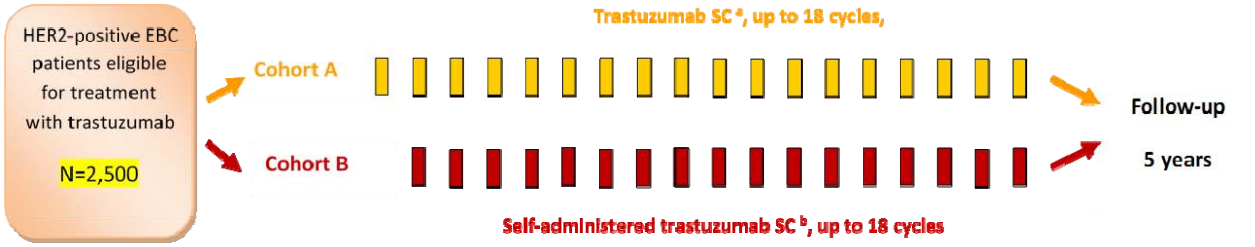
Patients will undergo a Safety Follow-up visit 4 weeks after their last dose of study treatment, with further follow-up according to the American Society of Clinical Oncology (ASCO) 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting (Khatcheressian et al. 2006) *or investigator's routine practice.* All patients will be followed-up for cancer recurrence and survival until study end. 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 progression, patients will be managed as per local practice and followed for survival only.

In some countries and sites, MCU (e.g., time and motion) and/or pharmacoeconomic substudies will be conducted. Details of the substudies will be described in separate protocols.

The primary analysis of safety endpoints and a preliminary analysis of efficacy (DFS and 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 OS and DFS 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 enrollment 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. The study design is shown in Figure 4 and the Schedule of Assessments in Appendix 1.

3.1.1 Overview

Figure 4 Study Design



EBC = early breast cancer; HCP = healthcare provider; HER2 = human epidermal growth factor receptor-2; SC = subcutaneous; SID = single-use injection device.

Notes: Participating investigators must opt for one route of administration per patient. For enrollment to **Cohort B**, patients need to be willing to self-administer the study drug based on the instructions for use supplied with the SID and personal instructions provided by an HCP during the first assisted administration. All trastuzumab SC administrations will occur in a hospital setting. Patients in both cohorts will receive trastuzumab SC 3-weekly, for a total of 18 cycles, unless disease recurrence, unacceptable toxicity or patient withdrawal necessitates early cessation of treatment. If trastuzumab SC is initiated in the neoadjuvant phase, surgery should be programmed after the dosing at Cycle 8, without interruption of trastuzumab treatment.

[a] **Cohort A**: Trastuzumab SC 600 mg will be injected by an HCP into the thigh over a period of approximately 5 minutes using a conventional handheld syringe with a gauge 25 or 27 hypodermic needle.

[b] **Cohort B**: Trastuzumab SC 600 mg will be injected into the thigh over a period of approximately 5 minutes using the SID. The first injection will be administered by a trained HCP (physician or nurse). Patients assessed by the investigator as competent to self-administer the study drug using the SID and are willing to will be allowed to self-administer the remaining trastuzumab SC doses under the direct supervision of a HCP. Patients not deemed competent to self-administer the study drug, or are not willing will have all their trastuzumab SC doses administered by a trained HCP (physician or nurse).

3.1.2 Steering Committee

A Steering Committee is established to provide scientific oversight and to ensure that the risk-benefit assessment is maintained during the total duration of the trial. Responsibilities of the Steering Committee include recommendation to the Sponsor of any protocol amendments, monitoring of accrual, compliance and safety during the conduct of the trial, and reviewing the results of three interim safety analyses when approximately 500, 1000, and 2500 patients have received at least one trastuzumab SC injection. Upon study completion, the Steering Committee will provide its interpretation of the results to the Sponsor, including their proposal for publications. Timing and type of publications generated by the SafeHer study will be defined in conjunction with the Sponsor.

The SafeHer Steering Committee is made up of investigators and Roche representatives and meets at regular intervals. The committee is composed of up to 10 members, including the Chairperson. The Chairperson of the Steering Committee is responsible for scheduling and conducting the meetings. Decisions of the Steering Committee are based on a majority vote.

Refer to the SafeHer Steering Committee Charter for further details.

3.2 END OF STUDY

End of study is defined as the last patient last visit in the follow-up period. The study will end when all patients have been followed for approximately 5 years 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 final analysis of OS and DFS and updated summaries for safety parameters will be performed at this stage.

The study is estimated to last approximately 8 years.

3.3 RATIONALE FOR STUDY DESIGN

This Phase III prospective, two-cohort non-randomized, multicenter, multinational, open-label study will assess the overall safety and tolerability of two SC administration methods of trastuzumab (assisted administration using a conventional needle and syringe and self-administration using a SID) in HER2-positive EBC patients. The safety and tolerability of the two SC administration methods will be evaluated over a standard treatment period of 18 cycles (administered every 3 weeks). With this comprehensive approach, any potential problems associated with multiple administrations (e.g., positioning the SID to avoid previous sites of administration) will also be assessed.

Patients will be allocated to **Cohort A** or **B** at the investigator's discretion. For enrollment into **Cohort B**, patients need to be willing to self-administer the study drug from the SID based on personal instructions/training provided by an HCP during the first assisted administration in addition to a quick reference guide and an instructional

animation describing the injection device handling and use, including how to respond if the SID loses sufficient contact with the body.

Administration by the SID could enable self-administration of trastuzumab in the future. The SID satisfaction questionnaire used in this study and the device usability monitoring questionnaire has been developed specifically for this purpose.

3.3.1 Rationale for Test Product Dosage

Subcutaneous trastuzumab will be given Q3W at a fixed dose of 600 mg in both cohorts. Use of a fixed dose for all patients and all cycles greatly simplifies dosing, reduces the potential for error, and reduces wastage. Fixed doses have been used for other therapeutic monoclonal antibodies, particularly in chronic conditions, such as rheumatoid arthritis (e.g., adalimumab). The fixed dose of trastuzumab for SC administration was selected with the aim of achieving trastuzumab serum trough concentrations (C_{trough}) that are non-inferior to those obtained with Q3W trastuzumab IV administration. The fixed (600 mg) dose of trastuzumab used in this study was calculated based on PK modelling of preliminary data from the BP22023 study (see Section 1.2.2.3.1), which showed that 600 mg doses of trastuzumab SC were able to achieve serum C_{trough} levels at least as high as those achieved with standard weight-adjusted trastuzumab IV dosing. Trastuzumab exhibits linear pharmacokinetics in the clinical dose range, which is an indication that target receptors are saturated. Therefore, achieving C_{trough} levels with SC administration that are at least as high as with the IV dosing, indicates that efficacy should be comparable. Patients with lower body weight may be exposed to higher C_{trough} levels than if they were dosed on a weight-adjusted basis. However, studies in which higher than standard (or more frequent) doses of trastuzumab were given (Clinical Study Report 1026709; Vogel et al. 2002) and reports of patients accidentally overdosed with trastuzumab IV do not indicate any detrimental effect on patient safety. Moreover, based on data from the BP22023 study, the predicted maximal concentrations following eight Q3W cycles of 600 mg are expected to be below the C_{max} of trastuzumab IV observed in the MO16982 study (range 199–375 mg/L). In Study MO16982, patients were initially dosed with 6 mg/kg weekly, and no increase in AEs was observed (Clinical Study Report 1026709). More recently, results of the HannaH study (BO22227) have been released. The study met its two co-primary endpoints, i.e. observed trastuzumab C_{trough} after 7 cycles and the primary efficacy variable of pathological complete response, thereby demonstrating comparable bioavailability and efficacy of the SC and IV formulations of trastuzumab.

The fixed dose of 600 mg of trastuzumab SC will be administered with a fixed dose of 10,000 U of rHuPH20 (2000 U/mL). The dose of rHuPH20 was selected based on nonclinical PK studies with a number of antibodies, including trastuzumab. These studies showed a trend for increasing dispersion and absorption with increasing concentrations of rHuPH20 (Clinical Study Report 1029906; Halozyme Study Report 09520). Of note, a higher amount of rHuPH20 (6000 U/mL) did not improve the

absorption of trastuzumab as compared to a formulation containing 2000 U/mL rHuPH20. The selected rHuPH20 concentration was further verified in clinical studies for satisfactory absorption parameters. Nonclinical and clinical data demonstrate that the selected amount of rHuPH20 contained in the trastuzumab SC formulation is well tolerated.

3.3.2 Rationale for the Patient Population

Adjuvant systemic therapies for early breast cancer have contributed to the substantial decline in breast cancer mortality in the past couple of decades (Verma et al. 2010; Colozza et al. 2006). The introduction of trastuzumab has particularly improved the outcome for early breast cancer patients with HER2-positive disease. Since its initial approval in 1998, trastuzumab has become standard of care for patients with HER2-positive breast cancer and is widely used for its approved indications in both the adjuvant and metastatic settings (Ross et al. 2009; NCCN 2010; Gnant et al. 2011; Aebi et al. 2011).

HER2 positivity, defined as the over-expression or amplification of HER2, is a prerequisite for the use of trastuzumab. Recent reports indicate that approximately 15%–20% of breast cancers are HER2-positive (Ross et al. 2009; Lund et al. 2010). Patients with HER2-positive early breast cancer frequently require extensive treatment lasting months or years. Many require surgery, adjuvant chemotherapy (usually given intravenously for 4–6 months) and/or hormonal therapy (given for 5–7 years), and radiotherapy (often given daily for 4–6 weeks), as well as trastuzumab. Adjuvant trastuzumab is given IV every week or every three weeks for a total of one year.

Although trastuzumab in combination with chemotherapy is now standard of care for patients with HER2-positive EBC larger than 1 cm, its role in the management of small (≤1 cm) HER2-positive tumors has not been established. There are two main reasons for this gap: first of all, most small breast cancers have a good prognosis and adjuvant chemotherapy is not routinely recommended for their management. In addition, due to this perceived good prognosis, patients with small (<1 cm, T1a,b) node-negative (N0) HER2-positive cancers were largely excluded from the pivotal adjuvant trastuzumab trials (Constantinidou and Smith 2011). However, recent data from several retrospective analyses suggest that small HER2-positive cancers might have a worse clinical outcome than previously estimated, and that more active adjuvant treatment including anti-HER2 therapy may be warranted in these cases (Amar et al. 2010; Tanaka et al. 2011; Constantinidou and Smith 2011). Subset analysis of one trastuzumab trial (HERA) demonstrated that patients with 1–2 cm cancers derived at least as much clinical benefit from 1 year of adjuvant trastuzumab with chemotherapy as the overall cohort (Piccart et al. 2005; Smith et al. 2007; Untch et al. 2008), and 2 retrospective studies have confirmed the same observation (McArthur et al. 2009; Rodrigues et al. 2010). These findings raise a key, but currently unanswered, clinical question of whether patients with small HER2-positive cancers should be offered adjuvant trastuzumab and

chemotherapy (Banerjee and Smith 2010; Constantinidou and Smith 2011). The importance of this issue is underscored by the steady increase in the number of women being diagnosed with T1a,bN0 primary tumors, which is largely due to the introduction of mammography screening programs and increased breast cancer awareness (Banerjee and Smith 2010; Fracheboud et al. 2004).

In addition to patients with small HER2-positive tumors, there are other relevant subpopulations with HER2-positive EBC who do not receive adjuvant chemotherapy. These include elderly patients and patients refuse chemotherapy due to the associated toxicities. Elderly patients with hormone-sensitive HER2-positive EBC may show benefit from endocrine treatment in combination with trastuzumab only (Constantinidou and Smith 2011).

In the current study, patients with HER2-positive EBC treated without neoadjuvant or adjuvant chemotherapy (such as patients with low-risk node-negative tumors $\leq$1.0 cm, elderly patients [$>$65 years of age], or patients who refuse chemotherapy) will comprise approximately 10% of the overall study population. Importantly, a prospectively planned subgroup analysis is expected to produce relevant data on the efficacy and safety of trastuzumab SC in this important subset of patients.

3.3.3 Rationale for Control Group

Not applicable; no formal statistical comparison of **Cohort A** and **Cohort B** is planned.

3.3.4 Rationale for Immunogenicity and Pharmacokinetic Assessments

With the introduction of a SC administration route, there is a potential that the previously observed very low incidence of HAHA formation (1 of 903 patients in previous clinical trials) could be increased. Based on published studies comparing IV and SC administration of protein drugs, there were either no significant increases in the incidence of HAHA following SC administration, or, in cases where increased immunogenicity was observed, the magnitude of the increase was small, i.e. less than 2-fold (Hale et al. 2004; Srinivas et al. 1997).

Immunogenicity testing is included in this study to determine whether HAHAs against trastuzumab or rHuPH20 develop, and whether these affect the safety and/or efficacy of trastuzumab SC. Samples for immunogenicity testing will be collected from a subset of patients enrolled in **Cohort B** at select sites (see Section 3.4.4).

3.3.5 Rationale for Observation Time Assessments

One of the exploratory objectives of the study is to collect additional safety data over a specified observation time (according to trastuzumab EU SmPC) following trastuzumab administrations in patients using the SID (**Cohort B**).

It will be assessed whether the prolonged observation time of the patients following trastuzumab SC administration (during the pre-specified time as per SmPC) is required for patients' safety. It is anticipated there may be a higher possibility of AEs following the first administration of trastuzumab. Therefore, the patient will be required to remain at site for 6 hours after start of the first trastuzumab administration. For all subsequent trastuzumab applications, patients will be required to remain onsite for 2 hours after start of drug administration. However, the patient may be required to remain onsite for an extended period of time if considered clinically necessary by the investigator. During this time, detailed information on 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 premedications prior to trastuzumab administration will be collected. Also, in addition to the date, the onset and resolution time of the treatment of AEs occurring during the observation time will be investigated. At the discretion of the investigator, patients will have the opportunity to self-administer trastuzumab via the SID; therefore, the SID performance under self-administration conditions will be monitored.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

The efficacy outcome measures will be analyzed as secondary endpoints in this study and are defined as follows:

- DFS: time from the date of first treatment to the date of local, regional or distant recurrence, contralateral breast cancer or death due to any cause. The DFS rate at 2 years and yearly up to 5 years will also be presented.
- OS: time from the date of first treatment until date of death, regardless of the cause of death. The OS rate at 2 years and yearly up to 5 years will also be presented.

Patients in **Cohort B**, who went on to self-administration of the study drug will be asked to rate their overall satisfaction with trastuzumab SC administrations using the SID by completing a 5-item SID satisfaction questionnaire. The questionnaire will be completed after the 4th cycle and at the Safety Follow-up visit (or at least 1 day after the last trastuzumab SC injection), after a minimum of 2 successful self-administrations of the study drug.

The SID satisfaction questionnaire was created specifically for this trial (see Appendix 6).

3.4.2 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- All clinical adverse events (AEs) and serious adverse events (SAEs), as well as abnormal laboratory values, will be recorded and graded according to the National

Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0.

- Cardiac function will be evaluated by measuring left ventricular ejection fraction (LVEF) (using echocardiography, Multi Gated Acquisition (MUGA) scan or Magnetic Resonance Imaging [MRI]) and ECG. Symptomatic left ventricular dysfunction (CHF) will be graded according to NCI-CTCAE, version 4.0 and the NYHA functional classification.
- All concomitant medication will be recorded between the Screening and the Safety Follow-up visits. Thereafter, 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*.

3.4.3 Patient-Reported Outcome Measures

Not applicable.

3.4.4 Exploratory Outcome Measures

Immunogenicity of trastuzumab and rHuPH20 will be tested in a subset of patients enrolled in **Cohort B** at select sites. 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 at least 6 months after the end of treatment for testing in a central laboratory.

In addition to the study assessments described in Appendix 1, all clinical AEs that occur during the observation period will be collected for all patients in **Cohort B** (within 6 hours after start of the first trastuzumab administration or within 2 hours after start of following trastuzumab administrations). Data collected during the observation period will include: frequency, incidence, and grade of AEs; onset and resolution times of AEs (dd:mm:yyyy:hh:mm); outcome of AE; and details of treatments provided following AEs during the observation period.

Information on the usability of the SID will be collected via SID monitoring questionnaire (Appendix 7), 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 observation of the HCP. The SID Device Observation is to be completed by HCPs.

The exploratory MCU and/or pharmacoeconomic parameters will be described in separate substudy protocols.

4. MATERIALS AND METHODS

4.1 PATIENTS

The study will recruit adult consenting patients with newly diagnosed HER2-positive (IHC 3+ or HER2-positive in situ hybridization [ISH]) early breast cancer who are eligible for treatment with trastuzumab (e.g., clinical Stage I [T1, N0, M0] to IIIC [any T, N3, M0]). Patients treated without neoadjuvant or adjuvant chemotherapy, such as patients with low-risk node-negative tumors ≤ 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 enrollment will be limited to approximately $\leq 10\%$ of the total study population.

Under no circumstances are patients who enroll in this study permitted to be re-enrolled to the same study for a second course of treatment.

4.1.1 Inclusion Criteria

Patients must meet ALL of the following criteria to be eligible for participation in this study according to the timing specified in the schedule of assessment:

1. Signed written informed consent approved by the reviewing independent Ethics Committee (EC)
2. Female or male aged 18 years or above
3. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
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 treatment with trastuzumab

   Note: Patients treated without neoadjuvant or adjuvant chemotherapy, such as patients with low-risk node-negative tumors ≤ 1.0 cm, elderly patients (>65 years of age), or patients with HER2-positive EBC but denying chemotherapy, will also be eligible to participate in the study, but their enrollment will be limited to approximately $\leq 10\%$ of the total study population.
5. HER2-positive EBC, defined as IHC 3+ or positive in situ hybridization (ISH testing) by validated and approved methods within a certified laboratory
6. Screening left ventricular ejection fraction (LVEF) $\geq 55\%$ as measured by echocardiography, multi-gated acquisition (MUGA) scan, or Magnetic Resonance Imaging (MRI) per local practice
7. Agreement to use an adequate, nonhormonal means of contraception by women of childbearing potential (defined as premenopausal 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 intrauterine device, a barrier method (condoms or diaphragm) in conjunction with spermicidal jelly, or total abstinence. Oral, injectable, or implant hormonal contraceptives are not acceptable for females participating in the study.

8. Intact skin at site of SC injection on the thigh

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will not be eligible for participation in this study:

Cancer-related Criteria:

1. Previous neoadjuvant or adjuvant breast cancer treatment with an approved or investigational anti-HER2 agent
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 other than breast cancer who have been disease-free for at least 5 years are eligible.
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.
4. Metastatic disease

Hematological, Biochemical, and Organ Function:

5. Inadequate bone marrow function (as indicated by any of the following):
   - Total white blood cell count (WBC) $< 2500/mm^3$ ($< 2.5 \times 10^9/L$)
   - Neutrophil count $< 1500/mm^3$ ($< 1.5 \times 10^9/L$)
   - Platelets $< 100{,}000/mm^3$ ($< 100 \times 10^9/L$)
   - Hemoglobin < 10 g/dL
6. Impaired hepatic function (as indicated by any of the following):
   - Serum total bilirubin $> 1.5 \times$ upper limit of normal (ULN)
   - Alanine amino transferase (ALT) $> 2.5 \times$ ULN
   - Aspartate amino transferase (AST) $> 2.5 \times$ ULN
   - Alkaline phosphatase (ALP) $> 2.5 \times$ ULN
7. Impaired renal function, as indicated by serum creatinine $> 1.5 \times$ ULN

Other Study Drug-related Exclusion Criteria:

8. Serious cardiac illness or medical conditions including but not confined to:
   - 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 consistently over 140/90 mmHg, despite treatment) or history of hypertensive crisis or hypertensive encephalopathy

9. Other concurrent serious diseases that may interfere with planned treatment including severe pulmonary conditions/illness
10. Prior maximum cumulative dose of doxorubicin >360 mg/m^2 or maximum cumulative dose of epirubicin >720 mg/m^2 or equivalent
11. Known hypersensitivity to trastuzumab, murine proteins, or excipients, or a general hypersensitivity to adhesives (**Cohort B** only)
12. History of severe allergic or immunological reactions, for example, difficult to control asthma.

General Exclusion Criteria:

13. Pregnancy or lactation
14. Unable or unwilling to comply with the requirements of the protocol, as assessed by the investigator
15. Concurrent enrollment 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
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.
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.
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

No exceptions or waivers will be granted for the above listed inclusion and exclusion criteria.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

It is anticipated that approximately 2500 patients will be recruited into the study. Eligible patients with HER2-positive EBC will be allocated to one of the two following cohorts at the investigator's discretion:

- **Cohort A** (approximately 1800 patients): trastuzumab SC 600 mg via assisted administration into the thigh over a period of approximately 5 minutes using handheld syringes with hypodermic needles
- **Cohort B** (approximately 700 patients): trastuzumab SC 600 mg, first assisted, then self-administered into the thigh over a period of approximately 5 minutes using the SID. For enrollment into **Cohort B**, patients need to be willing to self-administer the study drug from the SID based on personal instructions/training provided by an HCP during the first assisted administration in addition to a quick reference guide and an instructional animation describing the injection device handling and use, including how to respond if the SID loses sufficient contact with the body.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

The investigational medicinal product (IMP) for this study is trastuzumab SC 600 mg supplied as vial and SID formulations:

- **Cohort A:** RO 045.2317/F07, manual SC injection formulation: trastuzumab SC 600 mg/5 mL vial
- **Cohort B:** RO 045-2317/F06, device formulation: trastuzumab SC 600 mg/5 mL prefilled, single-use injection device

According to the Medical Device Directive, the drug/device combination is considered an integral medicinal product and, therefore, as a single IMP for this study.

The drug product in the vials for manual injection (**Cohort A**) and in the SID (**Cohort B**) contains 120 mg/mL trastuzumab and 2000 U/mL rHuPH20 (manufactured in a Chinese hamster ovary cell line) acting as a permeation enhancer, histidine/histidine-HCl (buffer), alpha,alpha-trehalose dihydrate (bulking agent), methionine (stabilizer), and polysorbate 20 (stabilizer/emulsifier) in water for injection (WFI) at a pH of 5.5 ± 0.3.

The recommended storage conditions are 2–8°C protected from light for both trastuzumab SC formulations. Batch-specific details and information on shelf-life are given in the packaging label.

Trastuzumab for SC administration will be supplied by Roche. Packaging of trastuzumab for SC use will be overseen by the Roche Clinical Trial Supplies department. Each IMP unit will bear a label with the identification required by local law, the protocol number, drug identification, and dosage. The packaging and labelling of trastuzumab SC will be in accordance with Roche standard and local regulations.

For further details, refer to the Herceptin (RO 45-2317, Trastuzumab) IB.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Preparation and Administration of Trastuzumab for SC Injection

Cohort A: Trastuzumab SC for manual injection will be supplied in a vial containing a ready-to-use solution with a nominal content of 600 mg of trastuzumab. The solution is injected using a conventional handheld syringe fitted with a hypodermic needle. Further information on the preparation and administration is provided as a separate instruction leaflet.

Cohort B: Trastuzumab SC is supplied in a SID. The cartridge included in the device contains a nominal content 600 mg of trastuzumab. Information on the preparation and use of the SID is provided in the quick reference guide supplied with the SID.

The drug product must not be diluted and should be used according to the instructional leaflet provided separately. The solution should not be administered at 2–8°C. Details for equilibration of the device to room temperature can be found in the quick reference guide supplied with the SID.

The total time that trastuzumab SC (for manual injection and in a SID) is stable outside the fridge is 6 hours. Trastuzumab should be allowed to equilibrate prior to injection. The drug may be returned to the fridge if necessary, but it must be allowed to reach room temperature prior to administration, and the total time out of the fridge prior to administration must not exceed 6 hours.

Patients will be enrolled into one of two cohorts at the investigator's discretion.

All study treatment administrations will occur in a hospital setting as follows:

- **Cohort A**: Trastuzumab SC 600 mg 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 600 mg will be injected subcutaneously into the thigh over a period of approximately 5 minutes using the SID. The first administration will be assisted (performed by a HCP [physician or nurse]), and then following administrations may be self-administered into the thigh (if the patient is willing and judged competent by the HCP) over a period of approximately 5 minutes using the SID. During HCP-assisted administration, the HCP will assist the patient to use the SID to self-administer the dose. The HCP should moderate the level of assistance provided with an assessment of the patient's competence. Competent subjects will be asked if they are willing to continue by self-administration of the study drug from the SID. Willing patients will be allowed to self-administer the remaining trastuzumab SC doses under the direct supervision of a HCP. Patients assessed as not competent or are not willing to self-administer the study drug from the SID will have all the remaining trastuzumab SC doses administered by the HCP.

Those patients judged competent by the investigator and willing to self-administer remaining doses with the SID will be provided with training from the HCP during the first assisted administration and will be provided with instructional materials (a quick reference guide and an instructional animation describing the injection device handling and use, including how to respond if the SID loses sufficient contact with the body).

Patients will remain onsite to be observed for a period of 6 hours after start of their first trastuzumab administration and for 2 hours after the start of each subsequent trastuzumab administrations. Patients may be required to remain onsite for an extended period of time if considered clinically necessary by the investigator (e.g., emergence of AEs).

In addition to the study assessments described in Appendix 1, all clinical AEs that occur during the observation period, onset and resolution dates and times of AEs, the collection of detailed information about premedications prior to trastuzumab administration, and in addition to the date, the onset and resolution time of treatment of AEs occurring during the observation time will be collected.

The SID satisfaction questionnaire will only be completed by patients who have successfully completed a minimum of 2 self-administrations of the study drug in **Cohort B**.

For SID usability 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 (see Appendix 7).

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 Section 5.4.4). The device must then be returned via courier to Roche for assessment. In case of multiple (>1) device failures at different treatment cycles, 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.

Any injection-related symptoms must have resolved before the patient is discharged, unless deemed clinically insignificant by the investigator. Patients who experience injection-related symptoms may be premedicated with paracetamol and antihistamines for subsequent injections.

4.3.2.2 Dose and Schedule of Trastuzumab SC

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. In case of sequential treatment, the interval between the last dose of chemotherapy and the first dose of trastuzumab SC should not be longer than 12 weeks. For patients receiving trastuzumab SC with adjuvant chemotherapy, trastuzumab SC must be administered first, followed by the administration of chemotherapy. For patients receiving trastuzumab SC without neoadjuvant or adjuvant chemotherapy, the start of trastuzumab SC should be within a maximum of 3 months following surgery.

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.

Hormonal therapy and radiotherapy (if applicable) may be given concomitantly with trastuzumab SC, as per local guidelines.

Recommended chemotherapy regimens with trastuzumab to be followed in the adjuvant setting are as stated in the pivotal trials (see Table 1: sequential trastuzumab; HERA and NCCTG N9831: and concurrent trastuzumab; NSABP B31, B31 + N9831 and BCIRG 006). In the neoadjuvant-adjuvant setting, clinical Study MO16432 (NOAH), trastuzumab was administered concurrently with chemotherapy.

For neoadjuvant treatment, the following will be applied:

- 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).
- 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.
- After the neoadjuvant phase (8 cycles) of trastuzumab SC, patients will undergo surgery without interruption of trastuzumab treatment. After surgery, patients will receive additional 10 cycles of SC trastuzumab to complete 1 year of treatment with trastuzumab.
- Surgery should be planned after dosing at Cycle 8 without interruption of trastuzumab treatment.

4.3.2.3 Dose Modifications, Interruptions, and Delays

Administration of trastuzumab SC may be delayed to assess or treat adverse events, as detailed in Table 8.

Table 8 Management of Trastuzumab-Related Toxicity

Toxicity Related to Study Treatment	Action
Hematological and non-hematological, Grade 1 or 2 (excluding cardiac) toxicity	Continue with study treatment (all medication in the cycle)
Hematological and non-hematological, Grade 3 or 4 (excluding cardiac) toxicity	Hold study treatment (all medication in the cycle) until recovery to Grade ≤ 2. Toxicity resolved to Grade ≤ 2 within a maximum of 5 weeks calculated from last administration: Resume study treatment. Toxicity did NOT resolve to Grade ≤ 2 within a maximum of 5 weeks calculated from last administration: Discontinue trastuzumab permanently. Take patient off study drug. Continue treatment as deemed suitable by local investigator.
Recurrence of non-hematological, Grade 3 or 4 (excluding cardiac) toxicity upon re-challenge	Discontinue trastuzumab permanently. Take patient off study drug. Continue treatment as deemed suitable by local investigator.
Cardiac toxicity (significant asymptomatic drop in LVEF (≥ 10 percentage points from baseline and to a LVEF $< 50\%$)	Study treatment (all medication in the cycle) to be held, continued or resumed according to the algorithm depicted in Appendix 5.
Cardiac toxicity (symptomatic congestive heart failure)	Trastuzumab to be discontinued permanently (patient to be taken off study)
Cardiac toxicity (other than significant asymptomatic LVEF drop or CHF)	Actions must follow rules 1 to 3. For non-hematological toxicities
Hematological toxicity: Neutropenia $< 1.5 \times 10^9$/L	Hold study treatment (all medication in the cycle) until neutrophils $\geq 1.5 \times 10^9$/L.

For toxicity related to concurrently administered chemotherapy, specific instructions/actions should be followed in the relevant SmPC. In the case of chemotherapy-related hematological or non-hematological toxicity, the following action should be applied:

- Grade 1 or 2, continue trastuzumab treatment
- Grade 3 or 4, hold trastuzumab treatment until recovery to $\leq$ Grade 2

If the patient misses a dose of trastuzumab SC, then the usual dose 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 (600 mg) 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 premedicated with paracetamol and antihistamines for subsequent infusions/injections.

4.3.3 Name of Additional Required Medication

Not applicable.

4.3.4 Investigational Medicinal Product Accountability

The investigator is responsible for the control of the drugs under investigation. Adequate records for the receipt (e.g., Drug Receipt Record) and disposition (e.g., Drug Dispensing Log) of the IMP must be maintained. Accountability and patient compliance will be assessed by maintaining adequate drug dispensing and return records.

Accurate records must be kept for each IMP provided by the Sponsor. These records must contain the following information:

- Documentation of IMP shipments received from the Sponsor (date received, quantity, and batch number)
- Disposition of unused IMP not dispensed to a patient
- A Drug Dispensing Log must be kept current and should contain the following information:

  Identification of the patient to whom the IMP was dispensed

  The date(s), quantity, and batch number of the IMP dispensed to the patient

4.3.4.1 Assessment of Compliance

The investigator is responsible for ensuring that the study drug is administered in compliance with the protocol. Delegation of this task must be approved by the investigator and clearly documented. Patient compliance will be assessed by maintaining adequate study drug dispensing records. All records and drug supplies must be available for inspection by the Roche Study Monitor at every monitoring visit.

Copies of the dispensing & inventory logs will be retrieved by the Monitor at study end.

4.3.4.2 Destruction of the IMPs

Used and unused IMP will be kept at the site (or designated pharmacy, depending on local practice) for accountability and destruction. Local or institutional regulations may require immediate destruction of used IMPs for safety reasons (e.g., cytotoxicity). In these cases, it may be acceptable for the investigational site staff to destroy the dispensed IMP before inspection by the Monitor, provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned, and destroyed. Written authorization must be obtained from the Sponsor at study start up before destruction of unused trastuzumab SC can take place at a site.

Written documentation of destruction must contain the following:

- Identity (batch numbers and patient numbers) of the IMP(s) destroyed
- Quantity of the IMP(s) destroyed

- Date of destruction (date discarded in designated hazardous container for destruction)
- Method of destruction (the site must provide the Sponsor with documentation of their institutional policy and procedures for handling and disposing of hazardous drugs); it is recommended to burn the vials and SIDs at 1200°C.
- Name and signature of responsible person who discarded the IMP in a hazardous container for destruction

4.3.5 Post-Trial Access to Trastuzumab

Trastuzumab SC will only be provided to study patients for the protocol-defined 18 cycles. Subsequent treatment will be at the investigator's discretion and according to local practice.

4.4 CONCOMITANT THERAPY

All concomitant medications and prior treatments for breast cancer must 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

Any additional medication that is necessary for the management of the patient may be used at the discretion of the investigator.

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

4.4.1 Permitted Therapy

In this study, 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 tumors >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 (estrogen 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 or 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).

4.4.2 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 of anthracyclines with trastuzumab in the adjuvant setting

4.5 STUDY ASSESSMENTS

4.5.1 Description of Study Assessments

4.5.1.1 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), and all medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, and nutritional supplements) used by the patient starting from the Screening visit.

Demographic data will include age, gender, and self-reported ethnic origin.

4.5.1.2 Vital Signs

Vital signs include blood pressure, heart rate, and temperature measurements 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. Vital signs measurements will be taken while the patient is in a seated position.

4.5.1.3 Physical Examinations

A general physical exam (including a general neurological exam, as clinically indicated) will be performed at screening, approximately 3-monthly during trastuzumab SC treatment (at Week 13/Cycle 5, Week 25/Cycle 9, Week 37/Cycle 13, and Week 52/Cycle 18), at the post-treatment Safety Follow-up visit, and subsequently according to the ASCO 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting (Khatcheressian et al. 2006) *or investigator's routine practice.* Physical examinations will be performed according to local practice; however, particular attention should be given to the cardiovascular system.

Any abnormality identified at screening should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits, new or worsened abnormalities should be recorded as AEs on the Adverse Event eCRF.

4.5.1.4 Electrocardiograms

A standard 12-lead ECG needs to be performed as specified in Section 5.1.2 and in Appendix 1, Schedule of Assessments.

4.5.1.5 Performance status

Performance Status (PS) will be evaluated using the Eastern Cooperative Oncology Group (ECOG) PS Scale (see Appendix 2). The assessment will be performed at screening, approximately 3-monthly (every 4 cycles) during study treatment, and at the post-treatment Safety Follow-up visit, as specified in Appendix 1, Schedule of Assessments.

4.5.1.6 Other Clinical Safety Assessments

Refer to Section 5.1.2 for a description of cardiac safety assessments and Section 5.2.1 for instructions on documenting and handling adverse events.

4.5.1.7 Laboratory Assessments

4.5.1.7.1 HER2 Testing for Eligibility

To be eligible for the study, patients must have confirmed HER2 overexpression (by IHC) or HER2 gene amplification (by validated and approved methods at the local laboratories) in the invasive part of the tumor, defined as one of the following:

- A score of 3+ by IHC
- A positive ISH result

HER2 should be assessed in specialized local laboratories with an accurate and validated assay according to recommendations outlined in the SmPC for trastuzumab IV (Herceptin). HER2 status needs to be assessed prior to the first dose of study drug, but otherwise, there is no time limit for when this is to be performed.

4.5.1.7.2 Safety Laboratory Assessments

All hematology and blood chemistry laboratory tests will be completed at local laboratories. Normal ranges for a study site's local study laboratory parameters must be supplied to the Sponsor before the study starts.

Blood samples for hematology and biochemistry are scheduled at screening, on Day 1 of Cycles 9 (Week 25) and 18 (Week 52) of study treatment, and at the Safety Follow-up visit. Screening safety laboratory tests should be completed within 28 days prior to the first study treatment and should allow for an evaluation of all laboratory exclusion criteria as outlined in Section 4.1.2. Screening values should be used to confirm eligibility.

- Hematology tests include: hemoglobin, WBC and differential, ANC, and platelet count.
- Biochemistry tests include: creatinine, urea/blood urea nitrogen (BUN), serum ALT/glutamic pyruvic transaminase (SGPT), AST/serum glutamic oxaloacetic transaminase (SGOT), total bilirubin, ALP, albumin, sodium, potassium, and calcium.

For the purposes of this study, no additional samples are scheduled. However, additional assessments may be performed as per institutional practice, as clinically indicated. Results for samples other than those specified above (and listed in Appendix 1, Schedule of Assessments) will only be collected if associated with an AE.

4.5.1.7.3 Pregnancy Testing and Contraception

Females of childbearing potential (defined as premenopausal and not surgically sterilized or less than 1 year after the onset of menopause) will undergo a serum pregnancy test within 7 days prior to the first dose of trastuzumab SC. A positive pregnancy test at screening will lead to the exclusion of the patient. 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 trastuzumab SC.

Women of childbearing potential and male participants with partners of childbearing potential must agree to use contraception during study treatment and for at least 7 months post-study treatment. Acceptable methods of contraception include:

- Complete abstinence* (if consistent with the preferred and usual lifestyle of the patient). Note: periodic abstinence (e.g., calendar, ovulation, symptothermal post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Male sterilization* (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients, the vasectomized male partner should be the sole partner.
- Non-hormonal intrauterine device or intrauterine system
- Barrier method:
    - Condom with spermicidal foam/gel/film/cream/suppository
    - Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository

    *Considered highly-effective forms of contraception resulting in a low failure rate (i.e., less than 1% per year)

The following birth control methods are not considered acceptable in this study:

- Hormonal contraceptives (for females participating in the study)
- Periodic abstinence (e.g., calendar, ovulation, symptothermal post-ovulation methods) and withdrawal
- Single barrier methods (e.g., spermicides alone)

4.5.1.7.4 Immunogenicity and PK assessments (Subset of Cohort B)

Immunogenicity of trastuzumab SC and recombinant human hyaluronidase (rHuPH20) will be tested in a subset of patients enrolled in **Cohort B** at select sites. Sites interested in participating in the immunogenicity assessments will be selected and approved by Roche. Serum samples (for anti-trastuzumab antibody analyses) 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 at least 6 months after the end of treatment. Since the evaluation of anti-trastuzumab assay results requires corresponding serum trastuzumab concentrations, the anti-trastuzumab analyses will be coupled with PK assessments.

The total blood loss for immunogenicity testing during the study is 18 mL. At each of the three assessment timepoints, approximately 6 mL of blood will be required for the rHuPH20 antibody analysis and trastuzumab antibody analysis, including confirmation of the presence of trastuzumab and the titer in serum.

The date/time of immunogenicity and PK sampling must be carefully recorded in all cases. On non-dosing days, the timing of sampling during the day will be at the investigator's discretion. Fasting is not a requirement for sampling.

In the event of an injection-related reaction, the blood samples for immunogenicity testing must be drawn within 8 hours following the reaction (see Appendix 1, Schedule of Assessments).

The serum and plasma samples (for anti-trastuzumab antibody and anti-rHuPH20 antibody analyses, respectively) will be stored on dry ice until shipment in batches can be arranged to the designated central laboratory. Details of sampling, handling, storage, and shipping are described in the study's Sample Handling and Logistics Manual.

A three-tiered analytical testing approach will be performed for HAHAs against both trastuzumab and rHuPH20. Screening for the potential emergence of antibodies will use bridging immunoassays. Any samples testing positive will be subsequently re-tested in a confirmatory assay. Finally, confirmed positives will be tested for the presence of neutralizing antibodies.

Samples will be kept for re-testing (if required) at the central laboratory and will be destroyed no later than 12 months after the Clinical Study Report (CSR) is finalized.

4.5.1.8 Breast Cancer Evaluations and Follow-Up

Patients will be assessed for residual disease (as per institutional practice) not more than 4 weeks before the first dose of study drug. Screening radiologic examinations to exclude metastatic disease should include a bilateral mammogram or breast MRI, and chest X-ray (CXR) or breast ultrasound. Should a previously taken chest CT or PET scan be available, then these results can also be used for eligibility assessment. These imaging tests do not need to be repeated if completed within 12 months prior to the first study treatment. In addition, bone scan and liver imaging should be performed if clinically indicated. During study treatment and the post-treatment follow-up period, patients will be followed for disease recurrence according to the American Society of Clinical Oncology (ASCO) 2006 Guideline for Breast Cancer Follow-up (Khatcheressian et al. 2006) *or investigator's routine practice* (see Appendix 1, Schedule of Assessments). In brief, the ASCO 2006 guidelines recommend:

- History/physical examination: every 3–6 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 led 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.

- Routine blood tests: full blood counts and liver function tests are not recommended.
- Imaging studies: chest x-ray, bone scans, liver ultrasound, computerized tomography (CT) scans, fluorodeoxyglucose-positron emission tomography (FDG-PET) scans, and breast magnetic resonance imaging (MRI) are not recommended.
- Tumor markers: CA 15-3, CA 27.29, and CEA are not recommended.
- Accordingly, assessments for recurrence/relapse will be primarily by physical examination and questioning the patient, with additional tests as clinically indicated and according to routine practice.

4.5.1.8.1 Assessment of Recurrence

Disease-free survival (DFS) is a secondary endpoint in this study. DFS is defined as time from the date of first treatment to the date of local, regional, or distant recurrence; contralateral breast cancer; or death due to any cause.

The diagnosis of a first breast cancer recurrence or second primary cancer can be made only when clinical, radiological, and laboratory criteria are met. Acceptable methods of confirmation of recurrence include radiology, CT scan, brain scan, ultrasound, or cytology, as per local practice. In case of uncertainty, disease relapse should be confirmed by histological or cytological examination of a suspicious lesion, if possible. Some patients may develop a suspicious recurrence that leads to death quite quickly without having the possibility to confirm relapse of disease. Efforts should be made to obtain an autopsy report in such patients.

The earliest date of diagnosis of recurrent disease should be used and recorded. This should be based on clinical, radiological, histological, or cytological evidence. The recurrence of disease has to be backdated to the date of the first diagnosis of lesion (i.e., an objective finding), not to the date of occurrence of the first symptom.

Recurrent disease includes: local, regional, distant recurrence and contralateral breast cancer.

a) **Local recurrence**: In the ipsilateral breast after surgery:

In case of conservative surgery (lumpectomy): defined as evidence of tumor, except lobular carcinoma in situ, in the ipsilateral breast after mass excision.

In case of mastectomy, local recurrence (other than ipsilateral breast after lumpectomy): defined as evidence of tumor in any soft tissue or skin of the ipsilateral chest wall after mastectomy.

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

c) **Contralateral invasive breast cancer:** Defined as development of invasive lobular or invasive ductal cancer in the contralateral breast (Hudis et al. 2007).

d) **Distant recurrence:** Defined as evidence of tumor in any area other than those described in subsections a) to c) above and the following:

- Skin, subcutaneous tissue, and lymph nodes (other than local or regional)
- Bone
- Bone marrow
- Lung
- Liver
- Central nervous system

4.5.1.9 Treatment Satisfaction with the SID

Patients in **Cohort B**, who went on to self-administration of the study drug will be asked to rate their overall satisfaction with trastuzumab SC administrations using the SID by completing a five-item SID satisfaction questionnaire. The questionnaire will be completed after the 4th cycle and at the Safety Follow-up visit (or at least 1 day after the last trastuzumab SC injection), after a minimum of 2 successful self-administrations of the study drug.

The questionnaire includes five items (level of comfort with the self-administration after training by a physician/nurse, convenience and ease of use, confidence with the administrations, overall satisfaction, and feedback on whether the SID would be chosen in the future), which will be rated on a 5-point Likert scale (from 1 = strongly disagree to 5 = strongly agree; see Appendix 6).

Completion of the questionnaire should take about 5 minutes.

For patients in **Cohort B** who discontinue study treatment prematurely for any reason, all efforts should be made to complete this questionnaire as part of the final assessment.

4.5.1.10 Pharmacoeconomic Assessments and Medical Care Utilization

In some countries and sites, MCU (e.g., time and motion) and/or pharmacoeconomic substudies will be conducted. Details of the substudies will be described in separate protocols.

4.5.2 Timing of Study Assessments

4.5.2.1 Screening and Pre-treatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

After consenting, patients will undergo the following screening procedures and assessments within 28 days prior to the first study treatment (denoted as Day 1), unless

otherwise specified or unless the procedure/assessment has already been conducted during this time period as part of the patient's routine clinical care:

- Demographics, complete medical history, and concomitant medications
- HER2 determination (Note: HER2 status needs to be assessed prior to the first dose of study drug, but otherwise there is no time limit for when this is to be performed.)
- General physical examination (including neurological examination, if clinically indicated)
- Measurement of vital signs (blood pressure, heart rate, and temperature), weight, and height
- ECOG performance status
- Cardiac assessments
    - Standard 12-lead ECG
    - LVEF is to be assessed within 14 days prior to the first study treatment if patients received anthracycline or 28 days prior to first study treatment for patients who received anthracycline-free regimens. Assessment should be performed by echocardiography (ECHO), multigated acquisition (MUGA) scan, or MRI (Note: ECHO is the preferred method).
    - Cardiac signs and symptoms
- Clinical laboratory testing (hematology, serum biochemistry) with results available prior to enrollment into the study to confirm patient eligibility (to be done in the allowed screening period of 28 days).
- Women of childbearing potential (defined as premenopausal, less than 1 year after the onset of menopause, or not surgically sterilized) will undergo a serum pregnancy test (β-HCG) within 7 days prior to the first dose of study treatment.
- **Cohort B** (selected sites only): Blood sample for immunogenicity testing (includes trastuzumab PK assessment)
- Imaging scan to exclude residual/recurrent disease per Section 4.5.1.8 (Note: results of imaging scans performed prior to obtaining informed consent and within 12 months prior to Day 1 may be used, i.e., such tests do not need to be repeated for screening.)
- Assessment of any SAEs caused by a protocol-mandated procedure

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment (also referred to as registration). The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or document reasons for screening failure, as applicable. Data of patients who fail screening will not be entered into the eCRF and the clinical trials database.

Eligible patients will be allocated to either **Cohort A** or **Cohort B** at the investigator's discretion. For enrollment into **Cohort B**, patients need to be willing to self-administer

the study drug based on the instructions for use supplied with the SID and personal instructions provided by an HCP during the first assisted administration.

Upon enrollment, patients will be assigned a unique study patient identification number. A Patient Enrollment List must be maintained by the investigator. Enrollment and the start of study medication (Day 1) occur on the same day.

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

4.5.2.2 Assessments during Treatment

All assessments must be performed on the day of the specified visit, unless a time window is specified in the schedule of assessments (see Appendix 1). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the schedule of assessments.

The following assessments must be performed prior to the respective treatment visits, so that results are available prior to dosing: hematology and biochemistry, LVEF, and routine breast cancer follow-up assessments.

Patients will undergo the following assessments during the study treatment period:

Assessments performed at each treatment visit:

- Assessment of AEs (including SAEs)
- Observation time for patients in **Cohort B**
- SID monitoring for subgroup of patients in **Cohort B**
- Treatment compliance
- Concomitant medication
- Survival follow-up

Assessments performed at specified intervals:

- Routine breast cancer follow-up, performed according to the ASCO 2006 Guideline for Breast Cancer Follow-up (Khatcheressian et al. 2006) *or investigator's routine practice* and reported every 6 months or per institutional standard practices (see Section 4.5.1.8)
- General physical examination (including neurological examination, if clinically indicated) will be performed on a 3-monthly basis (every 4 cycles).
- Weight will be measured for all patients at screening. For **Cohort B** patients participating to immunogenicity and PK testing at Cycle 9 (Week 25).
- Vital signs measurement (blood pressure, heart rate, and temperature) pre- and immediately post-trastuzumab SC administration on a 3-monthly basis (every 4 cycles; i.e., at Cycles 1, 5, 9, 13, and 18).

- Cardiac assessment (ECG, LVEF, and cardiac signs and symptoms) and evaluation of ECOG performance status performed on a 3-monthly basis (every 4 cycles);
- Hematology and biochemistry at Cycles 9 (Week 25) and 18 (Week 52);
- Blood samples for immunogenicity and PK testing (a subset of **Cohort B** patients at selected study sites) prior to Cycle 9 (Week 25)
- SID satisfaction questionnaire after the 4th treatment cycle (**Cohort B** patients who have successfully completed a minimum of 2 self-administrations of the study drug)
- Pregnancy test completed as clinically indicated

Please see Appendix 1 for the schedule of assessments performed during the treatment period.

4.5.2.3 Assessments at Treatment Completion/Early Termination: Safety Follow-Up Visit

Patients who complete the study treatment period (18 cycles of trastuzumab SC) or discontinue the study treatment early will be asked to return to the clinic 4 weeks after their last dose of trastuzumab SC for a Safety Follow-up visit. The following assessments will be completed at the Safety Follow-up:

- Physical exam (including neurological examination, if clinically indicated)
- Vital signs (blood pressure, heart rate, and temperature), ECOG performance status
- Assessment of AEs (including SAEs) and concomitant medication
- Cardiac safety assessments, if clinically indicated (see Section 5.1.1.2 for details)
- Clinical laboratory testing (hematology and serum biochemistry)
- SID satisfaction questionnaire (**Cohort B** patients only who have successfully completed a minimum of 2 self-administrations of the study drug) at least 1 day after the last trastuzumab SC injection

4.5.2.4 Post-treatment Follow-up Visits (minimum 5 years)

All patients will be followed-up for cancer recurrence and survival till study end (i.e., until all patients have had a minimum 5-year follow-up) yearly or at higher frequency based on the site standard of care. The duration of follow-up will be at least 5 years after the last study treatment or until withdrawal from the study, lost to follow-up, or death, whichever occurs first. During this post-treatment follow-up period, patients will undergo the following assessments:

- Breast cancer follow-up according to the ASCO 2006 Guideline for Breast Cancer Follow-up (Khatcheressian et al. 2006) and reporting every 6 months or as per institutional standard practices (see Section 4.5.1.8 for details)
- Blood samples for immunogenicity and PK analyses will be collected from a subset of **Cohort B** patients (at selected sites only) 6 months after their last study treatment.

- Patients' weight must also recorded 6 months after their last study treatment if participating to immunogenicity and PK testing.
- Pregnancy test as clinically indicated up to *7* months after last study treatment
- AE follow-up: *After initiation of study drug,* all AEs/SAEs (except unrelated non-cardiac AEs in the follow-up period), regardless of relationship to study drug, will be reported until study closure. The investigator does not need to actively monitor subjects for AEs once the trial has ended. However, if becoming aware of any serious adverse events and non-serious adverse events of special interest occurring to a subject, the investigator should report those to the sponsor (see Section 5.6).
- Concomitant medications: 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*; refer to Section 4.4 for details.
- Cardiac safety assessments will be performed at 6, 12, and 24 months and at yearly intervals until 5 years after treatment cessation (see Section 5.1.1.2 for details);
- Survival: After disease progression, patients will be managed as per local practice and followed for survival only.

After study treatment completion (or early discontinuation), AEs should be followed as outlined in Section 5.5 and Section 5.6.

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

4.5.2.5 Assessments at Unplanned Visits

Assessments other than those specified in Appendix 1, Schedule of Assessments, may be performed as clinically indicated and need to be adequately documented.

4.6 PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Patients should be informed of circumstances under which their participation may be terminated by the investigator or the study Sponsor without the patient's consent and in case of such withdrawal, the reason(s) for withdrawal must be documented and explained to the patient.

Patients have the right to withdraw from the study at any time for any reason. Should a patient decide to withdraw, all efforts should be made to complete and report the observations prior to withdrawal as thoroughly as possible. Patients will not be followed for any reason after consent has been withdrawn.

4.6.1.1 Discontinuation from Study Drug

Reasons for study drug discontinuation may include, but are not limited to the following:

- Withdrawal of consent by the patient
- Pregnancy
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if she or he continues receiving the study drug
- Investigator or Sponsor determines it is in the best interest of the patient
- Intercurrent illness
- AE(s)
- Treatment failure
- Protocol violation
- Lack of compliance with the study and/or study procedures (e.g., dosing instructions or study visits)
- Cure

Patients refusing further study treatment should be asked if they can still be contacted for further information after treatment cessation. The outcome of that discussion should be documented in both the medical records and in the eCRF.

Patients who discontinue study treatment prematurely due to lack of tolerability will be clinically managed as per local practice and followed as outlined in the Schedule of Assessments, Appendix 1. If the reason for treatment discontinuation is an AE, the principal specific event will be recorded in the eCRF.

All prematurely withdrawn patients who have received at least one dose of trastuzumab should continue to be monitored for cardiac function as described in the Herceptin SmPC, within or outside the study, as appropriate.

4.6.1.2 Withdrawal from Study

Reasons for withdrawal from the study may include, but are not limited to, the following:

- Withdrawal of consent by the patient
- Treatment failure
- Protocol violation

An excessive rate of withdrawals can render the study non-interpretable; therefore, unnecessary withdrawal of patients should be avoided, and all withdrawals should undergo a complete final evaluation at the time of termination, which should include documentation and an explanation of the reason for withdrawal.

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

appropriate eCRF. If lost to follow-up, the investigator should contact the patient or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal.

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

4.6.2 Study and Site Discontinuation

The Sponsor and study Steering Committee have the right to terminate the study at any time. Should this be necessary, the required procedures will be implemented after review and consultation with the Steering Committee. In terminating the study, Roche and the investigators will assure that adequate consideration is given to the protection of the patient's interests. The appropriate IEC and Regulatory Agencies will be informed accordingly.

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

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Noncompliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

5.1.1 General Safety Assessments

Patients will be assessed by prior medical history, vital signs (including blood pressure, heart rate, temperature), weight and height (screening only), physical examination, adverse events, and concomitant medications. A complete medical history (including demographic profile and prior treatments for cancer) will be documented at screening. A general physical exam (including general neurological exam, as clinically indicated) will be performed at screening, approximately 3-monthly (every 4 cycles) during trastuzumab SC treatment, at the post-treatment Safety Follow-up visit, and subsequently according to the ASCO 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting (Khatcheressian et al. 2006) *or investigator's routine practice* during the 5-year follow-up period (see Appendix 1, Schedule of Assessments). During physical examination, particular attention should be given to the cardiovascular system. Apart from physical exams, SC injection sites will be checked at every visit, and blood pressure will be measured before and after trastuzumab SC administration every 4 cycles, as specified in Appendix 1, Schedule of Assessments.

Adverse events will be monitored and documented continuously during study (at each 3-weekly treatment visit and during the post-treatment follow-up, as detailed in Section 5.3.1). Serious adverse events will also be monitored, documented, and reported; refer to Section 5.4.2 and Section 5.5 for details on SAE reporting and follow-up requirements, respectively. All AEs and SAEs (including patients' symptoms and signs of toxicity and clinically significant hematological and biochemical parameters) will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (see Appendix 5). Changes in concomitant medication will be recorded at each study visit.

5.1.1.1 Observation Time Assessment

In addition to the study assessments described in Appendix 1, all clinical AEs that occur during the observation period will be collected for all patients in **Cohort B** (within 6 hours after start of the first trastuzumab administration or within 2 hours after start of following trastuzumab administrations). Data collected during the observation period will include: Frequency, incidence, and grade of AEs; onset and resolution times of AEs (dd:mm:yyyy:hh:mm); outcome of AEs; and details of treatments provided following AEs during the observation period.

5.1.1.2 Cardiac Safety Assessments

Cardiac function will be evaluated regularly throughout the study by measuring LVEF using echocardiography, MUGA scan, or MRI (method selected according to local practice); ECG; and assessment of cardiac signs and symptoms.

Cardiac safety assessments will be performed at screening, approximately 3-monthly during trastuzumab SC treatment (at Week 13/Cycle 5, Week 25/Cycle 9, Week 37/Cycle 13, and Week 52/Cycle 18; with the results available prior to trastuzumab administration) and then at 6, 12, and 24 months, and 3, 4, and 5 years after treatment cessation (see Appendix 1, Schedule of Assessments). LVEF assessment should be performed at the Safety Follow-up visit (4 weeks after the end of treatment) only if clinically indicated.

5.1.1.3 LVEF Assessment

The screening LVEF assessment should be performed within 14 days for prior anthracycline use or within 28 days prior to the first trastuzumab SC administration for anthracycline-free regimens, and the LVEF must be $\geq$55% for the patient to be eligible for participation in this study. The method of assessment (echocardiography, MUGA, or MRI) is at the investigator's discretion; however, to the extent possible, the same imaging technique is to be used for each patient throughout the study. LVEF assessment results must be available before/on the day of the next scheduled trastuzumab administration, and, should a reduction in LVEF be noticed compared to screening, a decision to give or hold that dose must be made based on the algorithm provided in Appendix 4. In addition, any patient who develops clinical signs or symptoms suspicious of cardiac failure at any time during the study should undergo an

LVEF assessment immediately. If a patient has an LVEF result between 45%–49%, a drop of ≥10% and is symptomatic, or is a patient for whom the study drug was permanently stopped due to a significant drop in LVEF, then a repeat LVEF should be performed as clinically indicated, with a minimum repeat LVEF within 3 weeks.

Of note, if MUGA scans are chosen, investigators must be aware that there may be local guidelines which govern how many MUGA scans (or the amount of irradiation) a patient is allowed to have in a year and must ensure that patients are able to adhere to the cardiac assessment schedule as outlined in Appendix 1. In case additional LVEF assessments become necessary for the medical management of a patient, the investigator may use echocardiography instead of a MUGA scan to remain within the locally accepted amount of irradiation.

Symptomatic left ventricular dysfunction (congestive heart failure) will be graded according to NCI-CTCAE version 4.0 (Appendix 5) and the New York Heart Association (NYHA) functional classification (Appendix 3).

5.1.2 Management of Specific Adverse Events

Cardiac safety will be monitored throughout the study, as described in Section 5.1.1.2. In addition to the scheduled assessments, any patient who develops clinical signs or symptoms suspicious of cardiac failure at any time during the study should undergo an LVEF assessment immediately. Patients whose LVEF falls ≥10 percentage points from screening and to a LVEF <50% may require temporary or permanent cessation of trastuzumab in accordance with the treatment continuation/discontinuation algorithm shown in Appendix 4. A repeat LVEF assessment should be performed approximately 3 weeks later. If the LVEF has not improved or has declined further, trastuzumab should be discontinued. All such patients should be referred for assessment by a cardiologist and followed up. Trastuzumab should also be discontinued in any patient who develops clinically significant heart failure see (Section 4.3.3).

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.8 and Section 5.3.5.9
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.1.1 Laboratory Test Abnormalities

Local laboratories will be used for all safety laboratory tests. Laboratory test reports should be included in the patient chart and made available for routine monitoring and source document verification.

Any treatment-emergent abnormal laboratory result that is clinically significant should be recorded as a single diagnosis on the AE page in the eCRF. Clinical significance is defined as meeting one or more of the following conditions:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g., dose modification, interruption, or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy, or treatment)

Laboratory test value abnormalities that are not considered clinically significant should not be recorded as AEs in the eCRF. Laboratory test results obtained at timepoints other than those specified in Appendix 1 will only be recorded on the laboratory results e-form of the eCRF, if they are associated with an AE.

Any laboratory result abnormality fulfilling the criteria for an SAE should be reported as such, in addition to being recorded as an AE in the eCRF.

5.2.2 Serious Adverse Events (Immediately Reportable to Roche)

A SAE is an experience that suggests a significant hazard, contraindication, side effect, or precaution. It is any AE that at any dose fulfils at least one of the following criteria:

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

  This refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The term sudden death should be used only when the cause is of a cardiac origin as per standard definition. The terms death and sudden death are clearly distinct and must not be used interchangeably.

Please refer to Section 5.4 and Section 5.5 for details on how these events should be reported and followed up, respectively.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to NCI-CTCAE criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings). Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF. Serious adverse event s are required to be reported by the investigator to the Sponsor within 24 hours after learning of the event (see Section 5.4.2 for reporting instructions).

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4 to Section 5.6.

For each AE recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

The investigator is also responsible for reporting medical device complaints, regardless whether they are associated with adverse events or not (see Section 5.4.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies). All other adverse events will be recorded as medical history.

After initiation of study drug, all AEs/SAEs *(except unrelated non-cardiac AEs in the follow-up period)*, regardless of relationship to study drug, will be reported until study closure. The investigator does not need to actively monitor subjects for AEs once the trial has ended. However, if becoming aware of any serious adverse events and non-serious adverse events of special interest occurring to a subject, the investigator should report those to the Sponsor (see Section 5.6).

Any injection-site reactions are considered to be related AEs/SAEs and should be reported accordingly.

Symptomatic congestive heart failure must be reported irrespective of causal relationship during the full course of the study, even if the patient starts a new anticancer regimen.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of nondirective questioning should be adopted for eliciting adverse event information at all patient evaluation time points. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The intensity of all adverse events will be graded according to the NCI-CTCAE, version 4.0 on a five-point scale (Grade 1 to 5) and reported in detail on the eCRF.

Table 9 will be used for assessing severity for AEs that are not specifically listed in the NCI-CTCAE.

Table 9 Assessment of AE Severity

CTC Grade	Equivalent To:	Definition
Grade 1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
Grade 2	Moderate	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
Grade 3	Severe	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
Grade 4	Life threatening	Life-threatening consequences or urgent intervention indicated [d]
Grade 5	Death	Death related to adverse event [d]

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of SAE in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving trastuzumab SC concurrently with adjuvant chemotherapy, causality will be assessed individually for each therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct English medical terminology/concepts when recording AEs on the Adverse Event eCRF. Colloquialisms and abbreviations should be avoided.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

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

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF.

For example:

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

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

Recurrence of breast cancer (as defined in Section 4.5.1.8.1) should not be reported as an AE since this is clearly consistent with progression/relapse of the underlying disease. Hospitalization due solely to the relapse of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of relapse may be reported as AEs if the symptom cannot be determined as exclusively due to the relapse of the underlying malignancy or does not fit the expected pattern of relapse for the disease under study.

If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent adverse event is one that resolves between patient evaluation time points and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated

potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator’s judgment

It is the investigator’s responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor within 24 hours after learning of the event, as a serious AE (see Section 5.4.2).

5.3.5.7 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur prior to study closure that are attributed by the investigator solely to progression of EBC should be recorded only on the *Death* eCRF *page*. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

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

During study survival follow-up, deaths attributed to progression of EBC should be recorded only on the *Death* eCRF *page*.

5.3.5.8 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A pre-existing medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of the Underlying Condition

Medical occurrences or symptoms of deterioration that are anticipated as part of the patient's underlying breast cancer should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of breast cancer on the Adverse Event eCRF, it is important to convey the concept that the

condition has changed by including applicable descriptors (e.g., “accelerated breast cancer”).

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. The determination of clinical progression will be based on objective evidence and/or symptomatic deterioration. Every effort should be made to document progression using objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be serious adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration)
- Hospitalization for a pre-existing condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not suffered an adverse event
- Hospitalization due solely to progression of the underlying cancer

5.3.5.11 Overdoses

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfils serious criteria, the event should be reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

The investigator must report the following events to the Sponsor within 24 hours after becoming aware of the event, regardless of relationship to study drug:

- SAEs (see definition in Section 5.2.2)
- Pregnancies (for female study patients and female partners of male study patients)
- Device complaints

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

Serious adverse events regardless of the relationship to the study drug ***MUST*** be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed. All participating investigators and the respective independent Ethics Committees (ECs) will be notified of all Suspected Unexpected Serious Adverse Reactions (SUSARs) that are reported during the study. An AE only qualifies as a SUSAR when all of the following conditions are met:

- The event is serious (SAE);
- The event is deemed related to the study drug, according to the criteria provided in Section 5.3.4. (Note: any suspicion of a causal relationship should lead to an assessment of 'related');
- When assessed against the known safety profile of trastuzumab SC (as described in the IB), the event is considered unexpected (not foreseen in the IB).

When all patients at a particular site are off treatment as defined by the protocol:

- Individual SUSAR reports originating in that particular trial will be forwarded to all participating investigators and the IECs associated with their sites, on an expedited basis;
- Individual SUSARs considered to be a significant safety issue and/or which result in Roche recommending a change to the Informed Consent Form (ICF), will be reported in an expedited manner to all investigators and reviewing IECs;
- SUSAR reports originating from other trials using the same IMP will be provided as six-monthly SUSAR Reports (SSRs) to all investigators and IECs where long-term follow-up studies are carried out.

5.4.1 Emergency Medical Contacts

Medical Monitor (Roche Medical Responsible) Contact Information

Primary Contact

Medical Monitor: [redacted] M.D.

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Secondary Contact

Medical Monitor: Dr. [redacted] M.D.

Telephone No.: *+650 225-1000*

Office Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Centre Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Centre Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.2 Reporting Requirements for Serious Adverse Events

For reports of serious adverse events, investigators should record all case details that can be gathered within 24 hours on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management or its designee by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event CRF and Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee within 24 hours after learning of the event, using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

The investigator should report all complaints relating to the medical device used to administer the study treatment to Roche. The investigator must document as much information as possible (based on the *Medical Device Complaint Form*) including the batch number and expiration date of the device and forward this to Roche Safety Risk Management or its designee within 24 hours of becoming aware of the complaint. The investigator may also be requested to forward defective medical device samples to Roche.

If the medical device complaint results in an AE, the information should be captured on the patient eCRF. If the medical device complaint results in an SAE, the investigator should also complete an *SAE Reporting Form* and forward it to Roche Safety Risk Management within 24 hours of becoming aware of the event.

According to Roche standard procedures, all AE reports/complaints from the use of investigational medicinal products (IMPs) that are associated with a Medical Device which is used to administer the IMP must be forwarded to Drug Safety and all AE reports/complaints associated with a Medical Device, and all Medical Device SAEs must

be forwarded to the Local Complaint Manager/relevant department for complaint management. In addition, all medical device SAEs need to be reported within 24 hours to Roche Safety Risk Management or its designee.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

For women of childbearing potential (defined as premenopausal, less than 1 year after the onset of menopause or not surgically sterilized), appropriate contraceptive measures are mandatory during study treatment (see Section 4.5.1.7.3). Based on pharmacokinetic considerations, contraceptive measures are recommended for at least 7 months following the last dose of trastuzumab.

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 7 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator within 24 hours after learning of the pregnancy and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue the study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

In the event that the EDC system is unavailable, a Pregnancy Report worksheet and Pregnancy Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee within 24 hours after learning of the pregnancy, using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). As soon as the EDC system is operating, the Pregnancy Report eCRF will be completed.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 7 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator within 24 hours after learning of the pregnancy and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Abortions

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

5.4.4 Reporting Requirements for Medical Device Complaints

The investigator must report all medical device complaints to Roche Safety Risk Management. The investigator should document as much information as possible on the Medical Device Complaint Form, including the product batch number and expiration date and forward this to Roche Safety Risk Management within 24 hours of knowledge of the complaint. The investigator may also be requested to forward defective medical device samples to Roche.

If the medical device complaint results in an AE, the Medical Device Complaint eCRF must be completed and submitted through the EDC within 24 hours after learning of the event. The AE must be reported on the Adverse Event eCRF. If the medical device complaint results in an SAE, the investigator should also complete an *SAE Reporting Form* and forward it to Roche Safety Risk Management within 24 hours of knowledge, as outlined in Section 5.4.2.

In the event of a device failure, the complaint must be reported to Roche Safety Risk Management. The device must also be returned via courier to Roche for assessment. Supplemental dosing requirements for the patient will be assessed by the investigator as per the instructions provided. In the case of a patient experiencing more than one device failure the patient will revert to SC trastuzumab for all remaining cycles to complete 18 cycles in total as part of the study.

The investigator should report all complaints relating to the medical device used to administer the study treatment to Roche Safety Risk Management. The investigator must document as much information as possible (based on the Medical Device Complaint Form [gcp_for000447]) including the batch number and expiration date and forward this to Roche Safety Risk Management within 24 hours of knowledge of the complaint. The investigator may also be requested to forward defective medical device samples to Roche.

If the medical device complaint results in an AE, the information should be captured on the patient eCRF. If the medical device complaint results in an SAE, the investigator should also complete an *SAE Reporting Form* [gcp_for004369] and forward it to Roche Safety Risk Management within 24 hours of knowledge.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all SAEs until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

The Investigator must report new significant follow-up information for these events to the Sponsor within 24 hours after becoming aware of the information. New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event (including outcome of a reported pregnancy, as applicable)

In an individual patient, AE follow-up will continue as follows:

Related *or cardiac* AEs and SAEs will be followed until one of the following occurs:

- Resolved or improved to baseline state
- Relationship is reassessed as unrelated
- Investigator confirms that no further improvement can be expected
- Start of a new anti-cancer regimen
- Death

Unrelated *non-cardiac* AEs *(Grade 3 or Grade 4)* and SAEs *(any grade)* will be followed until one of the following occurs:

- Resolved or improved to baseline state
- Severity improved to Grade 2
- Investigator confirms that no further improvement can be expected
- Start of new anti-cancer regimen
- Death

Unrelated *non-cardiac* AEs (Grade 1 or Grade 2) will be followed until 4 weeks after the last dose of study drug in an individual patient.

The final outcome of each adverse event must be recorded on the eCRF.

Follow-up of Abnormal Laboratory Test Values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range or baseline state and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

At the *final* follow-up visit *of the study*, the Investigator should instruct each patient to report to the Investigator any subsequent adverse events. The Sponsor should be notified if the Investigator becomes aware of any death or serious adverse event *related to study drug,* occurring at any time, after a patient has discontinued study participation, even after study closure. The investigator is not required to actively monitor patients after the study has ended.

The Sponsor should also be notified if the Investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study.

The Investigator should report these events to Roche Safety Risk Management on the Adverse Event eCRF. If the Adverse Event eCRF is no longer available, the Investigator should report these events, indefinitely, directly to Roche Safety Risk Management via telephone (see "Protocol Administrative and Contact Information & List of Investigators").

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, AND ETHICS COMMITTEES

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Herceptin (RO 45-2317, Trastuzumab) IB

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

A sample size of approximately 2500 patients is planned for this study (approximately 1800 patients in **Cohort A** and approximately 700 patients in **Cohort B**). There is no formal statistical hypothesis; hence, all safety (primary) endpoints results will be presented by 95% confidence intervals and descriptively explained.

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.

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

Table 10 Clopper-Pearson 95% Confidence Intervals for the Observed CHF-Related SAE Incidence

Cohort A: **Total number of patients: 1800**	
Number of patients with CHF-related SAEs (incidence rate)	**95% Clopper Pearson CI**
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% (Romand et al. 2005; Ewer and O'Shaughnessy 2007) and a sample size of 1800 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 is produced by the SAS program and nQuery Version 6.

The split of the two cohorts in the current study was based on the availability of the device, 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% (Romand et al. 2005; Ewer and O'Shaughnessy 2007) and a sample size of 700 patients for **Cohort B**, the upper limit of the 95% 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 (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.

Refer to the Statistical Analysis Plan (SAP) for further details.

6.2 SUMMARIES OF CONDUCT OF STUDY

This is a Phase III prospective, two-cohort, non-randomized, multicenter, multinational, open-label study. Eligible patients with HER2-positive EBC will be allocated to one of two cohorts at the investigators' discretion:

- **Cohort A** (approximately 1800 patients) will receive trastuzumab SC by assisted administration using a conventional syringe.
- **Cohort B** (approximately 700 patients) will receive trastuzumab SC, first assisted, then self-administered (select patients) using a SID.

Patients in both cohorts will receive a total of 18 cycles of trastuzumab SC, unless disease recurrence, unacceptable toxicity, or patient withdrawal necessitates earlier treatment cessation. During adjuvant therapy, patients will be assessed for safety and efficacy, as detailed in Appendix 1.

Safety endpoints are the primary objectives in this study. Secondary efficacy endpoints include DFS, OS (both cohorts), and patient satisfaction with trastuzumab SC administration using the SID (**Cohort B** patients who went on to self-administration only). In addition, immunogenicity of trastuzumab and rHuPH20 (with PK) will be analyzed in a subset of patients enrolled in **Cohort B** at select sites. There is no formal statistical hypothesis for the comparison of **Cohort A** and **Cohort B**. With the exceptions noted above, all summaries and analyses will be performed for **Cohort A** and for **Cohort B**.

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 OS and DFS 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 enrollment 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: There will be no adjustments for multiplicity of endpoints or within-subgroups comparisons.

Three interim safety analyses are planned for the study when approximately 500, 1000, and 2500 patients have received at least one trastuzumab SC injection. More details are provided in the Section 3.1.2 of the protocol and in the Steering Committee Charter.

A Clinical Study Report (CSR) will be written at the time of the primary endpoint analysis, and distributed to Health Authorities in keeping with the applicable regulatory requirements. All subsequent data analyses will be reflected in an addendum to the CSR.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Not applicable; no formal statistical comparisons of the two cohorts are planned.

6.4 SAFETY ANALYSES

6.4.1 Primary Safety Endpoint

Safety endpoints are the primary objectives in this study and will include: all AEs, Grade ≥3 AEs, SAEs, AEs leading to premature discontinuation of study treatment, AEs causing interruption of trastuzumab SC, cardiac AEs, CHF-related SAEs, premature withdrawals from study and study medication, exposure to treatment, laboratory parameters, LVEF, vital signs, ECG, weight, and ECOG performance status.

The primary analysis of the safety endpoints will be performed for the safety population (SP) defined as all enrolled patients who received at least one dose of study medication. There will be two safety populations, one for each cohort (SP1 for **Cohort A** and SP2 for **Cohort B**). The safety endpoints will be summarized for each cohort (SP1 and SP2) and overall (SP) as described below. The primary analysis of safety endpoints will take place when all patients have received 18 cycles of trastuzumab SC and have completed the post-treatment Safety Follow-up assessments. Updated summaries for safety parameters will be prepared 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.

The analysis of AEs will focus on treatment-emergent adverse events (TEAEs) i.e, AEs occurring on the day of or after first administration of study drug. Non-treatment emergent AEs (i.e., those occurring before commencement of study medication) will only be listed. The incidence of AEs, AEs leading to premature discontinuation or interruption of study treatment, SAEs, Grade 3 and 4, and cardiac AEs will be summarized according to the primary system-organ class (SOC) and within each SOC by MedDRA preferred term. The time to onset of the first episode of cardiac AEs will also be summarized using the Kaplan-Meier approach. The incidence of deaths and cause of deaths will be listed and summarized by treatment cohort and overall.

LVEF will be summarized over time by means of mean, median, and range (mean and maximum) and will be presented graphically for each trastuzumab SC cohort and overall. Vital signs, ECG, and weight will be summarized similar to LVEF.

Safety laboratory parameters (hematology, biochemistry, as defined in Section 4.5.1.7.2), will be presented in shift tables according to NCI CTC grade at screening versus worst grade during trastuzumab treatment for each trastuzumab SC cohort and overall. The summary of laboratory parameters will include means, standard deviation, minimum, and maximum values. Select laboratory parameters may also be displayed graphically. More details will be presented in the SAP.

Exposure to study treatment (number of cycles administered) and duration of treatment exposure (calculated from date of first study treatment to the last treatment date) will be summarized.

The number of patients who prematurely discontinue study treatment and the number of patients who withdrew from the study will be summarized, and reasons for withdrawal will be displayed.

ECOG performance status will be summarized by frequency tables over time, and percentage of patients in different categories will be presented by bar charts at different timepoints.

6.5 EFFICACY ANALYSES

6.5.1 Secondary Efficacy Variables

Secondary efficacy endpoints include disease-free survival (DFS) and overall survival (OS) and will be assessed in both cohorts.

- DFS is defined as the time from the date of first treatment to the date of local, regional, or distant recurrence; contralateral invasive breast cancer (including contralateral or ipsilateral ductal carcinoma in situ [DCIS]); or death due to any cause.
- OS is defined as time from the date of first treatment until date of death, regardless of the cause of death.

DFS and OS will be analyzed as a time-to-event variable for the ITT population (see Section 6.5.2).

In addition, patients' satisfaction with trastuzumab SC administration using the SID will be evaluated for **Cohort B** patients who went on to self-administration only.

6.5.2 Analyses of Efficacy Endpoints

The efficacy endpoints, DFS and OS, will be analyzed as a time-to-event variable for the ITT and PP populations and for each cohort. Estimates and corresponding 95% confidence intervals for the survivor function for the time-to-event variable will be

obtained by using the KM approach. A frequency table will be also provided for the type of DFS event (e.g., local, regional, or distant recurrence; contralateral *breast cancer*; or death).

A preliminary analysis of efficacy (DFS and 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 OS and DFS will take place 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 enrollment 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

Patients' satisfaction with trastuzumab SC administration using the SID (**Cohort B** patients who went on to self-administration only) will be summarized by frequency tables and presented graphically.

6.5.3 Other Analyses

Baseline characteristics will be summarized overall and for each treatment cohort. The demographic profile, medical history, HER2-positivity, and serum pregnancy test at screening will be listed and summarized using appropriate descriptive statistics: mean, standard, median, range (minimum and maximum), and 25th–75th quartiles for the continues variables and number/percentage of patients, medians, and ranges for the categorical variables.

Concomitant medications will be summarized by class and preferred term for the ITT and safety populations. Within each cohort, the number of cycles, as well as dosing information (e.g., dose interruptions, modifications, and delays), will be summarized by median and range.

More details about the planned analyses will be presented in the SAP.

6.6 ANALYSIS POPULATIONS

The Safety Population (SP) will include all enrolled patients who received at least one dose of study medication. There will be two safety populations, one for each cohort (SP1 for **Cohort A** and SP2 for **Cohort B**).

The intent to treat (ITT) population will include all patients enrolled in the study.

The per-protocol population (PP) will include all ITT patients who have received at least one dose of study medication and did not have major protocol violations (which will be defined in the SAP).

6.7 PHARMACOKINETIC ANALYSES

Pharmacokinetic assessments will be limited to the confirmation of the presence and titer of trastuzumab in the serum of a subset of patients enrolled in **Cohort B** at select sites, who will also undergo immunogenicity testing (anti-trastuzumab assay; see Section 6.9.1).

6.8 PATIENT–REPORTED OUTCOME ANALYSES

Not applicable.

6.9 EXPLORATORY ANALYSES

6.9.1 Immunogenicity

Immunogenicity assessments will be summarized for a subset of patients enrolled in **Cohort B** at selected sites. The percentage of patients who develop anti-human antibodies (HAHAs and ADAs) to trastuzumab SC or rHuPH20 or both will be presented. Serum trastuzumab concentration data will be used for the evaluation of the anti-trastuzumab assay.

Details about analysis methods are provided in the Statistical Analysis Plan (SAP).

6.9.2 Observation Time

Exploratory study analyses for all clinical AEs that occur during the observation period will be evaluated, analyzed, and presented, and further exploratory analysis will be performed for all patients in **Cohort B** (within 6 hours after start of the first trastuzumab administration or within 2 hours after start of following trastuzumab administrations). Details of the analysis will be documented in the Statistical Analysis Plan (SAP) and will include the following:

- Analysis of frequency, incidence, and grade of AEs during the observation period
- Analysis of time from last preceding administration of study drug to onset time of AE occurrence (dd:mm:yyyy:hh:mm) during the observation period
- Analysis of time to resolution (dd:mm:yyyy:hh:mm) and outcome of AEs observed during the observation period
- Analysis of treatments provided following AEs during the observation period

Exploratory analyses on the usability of the SID summarizing the parameters collected via SID monitoring questionnaire (Appendix 7) 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 observation of the HCP. The SID Device Observation is to be completed by HCPs.

6.9.3 Subgroup Analyses

Selected safety and efficacy summaries will be repeated for the subgroup of patients treated without neoadjuvant or adjuvant chemotherapy, such as patients with low-risk,

node-negative tumors ≤ 1.0 cm, elderly patients (> 65 years of age), or patients who refuse chemotherapy. Enrollment of patients treated without chemotherapy will be limited to ≤ 10% of the total study population. Details of the planned subgroup analyses will be provided in the SAP.

6.10 INTERIM SAFETY ANALYSES

Three interim safety analyses are planned when approximately 500, 1000, and 2500 patients have received at least one trastuzumab SC injection.

Details regarding the planned interim safety analyses will be provided in the Steering Committee Charter.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Roche will supply electronic eCRF specifications for the study. The overall procedures for quality assurance of clinical study data are described in the Roche Standard Operational Procedures and/or those of the global Contract Research Organization (CRO) designee.

Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system. eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

The responsible monitors (CRO designee) will visit the investigators and will be allowed, on request, to inspect the study records, provided that patient confidentiality is maintained in accordance with local requirements. It will be the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor must verify that the patient received the study drug as prescribed in the protocol. The monitor should have access to laboratory test reports and other patient records needed to verify the entries on the eCRF. The investigator (or deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

Roche will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically

transferred electronically from the CRO to Roche, and Roche's standard procedures will be used to handle and process the electronic transfer of these data.

For classification purposes, preferred terms will be assigned by the Sponsor (or CRO designee) to the original terms entered on the eCRF, using the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA) terminology for adverse events and diseases and the International Non-proprietary Name (INN) Drug Terms and Procedures Dictionary for treatments and surgical and medical procedures.

7.2 ELECTRONIC CASE REPORT FORMS

A global CRO will handle eCRF development and review, eCRF online monitoring/data management, statistics, preparation of the final statistical report and clinical study report (CSR). The CSR will be prepared when all patients have completed the Safety Follow-up visit (4 weeks after the last dose of study treatment). An addendum to the CSR will be prepared when the last patient has completed 5 years of post-treatment follow-up.

An eCRF must be completed for each enrolled (registered) patient. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. All eCRFs should be completed by designated, trained site staff, who will transcribe the collected patient data from paper source documents onto the eCRF. In no case is the eCRF to be considered as source data for this trial. eCRFs should be reviewed and electronically signed and dated by the investigator or an authorized designee. eCRFs will be submitted electronically to Roche and should be handled in accordance with instructions from Roche.

An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change. The data will be transferred directly to the clinical database.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc will be required.

7.3 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the accuracy of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and EC review. The investigational site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

Roche's sample Informed Consent Form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. Roche or its designee must review and approve any proposed deviations from Roche's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before EC submission. The final EC–approved Consent Forms must be provided to Roche for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised EC-approved Consent Forms must be provided to Roche for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the EC by the Principal Investigator and reviewed and approved by the EC before the study is initiated. In addition, any patient recruitment materials must be approved by the EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC. Investigators are also responsible for promptly informing the EC of any protocol amendments (see Section 9.5).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and EC. Investigators may receive written safety reports or other safety-related communications from Roche. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

Roche maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Roche location.

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

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

Data generated by this study must be available for inspection upon request by representatives of the national and local health authorities, Roche monitors, representatives, and collaborators, and the EC for each study site, as appropriate

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 SITE INSPECTIONS

Site visits will be conducted by Roche or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Roche monitors, representatives, and collaborators; and the ECs to inspect facilities and records relevant to this study.

9.3 ADMINISTRATIVE STRUCTURE

Please refer to the separate contact list for the contact information of the Sponsor and Global Roche Study Personnel.

This information can be found at the local Roche affiliate office, and within the Investigator Site File.

9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to Roche prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

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

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Roche personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Roche personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

9.5 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Investigators are responsible for promptly informing the EC of any amendments to the protocol.

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

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Appendix 1
Schedule of Assessments

	Screening	Study Treatment 3-weekly (18 cycles)				Safety Follow-Up Visit [q,r]	Follow-Up Visits [k,r]
Study Week (Treatment Cycle #)	**Day -28 to 1**	**Week 1 to 22 Cycles 1 to 8 [r,u]**	**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		Approximately 3-monthly (every 4 cycles) [p]				x [s]	Cardiac assessments at 6, 12 and 24 months, and at 3, 4 and 5 years following treatment cessation
12-lead ECG	x						
LVEF [f]	x [f]						
Signs/symptoms	x						
Pregnancy test [g]	x	As clinically indicated					

Appendix 1 Schedule of Assessments (cont.)

	Screening	Study Treatment 3-weekly (18 cycles)				Safety Follow-Up Visit [q,r]	Follow-Up Visits [k,r]
Study Week (Treatment Cycle #)	**Day -28 to 1**	**Week 1 to 22 Cycles 1 to 8 [r,u]**	**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)**
Blood samples for immunogenicity and PK testing [h]	x [h]		x [h]				x (6 months after last study treatment)
Hematology 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 monitoring questionnaire [w]		x	x	x	x		
Treatment compliance		x	x	x	x		
SID satisfaction questionnaire [o]		After Cycle 4 [o]				x	
Survival		x	x	x	x	x	x (at *12,* 24 months and at 3, 4, and 5 years after last treatment)

Note: First dose of study drug = study Cycle 1, Day 1.

[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 patient participating in PK sampling at Cycle 9 and 6 month after last study treatment. Height is only measured at screening.

[e] Vital signs include blood pressure, heart rate measurement and temperature at screening and 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 anthracycline regimens or 28 days prior to the first study treatment for 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 ≥ 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 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] Hematology: hemoglobin, 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 hematology 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 predose, 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 12 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 3–6 months for the first 3 years after primary therapy, every 6–12 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), tumor 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 SI 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 AEs, the collection of detailed information about premedications 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.

Appendix 2
ECOG Performance Status Scale

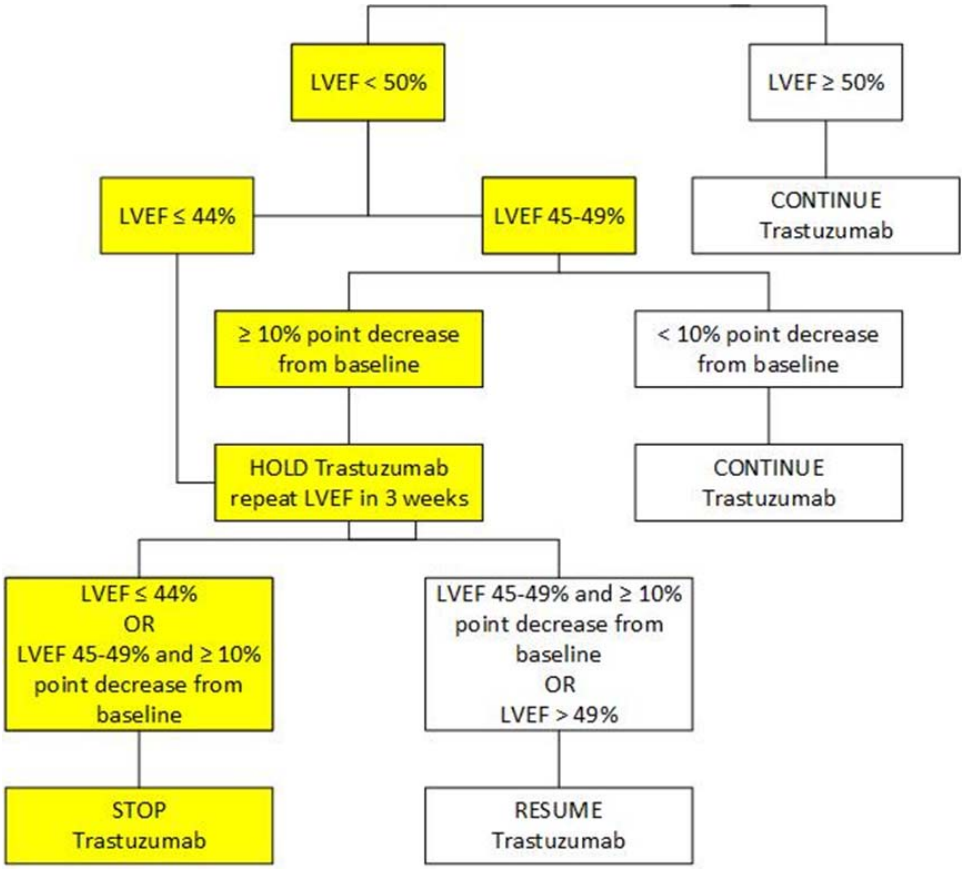
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work).
2	Ambulatory and capable of all selfcare, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

Source: Oken M et al. 1982.

Appendix 3
New York Heart Association (NYHA) Functional Classification System for Heart Failure

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Appendix 4
Algorithm for Continuation and Discontinuation of Trastuzumab SC Based on LVEF Assessment in Asymptomatic Patients



Appendix 5
Common Terminology Criteria for Adverse Events

Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0

Published: May 28, 2009 (v4.03: June 14, 2010)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health, National Cancer Institute

The CTCAE v4.0 manual can be found at the following URL:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Appendix 6
Single-Use Injection Device (SID) Satisfaction Questionnaire

The SID satisfaction questionnaire is to be completed by patients in **Cohort B** who completed a minimum of 2 (preferably 3) self-administrations of the study drug.

Please rate your level of agreement or disagreement with each the following statements, by placing an "X" in the appropriate box (one answer for each statement):

1. **Following the first injection given by the physician/nurse and training on how to use the SID, I felt comfortable injecting the study drug by myself.**

☐$_1$ Strongly Disagree ☐$_2$ Disagree ☐$_3$ Unsure ☐$_4$ Agree ☐$_5$ Strongly agree

2. **The SID was convenient and easy to use.**

☐$_1$ Strongly Disagree ☐$_2$ Disagree ☐$_3$ Unsure ☐$_4$ Agree ☐$_5$ Strongly agree

3. **I am confident giving myself an injection in the thigh with the SID.**

☐$_1$ Strongly Disagree ☐$_2$ Disagree ☐$_3$ Unsure ☐$_4$ Agree ☐$_5$ Strongly agree

4. **Taking all things into account, I find self-administration using the SID satisfactory.**

☐$_1$ Strongly Disagree ☐$_2$ Disagree ☐$_3$ Unsure ☐$_4$ Agree ☐$_5$ Strongly agree

5. **If given the opportunity, I would choose to continue self-injecting the study drug using the SID in the future.**

☐$_1$ Strongly Disagree ☐$_2$ Disagree ☐$_3$ Unsure ☐$_4$ Agree ☐$_5$ Strongly agree

Appendix 7
Single-Use Injection Device (SID) Observers Usability Questionnaire

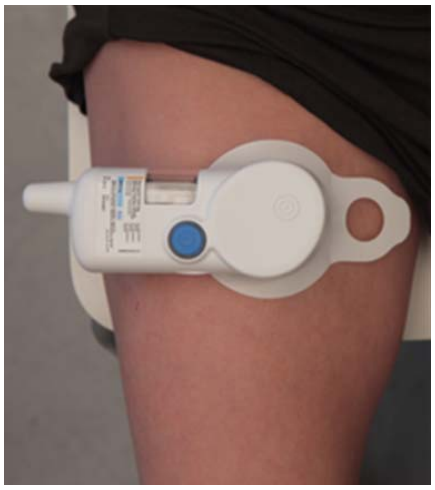
The SID Device Observation is to be completed by HCPs (physician or nurses) for 48 patients selected in **Cohort B** who were judged able, and were willing to self-administer remaining doses from the SID under direct observation of the HCP. Patients participating in the usability questionnaire must self-administer with the SID and no assistance is to be provided unless it was not possible for a user to use the SID correctly (in which case assistance is permitted). In this instance, the SID usability questionnaire must still be completed.

Positioning of device; body site selection and prepare skin

1. Does selection of body positioning of SID comply with instruction (semi-supine, anterior thigh)?
   (Circle the applicable answer)
   If NO please comment: **[YES] [NO]**
   _____
   _____
   _____

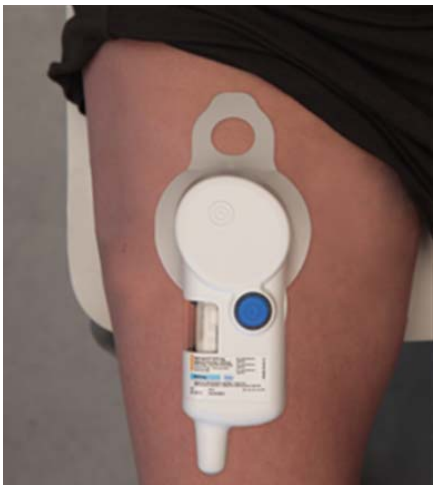
2. Which image below best describes the placement of the SID on the thigh of the patient? *(Circle the applicable answer)*.

[A]



[A] Across the Thigh

[B]



[B] Along the thigh

Appendix 7 Single-Use Injection Device (SID) Observers Usability Questionnaire (cont.)

3.	Was the body site dry before attaching the SID? *(Circle the applicable answer)*	**[YES]**	**[NO]**
4.	Was the SID stuck onto the skin with the adhesive pad removed? *(Circle the applicable answer)* If NO please comment: _____ _____	**[YES]**	**[NO]**
5.	**Was the full dose injected from the SID?** Piston at end position of cartridge at the end of injection. *(Circle the applicable answer)* If NO please comment: _____ _____	**[YES]**	**[NO]**
6.	**Did the SID stop at any time during administration?** This is indicated by the motor stopping and indicator light flashing alternating green and orange. *(Circle the applicable answer)* If YES please comment: _____ _____	**[YES]**	**[NO]**
7.	**IF the SID did stop during the administration -** **Was the problem corrected to resume delivery?** (To correct the SID was depressed onto the skin again within 10 seconds and pressure maintained until the status light resumed slowly flashing orange and injection continued).	**[YES]**	**[NO]**
8.	Following completion of the injection and removal of the SID from the body: **Did the needle automatically retract into SID?**	**[YES]**	**[NO]**
9.	Was there residual liquid left at the injection site? If **Yes**, please tick **one** of the options below: **1 to 5 drops [ ]** **More than 5 drops [ ]**	**[YES]**	**[NO]**

Appendix 7 Single-Use Injection Device (SID) Observers Usability Questionnaire (cont.)

10. Was assistance given to a user at any time during the self-administration? If YES please comment: _____ _____ _____ _____ _____ _____	**[YES]**	**[NO]**