

**Official Title:** NATIONAL PHASE IIIB PROSPECTIVE , TWO-COHORT NON-RANDOMIZED, MULTI-CENTRE, OPEN LABEL STUDY TO ASSESS THE SAFETY OF SUBCUTANEOUS TRASTUZUMAB AND MOLECULAR BIOMARKERS IN PATIENTS WITH EARLY AND LOCALLY ADVANCED HER2-POSITIVE BREAST CANCER

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# Statistical Analysis Plan

**F. HOFFMANN-LA ROCHE LTD**

**Herceptin SC ML28879/ NCT01940497**

Test Product: Trastuzumab SC (RO 45-2317)

National phase IIIb prospective, two-cohort non-randomized, multi-centre, open label study to assess the safety of subcutaneous trastuzumab and molecular biomarkers in patients with early and locally advanced HER2-positive breast cancer

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6<sup>th</sup> October 2016

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	Table 14.5.5	Added a graph to display LVEF (%) over time		

\* Provide person's initial and last name.

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## Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
BC	breast cancer
BSA	Body Surface Area
BUN	blood urea nitrogen
CHF	congestive heart failure
CI	confidence interval
C <sub>max</sub>	maximum concentration
CNS	central nervous system
CRO	contract research organization
CT	computed tomography
CTCAE	common terminology criteria for adverse events
DCIS	ductal carcinoma in situ
DBP	Diastolic Blood Pressure
DFS	disease free survival
DLT	dose-limiting toxicity
DoR	duration of response
eBC	early breast cancer
EC	Ethics Committee
ECG	electrocardiogram
ECHO	echocardiography
ECOG	Eastern Cooperative Oncology Group
(e)CRF	(electronic) Case Report Form
EDC	electronic data capture
EEA	European economic area
EGRF	epidermal growth factor receptor
EU	European Union
FDA	Food and Drug Administration
Hb	haemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIV	immunodeficiency virus
HCP	health care professional
HR	hazard ratio
ICH	International Conference on Harmonization
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug (application)
INR	international normalised ratio
IRB	Institutional Review Board
IRC	Independent Review Committee

IRR	infusion-related reaction
ISH	in situ hybridization
ITT	intent-to-treat
IV	intravenous
LABC	locally advanced breast cancer
LVEF	left ventricular ejection fraction
LPLV	last patient, last visit
MedDRA	Medical Dictionary for Regulatory Activities
m-ITT	modified intent-to-treat
MRI	magnetic resonance imaging
MUGA	multiple gated acquisition
NCI	National Cancer Institute
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival
pCR	pathological complete response
PD	progressive disease
PET	positron emission tomography
PFS	progression free survival
PK	pharmacokinetic
PPAS	per-protocol population analysis set
PR	partial response
PRO	patient-reported outcome
q3w	every 3 weeks
qw	weekly
RECIST	response evaluation criteria for solid tumours
rHuPH20	recombinant humanised hyaluronidase
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SID	single-use injection device
SBP	Systolic Blood Pressure
SI	standard international
SOC	system-organ class
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse event
ULN	upper limit of normal
WBC	white blood cells
WHO	World Health Organization



# 1 Introduction

This document describes the statistical methods to be used during the analyses and reporting of study ML28879. This SAP includes all details for the analysis and reporting (tables, listings and graphs) of the data collected as part of this protocol.

This Statistical Analysis Plan is based on the protocol version Final 2.0, dated 27 May 2014.

## 2 Study Objectives

### 2.1 Primary Objective

The primary objective of the study is to assess the safety and tolerability of trastuzumab solution injected subcutaneously (vial or single-use injection device [SID]) in patients with HER2-positive early breast cancer (eBC) or locally advanced breast cancer (LABC).

### 2.2 Secondary Objectives

The secondary safety objectives for this study are to assess:

- Exposure to study medication
- Duration of treatment and follow-up
- ECOG
- Vital sign, physical examination and laboratory parameters
- Concomitant medication
- Premature withdrawals and major protocols violation

The secondary efficacy endpoint will be:

- Disease Free Survival (DFS)
- Overall Survival (OS)
- For neo-adjuvant setting, incidence of pathological Complete Response (pCR) in breast and in nodes (ypT0-is ypN0)
- Patient Satisfaction using SID (single use injection device)
- HCP satisfaction

Furthermore, will be implemented an Explorative Analysis on the central HER2 positive cases to evaluate the association of PI3K mutation status in tumor tissues and in circulating free DNA (cfDNA) in blood. We performed the following assessment:

- Agreement evaluation at baseline and at Cycle 5 between PI3K mutation assessment in tumor tissue (gold standard) and in circulating free DNA (experimental)
- Association between the baseline mutation status with pCR in neo-adjuvant arm

- Association between pharmacodynamics change (baseline, Cycle 1, Cycle 5) of the cfDNA before and after treatment with clinical outcomes

A sensitivity analysis will be performed on the HER2 positive cases confirmed by the Central Laboratory (IHC=3+ or FISH=Amplified).

## 3 Study Design

### 3.1 Primary Objective

The primary objective of this study is to assess the safety and tolerability of trastuzumab solution injected subcutaneously in patients with HER2-positive eBC or LABC.

The primary analysis of safety endpoints, the analysis of efficacy (pCR) and the 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 with the summaries for safety parameters will be performed when the last patient has been followed up for at least 24 months 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 5 years after the enrolment of the first patient, based on an expected 18-month recruitment period per cohort, 15 months of study treatment and 2 years of follow-up after the last study treatment of the last patient. There will be no adjustments for multiplicity of endpoints or within-subgroups comparisons.

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.

### 3.2 Overview of Study Design

This study is a part (Daughter study) of Global (Umbrella) Study.

This is a prospective, two-cohort, non-randomized, multicenter, open-label study to assess the safety and tolerability of trastuzumab solution injected subcutaneously (vial or single-use injection device [SID]) in approximately 240 patients with HER2-positive eBC or LABC who are eligible for anti-HER2 therapy.

The patients will be enrolled in two sequential cohorts.

The first 120 patients will be treated with trastuzumab SC 600 mg/5ml vial (Cohort A) and the subsequent 120 patients will be treated with trastuzumab SC 600 mg/5ml prefilled single use injection device - SID (Cohort B).

In each cohort (A and B), patients will be allocated to adjuvant or neoadjuvant treatment, with pragmatic selection according to conventional clinical criteria and physician choice:

- Group 1 = Adjuvant chemotherapy + trastuzumab SC
- Group 2 = Neoadjuvant chemotherapy + trastuzumab SC

In both groups the planned treatment will require sequential chemotherapy regimens containing 4 cycles of Anthracyclines followed by 4 cycles of Taxanes based chemotherapy administered in combination with trastuzumab SC followed by trastuzumab alone.

Here below the detailed schemas:

Adjuvant Schema

Surgery → CT x 4 cycles (Cycles A1 to A4) → CT + Trastuzumab SC x 4 cycles (Cycles 1 to 4) → Trastuzumab SC x 14 cycles (Cycles 5 to 18)

Neoadjuvant Schema

CT x 4 cycles (Cycles A1 to A4) → CT + Trastuzumab SC x 4 cycles (Cycles 1 to 4) → Surgery → Trastuzumab SC x 14 cycles (Cycles 5 to 18)

### 3.3 Schedule of Assessments

#### 3.3.1 Adjuvant patients schedule of Assessments

	Screening	Baseline	Treatment Period													Safety Follow-up	Follow-up visits
Day  (Treatment Cycle #)	Days -28 to -1	Days -7 to -1	Anthracycline containing regimens			Starting trastuzumab (+ taxanes)		Trastuzumab ± RT ± hormonal therapy								4 weeks after last study treatment	Continuing for 24 months after safety follow (months 6,12,18,24)
			A1	A2, A3	A4	1	2, 3, 4	5	6, 7, 8	9	10, 11, 12	13	14, 15, 26	17	18		
Explain study and obtain signed Informed Consent [a]	X																
Demographics and medical history [b, c]	X																
HER2 determination [d]	X																
Baseline Breast Cancer evaluation [e]	X																
Review inclusion/exclusion criteria	X																
Vital signs, physical examination [f], weight, and height [g]	X	x	x	x	x	x	x	x	x	X	x	x	x	x	x		
ECOG performance status	X		x			x		x		X		x		x		x	x

	Screening	Baseline	Treatment Period													Safety Follow-up	Follow-up visits
Day (Treatment Cycle #)	Days -28 to -1	Days -7 to -1	Anthracycline containing regimens			Starting trastuzumab (+ taxanes)		Trastuzumab ± RT ± hormonal therapy								4 weeks after last study treatment	Continuing for 24 months after safety follow (months 6,12,18,24)
			A1	A2, A3	A4	1	2, 3, 4	5	6, 7, 8	9	10, 11, 12	13	14, 15, 16	17	18		
Cardiac monitoring [p]																	
12-lead ECG	X					X		x		X		x		x		x	x
LVEF	X					X		x		X		x		x		x	x
Signs/symptoms	X					X		x		X		x		x		x	x
Pregnancy test [i]		x				x		x		x		x		x			x
Hematology and biochemistry [j]	X		x	x	x	x	x	x		X		x		x		x	
Biomarkers blood sample collection *		x				x*		x*									
Tissue collection **		x															
Routine breast cancer follow-up [k]	X		Assessment as per institutional practice or ASCO adjuvant follow-up Guidelines 2006 to be reported 6-monthly														
AEs and SAEs [l]	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x
Past and Concomitant medications [m]	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x <sup>i</sup>
Anthracycline-containing regimen			x	x	x												
Taxane						x	x										
Trastuzumab [n]						x	x	x	x	X	x	x	x	x	x		

### 3.3.2 Neoadjuvant patients schedule of Assessments

	Screening	Baseline	Pre-Surgery Treatment Period					Surgery	Post-Surgery Treatment Period								Safety Follow-up	Follow-up visits
Day  (Treatment Cycle #)	-28 to 1	-7 to 1	Anthracycline containing regimens			Starting trastuzumab (+ taxanes)			Trastuzumab ± RT ± hormonal therapy								4 weeks after last study treatment	Continuing for 24 months after safety follow (months 6,12,18,24)
			A1	A2, A3	A4	1	2, 3, 4		5	6, 7, 8	9	10, 11, 12	13	14, 15, 16	17	18		
Explain study and obtain signed Informed Consent [a]	x																	
Demographics and medical history [b, c]	x																	
HER2 determination [d]	x																	
Review inclusion/exclusion criteria	x																	
Baseline Breast Cancer evaluation [e]	x																	
Vital signs, physical examination [f], weight, and height [g]	x	x	x	x	x	x	x		X	x	x	x	x	x	x	x		
ECOG performance status	x		x			x			x		x		x		x		x	x
Cardiac monitoring [h,p]																		
12-lead ECG	x					x			X		x		x		x		x	x
LVEF	x					x			X		x		x		x		x	x
Signs/symptoms	x					x			X		x		x				x	x

	Screening	Baseline	Pre-Surgery Treatment Period					Surgery	Post-Surgery Treatment Period								Safety Follow-up	Follow-up visits
Day (Treatment Cycle #)	-28 to 1	-7 to 1	Anthracycline containing regimens			Starting trastuzumab (+ taxanes)			Trastuzumab ± RT ± hormonal therapy								4 weeks after last study treatment	Continuing for 24 months after safety follow (months 6,12,18,24)
			A1	A2, A3	A4	1	2, 3, 4		5	6, 7, 8	9	10, 11, 12	13	14, 15, 16	17	18		
Pregnancy test [i]		x				x			x		x		x		x			x
Hematology and biochemistry [j]	x		x	x	x	x	x		x		x		x		x		x	
Biomarkers blood sample collection *			x*			x*			x*									
Tissue collection **		x						x										
Routine breast cancer follow-up [k]	x				x <sup>j</sup>	x <sup>j</sup>		x <sup>j</sup>	Assessment as per institutional practice or ASCO adjuvant follow-up Guidelines 2006 to be reported 6 monthly									
AEs and SAEs [l]	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x	x	x
Surgery including Pathological Response Assessment [o]								x										
Past and Concomitant medications [m]	x	x	x	x	x	x	x		X	x	x	x	x	x	x	x		x <sup>i</sup>
Anthracycline-containing regimen			x	x	x													
Taxane						x	x											
Trastuzumab [n]						x	x		x	x	x	x	x	x	x	x		

## Notes

- [a] Written Informed Consent must be obtained before any study-specific assessments or procedures are performed  
[b] Demographic data including date of birth, gender, and self-reported ethnic origin where permitted by local regulations  
[c] Breast cancer disease history, including ER/PgR status, prior anticancer treatments, current medications and symptoms  
[d] HER2-positivity is defined as immunohistochemistry (IHC)3+ or gene amplification by in situ hybridization (ISH)

[e] Baseline breast cancer evaluation to be completed within 4 weeks before protocol related chemotherapy treatment start, with the following exceptions: Screening radiological examinations to exclude metastatic disease (chest X-ray, liver ultrasound, bone scan) do not need to be repeated if completed within 8 weeks prior to the first chemotherapy administration; Bilateral Mammography do not need to be repeated if completed within 6 weeks prior to the first chemotherapy administration.

[f] Vital signs and physical examination including pulse, blood pressure, and body temperature are measured at Screening, at every treatment cycle, and at the Safety Follow-up visit

[g] Weight is measured at baseline, at every treatment cycle, at the Safety Follow-up visit, and at each visit during follow-up period. Height is only measured at Screening

[h] LVEF assessments by either ECHO or MUGA Scan: the same imaging technique should be used per patient throughout the study. Echocardiography should be the method of choice for these assessments. LVEF assessment is mandatory at Screening. During treatment, a 3-monthly assessment should be performed or as per institutional practice and immediately as per Section 5.1.3 in case of cardiac failure

[i] Applicable to women of childbearing potential (premenopausal or less than 12 months of amenorrhea post-menopause, and who have not undergone surgical sterilization); a serum pregnancy test needs to be completed within 7 days prior to the first dose of first administration of the protocol required chemotherapy treatment. Testing should be repeated every 3 months 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. Additional 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.

[j] Hematology: hemoglobin, white blood cells (WBC) and differential, absolute neutrophil count (ANC), platelet count. Biochemistry: creatinine, urea (BUN), SGPT (ALT), SGOT (AST), total bilirubin, alkaline phosphatase, glycaemia, albumin, sodium, potassium and calcium. Additional hematology and biochemistry tests may be performed as per institutional practice, but these data will not be collected

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

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

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

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

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

In neoadjuvant setting mammogram and ultrasound have to be performed at Screening and before surgery. After first sequence comprehensive of Anthracycline (4 cycles, on day 1 of first cycle of subsequent sequence) the mammogram is optional.

[l] After informed consent, but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention will be collected. Before study closure, all AEs/SAEs will be reported regardless of the study drug relationship. After study closure, all SAEs will be reported indefinitely regardless relationship to the drug. NCI-CTCAE version 4 should be used for AE coding. All SAEs, and AEs that are not resolved after the end of study, should be followed-up until resolution. See section 5.3.1 for AEs reporting period.

[m] All concomitant medications and prior treatments for BC must be reported in the eCRF starting at the Screening visit. The year of start and end date (when applicable) of the past and current concomitant treatments for BC, as well as the route and dose, will be collected when available. All concomitant medication will be recorded between the Screening and the Safety Follow-up visits. Thereafter, only medication applicable for long-term



reporting 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 SAEs that are applicable for long-term reporting (e.g., treatment of heart failure)

[n] Trastuzumab is administered subcutaneously at a fixed dose of 600 mg, 3-weekly for a total of at least 18 cycles/1 year (regardless of body weight) starting after first chemotherapy sequence based on anthracycline ( 4 cycles).

[o] Pathological Response assessment to be performed using the resected tumor according to guidelines provided

[p] Approximately 3-monthly (every 4 cycles) refers to pre-study treatment administration at: Cycle 5 (after 4 cycles of anthracycline based chemotherapy), Cycle 9 (after 4 cycles of taxane based chemotherapy plus trastuzumab SC), Cycles 13, 17 and 21 and at safety follow-up visit (4 weeks after last study treatment). Cardiac assessments at follow-up visits have to be performed at 6, 12, 18 and 24 months following treatment cessation.

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

\* Local Blood samples will be obtained at the following time points:

Adjuvant:

1. basal (Day 1-7);
2. after first sequence comprehensive of Anthracycline containing regimens (on Day 1 of first cycle of Taxane + trastuzumab SC administration)
3. end of chemotherapy treatment (on Day 1 of C 5 before starting administration of Trastuzumab alone)

Neoadjuvant:

- 1 basal (Day 1-7);
- 2 after first sequence comprehensive of Anthracycline containing regimens (on Day 1 of first cycle of Taxane + trastuzumab SC administration)
- 3 end of chemotherapy treatment (8 cycles, on Day 1 of first cycle of subsequent sequence)

\* \*Local: Tissue samples will be obtained at the following points:

Neoadjuvant:

- basal (Day 1-7);
- at surgery

Adjuvant:

- at surgery

### 3.4 Sample Size

The estimation of sample size is based on the LVEF rate that is a safety endpoint of primary interest.

The tables provide below shows the resultant confidence intervals for various sample sizes and various event rates, according to the assumptions derived by previous studies. Assuming an observed LVEF Grade  $\geq 1$  rate of 25%, a LVEF Grade  $\geq 2$  of 4% and a LVEF Grade  $\geq 3$  of 2% a sample size of 240 will produce a 95% confidence interval deemed sufficiently precise to draw valid conclusions around the event rate. Safety results within each treatment group will be useful for descriptive purpose. The estimation of the confidence intervals will be performed using SAS based on Clopper-Pearson methodology.

**Table 1** Clopper-Pearson 95% Confidence Intervals for the incidence of different LVEF Grade

Number of Patients	LVEF Grade: Estimated Incidence		
	$\geq 3$ : 2%	$\geq 2$ : 4%	$\geq 1$ : 25%
50	0.1% - 10.6%	0.5% - 13.7%	14.6% - 40.3%
190	0.6% - 5.3%	1.8% - 8.1%	19.3% - 32.1%
240	0.7% - 4.8%	2.0% - 7.5%	19.7% - 31.0%

### 3.5 Study Endpoints

- Primary Safety Endpoints include:
  - Incidence and severity by NCI CTCAE version 4.0 of AEs and serious adverse events (SAEs);
  - Incidence of AEs leading to premature discontinuation of study treatment;
  - Cardiac safety
    - Incidence of Cardiac AEs (detected by *MedDRA system organ class: Cardiac Disorders*);
    - Incidence of CHF (according to NCI CTCAE version 4.0 and New York Heart Association [NYHA] Classification);
    - Change of LVEF over time. In the event of an asymptomatic decline in LVEF, an algorithm (see appendix 1 in this SAP) will be used to determine whether to continue trastuzumab SC treatment;
- Secondary Safety Endpoints include:
  - Exposure to study medication (overall and by cycle)
  - Duration of treatment period (days and cycles)
  - Duration of safety follow-up (days)
  - ECOG
  - Concomitant medication
  - Vital sign, physical examination and laboratory parameters

- Premature withdrawals and major protocols violation
- Secondary Efficacy Endpoints include:
  - DFS and OS
  - incidence of pathological Complete Response in breast and nodes (pCR) (ypT0-is ypN0). Residual in situ disease (ypTis) is considered as pCR (for the neo-adjuvant setting the activity of two sequential drug regimens).
  - Patients (using SID) and HCP satisfaction derived from questionnaires
- Secondary Explorative Endpoints include:
- for the E542K, E545K, H1047R gene expressions
  - frequency and percentage of the gene mutation in tumor tissue (baseline and Cycle 5) and in circulating free DNA (baseline, Cycle 1 and Cycle 5);
  - evaluation the agreement between the PI3K mutation assessment in tumor tissue and in circulating free DNA at baseline and at Cycle 5;
- for the most frequent gene expression
  - correlation, using univariate and multiple generalized linear model, of baseline mutation status (in tumor tissue and cfDNA) with clinical outcome (pathological response to treatment in the neoadjuvant arm).
  - correlation, using univariate and multiple generalized linear model, of pharmacodynamic change of the cfDNA before and after treatment with clinical outcome,

### 3.6 Study Visits

For each patient, the day of first Anthracycline administration will be considered study day 1.

Each assessment will be assigned a study day calculated as follows:

- If the date of assessment < date of study day 1 then
  - study day = (date of assessment – date of study day 1)
- If the date of assessment ≥ date of study day 1 then
  - study day = (date of assessment – date of study day 1) +1

In the same way reported above it is defined the day of first Trastuzumab SC administration, considered as study treatment day 1.

Each assessment will be assigned a study day calculated as follows:

- If the date of assessment < date of study treatment 1 then
  - treatment day = (date of assessment – date of treatment day 1)
- If the date of assessment ≥ date of study day 1 then
  - treatment day = (date of assessment – date of treatment day 1) +1

All efficacy and safety data will be listed as recorded on the CRF, sorted by site identifier, patient identifier, cycle identifier/study day/treatment day.

### 3.7 Randomization

Not applicable for this protocol. This is a non-randomized study.

## 4 Study Analysis Populations

Agreement and authorization of subjects included/excluded from each analysis set will be conducted prior to the database lock of the study.

There will be four populations defined for the study analyses. Other analysis populations may be defined based on more restrictive criteria, such as fulfilment of eligibility criteria or a minimum duration of the observation period. Such populations will be defined prior to the primary reporting event.

#### 4.1.1 Intent to treat Population (ITT)

The intent-to-treat (ITT) population will contains all enrolled patients.  
All baseline summaries will be based on the ITT.

#### 4.1.2 Modified Intent to treat Population (m-ITT)

The modified-Intent-to-Treat (m-ITT) population will be defined as all enrolled patients satisfying inclusion and exclusion criteria for eligibility. All efficacy analyses will be based on the m-ITT population.

#### 4.1.3 Safety Population (SAF)

The safety population will consist of all enrolled patients who received at least one dose of any study medication (trastuzumab). The Safety population will be the primary population used for safety analysis and summaries.

#### 4.1.4 Explorative Population (EXP)

The explorative population will consist of all enrolled patients belongs to neo-adjuvant setting who meet al inclusion and exclusion criteria for eligibility and received at least one dose of study medication (trastuzumab). The Explorative population will be the primary population used for the analysis of the translational study (explorative analysis).

#### 4.1.5 Patient Satisfaction Questionnaire Population (PSQ)

The Patient Satisfaction Questionnaire Population will consist of all enrolled patients belongs to Cohort B (use of Trastuzumab SC SID), who will be able to use SID, who will complete a minimum of 14 administrations of trastuzumanb SC using SID (at least 10 self- administered).

#### 4.1.6 Health Care Professional Questionnaire Population (HCPQ)

The Health Care Professional Questionnaire Population will consist of all Investigators and study nurses that will complete the questionnaire at each site when at least 4 patients from their site have received at least 5 cycles of adjuvant study treatment. For that recruit <4

patients, the investigators and a study nurses will each complete an HCPQ when the last patient at their site has received at least 5 cycles of study treatment.

## 4.2 Withdrawn Patients

Patients have the right to withdraw from the study at any time for any reason. Those who withdraw from the study will not be replaced.

## 4.3 Blinding

Not applicable. This study is open label.

# 5 Statistical Methodology

## 5.1 Data Quality Assurance

The data for this study will originate from a number of individual local studies and, once combined, will be stored in a global database in the form of SAS datasets. Data from this study will be transcribed by the site from the paper source documents to the eCRF (IDAS database). From the eCRF the data will be entered into database and from there, the pre-specified core data will be transferred to the central global Umbrella database. A comprehensive validation check has to be performed at the site to assure appropriate data quality.

## 5.2 Subgroups

Results, including demographic, patient characteristics, safety and efficacy, may be reported for individual subgroups, in addition to the analysis populations described above. Possible subgroups are listed below. The first list is defined at the patient level where each patient is either in or out of each subgroup. The second list is defined at the cycle level where patients can contribute to such a subgroup for one cycle but may not for a subsequent cycle.

Patient level subgroups (defined at time of enrolment):

- neo-adjuvant
- adjuvant

Cycle level subgroups:

- trastuzumab SC monotherapy
- trastuzumab SC combination therapy
- trastuzumab SC administered using vial
- trastuzumab SC administered using SID

The incidence of AEs, SAEs, AEs leading to premature discontinuation, specific cardiac AEs and SAEs will be analysed by taking into account the following subgroup:

- severity
- relation to study drug

There will be no adjustment for multiplicity of endpoints or within subgroup comparisons.

The decision on the subgroups and endpoints to be analysed will be made prior to the time of analysis based on considerations such as the number of patients in subgroups of interest.

### 5.3 Analysis Timing

The following analyses have been/will be performed for this study:

- Interim Analysis performed by the Global group and presented in Copenhagen at ESMO Congress.

Title of presented abstract is: 210P - An open-label, multinational, multicentre, phase IIIB umbrella study of subcutaneous trastuzumab with or without chemotherapy or pertuzumab in patients with HER2-positive early or metastatic breast cancer (UmbHER1):

Interim safety results from early breast cancer studies) patients enrolled by 27th November 2015 were included (719 of patients globally involved - 228 patients from ML28879)

All patient visits (treatment, unscheduled, end of study, withdrawal, follow up, AE, concomitant medications) that took place up to 27<sup>th</sup> November 2015 were included into the Interim Analysis.

- Primary Analysis

The primary analysis will be undertaken once all patients have completed the study (treatment phase and 28-days safety follow-up visit). A selection of tables, figures and listings will be presented for the primary analysis.

- Final Analysis

All final, planned analyses identified in this SAP will be performed following Sponsor Authorization of this Statistical Analysis Plan, Database Lock and Sponsor Authorization of Analysis Sets.

### 5.4 Baseline and Demographic Characteristics

Baseline, is defined as the last scheduled non-missing measurement taken prior to the first administration of any study drug.

All screening/baseline and demographic characteristics will be listed and/or summarised for the ITT population. Included will be:

- date of birth
- sex
- race
- ethnicity
- female reproductive status
- inclusion/exclusion criteria
- medical history and breast cancer history (including Stage/Pathological Stage TNM, Histological examination/subtype, Diagnostic Procedures)
- HER2 evaluation (Immunohistochemistry (IHC), In situ hybridization (ISH))
- physical examination
- vital signs (including: height, weight, body mass index (BMI), body surface area (BSA), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, temperature)
- ECOG
- radiological examination
- cardiac monitoring (12-lead ECG and LVEF examination)
- physical examination
- laboratory examination (haematology and biochemistry)
- baseline pregnancy test result will be summarised for females of child bearing potential

In general, continuous data will be summarized using: number of cases, mean, standard deviation, median, and range. Whereas, discrete data will be summarized using frequency counts and percentages.

Age will be calculated as the integer:  $((\text{date of consent} - \text{date of birth}) / 365.25)$ . If day of birth is missing it will be replaced with the 1st of the month; if the month is missing it will be replaced with January.

Medical history will be coded using MedDRA (the latest available version) and summarised by body system and preferred term.

## 5.5 Safety Analysis

Safety is the primary endpoint of this protocol. All safety variables will be presented for the safety population.

All AEs and laboratory variables will be assessed according to the National Cancer Institute Common Terminology Criteria for AEs (NCI CTC-AE) version 4.0 grading system. Cardiac AEs will additionally be graded using the NYHA class (I, II, III or IV).

### 5.5.1 Adverse events

Incidence of AEs will be presented for the entire study duration. Additionally, selected tables will be presented by subgroups as specified in section 5.2.

Both Treatment Emergent Adverse Events (TEAE - starting on the day of or after first administration of study drug (trastuzumab) and within 28 days after last study drug) and AE for the safety follow-up period (starting after last study drug and continuing to study end) will be

included in the summary tables. The general rule is that where an AE starts date is partially or fully missing, and it is unclear as to whether the AE started after the start of the study, it will be assumed to be on-study.

AEs and SAEs occurring prior to the first drug administration will be listed only.

For summaries by subgroup, an AE will be assigned to a specific study drug administration subgroup if it occurred on or after the first dose by that administration method and prior to the first (subsequent) date of a treatment by another administration method. If there is no subsequent treatment by another route then a 35 day cut off will be applied. Where an AE start date is partially or fully missing, and it is unclear to which subgroup the AE should be assigned, the AE will be assigned to all relevant subgroups.

Tables of nonserious adverse events (excluding any SAEs), organized by SOC, then preferred term, that occurred at a frequency of  $\geq 5\%$  in any treatment group, will be presented for TEAE and Related TEAE, with the following details:

- Total number of patients experiencing at least 1 nonserious AE by treatment group/arm, applying the 5% threshold;
- Number of PATIENTS with each nonserious AE preferred term by treatment group/arm.

Endpoints related to adverse events (incidence and severity), serious adverse events (incidence and severity), incidence of TEAEs/AEs that leading to premature discontinuation of study treatment, incidence of Cardiac TEAEs/AEs (detected by MedDRA system organ class: Cardiac Disorders), incidence of CHF (according to NCI CTCAE version 4.0 and New York Heart Association [NYHA] Classification) and Change of LVEF over time will be summarised by presenting the number and percentage of patients having any event. The proportions of patients experiencing the following will be summarised:

- Any adverse event
- Any serious adverse event
- Grade 3+ CHF
- Any administration associated reaction [defined in Appendix 2 Administration Associated Reactions2]
- Any adverse event by CTC grade (1, 2, 3, 4)
- Any serious adverse event by CTC grade (1, 2, 3, 4)
- Cardiac adverse events
- Cardiac serious adverse events
- Any cardiac adverse event by NYHA class (I, II, III, IV)
- Any serious cardiac adverse event by NYHA class (I, II, III, IV)
- Adverse events leading to discontinuation
- Serious adverse events leading to discontinuation

Summary tables by system organ class (SOC) and preferred term of the number and percentage of patients having events will be presented using the following displays:

- overall
- related AEs only
- by maximum intensity (CTC grade)



- by maximum class (NYHA classification) [for cardiac adverse events only]
- by anthracycline/taxane/trastuzumab administration [for Grade 3+ and of suspected cardiac origin AEs only]
- within/more than 28 days prior to the first trastuzumab administration [of suspected cardiac origin AEs only]
- by planned chemotherapy regimen [for Grade 3+ and of suspected cardiac origin AEs only]

The above outputs will be repeated for:

- all AEs
- Grade 3+ AEs (table by CTC grade not required)
- all SAEs
- Grade 3+ SAEs (table by CTC grade not required)
- all Administration Associated Reactions
- AEs of suspected cardiac origin (intensity summaries repeated for NYHA Class)
- AEs symptomatic of left ventricular systolic dysfunction (intensity summaries repeated for NYHA Class)
- AEs resulting in LVEF decrease (intensity summaries repeated for NYHA Class)
- SAEs of suspected cardiac origin (intensity summaries repeated for NYHA Class)
- SAEs symptomatic of left ventricular systolic dysfunction (intensity summaries repeated for NYHA Class)
- SAEs resulting in LVEF decrease (intensity summaries repeated for NYHA Class)
- AEs leading to study drug discontinuation
- AEs leading to study drug dose modification
- AEs leading to chemotherapy discontinuation
- AEs leading to chemotherapy dose modification
- AEs leading to death

Within a single summary table, patients with more than one occurrence of the same adverse event in a particular system organ class/preferred term will be counted only once in the total of those experiencing adverse events in that particular system organ class/preferred term.

Adverse events will also be summarised by relationship and by maximum CTC grade, where each patient's maximum CTC grade will be used in the summary. If a patient experiences the same adverse event at more than one CTC grade level, or with more than one relationship to study drug, the most severe rating or the stronger causal relationship to study drug will be given precedence. Any missing CTC grade, causality, or outcome will not be imputed but classed as unknown.

Related refers to those events that there is a reasonable suspected causal relationship to the study drug, or with an unknown relationship.

Adverse events will be coded using MedDRA (the latest available version) and all other information collected will be listed as appropriate.

### Deaths

A summary of deaths will be presented, tabulating the number and percentage of patients by primary cause of death and relationship to study drug. An AE and SAE summary of events with an outcome of death will be presented.

### Length of Time on Study

Length of time on study is defined as time from first study drugs dose (should be expected Anthracycline for both arms) to patient's last assessment.

Length of Study = (date of last assessment – date of first dose + 1) / 30.4375

[where 30.4375 = average number of days per month = 365.25/12]

Kaplan-Meier (KM) estimates of the median time to event and the corresponding two-sided 95% confidence interval will be presented along with the estimates for the 25th and 75th percentiles and the associated ranges (minimum, maximum). The survivor function will be displayed graphically using a Kaplan-Meier curve.

### **5.5.2 Previous and Concomitant Treatments**

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

The incidence of prior medications and of concomitant medications will be presented by preferred drug name. All medications other than study drugs will be summarised in this fashion.

Prior medications and of concomitant medications will be also presented for those patients with abnormality finding in ECG or LVEF at screening.

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

Previous and Concomitant Treatments will be presented for the ITT population and coded using WHO-DRL dictionary (the latest available version). Previous and Concomitant Treatments will be summarized by primary therapeutic subgroup (3rd level ATC code) and generic name.

### **5.5.3 Laboratory findings**

Results from the following laboratory parameters will be summarised for the safety population:

#### Haematology:

Haemoglobin, white blood cell (WBC) count and differential, and absolute neutrophil count (ANC) and platelet count.

#### Biochemistry:

Creatinine, blood urea nitrogen (BUN), urea, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), total bilirubin, glucose, alkaline phosphatase (ALP), albumin, sodium, potassium, calcium.

The following summaries will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements);
- Shift from baseline according to normal range criteria (for quantitative measurements and categorical measurements) according to the following classification: within normal range, below the normal range and above the normal range (Low/Normal/High)

#### Notes:

The data will be presented in the SI units (Appendix 3).

#### 5.5.4 Vital Signs

Vital signs and physical parameters will be summarised over time (including change from baseline) using descriptive statistics.

The following Vital Signs/physical parameters measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart Rate (bpm)
- Weight (kg)
- Height (cm) – only at screening/baseline
- BSA (m<sup>2</sup>) – calculated on the basis of Du Bois Du Bois formula as  $(\text{weight}^{0.425} \times \text{height}^{0.725}) \times 0.007184$

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit (for quantitative measurements)

#### 5.5.5 Pregnancy Tests

Pregnancy test results throughout the study will be listed only. Baseline results are summarised as part of demography and baseline characteristics.

#### 5.5.6 ECG

Abnormal results at each visit will be listed only.

#### 5.5.7 LVEF

LVEF percentage will be summarised over time (including change from baseline) using descriptive statistics. Categorical findings will also be summarised over time.

A comparison between Investigator's assessment of normality on LVEF percentage and assessment definition as per protocol will be performed over time.

As per protocol, LVEF percentage is assessed as "abnormal" if:

- LVEF (%)  $\leq$  44%

OR

- LVEF (%) between 45% and 49% with a baseline change of more than 10%.

If LVEF(%) is greater than or equal to 50%, normality is assessed.

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

#### 5.5.8 ECOG Performance Status

ECOG performance status (Grade 0 - Grade 5) will be summarised by visit by presenting the number and percentage of patients in each category.

### 5.5.9 Physical Examination

Abnormal results at each visit will be listed only.

## 5.6 Efficacy Analysis

The efficacy outcome measures of this study will be to collect data for subcutaneous administration of trastuzumab in the treatment of HER2-positive eBC and LABC. The efficacy analysis will be performed on the m-ITT population and will be presented by cohort (Cohort A: Trastuzumab SC 600 mg/5ml VIALS; Cohort B: Trastuzumab SC 600 mg/5ml SID) and groups (Group 1: Adjuvant chemotherapy and trastuzumab SC; Group 2: Neoadjuvant chemotherapy and trastuzumab SC.). No formal hypothesis testing, to evaluate the difference between cohorts/groups, is planned.

### 5.6.1 Overall Survival

Overall Survival (OS) is defined as time from first study drugs dose (should be expected Anthracycline for both arms) to death from any cause. Patients who have not died will be censored on the date they were last known to be alive. Time will be calculated in months as follows:

$$OS = (\text{date of death} - \text{date of first dose} + 1) / 30.4375$$

[where 30.4375 = average number of days per month = 365.25/12]

Kaplan-Meier (KM) estimates of the median time to event and the corresponding two-sided 95% confidence interval will be presented along with the estimates for the 25th and 75th percentiles and the associated ranges (minimum, maximum). The survivor function will be displayed graphically using a Kaplan-Meier curve.

A life-table of the number and percentage of patients who died and those at risk in 3-monthly time periods will also be presented.

### 5.6.2 Disease-free Survival

Disease free Survival (DFS) is defined as time from first study drugs dose (should be expected Anthracycline for both arms) to local, regional or distant recurrence or death from any cause (whichever occurs first). Patients who have neither had a recurrence nor died will be censored on the date of their last visit. Time will be calculated in months as follows:

$$DFS = (\text{date of recurrence/death} - \text{date of first dose} + 1) / 30.4375$$

Kaplan-Meier (KM) estimates of the median time to event and the corresponding two-sided 95% confidence interval will be presented along with the estimates for the 25th and 75th percentiles and the associated ranges (minimum, maximum). The survivor function will be displayed graphically using a Kaplan-Meier curve.

A life-table presenting the number and percentage of patients in each category (local recurrence, regional recurrence, distant recurrence, contralateral breast cancer, second non-breast malignancy and death) and the number at risk in 3-monthly time periods will also be presented.

### 5.6.3 Pathological Complete Response (pCR)

The incidence of pCR in breast and nodes (ypT0-is ypN0), in Neoadjuvant group only, will be presented as proportion with relative 95% confidence interval.

#### **5.6.4 Patients (using SID) and HCP satisfaction derived from questionnaires**

Patient Satisfaction will be assessed by Patient Satisfaction Questionnaire only in Cohort B (use of Trastuzumab SC SID) and Health Care Professional (HCP) satisfaction will be assessed by a Health Care Professional Questionnaire (HCPQ).

Answers will be summarized using frequency counts and percentages. Open questions will not be summarized.

### **5.7 Explorative Analysis**

For the explorative analysis, the association of PI3K mutation status at baseline and pCR (only for the neoadjuvant arm) will be assessed by means of a univariate and multiple generalized linear model, with binomial link function, where the odds of pCR will be modelled as function of the marker and adjusted by baseline factors relative to tumor and patients characteristics. The best model will be selected by means of stepwise procedure. The cut-off value for statistical significance will be set  $\alpha=0.05$  two tails.

Also, the association between the pharmacodynamics change of the PI3K mutation assessment in cfDNA, pre and post treatment, and pCR will be performed as described above.

An association between PI3K mutation assessment in tumor tissue collected at baseline (gold standard) and in cfDNA (experimental) will be performed by means of the Pearson Correlation.

Incidence of pathological complete response (pCR) of invasive tumor in breast and axilla. Patients progressed under treatment or for which surgery will not be feasible at the end of treatment will be considered as not having achieved a pCR.

The data will also be analysed in subgroups defined, according to study design, patient population, and other relevant factors.

### **5.8 Disposition of Patients**

The following will be summarised for the safety, ITT and m-ITT populations:

- number and percentage in each analysis population
- number and percentage completing treatment (Yes, No)
- number and percentage completing follow-up (Yes, No)
- reasons for discontinuation of treatment and follow-up

The number and percentage of screen failures overall and by reason for failure will be presented

## 5.9 Exposure

Exposure will be summarised as set out in the following sections using the safety population.

### 5.9.1 Extent of Exposure to Trastuzumab SC

Exposure to trastuzumab SC will be summarised overall and also within each of the study drug related subgroups listed in section 5.2.

The total number of cycles received will be summarised both by descriptive statistics and frequency counts. Trastuzumab SC will be counted as being taken within a cycle if any dose administered during that cycle.

Trastuzumab SC administration details will be summarised by cycle and overall and will include, duration of injection, dose injected, percentage of injections delayed (by reason), vial /SID, and administrator (self / HCP, only over time).

Summary statistics, overall and by cycle for the Actual Total Dose Delivered (mg), Dose Intensity (mg/kg/week), and Relative Dose Intensity (%) will be presented and calculated as follow:

**Actual Total Dose Delivered (mg)** = sum over all cycles of actual dose received (mg).

**Dose Intensity: DI (mg/kg/week)** = [Actual Total Dose Delivered (unit/kg)/Duration of exposure (week)].

**Planned Dose Intensity: PDI (mg/kg/week)** = [Sum of planned doses (mg/kg)/Duration of exposure (week)]. Planned dose intensity (PDI) will be the assigned dose per week planned to be given to patients as per protocol.

**Relative Dose intensity: RDI (%)** = [DI (mg/kg/week) / PDI (mg/kg/week)] x 100

### 5.9.2 Extent of exposure to other non-study drug medications

Exposure to other treatments given for eBC other than trastuzumab SC will be summarised overall.

The following medications will be summarised with the total n for each being defined as the number of patients receiving at least one dose of the medication in question:

- doxorubicin
- epirubicin
- cyclophosphamide
- fluorouracil
- docetaxel

For these medications the total number of cycles received will be summarised both by descriptive statistics and frequency counts. Dose and delays will be summarised by cycle and overall. The following medications are collected for the study period rather than by cycle:

- hormone therapy
- radiotherapy
- chemotherapy

Daily dose of hormone therapy will be summarised by treatment. Total dose of radiotherapy will be summarised overall and by site. Total dose per cycle of chemotherapy will be summarised by treatment.

Other non-study drug medications will be presented for the ITT population and coded using WHO-DRL dictionary (the latest available version). These medications will be summarized by primary therapeutic subgroup (3rd level ATC code) and generic name.

### **5.10 Survival Follow-up**

The length of time patients were on study (last visit date – informed consent date + 1) will be summarised overall using ITT population.

In addition a reverse Kaplan Meier curve will be constructed using the overall survival data where deaths will be censored and the original censored observations will count as events. This will give a good indication of median follow-up.

### **5.11 Protocol Violations**

Patients who meet any of the following criteria will be summarised, listed and presented in the study report:

- non-compliance with inclusion criteria
- non-compliance with exclusion criteria
- non-compliance with study medication
- use of disallowed concomitant medication

The following treatment are not permitted:

- Concurrent treatment with other systemic HER2-directed immunotherapy
- Concurrent investigational agents of any type
- Hormonal treatment concomitant with neoadjuvant chemotherapy (even with the purpose of fertility preservation).
- Other chemotherapy regimens than those specified at paragraph 3.1 of the Protocol.

Full details of these criteria will be finalised prior to the primary analysis time point.

## **5.12 Missing Values – Missing Visits**

Missing, unused and spurious data will be dealt with as such. There is no intention to implement any procedure for replacing missing data.

## **5.13 Deviations from SAP**

Any deviations from the original statistical plan will be described and justified in the final clinical study report.



## 6 Tables and Listings

### 6.1 Table Format

All output will be produced using SAS version 9.4 or a later version.

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

The last row(s) of footnotes will contain the following information:

- SAS program name
- the date and time of creation of table/listing

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

In listings every effort will be made to contain a patient's data to a single page. In the case that a patient's record has to be continued to the next page, an appropriate identification (e.g., the patient ID number) must be presented at the beginning of that page.

### 6.2 Conventions

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

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

Summaries will generally be based on non-missing data with the number of patients with missing data also presented. To this end, the number of patients contributing to the summaries plus the number with missing data should add to the top-line 'N' for the table.

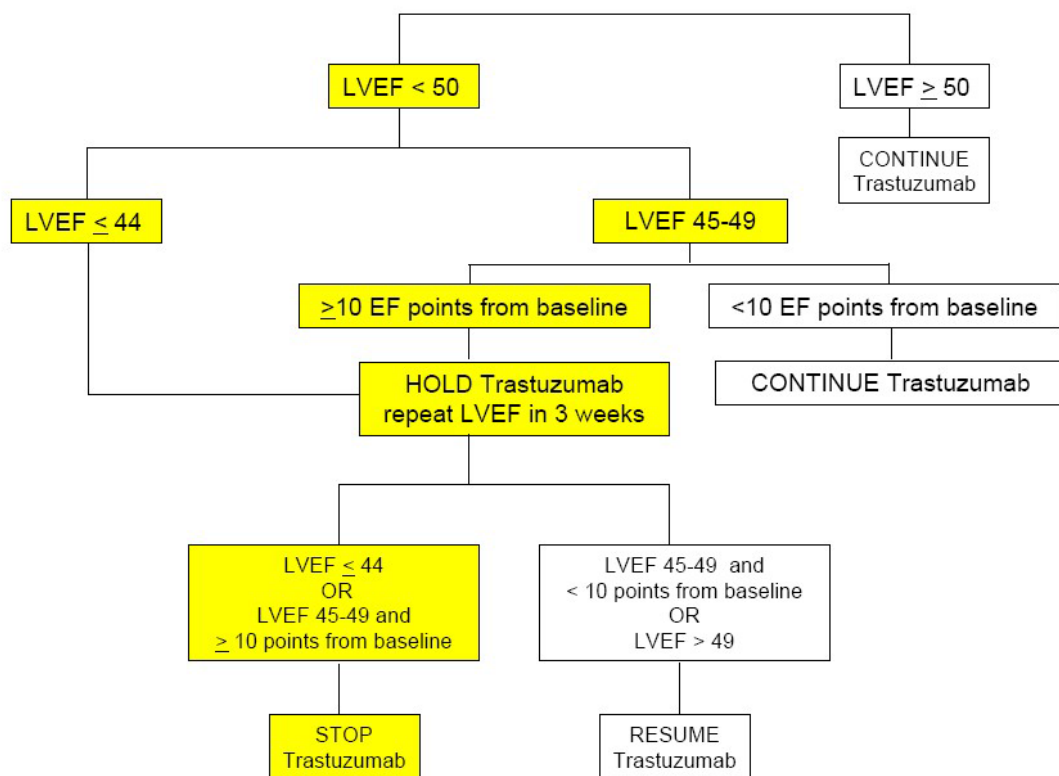
P-values, if applicable, will be presented to 4 decimal places. If the p-value is less than 0.0001 then it will be presented as <.0001. If the rounded result is a value of 1.000, it will be displayed as >.9999. Any date information in the listing will use the *date9.* format, for example, 07MAY2002. In the listing, a unit associated with a variable will be presented only once within parentheses either below or next to that variable in the heading portion.

Listings should be sorted by treatment group, patient and visit.

### 6.3 References

None.

# APPENDIX 1 Algorithm for continuation and discontinuation of trastuzumab SC or IV based on LVEF assessment in asymptomatic patients



## Appendix 2 Administration Associated Reactions

Defined using Standardised MedDRA Query (SMQ20000021w). The following preferred terms are defined as Administration Associated Reactions (note that this list may be updated with future MedDRA releases):

ACUTE RESPIRATORY FAILURE	CYANOSIS
ALLERGIC OEDEMA	DIASTOLIC HYPOTENSION
ANAPHYLACTIC REACTION	DRUG HYPERSENSITIVITY
ANAPHYLACTIC SHOCK	DYSPNOEA
ANAPHYLACTIC TRANSFUSION REACTION	ERYTHEMA
ANAPHYLACTOID REACTION	EYE OEDEMA
ANAPHYLACTOID SHOCK	EYE PRURITUS
ANGIOEDEMA	EYE SWELLING
ASTHMA	EYELID OEDEMA
BLOOD PRESSURE DECREASED	FACE OEDEMA
BLOOD PRESSURE DIASTOLIC DECREASED	FIRST USE SYNDROME
BLOOD PRESSURE SYSTOLIC DECREASED	FIXED ERUPTION
BRONCHIAL OEDEMA	FLUSHING
BRONCHOSPASM	GENERALISED ERYTHEMA
CARDIAC ARREST	HYPERSENSITIVITY
CARDIO-RESPIRATORY ARREST	HYPERVENTILATION
CARDIO-RESPIRATORY DISTRESS	HYPOTENSION
CARDIOVASCULAR INSUFFICIENCY	INFUSION RELATED REACTION
CHEST DISCOMFORT	INJECTION SITE HYPERSENSITIVITY
CHOKING	INJECTION SITE URTICARIA
CHOKING SENSATION	KOUNIS SYNDROME
CIRCULATORY COLLAPSE	LARYNGEAL DYSPNOEA
CIRCUMORAL OEDEMA	
COUGH	
LARYNGEAL OEDEMA	REVERSIBLE AIRWAYS OBSTRUCTION
LARYNGOSPASM	SENSATION OF FOREIGN BODY
LARYNGOTRACHEAL OEDEMA	SHOCK
LIP OEDEMA	SKIN SWELLING
LIP SWELLING	SNEEZING
NASAL OBSTRUCTION	STRIDOR
OCULAR HYPERAEMIA	SWELLING
OEDEMA	SWELLING FACE
OEDEMA MOUTH	SWOLLEN TONGUE
OROPHARYNGEAL SPASM	TACHYPNOEA
OROPHARYNGEAL SWELLING	THROAT TIGHTNESS
PERIORBITAL OEDEMA	TONGUE OEDEMA
PRURITUS	TRACHEAL OBSTRUCTION
PRURITUS ALLERGIC	TRACHEAL OEDEMA
PRURITUS GENERALISED	TYPE I HYPERSENSITIVITY
RASH	UPPER AIRWAY OBSTRUCTION
RASH ERYTHEMATOUS	URTICARIA
RASH GENERALISED	URTICARIA PAPULAR
RASH PRURITIC	WHEEZING
RESPIRATORY ARREST	
RESPIRATORY DISTRESS	
RESPIRATORY FAILURE	

## Appendix 3

### Laboratory Specific Derivations

To convert from the conventional unit to the SI unit, **multiply** by the conversion factor:

Parameter	Conventional Unit	Conversion Factor	SI Unit
Hematology			
Hemoglobin	g/dL	10	g/L
WBC count	$\times 10^3/\mu\text{L}$	1	$\times 10^9/\text{L}$
Neutrophils	$\times 10^3/\mu\text{L}$	1	$\times 10^9/\text{L}$
Eosinophils	$\times 10^3/\mu\text{L}$	1	$\times 10^9/\text{L}$
Lymphocytes	$\times 10^3/\mu\text{L}$	1	$\times 10^9/\text{L}$
Monocytes	$\times 10^3/\mu\text{L}$	1	$\times 10^9/\text{L}$
Basophils	$\times 10^3/\mu\text{L}$	1	$\times 10^9/\text{L}$
Other cells	tbd	tbd	tbd
Platelets count	$\times 10^3/\mu\text{L}$	1	$\times 10^9/\text{L}$
Biochemistry			
Creatinine	mg/dL	76.25	$\mu\text{mol/L}$
Glucose	mg/dL	0.0555	mmol/L
Albumin	g/dL	10	g/L
BUN	mg/dL	0.357	mmol/L
Urea	mg/dL	0.357	mmol/L
ALP	U/L	1	U/L
ALT	U/L	1	U/L
AST	U/L	1	U/L
Sodium	mEq/L	1	mmol/L
Calcium	mg/dL	0.25	mmol/L
Potassium	mEq/L	1	mmol/L

## APPROVAL SIGNATURES

Study Biostatistician:	Name: [REDACTED] Title: [REDACTED]		[REDACTED]
	[REDACTED]		[REDACTED]
	Signature		Date
Reviewer:	Name: [REDACTED] Title: [REDACTED]		
	[REDACTED]		[REDACTED]
	Signature		Date
Approved by:	Name: [REDACTED] Title: [REDACTED] - Italy		
	[REDACTED]		[REDACTED]
	Signature		Date
Approved by:	Name: [REDACTED] Title: [REDACTED] - Italy		
	[REDACTED]		[REDACTED]
	Signature		Date