SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL WA20499/ACT4071G)

COMPANY: F. Hoffmann-LaRoche Ltd/Genentech Inc. NAME OF FINISHED PRODUCT: Ocrelizumab NAME OF ACTIVE SUBSTANCE(S): Ocrelizumab	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A Randomised, Double-Blind, Placebo Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Two Doses of Ocrelizumab in Patients with Active Systemic Lupus Erythematosus / [redacted] / June 2010		
INVESTIGATORS / CENTERS AND COUNTRIES	19 investigators / centers in 7 countries (Argentina, Canada, Colombia, France, Hungary, Malaysia, and US)		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	03 December 2007 to 22 March 2010 (data cut-off)	CLINICAL PHASE	III
TERMINATION OF STUDY	[redacted] In this study, a total of 33 patients were randomized and received at least one infusion of either ocrelizumab (OCR) or placebo, before being transferred into the safety follow-up period. The earliest recruited patient reached the Week 20 time point. No patients had a visit in the double blind treatment period beyond Week 20. At the time of this study report, four patients [redacted] in the OCR 1000 mg group continue to participate in the safety follow-up period. Data from these four patients (up to the cut-off date of 22 March 2010) are included in all safety analyses for this study report. An addendum to this report will be written once the final safety data are available for these four patients.		
ABBREVIATED REPORT	The clinical study report has been abbreviated to only include full summaries of safety data. Since efficacy, pharmacokinetic (PK)/ pharmacodynamics (PD), and exploratory analyses were not completed, these data are provided as selected listings in the appendices of this report. No efficacy analyses were performed.		

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OBJECTIVES	**Primary:** to investigate the ability of the OCR regimen in combination with the standard-of-care treatment to improve the signs and symptoms of moderate to severe SLE in patients with active disease. **Secondary:** • To assess the safety and tolerability of OCR in combination with standard of care • To evaluate the pharmacokinetics, immunogenicity, and pharmacodynamic effects of OCR in this population • To evaluate corticosteroid sparing in patients receiving OCR • To evaluate the effect of OCR on the frequency of disease flares • To evaluate the impact of OCR on symptoms and patient functioning using the SF-36, FACIT Fatigue, and Modified Brief Pain Inventory (mBPI-SF)
STUDY DESIGN	Phase III, randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of OCR compared to placebo when combined with a single stable background immunosuppressive medication and a corticosteroid regimen.
NUMBER OF SUBJECTS	A total of 423 patients were originally planned for enrollment. A total of 33 patients were actually randomized in a 1:1:1 ratio [redacted]. At the time of this report, four patients remain in the safety follow-up period of the study.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Men and women, ≥ 16 years old, diagnosed with definite SLE according to the American College of Rheumatology (ACR) criteria were eligible for this study. At least four of the ACR criteria had to be present, one of which was a positive ANA test. Additionally, patients had to have active disease, defined as either a BILAG A score in at least one organ domain (other than the renal system) OR BILAG B scores in at least two organ system

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	domains. Patients also had to be on one background immunosuppressive regimen (either AZA, MMF, or MTX) and doses could not be changed by more than 50 mg of AZA daily, 500 mg MMF daily, or 5 mg MTX weekly in the 30 days prior to Day 1.
TRIAL DRUG / STROKE (BATCH) No.	OCR i.v./ [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Arm A: OCR 1000 mg i.v. on Days 1 and 15, followed by 1000 mg i.v. at Week 16 and then every 16 weeks plus background AZA, MMF, or MTX. Arm B: OCR 400 mg i.v. on Days 1 and 15, followed by 400 mg i.v. at Week 16 and then every 16 weeks plus background AZA, MMF, or MTX.
REFERENCE DRUG / STROKE (BATCH) No.	Placebo i.v. / [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Arm C: Placebo infusions on Days 1 and 15, followed by placebo infusion at Week 16 and then every 16 weeks plus background AZA, MMF, or MTX.
CRITERIA FOR EVALUATION	
EFFICACY:	The primary outcome measure was the clinical response based on the monthly assessments using the BILAG 2004 instrument. • Efficacy was to be assessed as the proportion of patients who achieved a clinical response in each of the following mutually exclusive categories: 1. Major Clinical Response (MCR), Partial Clinical Response (PCR), and No Clinical Response (NR).

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	2. The proportion of patients who achieved an MCR at Week 48. 3. The proportion of patients who achieved a Major or a Partial Clinical Response at Week 48 (PCR plus MCR proportion). • BILAG • SLEDAI-2K
PHARMACOKINETICS/ /PHARMACODYNAMICS:	The PK and key PD outcome measures were to include the following: • Serum levels of OCR • Circulating B-cell counts • Human anti-human antibodies (HAHA) rate and level
SAFETY:	Safety was assessed through regular physical examinations, vital signs and occurrence of adverse events (AEs): • Incidence of AEs graded according to the NCI CTC AE (Version 3.0) • Incidence of clinical laboratory abnormalities • Incidence of HAHAs
EXPLORATORY:	Health related quality of life were to be assessed using the following scales: • SF-36 • FACIT Fatigue • Modified Brief Pain Inventory • EQ-5D • Health Care Utilization
STATISTICAL METHODS	This section describes the statistical analyses that were originally planned for this study. [redacted] efficacy analyses, PK/PD analyses, and exploratory analyses were not performed as originally planned and outlined below for this study. The difference in the clinical response (MCR, PCR, and NR) at Week 48 was to be analyzed using a stratified Wilcoxon rank sum

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test, adjusting for race and initial assigned corticosteroid use. In order to control the type I error rate, a Hochberg step-up procedure was to be applied to evaluate the efficacy of the two dose levels versus the control arm (two pairwise comparisons).

All efficacy and safety data were to be listed on a by-patient basis and to include a reference to the center at which the patient was enrolled. Screening (pre-steroid) measurements were taken as the baseline for the purpose of the statistical analyses. All analyses, summaries, and listings were performed using SAS® software (version 8.2 or higher in a UNIX environment).

[redacted] the safety analysis included all safety data for the 33 randomized patients that were available up to the data cut-off date (22 March 2010). Safety data were summarized descriptively for AEs, clinical laboratory abnormalities, and HAHA levels.

METHODOLOGY:

The study was to be divided into four periods:

- Period 1: The Double-Blind Treatment Period.
- Period 2: The Study Extension Treatment Period (after the Week 48 assessments). **Note:** No patients entered this period of the study.
- Period 3: In the Open-Label Period. **Note**: No patients entered this period of the study.
- Period 4: The Safety Follow-Up Period. **Note:** All 33 patients who entered the study and received at least one dose of OCR had been transferred into the safety follow-up period [redacted] (09 May 2008).

Evaluation of the primary and some secondary endpoints was to occur at Week 48 with further analyses conducted at Week 96. [redacted], the analysis of the primary and secondary endpoints were not conducted. [redacted] patients were unblinded to the sponsor and all patients had a withdrawal visit. Patients who received OCR were followed, per protocol, for a minimum of 48 weeks and until their B cells returned to their baseline value, or the lower limit of normal.

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EFFICACY RESULTS:

[redacted], efficacy analyses were not performed.

PHARMACOKINETIC / PHARMACODYNAMIC RESULTS:

[redacted], PK/PD analyses were not performed.

SAFETY RESULTS:

[redacted] All 33 patients enrolled in this study were included in the safety analysis population.

- A total of 23/33 patients experienced at least one AE: 5/10 patients in the placebo group, 10/11 patients in OCR 400 mg group, and 8/12 patients in the OCR 1000 mg group.
- Two patients, both in the OCR 400 mg group, died in this study. Patient [redacted] due to an upper respiratory infection and patient [redacted] due to pneumoncystis.
- A total of 9/33 patients experienced at least one SAE: no patients in the placebo group, 6/11 patients in OCR 400 mg group, and 3/12 patients in the OCR 1000 mg group.
- Two patients required a dose modification (reduction) due to infusion-related reactions [redacted]
- Two patients, both in the OCR 400 mg group, experienced infusion-related reactions and symptoms. Patient [redacted] had a symptom of mild hypotension, and patient [redacted] had the symptoms of laryngeal/throat irritation, nausea, throat itching, reflux, cough, throat tightness, and chest tightness (all moderate) at 25 mL/hr. Both of these events led to a dosage adjustment, and resolved without sequelae that same day.
- A total of 18 patients experienced an infection (including those reported under body systems other than 'infections and infestations' class). The most commonly reported infections were upper respiratory tract infection, urinary tract infection, and sinusitis.
- Of the 18 patients who experienced infections, two patients in the OCR 400 mg group experienced opportunistic infections [redacted] had pneumocystis jiroveci pneumonia and patient [redacted] had cytomegalovirus [CMV]).
- Three patients experienced serious infections. Two of the patients were the deaths noted above. The other patient [redacted] in the OCR 1000 mg group experienced the SAE pneumonia, which resolved without sequelae.
- No patients withdrew from the study due to an AE.

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- No safety signals or clinically meaningful trends were observed for the laboratory parameters, ECGs, chest x-rays, or physical examinations.

EXPLORATORY RESULTS:

[redacted] The exploratory measures were not analyzed.

CONCLUSIONS:

[redacted]

Since the efficacy, PK/PD, and exploratory data were not analyzed[redacted] no conclusions can be drawn. Furthermore, due to the low number of patients enrolled in this study and short safety follow-up period, no clinically relevant conclusions can be drawn across treatment groups in regards to the safety profile of OCR 1000 mg and OCR 400 mg compared to placebo.