SYNOPSIS OF RESEARCH REPORT [redacted]
(PROTOCOL BO18414)

COMPANY: F. Hoffmann-La Roche NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S): Ocrelizumab (rhuMAb 2H7, RO4964913, PRO70769)	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	An open-label, multicentre, dose-escalating phase I/II trial of 3-weekly ocrelizumab in patients with follicular non-Hodgkin's lymphoma (NHL). Roche Report No [redacted] December 2008		
INVESTIGATORS / CENTERS AND COUNTRIES	19 centers in six countries (3 Australia, 3 Canada, 5 France, 3 Italy, 3 Sweden and 2 Switzerland).		
PUBLICATION (REFERENCE)	Morschhauser F et al. Interim results of a phase I/II study of ocrelizumab, a new humanised anti-CD20 antibody in patients with relapsed/refractory follicular non-Hodgkin's lymphoma. Blood. 2007; 10 (11) abstract 645.		
PERIOD OF TRIAL	1st patient screened: May 5, 2005 1st patient enrolled: May 18, 2005 Last patient last visit: January 21, 2008.	CLINICAL PHASE	I/II
OBJECTIVES	**Primary**: - To evaluate the safety and tolerability of escalating intravenous (IV) doses of ocrelizumab given every 3 weeks in patients with CD20+, follicular NHL whose disease had progressed after prior rituximab-containing therapy **Secondary**: - To characterize the pharmacokinetics of ocrelizumab in patients with follicular NHL - To examine peripheral blood B-cell depletion with increasing doses of ocrelizumab - To obtain preliminary data on the anti-tumour efficacy of ocrelizumab by evaluating o overall response rate (ORR) o progression-free survival (PFS) o event-free survival (EFS) - To explore pharmacogenetic parameters (notably FcγR IIa and IIIa polymorphisms at baseline) and a pharmacodynamic parameter (notably bcl-2 rearrangements at baseline, during and after treatment) in relation to efficacy.		
STUDY DESIGN	open-label, multi-center		

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NUMBER OF SUBJECTS	45 planned, 48 enrolled, 47 treated
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Male or female adult patients with CD20+, follicular NHL, whose disease had progressed or relapsed after prior therapy. Patients could have received several chemotherapies and could have been refractory to prior chemotherapy. Patients must have received at least one course of rituximab, given either as monotherapy or in combination with standard chemotherapies and their last treatment before enrolment must have been rituximab or a rituximab containing regimen. Moreover, they must have responded to their last rituximab or rituximab-containing regimen for > 6 month, with response being defined as complete response (CR), complete response unconfirmed (CRu), partial response (PR) or stable disease (SD).
TRIAL DRUG / STROKE (BATCH) No.	Ocrelizumab solution for injection (20 mg/mL). Formulation No: [redacted]; Batch Nos: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	A single intravenous infusion given at 3 week intervals for a maximum of eight cycles at doses of: Cohort A - 200 mg/m^2 (8 doses) Cohort B - 375 mg/m^2 (8 doses) Cohort C - 375 mg/m^2 (1 dose) followed by 750 mg/m^2 (7 doses)
REFERENCE DRUG / STROKE (BATCH) No.	Not applicable
DOSE / ROUTE / REGIMEN / DURATION	Not applicable
CRITERIA FOR EVALUATION	
EFFICACY:	– Overall response rate (ORR) – Progression-free survival (PFS) – Event-free survival (EFS)
PHARMACODYNAMICS:	- Peripheral blood B-cell depletion - Bcl-2 re-arrangements
PHARMACOKINETICS:	- $AUC_{(0-28)}$ - area under the plasma concentration-time curve from time 0 to day 28

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	- $AUC_{(0\text{-inf})}$ - area under the plasma concentration-time curve from time 0 to infinity - C_{max} - maximum plasma concentration - Clearance (CL) - Steady-state volume of distribution (Vss) - $t_{1/2}$ - half life
SAFETY:	- Adverse events (graded according to NCI-CTC version 3) - Serious adverse events - Blood chemistry and hematology - HACA (baseline only), HAHA - Immunology (immunogloblins and complement C3 and C4)
OTHER	Blood samples were collected under sub-study protocol BO18414RG for pharmacogenetic / pharmacogenomic analysis. The results from this sub-study will be reported separately. Fc γR IIa and IIIa polymorphism at baseline will be evaluated in relation to efficacy.
STATISTICAL METHODS	For response rate, the best confirmed and last response rates are provided together with the 95% confidence intervals. PFS and EFS - time to event parameters were estimated using Kaplan and Meier methodology.

METHODOLOGY:

Written informed consent was obtained before any study-specific procedures were performed. Eligible patients were then enrolled into one of three treatment cohorts in a partially sequential, partially randomised manner. Patients in each cohort received a total of eight infusions of ocrelizumab (unless they experienced disease progression, unacceptable toxicity or declined further treatment) given at intervals of 3 weeks. After cycles 4 and 8, patients were assessed for tumour response according to the report from an International Workshop to standardise response criteria for NHL. A follow-up visit was performed 28 days after the last dose. Additional follow-up visits were scheduled every 3 months until one year and then every 6 months until 2 years after enrollment. Although the protocol specified that all patients would be followed until death, disease progression, initiation of new lymphoma treatment, or until 2 yrs after the last patient was enrolled, this was not done. Patients were in fact followed up until disease progression, death or until 2 years after they were enrolled into the study. Data on new lymphoma treatment were also not recorded in the CRF. Adverse events, including serious adverse events, were collected throughout the study up to 4 weeks after the last dose of study treatment. Related serious adverse events were collected

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indefinitely.

DEMOGRAPHIC CHARACTERISTICS:

A total of 48 patients with a mean age of 58 years (range 38 to 83 years) were enrolled into three cohorts; of these, 47 received study treatment. The majority of patients had stage Ann Arbor III-IV disease and WHO histologic grade 1 or 2. According to the FLIPI score, 21 patients (45%) were considered to have intermediate to high risk disease. As specified in the study protocol, all patients had an ECOG performance status of 0 or 1 at baseline. There were no clinically relevant differences in demographic or disease characteristics between the cohorts.

EFFICACY RESULTS:

Ocrelizumab demonstrated efficacy (with respect to ORR, median PFS and median EFS) in patients with relapsed NHL. The best efficacy results were observed at a dose of 375 mg/m2 (cohort B), although there was no obvious difference in baseline disease characteristics in this group that would account for this observation. However, the mean duration of study treatment was longer in arm B compared with the other arms. For ORR, the higher response in cohort B was accounted for by more patients achieving a CR/CRu.

	Cohort A N=15	**Cohort B N= 16**	**Cohort C N=16**
Last overall response rate	4 (27%)	8 (50%)	6 (38%)
95% CI	8%-55%	25%-75%	15%-65%
CR	0	2	0
CRu	2	2	1
PR	2	4	5
SD	6	6	5
PD	5	2	4
Missing*	0	0	1
Best overall response rate	6 (40%)	9 (56%)	6 (38%)
95% CI	16%-68%	30%-80%	15%-65%
CR	1	3	2
CRu	1	1	0
PR	4	5	4
SD	5	7	6
PD	4	0	3
Missing	0	0	1
Median progression-free survival, months (95%CI)	9.4 (4.7-12.0)	17.2 (8.6-23.5)	17.2 (5.8-N.E.)
1-yr event-free rates	0.22	0.60	0.53
Median event-free survival, months (95% CI)	6.7 (2.2-11.8)	17.1 (8.6-23.5)	5.8 (2.6-23.2)
1-yr event free rates	0.20	0.56	0.42

N.E. not estimable

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Subgroup analysis showed a comparable ORR (last assessment) in the subgroups with the low affinity (FF/FV) and high affinity (VV) variants of the FCγIIIa receptor (39% and 43%, respectively). Similar ORRs were also observed in the two Fcγ IIa receptor subgroups (42% and 41% with the RR and HR variants, respectively). ORR was higher in patients who had achieved a response of CR, CRu or PR to their last rituximab regimen compared with those who only achieved SD (41% vs 17%, respectively).
In a small group of 11 patients positive for BCL2 in blood at baseline and who had a valid post treatment sample, the rate of BCL2 rearrangement was 45% (5 of 11 patients).

PHARMACOKINETICS RESULTS:

Maximum serum concentrations (Cmax) of ocrelizumab increased with increasing doses. The mean steady-state Cmax was approximately 125±57 (n=3), 335±76 (n=5) and 455±67 (n=4) µg/ml and the mean terminal t½ was estimated to be approximately 22.9±12.5 (n=5), 27.6±4.1 (n=7), and 25.9±8.9 (n=6) days for cohorts A, B and C, respectively.

SAFETY RESULTS:

An overview of the safety experience in this study is shown below.

	Cohort A N=15 N (%)	Cohort B N= 16 N (%)	Cohort C N=16 N (%)
All AEs	12 (80)	16 (100)	15 (94)
Related AEs	12 (80)	14 (88)	12 (75)
Serious AEs	1 (7)	3 (19)	2 (13)
Serious related AEs	1 (7)	3 (19)	-
Grade 3 or 4 AEs	1 (7)	1 (6)	4 (25)
Grade 3 or 4 related AEs	1 (7)	1 (6)	2 (13)
AEs leading to withdrawal	1 (7)	-	2 (13)
Death	1 (7)	-	1 (6)

Ocrelizumab was generally well tolerated and no dose limiting toxicities were observed. The maximum tolerated dose was not reached in this study. The most commonly reported AE was infusion related reactions (IRR) the incidence of which was highest in the first treatment cycle (70) and decreased over time (25% from cycle 3 and beyond). Typical symptoms associated with IRR included pyrexia, chills, nausea, headache and hypotension. Most IRRs were of grade 1 or 2 severity and all were manageable by interruption and/or reduction in the rate of infusion. One patient prematurely discontinued study treatment due to an IRR; the patient experienced a grade 2 event in the first treatment cycle.

Other AEs were reported at low incidence with no discernable dose relationship and the majority were of grade 1 or 2 severity. The only AEs reported by more than 10% of the overall study population were

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asthenia and nasopharyngitis. Six patients (1, 3 and 2 in cohorts A, B and C, respectively) experienced serious AEs (obliterative bronchiolitis in cohort A; 2 cases of IRRs and bone pain in cohort B; pleural effusion and malignant neoplasm in cohort C). Two deaths occurred during the study period; one death was NHL-related and the other was due to a pulmonary embolism (considered by the investigator as remotely related to study treatment). The overall incidence of premature withdrawal from study treatment for safety reasons was low. Three patients prematurely stopped ocrelizumab treatment due to AEs; the events were obliterative bronchiolitis in cohort A (which culminated in a fatal pulmonary embolism some 10 months later); IRR and malignant neoplasm in cohort C.

CD19+ B cells decreased following ocrelizumab administration with more pronounced effects in the high dose cohorts (B and C). A few patients remained B-cell depleted up to 6 months following cessation of ocrelizumab therapy.

There were no noteworthy changes over time or differences between the study arms in median value for vital signs parameters or blood chemistry, haematology or immunology (complement C3 and C4, IgG, IgM, IgA) parameters. The only grade 3 or 4 laboratory abnormality of clinical concern was neutropenia, which occurred at a low incidence (6 of 317 infusions). Three patients were positive for HACA at baseline. No patient developed HAHA following treatment with ocrelizumab (although one patient was positive at baseline).

CONCLUSIONS:

Ocrelizumab was safely administered to patients with relapsed follicular NHL. Study treatment was generally well tolerated and there were no dose limiting toxicities observed. The maximum tolerated dose was not reached in this study. The most commonly reported AE was IRR with the majority of cases being of grade 1 or 2 severity and manageable by interruption and/or reduction of the rate of infusion. The incidence of IRR tended to decrease over time. Few patients discontinued treatment for safety reasons.

Administration of ocrelizumab resulted in B-cell depletion with more pronounced effects being observed in the higher dose cohorts.

The estimated t½ of ocrelizumab was between 23 and 28 days depending on the dose; this is consistent with that of other IgG monoclonal antibodies.

Ocrelizumab demonstrated efficacy in patients with relapsed follicular NHL who were previously treated with rituximab-containing therapies with a trend for better efficacy in the 375 mg/m2 cohort (B). The ORR in the pooled population was 38%. Safety and efficacy of ocrelizumab are in line with expectations. In the absence of randomized data for ocrelizumab against rituximab and other CD20 antibodies it is difficult to conclude that either antibody would be superior over the other, however, it can be concluded that a clear superiority claim for ocrelizumab over rituximab can not be made based on these data.