SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL WA18230)

COMPANY: NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A randomized placebo-controlled, multicenter, Phase I/II study of the safety of escalating single intravenous doses of ocrelizumab (rhuMAb 2H7, RO4964913, PRO70769) in patients with moderate to severe rheumatoid arthritis receiving stable doses of concomitant methotrexate but with unsatisfactory clinical response. Final Clinical Study Report. Report No. [redacted], May 2013.		
INVESTIGATORS / CENTERS AND COUNTRIES	40 centers in 8 countries (United Kingdom [11 centers], Spain [10 centers], Canada [7 centers], Russia [6 centers], Belgium [2 centers], New Zealand [2 centers], Netherlands [1 center] and Australia [1 center]).		
PUBLICATION (REFERENCE)	NA		
PERIOD OF TRIAL	First patient entered: 26th October 2005 Reporting period: Date of last clinical cut-off 19th July 2011 to last patient last visit 6th February 2013	CLINICAL PHASE	I/II
OBJECTIVES	PRIMARY: • To evaluate the safety and tolerability of escalating single intravenous (iv) doses of ocrelizumab (OCR) in combination with methotrexate (MTX) in patients with moderate to severe rheumatoid arthritis (RA). SECONDARY: • To evaluate the efficacy of OCR in combination with MTX in patients with moderate to severe RA at 24 weeks. • To characterize the pharmacokinetics of OCR. • To characterize the pharmacodynamics of OCR by evaluation of the relationship between the dose of OCR and the onset, extent and duration of peripheral B-cell depletion. • To collect research samples for evaluation of potential biomarkers, which may be predictive of response to OCR treatment. • To evaluate the effect of infusion time on the safety of administration of OCR.		

STUDY DESIGN	Randomized, placebo-controlled, multicenter phase I/II study in 2 parts. The sponsor, investigator and patients were blinded to treatment assignment, but not to dose level. Part I - Dose Escalation Patients received a single iv infusion of OCR or placebo equivalent at one of the following dose levels: Group 1: 400 mg Group 2: 1000 mg Group 3: 1500 mg Group 4: 2000 mg Part II After the review of data from Part I of the study, approximately 120 (96 active, 24 placebo) additional patients were to be randomized to the following 3 dose levels: 400 mg, 1000 mg, and 1500 mg. Once patients had reached and completed the Week-24 visit they were eligible for additional treatment based on the need to provide control of disease activity.
NUMBER OF SUBJECTS	Planned: 40 in Part I; 120 in Part II Actual: Part I: 40 (8 patients in each of the placebo + MTX, OCR 400 mg + MTX, OCR 1000 mg + MTX, OCR 1500 mg + MTX and OCR 2000 mg + MTX groups). Part II: 135 (27 patients in the placebo + MTX group, 35 patients in the OCR 400 mg + MTX group, 36 patients in the OCR 1000 mg + MTX group and 37 patients in the OCR 1500 mg + MTX group).
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	• Adult patients (aged 18-80 years inclusive). • Moderate to severe RA diagnosed according to the revised 1987 American College of Rheumatology criteria for classification of RA. • Failed (through lack of efficacy or tolerability) one disease-modifying anti-rheumatic drug (DMARD) or biologic, but had not failed more than 6 of these agents, including MTX. • Was currently receiving MTX, but had shown unsatisfactory clinical responses to treatment with MTX (i.e. partial responders).
TRIAL DRUG / STROKE (BATCH) No.	Batch numbers of OCR used in the study: Part I: [redacted] Part II: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Single iv infusion of OCR 400, 1000, 1500 or 2000 mg. Patients who completed the Week 24 visit were eligible for additional treatment on the basis of need to provide control of disease activity. OCR was given in combination with weekly MTX at a stable dose of 10-25 mg/week (oral or parenteral).

REFERENCE DRUG / STROKE (BATCH) No.	Batch numbers of matching placebo used in the study: Part I: [redacted], [redacted] Part II: [redacted], [redacted], [redacted], [redacted], [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Single iv infusion of matching placebo. Patients who completed the Week 24 visit were eligible for additional treatment subject to meeting certain criteria, until the study was unblinded. Matching placebo was given in combination with weekly MTX at a stable dose of 10-25 mg/week (oral or parenteral).
CRITERIA FOR EVALUATION	
SAFETY:	Adverse events (AEs) reported by patients remaining in follow-up at the date of the last clinical cut-off are presented in this final CSR.
STATISTICAL METHODS	The main safety analyses presented in previous CSRs (Report Numbers [redacted], [redacted] and [redacted]) were based on all patients who were randomized and received at least one dose of study drug (N=154). This final CSR lists safety information for the 19 patients who completed the study after the last clinical cut-off date (CCOD).

METHODOLOGY

Following analyses of all available safety data from the phase III RA clinical trials at 72 weeks of follow-up since the last patient received the last infusion of OCR in each study, it was concluded that continuation of safety follow-up (SFU) would not provide a benefit to patients above and beyond the management of the patient's RA through usual standard of care, and would not add to the understanding of the safety of OCR. The Sponsor considered it appropriate to terminate the B-cell follow up in patients treated with OCR in RA clinical trials. This abbreviated format clinical study report (CSR) presents an update from the CCOD (19th July 2011) to the date of last patient last visit (LPLV) (6th February 2013).

SAFETY RESULTS

Nineteen patients were continuing in SFU at the last CCOD (19th July 2011) and 10 of these patients reported a total of 23 AEs (11 AEs with date of onset after the CCOD and 12 AEs with date of onset before the CCOD), including 2 SAEs in the same patient, recurrent bladder transitional cell carcinoma and squamous cell lung carcinoma, considered by the investigator to be unrelated to treatment with OCR. All other events were of mild or moderate intensity and most of them were considered unrelated to treatment with OCR by the investigators.

CONCLUSIONS

No new safety signals related to OCR were observed during the follow-up period of this report from the last CCOD (19th July 2011).