SYNOPSIS OF RESEARCH REPORT [redacted]
(PROTOCOL WA20495)

COMPANY: Hoffmann-La Roche Ltd. NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S): ocrelizumab	(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 who have an inadequate response to at least one anti-TNF-α therapy. Research Report [redacted] December 2010. This clinical study report covers the double-blinded treatment phase of the study (Day 1 to Week 48).		
INVESTIGATORS / CENTERS AND COUNTRIES	227 centers in 25 countries worldwide: Argentina (3 centers), Australia (3 centers), Belgium (5 centers), Brazil (5 centers), Canada (14 centers), Czech Republic (1 center), France (9 centers), Germany (6 centers), Hungary (4 centers), Israel (5 centers), Italy (4 centers), Japan (14 centers), Mexico (4 centers), Netherlands (1 center), New Zealand (1 center), Panama (1 center), Peru (3 centers), Poland (2 centers), Slovakia (1 center), Slovenia (1 center), Spain (8 centers), Sweden (2 centers), Taiwan (1 center), and USA (127 centers).		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	08 Jun 2007 – 21 Jan 2010	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 or leflunomide in patients with active RA who have an inadequate response to at least one anti-TNF-α agent. **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 (PK) and pharmacodynamics (PD) of ocrelizumab.		

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STUDY DESIGN	Randomized, double-blind, multicenter, parallel group study with three treatment arms: placebo + non-biologic DMARD therapy (placebo), ocrelizumab 200 mg + non-biologic DMARD therapy (OCR 200 mg) and ocrelizumab 500 mg + non-biologic DMARD therapy (OCR 500 mg). The study included three phases: a double-blind treatment period (Day 1 to Week 48), a study extension period where eligible patients received open-label treatment with ocrelizumab (500 mg x 2) and a safety follow-up phase of at least 48 weeks for patients who withdrew from either of the treatment periods (double-blind or study extension).
NUMBER OF SUBJECTS	800 patients were planned; 840 enrolled (277 in the placebo group, 278 in the OCR 200 mg group and 285 in the OCR 500 mg group).
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Adult patients with active RA of at least 3 months who have had an inadequate response to previous or current treatment with one or more anti-TNF-α therapies (toxicity or inadequate efficacy). Those patients receiving MTX, leflunomide or other non-biologic DMARD therapy, and 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 (RoW): [redacted] Batch Numbers (US) [redacted]
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 a background medication consisting of either leflunomide (10-20 mg once daily) or methotrexate (7.5 - 25 mg oral or parenteral weekly) given either alone or in combination

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	with other non-biologic DMARDs.
REFERENCE DRUG / STROKE (BATCH) No.	Matching Placebo Batch Numbers (RoW): [redacted] Batch Numbers US: [redacted]
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 a background medication consisting of either leflunomide (10-20 mg once daily) or methotrexate (7.5 - 25 mg oral or parenteral weekly) given either alone or in combination with other non-biologic DMARDs.
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. • 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

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	mTSS at Week 48 **Exploratory** • The proportion of patients achieving an ACR90 response at Weeks 24 and 48. • 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 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 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 both active arms, OCR 200 mg and OCR 500 mg. The difference in ACR response was analyzed using the CMH test stratified by region (US, ROW) and baseline DMARD therapy. To control the type I

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error rate for the primary analyses, the following procedure was to be 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 to be 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 are < 0.05, then both doses were to be declared efficacious.

To control the type I error for secondary analyses, a hierarchy of four key secondary analyses has been 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 difference in ACR response are 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 have been 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. In addition, the study medication was given together with a background medication consisting of either leflunomide 10-20 mg once daily or methotrexate (7.5 - 25 mg oral or parenteral weekly) given either alone or in combination with other non-biologic DMARDs. Each infusion of study treatment was preceded by prophylactic treatment with 100 mg of methyl prednisolone. 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 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 patients were eligible to receive open-label OCR 500 mg, at the discretion of the investigator.

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

Patients who withdrew from the study at anytime during the 48-week period, 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.

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 12-13 years across treatment groups (median was 10-12 years) and mean DAS28 at baseline was high at 6.4-6.5 in all three groups reflecting severe disease in this patient population.

Of the 840 patients enrolled, four did not receive treatment and 85 withdrew from trial treatment prior to Week 48: 35 (12.6%) in the placebo group, 29 (10.5%) in the OCR 200 mg and 21 (7.4%) 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 196 patients: 110 (39.7%) from the placebo group, 41 (14.7%) from the OCR 200 mg group and 45 (15.8%) from the OCR 500 mg group. Most of the patients who received rescue therapy did not withdraw from the treatment period.

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The ITT and safety populations consisted of 836 patients with 277, 277 and 282 assigned to the placebo, OCR 200 mg and OCR 500 mg groups, respectively. The PP population comprised 665 patients (79% of the ITT population); 215 patients in the placebo group, 221 patients in the OCR 200 mg group and 229 patients in the OCR 500 mg group.

EFFICACY RESULTS:

At Week 24, the proportion of ACR20 responders was 22.0% in the placebo group, 42.2% in the OCR 200 mg group and 47.9% in the OCR 500 mg group. The proportion of ACR20 responders at Week 48 was 19.5% in the placebo group compared with 48.7% in the OCR 200 mg group and 50.7% in the OCR 500 mg group. 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 and PP population.

Logistic regression analysis at Week 24 indicated that the odds for achieving an ACR20 response was 2.63 and 3.25 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 1.93 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 4.04 and 4.27 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 the majority of secondary endpoints related to disease activity. Exceptions to this were: change in ACR core parameters SJC at Weeks 24 and 48, physicians global assessment at Week 24, and DAS28 remission at Week 24. The change in mTSS was not significant in the OCR 200 mg group, therefore, significance could not be claimed for any radiographic endpoints in the OCR 200 mg group due to the hierarchy of testing, or for major clinical response at Week 48 in the 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	22.0	42.2	< 0.0001	47.9	< 0.0001
Week 48	19.5	48.7	< 0.0001	50.7	< 0.0001
Secondary endpoints					
ACR50 (%)					
Week 24	7.9	21.3	< 0.0001	24.8	< 0.0001
Week 48	9.0	28.5	< 0.0001	30.9	< 0.0001
ACR70 (%)					
Week 24	2.9	7.6	0.0203	9.9	0.0014
Week 48	4.3	11.2	0.0042[#]	18.1	< 0.0001[#]
Change in ACR core set (adjusted mean)					
Week 24					
SJC	-5.7	-6.8	0.1770	-7.9	0.0063
TJC	-8.5	-11.1	0.0314	-13.6	< 0.0001
Patient's global assessment	-18.8	-25.8	0.0038	-29.6	< 0.0001
Physician's global assessment	-23.2	-27.1	0.0051	-29.8	0.0016
Patient's pain assessment	-15.2	-22.6	0.0016	-25.7	< 0.0001
CRP	-0.5	-1.2	< 0.0001	-1.5	< 0.0001
HAQ-DI	-0.3	-0.4	0.0010	-0.5	< 0.0001
ESR	-4.3	-15.3	< 0.0001	-18.4	< 0.0001
Week 48					
SJC	-7.1	-8.7	0.0531	-9.6	0.0017
TJC	-9.8	-13.6	0.0032	-15.7	< 0.0001
Patient's global assessment	-19.8	-31.0	< 0.0001	-34.3	< 0.0001
Physician's global assessment	-22.8	-32.7	< 0.0001	-34.2	< 0.0001
Patient's pain assessment	-17.1	-28.6	< 0.0001	-31.0	< 0.0001
CRP	-0.5	-1.6	< 0.0001	-1.7	< 0.0001
HAQ-DI	-0.2	-0.5	< 0.0001	-0.6	< 0.0001
ESR	-2.8	-18.9	< 0.0001	-23.1	< 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)	1.8	4.0	0.1885	5.7	0.0330
DAS28 remission					
Week 24	1.8	5.8	0.0175	6.0	0.0134
Week 48	1.4	11.9	<0.0001	12.1	<0.0001
EULAR response, good and moderate (%)					
Week 24	31.4	54.2	-	61.0	-
Week 48	24.9	58.8	-	60.3	-
Mean change from baseline in mTSS					
Week 24	1.23	1.12	0.7924[a]	0.67	0.4608[a]
Week 48[b]	2.58	1.84	0.2349[a]	1.00	0.0017[a]
Proportion of Patients without Radiographic Progression (%)					
Week 24	35.1	46.0	0.0142	44.4	0.0313*
Week 48	23.8	37.9	0.0004	42.9	< 0.0001*

*, P-values from CMH analysis stratified by region (US vs ROW) and DMARD (MTX or leflunomide). P-values for continuous endpoints from an analysis of variance. Model contains region (US, ROW), baseline DMARD, baseline ACR core set parameter and treatment. P-values are vs placebo.

[#] P-value unadjusted for Intersection of Union Testing

[a], All comparisons to placebo x 2 + MTX using Van Elteren's test stratified by region (US, ROW) and baseline DMARD therapy (MTX, leflunomide).

[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-(1.83/2.61)]*100 = 30% 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 statistically significant at Week 24 but achieved

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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:

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	3.85	6.74	-	8.29	-
Week 48	3.59	7.69	-	8.60	-
Change in SF-36 domains (adjusted means)					
Mental health					
Week 24	3.35	4.94	0.0822	5.05	0.0332
Week 48	3.04	5.37	0.0099	5.39	0.0058
Physical health					
Week 24	2.90	6.15	<0.0001	7.93	<0.0001
Week 48	3.55	7.77	<0.0001	9.17	<0.0001

*, P-values from an analysis of variance controlling for region (US, ROW) and baseline DMARD

PHARMACODYNAMIC RESULTS:

Post-initiation of treatment, a rapid depletion of CD19+ B-cells was observed in the OCR groups as early as 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 they returned to baseline values within approximately 2 weeks.

The levels of all three classes of immunoglobulin levels 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.

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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 62.7 (± 31.4) µg/mL and 75.9 (± 25.1) µg/mL, respectively, for the OCR 200 mg dose group. Mean (± SD) C_{first} and C_{second} were 157 (± 66.0) µg/mL and 189 (± 62.8) 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 72.2 (± 24.3) µg/mL and 84.2 (± 25.6) µg/mL, respectively, for the OCR 200 mg dose group. Mean (± SD) C_{first} and C_{second} were 176 (± 49.3) µg/mL and 216 (± 60.9) µg/mL, respectively, for the OCR 500 mg dose group.

Mean terminal elimination half-life after the second infusion ranged from 16 to 18 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 approximately dose proportional over the limited dose range studied. Maximum concentrations following the second infusion of each course were approximately 17% - 23% 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 IRRs. Infections and infestations were reported with a higher frequency in the OCR groups (53 – 56%) compared with placebo (49.1%). In all three groups, the majority of AEs were of Grade 1 or 2 intensity.

A marginally higher percentage of patients experienced at least one SAE in the OCR 200 mg group (14.4%) compared with the placebo (11.6%) and OCR 500 mg (11.3%) groups with more serious related events reported in the OCR groups (7 events in the placebo group, 12 events in the OCR 200 mg and 13 events in the OCR 500 mg group).

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

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Number (%) of patients with:	Placebo N = 277	OCR 200 mg N = 277	OCR 500 mg N = 382
Any AE	227 (81.9%)	232 (83.8%)	238 (84.4%)
Grade 3	28 (10.1%)	25 (9.0%)	28 (9.9%)
Grade 4	1 (<1%)	2 (<1%)	3 (1.1%)
Related	127 (45.8%)	153 (55.2%)	166 (58.9%)
Serious	32 (11.6%)	40 (14.4%)	32 (11.3%)
Serious Related	7 (2.5%)	12 (4.3%)	13 (4.6%)
AE leading to withdrawal from Treatment	10 (3.6%)	11 (4.0%)	7 (2.5%)
Any Deaths	1 (<1%)	0	0
Any Infusion Related Reaction	30 (10.8%)	53 (19.1%)	67 (23.8%)
Serious	0	0	0
Any infection	143 (51.6%)	150 (54.2%)	164 (58.2%)
Serious	7 (2.5%)	14 (5.1%)	12 (4.3%)
Any Malignancies	5 (1.8%)	7 (2.5%)	2 (<1%)

The incidence of infusion-related reactions (IRR) was higher in the OCR groups than in the placebo group and the 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 one patient in the placebo group and two patients in the OCR 200 mg group. No patients had a serious IRR.

Overall, infections were experienced more frequently in the OCR treatment groups compared with placebo (51.6% in the placebo group, 54.2% in the OCR 200 mg group and 58.2% in the OCR 500 mg group). The most common infections in all groups were upper respiratory tract infections, nasopharyngitis, urinary tract infection and bronchitis. Thirty-three patients had at least one serious infection event with more events reported in the OCR 200 mg (5.1%) and OCR 500 mg (4.3%) groups compared with the placebo group (2.5%). A total of six infections led to discontinuation from study treatment (two in each group).

Thirteen patients had a malignancy as an AE: four from the placebo group, seven from the OCR 200 mg group and two from the OCR 500 mg group. All malignancies were single occurrences. 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.

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CONCLUSIONS:

- OCR 200 mg x 2 and OCR 500 mg x 2 administered together with MTX or leflunomide alone or in combination with other non-biologic DMARDs met the primary endpoint and significantly decreased disease activity over 48 weeks in RA patients who had previously experienced an inadequate response to therapy with at least one anti-TNF-α agent.
- Both doses were associated with clinically and statistically significant improvement in ACR20 response at Weeks 24 and 48 (primary efficacy endpoint).
- Ocrelizumab showed statistically 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 DAS28 remission at Week 48; changes in HAQ-DI at Week 24 as well as proportion of patients with clinically relevant improvement in HAQ –DI.
- 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. Only the OCR 500mg dose demonstrated an effect on X-ray (change in mTSS at Week 48).
- Most common adverse events were IRRs, which were mostly manageable with symptomatic treatment, as well as infections.
- Serious infection rates per 100 patient years were similar between OCR 200 mg and OCR 500 mg groups but higher than those in the placebo group. In both dose groups, higher rates of serious infections were primarily driven by Asia (Japan).