SYNOPSIS OF RESEARCH REPORT [redacted]

(PROTOCOL BO22227)

COMPANY: F. Hoffmann – La Roche Ltd NAME OF FINISHED PRODUCT: Herceptin® NAME OF ACTIVE SUBSTANCE(S): Trastuzumab	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Protocol BO22227 - A phase III, randomized, open-label study to compare pharmacokinetics, efficacy and safety of subcutaneous (SC) trastuzumab with intravenous (IV) trastuzumab administered in women with HER2-positive early breast cancer (EBC). Research Report [redacted] January 2012.		
INVESTIGATORS / CENTERS AND COUNTRIES	81 centers in 24 countries (Brazil 6 centers, Canada 1, China 1, Colombia 3, Czech 2, Estonia 1, France 5, Germany 8, Guatemala 1, Hungary 3, Italy 3, Korea 3, Mexico 1, Panama 1, Peru 5, Poland 3, Russia 10, Slovakia 2, South Africa 4, Spain 5, Sweden 2, Taiwan 4, Thailand 4, Turkey 3) **Principal Investigators:** [redacted], Germany [redacted] Brazil		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	October 19, 2009-July 12, 2011 (1st patient randomized-clinical cut-off)	CLINICAL PHASE	III
OBJECTIVES	**Primary Objectives** To compare the following parameters between trastuzumab IV and trastuzumab SC in the neoadjuvant setting: • Serum trough concentrations (C_{trough}) observed pre-surgery • Efficacy (pathological complete response, pCR) **Secondary Objectives** To compare the following parameters between trastuzumab IV and trastuzumab SC: • Observed C_{trough} concentrations post-surgery • Predicted C_{trough} concentrations pre-surgery and post-surgery • Pharmacokinetic (PK) profile		

	To evaluate the following parameters in the trastuzumab IV and trastuzumab SC arm: total pathological complete response (tpCR), overall response rate (ORR), time-to-response (TTR), event-free-survival (EFS), overall survival (OS), safety and tolerability, immunogenicity
STUDY DESIGN	Randomized, open-label multi-center Phase III trial in the neoadjuvant setting
NUMBER OF SUBJECTS	596 patients: 299 patients randomized to the trastuzumab IV arm and 297 patients in the trastuzumab SC arm
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	1. Patients had to sign and date an informed consent form 2. Female 3. Age ≥ 18 years 4. Non-metastatic primary invasive adenocarcinoma of the breast which was clinical stage I (T1, N0, M0) to IIIC (any T, N3, M0) including inflammatory and multicentric/multifocal breast cancer a. with tumor size ≥ 1 cm by ultrasound or ≥ 2 cm by palpation b. histologically confirmed c. centrally confirmed HER2-positive (immunohistochemistry [IHC] 3+ or in situ hybridization [ISH]+) 5. At least one measurable lesion in breast or lymph nodes (≥ 1 cm by ultrasound or ≥ 2 cm by palpation), except for inflammatory carcinoma (T4d) 6. Performance status Eastern Cooperative Oncology Group (ECOG) of 0 or 1 7. Baseline left ventricular ejection fraction (LVEF) ≥ 55% measured by echocardiography or multiple-gated radionuclide angiography (MUGA) scan prior to first dose of trastuzumab
TRIAL DRUG / STROKE (BATCH) No.	Neoadjuvant trastuzumab plus neoadjuvant chemotherapy (docetaxel followed by 5-fluorouracil, epirubicin, cyclophosphamide), then adjuvant trastuzumab up to 1 year. Batch details within the clinical study report.
DOSE / ROUTE / REGIMEN / DURATION	• Trastuzumab SC: fixed dose of 600 mg SC irrespective of the patient's body weight was administered every three weeks throughout the treatment phase • Trastuzumab IV: loading dose of 8 mg/kg infused over a 90-min period. All subsequent doses were 6 mg/kg and these could be administered over a 30-min period if the first administration was well-tolerated • Docetaxel (75 mg/m^2 IV infusion) after completion of trastuzumab administration, every 3 weeks for 4 cycles • FEC: 5-Fluorouracil (500 mg/m^2 IV bolus or infusion), epirubicin (75 mg/m^2 IV bolus or infusion) and cyclophosphamide (500 mg/m^2 IV bolus or infusion), every 3 weeks for 4 cycles.

REFERENCE DRUG / STROKE (BATCH) No.	Trastuzumab IV is given as detailed above
PHARMACOKINETICS:	C_{trough} at pre-Cycle 8 and pre-Cycle 13, maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the serum concentration-time curve (AUC)
EFFICACY:	**Primary parameter:** pathological complete response (pCR in breast) **Secondary parameters:** tpCR, ORR, TTR, EFS, OS
SAFETY:	Adverse events (AEs) graded according to NCI-CTCAE version 3.0 criteria (Grade 1 to 5), serious adverse events (SAEs), laboratory parameters, vital signs, left ventricular ejection fraction and ECG, deaths, withdrawals and anti-drug antibodies testing.
STATISTICAL METHODS	**Pharmacokinetics:** The geometric mean ratio C_{trough}SC/C_{trough}IV of the SC dose of trastuzumab relative to the IV dose was estimated together with the 90% confidence interval. Non-inferiority was concluded if the lower bound of the confidence interval was equal or greater than 0.8. All pharmacokinetic variables were presented by descriptive summary statistics including arithmetic mean, median, range, standard deviation and coefficient of variation. **Efficacy:** Non-inferiority in pCR rate was concluded if the lower limit of one-sided 97.5% confidence interval using the the method of Anderson and Hauck (1986) for the difference in pCR rate is greater than -12.5. All efficacy variables were summarized by descriptive statistics. Exploratory analyses including multiple logistic regressions on pCR were performed. **Safety:** parameters were analyzed descriptively.

PHARMACOKINETIC RESULTS:

The results for the pharmacokinetic co-primary endpoint, C_{trough} pre-dose Cycle 8, demonstrate that trastuzumab SC is non-inferior compared to trastuzumab IV with respect to PK. The lower boundary of the two-sided 90% confidence interval for the geometric mean ratio of the trastuzumab SC and trastuzumab IV arms was 1.24, ie, greater than the pre-specified non-inferiority margin of 0.8.

The point estimates for the pharmacokinetic endpoints, observed and predicted C_{trough} pre-dose at Cycle 8 and Cycle 13, were higher in the trastuzumab SC arm. Overall serum trastuzumab exposure assessed by AUC at Cycle 7 and Cycle 12 was comparable between both arms.

EFFICACY RESULTS:

The results for the efficacy co-primary endpoint, pCR, confirm the non-inferiority of trastuzumab SC compared to trastuzumab IV for both the EPP and ITT populations. In the EPP, the lower CI boundary of the difference in pCR rate between trastuzumab SC and trastuzumab IV was -4, ie, greater than the pre-defined margin of -12.5.

The number of responders for ORR was comparable between the treatment arms (EPP: 88.8% in the trastuzumab IV arm and 87.2% in the trastuzumab SC arm). The median time to clinical response in the EPP population was 6 weeks in each arm.

EFS and OS were not sufficiently mature at the time of the clinical cut-off date for the primary analysis

Table 1: Summary of Overall Efficacy (Clinical Cut-off July 12, 2011; Efficacy Per Protocol)

Parameter	Trastuzumab IV N = 263		Trastuzumab SC N = 260
Pathological Complete Response			
Patients (%)	107 (40.7%)		118 (45.4%)
95% CI for the Rate	[34.7; 46.9]		[39.2; 51.7]
Difference in pCR (SC - IV arm)		4.70	
Lower bound one-sided 97.5% CI		-4.0	
Total Pathological Complete Response			
Patients (%)	90 (34.2%)		102 (39.2%)
95% CI for the Rate	[28.5; 40.3]		[33.3; 45.5]
Difference in tpCR (SC - IV arm)		5.01	
Difference in tpCR rate (95%CI)		[-3.5; 13.5]	
Event-Free Survival			
Events (%)	15 (5.7%)		13 (5.0%)
Overall Survival			
Events (%)	1 (0.4%)		1 (0.4%)

SAFETY RESULTS:

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 (Table 2).

With the exception of SAEs, there was no notable difference in the types of incidence of all-grade AEs across study arms; the most frequently occurring AEs were alopecia, nausea, neutropenia, diarrhea, asthenia, fatigue and vomiting. The incidence of Grade ≥ 3 events (severe) was similar across arms (52% in both arms). Overall, there were 12% of patients in the trastuzumab IV arm who experienced an SAE compared to 21% in the trastuzumab SC arm. Four fatal AEs were reported, all of which occurred during the neoadjuvant phase of the study: two infections (one in each arm), myocardial ischemia and sudden death in the trastuzumab SC arm in patients with recognized cardiovascular risk factors.

In the trastuzumab IV arm, 2% of patients were withdrawn from study treatment due to AEs compared to 6% in the trastuzumab SC arm. The imbalance was mainly attributable to cardiac AEs most notable left ventricular dysfunction. In contrast to the trastuzumab IV arm, several

patients in the trastuzumab SC arm were withdrawn for single left ventricular ejection fraction (LVEF) decrease which was not in line with the recommendations of the study protocol. The incidence of confirmed significant LVEF decrease was similar across arms.

The overall cardiac safety of the trastuzumab SC regimen was similar to that of the trastuzumab IV regimen. A similar proportion of patients in each arm experienced significant decreases in LVEF. The incidence of symptomatic congestive heart failure (CHF) was low: two patients in the trastuzumab SC arm developed NYHA class II CHF – both had predisposing factors (obesity, hypertension). Both events improved following withdrawal of treatment. None occurred in the trastuzumab IV arm.

Trastuzumab SC injections were generally well-tolerated. As expected a higher rate of trastuzumab injection reactions was observed in the trastuzumab SC arm (0.3% vs 11% in the SC and IV arms, respectively). With the exception of two Grade 2 events, all events were of Grade 1 intensity.

Infusion-related reactions (IRR) were observed more commonly for trastuzumab SC (36% vs 44% in trastuzumab SC and IV, respectively) with erythema and cough being main AE contributors to the difference observed. In both study arms, the large majority of events (97%) were of Grade 1 or 2 intensity.

Table 2: Overview of Safety Profile (Safety Population)

	Trastuzumab IV N = 298	**Trastuzumab SC N = 297**
Any AEs	280 (94%)	289 (97%)
Grade ≥ 3 AEs (severe)	155 (52%)	154 (52%)
Serious AEs	37 (12%)	62 (21%)
AEs leading to treatment withdrawal	7 (2%)	17 (6%)
AEs leading to death	1 (< 1%)	3 (1%)

CONCLUSIONS:

The study demonstrated non-inferiority of PK and efficacy for trastuzumab SC versus trastuzumab IV. Point estimates of pathological complete response and total pathological complete response were in favor of trastuzumab SC.

Subcutaneous injections of trastuzumab were generally well-tolerated. Although more injection site reactions were reported in the trastuzumab SC arm, they were clinically insignificant. More SAEs (particularly infections) were reported in the trastuzumab SC arm. However, there was no pattern in SAE reports and no association with trastuzumab exposure. Severe IRRs were reported very infrequently and at a similar incidence in both treatment arms.

The overall safety profile of trastuzumab SC (including cardiac safety) was in line with the known safety profile of the IV formulation. No new safety findings were identified. Taking into account the favorable efficacy data of trastuzumab SC, this study established a favorable benefit:risk profile for the trastuzumab SC formulation which is similar to trastuzumab IV.