SYNOPSIS OF RESEARCH REPORT 1035307
(PROTOCOL WA20494)

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, double-blind, parallel group, international study to evaluate the safety and efficacy of ocrelizumab compared to placebo in patients with active rheumatoid arthritis continuing methotrexate (MTX) treatment. Report No. 1035307, September 2010. This clinical study report covers the double-blinded treatment phase of the study (Day 1 to Week 48).		
INVESTIGATORS / CENTERS AND COUNTRIES	209 centers in 24 countries worldwide: Argentina (4 centers), Australia (2 centers), Austria (3 centers), Belgium (3 centers), Brazil (6 centers), Canada (8 centers), China (4 centers in Hong Kong), France (7 centers), Germany (7 centers), Great Britain (5 centers), Greece (3 centers), Guatemala (1 center), Israel (3 centers), Korea (3 centers), Mexico (8 centers), New Zealand (3 centers), Panama (1 center), Peru (4 centers), Russia (10 centers), Spain (4 centers), Taiwan (4 centers), Thailand (4 centers), Ukraine (3 centers) and USA (109 centers).		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	Nov 30, 2006 to Oct 06, 2009	CLINICAL PHASE	III
OBJECTIVES	**Primary** To determine the efficacy and safety of ocrelizumab versus placebo in reducing the signs and symptoms of RA, when used in combination with MTX in patients with active RA who have an inadequate response to MTX therapy. **Secondary** • To assess the efficacy of ocrelizumab to slow or inhibit structural damage in these patients (using radiographs) • To assess the effect of ocrelizumab on physical function in this patient population. • To investigate the pharmacokinetics and pharmacodynamics of ocrelizumab.		
STUDY DESIGN	Randomized, double-blind, multicenter, parallel group study with three treatment arms: placebo + MTX (placebo), ocrelizumab 200 mg + MTX (OCR 200 mg) and ocrelizumab 500 mg + MTX (OCR 500 mg). The study included three phases: a double-blind treatment period (Day 1 to Week 48), a study extension period of at least 48 weeks (Week 48 to Week 96) where eligible patients received open label treatment with ocrelizumab (500 mg x 2) and a safety follow-up phase for patients who withdrew from either of the treatment periods (double-blind or study extension).		
NUMBER OF SUBJECTS	1000 patients were planned; 1015 enrolled (324 in the placebo group, 344 in the OCR 200 mg group and 347 in the OCR 500 mg group).		

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DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Adult patients with active RA of at least 3 months who have had an inadequate response to MTX therapy administered at a dose of 7.5-25 mg/wk for at least 12 weeks. As for patients receiving MTX therapy, those on corticosteroids (dose not exceeding 10 mg/day prednisolone or equivalent) or NSAIDs had to be on a stable dose of treatment for the 4 weeks prior to baseline.
TRIAL DRUG / STROKE (BATCH) No.	Ocrelizumab Batch Numbers: M32029, M31360, M31359, M58269, M58270, M52228, M52229, M52230, M73071, M73293, M86419, M86420, M86421, M86422, N03589, N02585, N25625, N35611, N42896, 705410, 705419, 705811, 708063, 737946, 737952, 765297, 775629, 787215, 805672, 797669, 809112, 831612, 852583, N57092, L13325, L13327, L13364, L13366, L13442, L13444, 705256 and 705255.
DOSE / ROUTE / REGIMEN / DURATION	Ocrelizumab: Double–blind treatment phase (Day 1 to Week 48): two intravenous (iv) infusions of either OCR 200 mg or OCR 500 mg given on study Day 1 and Day 15. Ocrelizumab was administered in combination with weekly oral or parenteral MTX at a stable dose of 7.5 – 25 mg/week.
REFERENCE DRUG / STROKE (BATCH) No.	Matching Placebo Batch Numbers: M31361, M35608, M62333, M52231, M73294, N04510, N03590, N42895, N54323, 700899, 702587, 704871, 705812, 741027, 781639, 792988, 851760, N57091, L13326, L13328, L13365, L13367, L13443, L13445, 705257 and 706659.
DOSE / ROUTE / REGIMEN / DURATION	Matching placebo: two iv infusions given on Day 1 and Day 15 of double-blind treatment phase. Matching placebo was given in combination with weekly oral or parenteral MTX at a stable dose of 7.5 – 25 mg/week as prescribed by the treating physician and in accordance with the local MTX label.
CRITERIA FOR EVALUATION	
EFFICACY:	**Primary endpoint** • The proportion of patients with an ACR20 response at Weeks 24 and 48. **Secondary endpoints** • The proportion of patients with a reduction ≥ 0.25 units in the HAQ-DI score at Weeks 24 and 48. • The change from baseline in mTSS at Week 24 and Week 48. • The proportion of patients with a major clinical response (ACR70 for ≥ 6 months) at Week 48.

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	• The proportion of patients achieving DAS28 remission (DAS <2.6) at Weeks 24 and 48. • The change in DAS28 from baseline at Weeks 24 and 48. • EULAR response rates at Weeks 24 and 48. • The proportion of patients achieving an ACR50 and ACR70 response at Weeks 24 and 48. • The change from baseline in the individual parameters of the ACR core set at Weeks 24 and 48. • The change from baseline in erosion score and the change from baseline in joint space narrowing. • The proportion of patients without radiographic progression at Week 24 and Week 48. • The proportion of patients with a reduction from baseline in mTSS at Week 48. **Exploratory endpoints** • The proportion of patients achieving low disease activity (DAS28 ≤ 3.2). • The ACRn score. • The area under the concentration versus time curve (AUC) of the ACRn. • Plots of cumulative density function of ACRn over time. • The proportion of patients achieving an ACR90 response at Weeks 24 and 48. • The proportion of patients who received rescue therapy. • Duration of DAS28 remission.
PHARMACOKINETICS/ PHARMACODYNAMICS:	Serum was obtained for PK assessments and for the analysis of PD parameters including the following: • Extent and duration of B-cell depletion. • Estimation of quantitative immunoglobulin levels, lymphocyte subtypes, rheumatoid factors, anti-CCP antibody, ANA and anti-tetanus and other antibodies. Exploratory analysis assessed the possible relationship between pharmacodynamic (PD) markers, pharmacokinetics (PK) and clinical response.
QUALITY OF LIFE/ PHARMACOECONOMICS	HAQ, SF-36, FACIT fatigue scale, BPI, Activity limitation and Disease status questions. HAQ, SF-36 and FACIT fatigue scales

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	were also efficacy parameters.
SAFETY:	Assessment of safety was based on the following: • Incidence of adverse events (AEs) graded according to the NCI CTC AE (Version 3.0). • Incidence of clinical laboratory abnormalities. • Incidence of human anti-ocrelizumab antibodies (HAHA).
STATISTICAL METHODS	The primary analysis was performed on the intent-to-treat (ITT) population. Using the Cochran-Mantel-Haenszel (CMH) test, the proportion of patients who achieved an ACR response at both 24 and 48 weeks was compared between placebo and OCR 200 mg and OCR 500 mg groups. The difference in ACR response analyzed using the CMH test was stratified by region (US, ROW) and baseline RF status (+, -). To control the type I error rate for the primary analyses, the following procedure was applied: step one of this procedure was to establish a p-value for the test of each dose on the basis of the principles of the intersection−union test. Accordingly, the maximum p-value obtained in the two tests for a dose at Week 24 and at Week 48 was to be taken as the p-value for that dose. In step two, a single Hochberg procedure using the intersection−union p-value for each dose was performed at $\alpha = 0.05$. According to this procedure (and assuming that all significant results support an advantage for ocrelizumab), if the intersection−union p-values for both doses were < 0.05, then both doses were to be declared efficacious. An intersection union test at Week 24 and Week 48 was also used to provide the p-values for the ACR50, ACR70 and ACR90 analyses. To control the type I error for secondary analyses, a hierarchy of four key secondary analyses was specified. Within each dose, results of a key secondary analysis had to be significant to continue hypothesis testing for key endpoints further down the hierarchy. The key secondary endpoints, in testing order, are HAQ-DI reduction ≥ 0.25 at Week 24, change from baseline in mTSS at Week 48, and proportion of patients with a major clinical response. Hypotheses were tested only for doses that were successful in the primary efficacy analysis. All secondary analysis hypothesis tests were performed at $\alpha = 0.05$. All endpoints were analyzed at Weeks 24 and 48. The differences in ACR response were expressed as proportions along with the 95% confidence interval for the treatment difference and corresponding p-value. Odds ratios with the corresponding 95% confidence interval for the odds ratio and associated p-value were produced for each OCR arm compared with placebo.

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METHODOLOGY:

Patients received a course (two iv infusions separated by 14 days) of OCR 200 mg or OCR 500 mg or placebo on Day 1 (baseline) and Day 15 and a repeat course at Weeks 24 and 26. Patients and investigators were blinded to the dose level. Each infusion of study treatment was preceded by prophylactic treatment with 100 mg of methylprednisolone and all patients were to be on a stable dose of 7.5 to 25 mg/week of MTX. Efficacy and safety assessments were scheduled 4-weekly from the baseline to Week 24 and every 8 weeks thereafter up to Week 48.

During the treatment period, patients were to remain on a stable dose of background medication for RA, where possible, and could receive protocol defined rescue medication for clinical need. For the primary efficacy analysis, patients who withdrew prematurely from the study, received sponsor-defined rescue therapy or had insufficient data were considered as non-responders.

After the completion of the Week 48 visit, patients could enter a study extension phase where some patients were eligible to receive open-label OCR 500 mg, at the discretion of the investigator.

Patients who withdrew from the study at anytime, were expected to enter safety follow-up for a period of at least 48 weeks from the first infusion of the last course of treatment or until their B-cell count had returned to baseline or the lower limit of normal, whichever was lower.

Oral corticosteroids ($\leq$ 10 mg /day of prednisolone or equivalent), NSAIDs and analgesics other than NSAIDs were permitted provided the maximum recommended dose was not exceeded.

STUDY POPULATION

At baseline, the three treatment groups were balanced with respect to general demographic and RA characteristics including mean values for ACR core variables, previous/concomitant rheumatoid diseases other than RA and the use of DMARDs, NSAIDs and corticosteroids. The mean duration of RA disease was approximately 7 years across treatment groups (median was 4.5 years) and mean DAS28 at baseline was high at 6.4 in all three groups reflecting severe disease in this patient population.

Of the 1015 patients enrolled, nine did not receive treatment and 74 withdrew from trial treatment prior to Week 48: 35 (10.9%) in the placebo group, 20 (5.8%) in the OCR 200 mg and 19 (5.5%) in the OCR 500 mg group. Patients withdrew due to safety and non-safety reasons which primarily included insufficient therapeutic response and treatment refusal.

Rescue therapy according to sponsor-specified criteria was initiated by a total of 149 patients: 90 (27.8%) from the placebo group, 31 (9.0%) from the OCR 200 mg group and 28 (8.1%) from the OCR 500 mg group. Most of the patients who received rescue therapy did not withdraw from the treatment period.

The ITT and safety populations consisted of 1006 patients with 320, 343 and 343 assigned to the placebo, OCR 200 mg and OCR 500 mg groups, respectively. The PP population comprised 806 patients (80% of the ITT population); 258 patients in the placebo group and 274 patients each, for both OCR groups.

EFFICACY RESULTS:

At Week 24, the proportion of ACR20 responders was 35.7% in the placebo group, 56.9% in the OCR 200 mg group and 54.5% in the OCR 500 mg group. The proportion of ACR20 responders at Week 48 was 27.6% in the placebo group compared with 58.3% in the OCR 200 mg and 62.1% in the OCR 500 mg groups, respectively. For both OCR groups, there was a highly statistically significant difference from placebo in the proportion of ACR responders at both Weeks 24 and 48, $p < 0.0001$ for both groups at both time points.

Consistent results were obtained in the sensitivity analyses on the ITT population as well as on the PP population.

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Logistic regression analysis at Week 24 indicated that the odds for achieving an ACR20 response was 2.38 and 2.15 times higher in patients receiving OCR 200 mg and OCR 500 mg, respectively, compared with patients receiving placebo. These analyses also showed that the odds of achieving an ACR20 response at Week 24 were 1.6 times higher for patients from the rest of the world (ROW) compared with patients from the US. The effect of treatment was more pronounced at Week 48 as reflected in the increase in the odds of achieving an ACR20 response for both active treatment groups compared to placebo from Week 24 to Week 48. At Week 48, the odds for the treatment comparisons were 3.78 and 4.43 for the OCR 200 mg and OCR 500 mg groups, respectively.

Secondary efficacy analyses were supportive of the primary endpoint. At Weeks 24 and 48, statistically significant differences from placebo were achieved for both OCR groups for all secondary endpoints related to disease activity, except for DAS28 low disease activity at Week 24 for the low dose OCR 200 mg group. In addition to the differences observed between active treatment and placebo at Weeks 24 and 48, the onset of response was apparent at Week 4/8 in the OCR-treated groups for a number of clinical parameters including ACR50, DAS28, change from baseline in ACR core set parameters and EULAR response.

Throughout the 48-week period, the two OCR groups performed similarly with respect to the primary and secondary efficacy endpoints. A summary of the key efficacy results at Weeks 24 and 48 for the OCR treatment groups vs placebo is shown in the table below:

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Key Efficacy Results at Weeks 24 and 48 (ITT Population)

ITT Population Results at Weeks 24 and 48	Placebo	OCR 200 mg		OCR 500 mg	
Primary endpoint			p-value*		p-value*
ACR 20 (%)					
Week 24	35.7	56.9	< 0.0001	54.5	< 0.0001
Week 48	27.6	58.3	< 0.0001	62.1	< 0.0001
Secondary endpoints					
ACR50 (%)					
Week 24	16.3	31.8	< 0.0001	31.2	< 0.0001
Week 48	12.9	39.9	< 0.0001	36.7	< 0.0001
ACR70 (%)					
Week 24	5.6	14.3	0.0002	12.2	0.0023
Week 48	6.6	20.7	< 0.0001#	22.4	< 0.0001#
Change in ACR core set (adjusted mean)					
Week 24					
SJC	-6.7	-9.1	0.0001	-9.0	0.0002
TJC	-10.8	-14.9	< 0.0001	-13.6	0.0047
Patient's global assessment	-23.0	-29.1	0.0036	-28.4	0.0104
Physician's global assessment	-24.9	-32.0	< 0.0001	-32.4	< 0.0001
Patient's pain assessment	-18.8	-24.4	0.0054	-24.7	0.0035
CRP	-0.4	-1.3	< 0.0001	-1.3	< 0.0001
HAQ-DI	-0.4	-0.5	0.0033	-0.6	< 0.0001
ESR	-7.4	-14.4	< 0.0001	-17.4	< 0.0001
Week 48					
SJC	-7.5	-10.9	< 0.0001	-11.4	< 0.0001
TJC	-11.4	-16.6	< 0.0001	-16.4	< 0.0001
Patient's global assessment	-22.9	-33.2	< 0.0001	-35.6	< 0.0001
Physician's global assessment	-27.3	-40.0	< 0.0001	-39.6	< 0.0001
Patient's pain assessment	-19.7	-29.3	< 0.0001	-30.6	< 0.0001
CRP	-0.3	-1.5	< 0.0001	-1.5	< 0.0001
HAQ-DI	-0.4	-0.6	0.0004	-0.7	< 0.0001
ESR	-8.6	-20.8	< 0.0001	-23.0	< 0.0001

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Key Efficacy Results at Weeks 24 and 48 (ITT Population) Cont.

ITT Population Results at Weeks 24 and 48	Placebo	OCR 200 mg		OCR 500 mg	
Key Secondary endpoint			p-value*		p-value*
Major clinical response (ACR70 for ≥ 6 months, Week 48 only)	0.9	6.1	0.0007	7.3	<0.0001
DAS28 remission					
Week 24	5.3	7.9	0.1472	10.8	0.0082
Week 48	5.3	16.0	<0.0001	17.5	<0.0001
EULAR response, good and moderate (%)					
Week 24	41.6	68.8	-	70	-
Week 48	35.3	65.9	-	72	-
Mean change from baseline in mTSS					
Week 24	1.04	0.34	0.0024[a]	-0.03	<0.0001[a]
Week 48[b]	1.74	0.26	<0.0001[a]	-0.03	<0.0001[a]

*, P-values from CMH analysis stratified by region (US vs ROW) and screening RF status. P-values for continuous endpoints from an analysis of variance. Model contains region (US, ROW), screening RF status, baseline ACR core set parameter and treatment. P-values are vs placebo.
[#], P-value unadjusted for Intersection-union test
[a], All comparisons to placebo x 2 + MTX using Van Elteren's test stratified by region (US, ROW).
[b], Inhibition was calculated using the formula [1-(Xa)/Xp)]*100. Xa = Mean Change from baseline in mTSS for the Active arm and Xp = Mean Change from baseline in mTSS for the Placebo arm. Therefore [1-(0.26/1.74)]*100 = 85% for OCR 200 mg at Week 48.

QUALITY OF LIFE RESULTS:

Patients in all the three treatment groups experienced improvement at Weeks 24 and 48 in self-assessment of fatigue, (based on the FACIT-fatigue assessment results) and in mental and physical health (based on the SF-36 health survey). The difference in adjusted means between placebo and the OCR groups, in the change from baseline in SF-36 mental component was not significant at Week 24 but achieved statistical significance at Week 48. Based on mean changes from baseline, both clinically relevant and statistically significant improvements in physical health score were observed at Weeks 24 and 48 for both OCR groups compared with placebo.

A summary of FACIT-fatigue and SF-36 results at Weeks 24 and 48 are shown below.

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Results at Weeks 24 and 48 (ITT)	Placebo	OCR 200 mg		OCR 500 mg	
Change in FACIT-fatigue (means)			p-value*		p-value*
Week 24	5.14	7.18	-	7.07	-
Week 48	5.39	8.01	-	8.41	-
Change in SF-36 domains (adjusted means)					
Mental health					
Week 24	4.8	6.0	0.1103	5.8	0.2011
Week 48	4.2	6.2	0.0186	6.3	0.0127
Physical health					
Week 24	6.0	7.5	0.0232	8.3	0.0006
Week 48	6.3	9.4	<0.0001	9.9	<0.0001

*, P-values from an analysis of variance controlling for region (US, ROW) and screening RF status

PHARMACODYNAMIC RESULTS:

Post-initiation of treatment, a rapid depletion of CD19+ B-cells was observed in the OCR groups as early as Week 2 (no measurement prior to week 2), in contrast to the placebo group. Other B-cell markers, CD19+CD27+ and CD19+CD27-, showed a similar pattern to that observed for CD19.

Lymphocyte subsets including CD3+, CD4+ and CD8+ T-cells were also reduced in the OCR groups compared with placebo, following the infusions, but returned to baseline values within approximately 2 weeks.

Mean levels of immunoglobulins (IgA, IgG, IgM) remained in the normal range and, at all time points after baseline, mean reductions in immunoglobulin levels were similar in the two OCR groups.

There was a marked decrease in rheumatoid factor and anti-CCP concentrations in the OCR groups, compared with relatively no change in the placebo group. A higher proportion of baseline RF+ patients became negative in the OCR groups compared with placebo at Week 24, with even higher proportions observed at Week 48. There was no difference between the two OCR groups with regard to the proportion of patients whose RF status changed from positive to negative over the course of the study.

PHARMACOKINETIC RESULTS:

For the first course of OCR treatment, mean (± SD) maximum serum concentrations following the first and second infusions (C_{first} and C_{second}) were 59.5 (± 17.6) μg/mL and 79.5 (± 27.1) μg/mL, respectively, for the OCR 200 mg dose group. Mean (± SD) C_{first} and C_{second} were 148 (± 42.0) μg/mL and 201 (± 1.2) μg/mL, respectively, for the OCR 500 mg dose group (first course).

For OCR re-treatment course at Week 24, mean (± SD) maximum serum concentrations following the first and second infusions (C_{first} and C_{second}) were 67.0 (± 30.6) μg/mL and 83.3 (± 32.0) μg/mL, respectively, for the OCR 200 mg dose group. Mean (± SD) C_{first} and C_{second} were 166 (± 59.3) μg/mL and 217 (± 71.5) μg/mL, respectively, for the OCR 500 mg dose group.

Mean terminal elimination half-life after the second infusion ranged from 17 to 19 days following the first course, and from 18 to 19 days following the first re-treatment course. Half-life was generally unchanged with dose level and did not appear to change upon re-treatment. Ocrelizumab PK (based on C_{max}) was

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approximately dose proportional over the limited dose range studied. Maximum concentrations following the second infusion of each course were approximately 24% - 34% higher on average than those seen after the first infusion. Ocrelizumab PK for first course and re-treatment course were comparable.

SAFETY RESULTS:

The incidence of AEs was balanced across treatment groups and the most common AEs in all groups were infections and infestations and infusion-related reactions (IRRs). Infections and infestations were reported with a similar frequency across treatment groups (53 – 55%). In all three groups, the majority of AEs were of Grade 1 or 2 intensity.

The incidence of serious adverse events was lower in the OCR 200 mg group compared with the placebo and OCR 500 mg groups with more serious drug-related events reported in the OCR 500 mg group these being infections and IRRs.

The number of AEs that led to study discontinuation was balanced across treatment groups and four patients died in the study during the 48-week period. A summary of the overall safety profile by treatment group (safety population) is provided below:

Number (%) of patients with:	**Placebo N = 320**	**OCR 200 mg N = 343**	**OCR 500 mg N = 343**
Any AE	254 (79.4%)	282 (82.2%)	287 (83.7%)
Grade 3	25 (7.8%)	20 (5.8%)	25 (7.3%)
Grade 4	2 (<1%)	2 (<1%)	2 (<1%)
Related	154 (48.1%)	165 (48.1%)	189 (55.1%)
Serious	37 (11.6%)	26 (7.6%)	38 (11.1%)
Serious Related	6 (1.9%)	7 (2.0%)	15 (4.4%)
AE leading to withdrawal from Treatment	5 (1.6%)	5 (1.5%)	6 (1.7%)
Any Deaths	1 (<1%)	0	3 (<1%)
Any Infusion Related Reaction	31 (9.7%)	69 (20.1%)	80 (23.3%)
Serious	0	1 (<1%)	2* (<1%)
Any infection	173 (54.1%)	188 (54.8%)	194 (56.6%)
Serious	10 (3.1%)	11 (3.2%)	21 (6.1%)
Any Malignancies	6 (1.9%)	3 (<1%)	4 (1.2%)

* Includes one event initially reported as anaphylactoid reaction.

The incidence of IRRs was higher in the OCR groups than in the placebo group and a majority of these reactions were experienced during the first infusion of the first course. The reactions were mostly of Grade 1 or 2 intensity with the exception of Grade 3 events experienced by two patients in the OCR 200 mg group. Three patients in the OCR-treated groups had events reported as serious IRRs, all of which resolved following symptomatic treatment.

The incidence of infections was similar across treatment groups and the most common infections in all groups were upper respiratory tract infections, nasopharyngitis and bronchitis. Except for pneumonia which was more frequent in the OCR 500 mg group than in the placebo and the OCR 200 mg groups, the

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incidence of all other infections was similar across groups with a majority of them being single occurrences. Forty-two patients had at least one serious infection event with more events reported in the OCR 500 mg group (6.1%) compared with the placebo group (3.1%) and the OCR 200 mg group (3.2%). A total of five infections led to discontinuation from study treatment (two, one and two experienced by patients from the placebo, OCR 200 mg and OCR 500 mg groups, respectively) and two patients had opportunistic infections; one case of Mycobacterium kansasii infection in the OCR 200 mg group and one case of fungal oesophagitis in the OCR 500 mg group.

Thirteen patients had a malignancy as an AE: six from the placebo group, three from the OCR 200 mg group and four from the OCR 500 mg group. All malignancies, with the exception of lung neoplasm (one event in each treatment group) and B-cell lymphoma (two cases, one each in the placebo and OCR 500 mg groups) were single occurrences. The events of lung neoplasm were incidental findings of pulmonary nodules in radiology examinations that did not lead to any clinical diagnosis. Overall there was no apparent imbalance in reporting of malignancies between ocrelizumab groups and placebo. There was no indication that ocrelizumab treatment may be associated with occurrence of certain type of cancers.

All laboratory parameters, with the exception of CRP and ESR, showed no clinically meaningful mean or median changes from baseline during the 48-week period. However, a trend towards a decrease in the mean and median lymphocyte and neutrophil counts was observed particularly in the OCR-treated groups.

CONCLUSIONS:

- Treatment with OCR 200 mg x 2 and OCR 500 mg x 2 in combination with MTX significantly decreased disease activity over 48 weeks in RA patients who had previously experienced an inadequate response to MTX.

  Both doses were associated with clinically and statistically significant improvement in ACR20 response at Weeks 24 and 48 (Co-Primary efficacy endpoints).

- Ocrelizumab showed significant improvement in signs and symptoms and physical function endpoints as indicated by: ACR50 and ACR70 response rates at Weeks 24 and 48; proportion of patients with Major Clinical Response at Week 48; proportion of patients with DAS28 low disease activity and DAS28 remission at Week 48; changes in HAQ-DI at Week 24 and Week 48.

- Overall, the OCR 200 mg and OCR 500 mg doses demonstrated comparable efficacy regarding signs and symptoms and patient reported outcomes. Additional efficacy benefit was seen at Week 48 in terms of both absolute response rates and treatment effect with both doses.

- Treatment with OCR 500 mg resulted in inhibition of progression of joint damage (100% inhibition of mTSS progression compared with placebo) as early as Week 24. OCR 200 mg dose showed significant improvement in progression of joint damage at Week 24, no further progression in mTSS from Week 24 onwards, achieving an inhibition of progression of mTSS of 85% by Week 48 compared with placebo.

- Ocrelizumab was well tolerated as indicated by comparable incidence of overall AEs and SAEs

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between the OCR groups and placebo.

- Most common adverse events were IRRs, which were manageable with symptomatic treatment as well as infections occurring with a similar frequency in all treatment groups.
- Serious infection rates per 100 patient years were similar between OCR 200 mg and placebo, but higher in OCR 500 mg.