SYNOPSIS OF RESEARCH REPORT NO. [redacted] (PROTOCOL WA20496)

COMPANY: F. Hoffmann-La Roche 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	Study WA20496: A Randomized, Double-Blind, Parallel-Group, International Study to Evaluate the Safety and Efficacy of Ocrelizumab Given as a Single Infusion or Dual Infusion Compared with Placebo in Patients with Active Rheumatoid Arthritis Who Have an Inadequate Response to Methotrexate Therapy / Report No. [redacted] / October 2010. This clinical study report covers the randomized, double-blinded placebo-controlled treatment phase of the study (up to Week 24) and the randomized not placebo-controlled period from 24 – 48 weeks.		
INVESTIGATORS / CENTERS AND COUNTRIES	Patients were recruited from 96 centers in 14 countries including Australia (2 centers), Canada (2 centers), France (4 centers), Germany (3 centers), Great Britain (4 centers), Italy (2 centers), Korea (2 centers), Mexico (4 centers), Poland (3 centers), Romania (4 centers), Spain (4 centers), Switzerland (1 center), Thailand (2 centers), and US (59 centers).		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	24 Apr 2008 to 26 Oct 2009	CLINICAL PHASE	III
OBJECTIVES	**Primary** To determine the efficacy and safety of 400 mg ocrelizumab (OCR), given as a single infusion, vs placebo, in combination with methotrexate (MTX), to reduce the signs and symptoms of Rheumatoid Arthritis (RA) at 24 weeks in patients with active RA who currently had an inadequate response to MTX therapy **Secondary** • To investigate and compare the PK and PD of a single and a dual infusion of ocrelizumab in this patient population • To assess the effect of a single infusion of ocrelizumab vs placebo on physical function in this patient population • To compare the safety and efficacy of single vs dual infusion at 24 and 48 weeks		
STUDY DESIGN	This was a randomized, double-blind, multicenter, placebo-controlled (up to Week 24), parallel-group study to investigate the efficacy and safety of a single infusion of OCR in combination with MTX. The target population for enrollment was patients with active RA (with or without previous exposure to biologic DMARDs) who had an inadequate clinical response to at least 12 weeks of prior MTX therapy. The study consisted of a 24-week double-blind, randomized,		

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	placebo-controlled treatment period and a subsequent 24-week double-blind, re-randomized (not placebo-controlled) treatment period, an open-label study-extension period, and a safety follow-up period. Only data up to Week 48 are presented in this report.
NUMBER OF SUBJECTS	A total of 314 patients were randomized into the study, 117 to OCR 400×1, 133 to OCR 200×2, and 64 to placebo. A total of 288 patients were re-randomized at Week 24: 109 to OCR 400/OCR 400, 61 to OCR 200/OCR 200, 61 to OCR 200/OCR 400, 29 to placebo/OCR 200, and 28 to placebo/OCR 400.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Eligible patients for this study included men and women ≥ 18 years of age, with active RA who currently had an inadequate clinical response to at least 12 weeks of prior MTX therapy. In addition to MTX, patients may have received other non-biologic and biologic DMARDs in the past. Eligible patients were positive for RF- or positive cyclic citrullinated peptide (CCP) antibody, or both; had ≥ four swollen joints and ≥ four tender joints; and had C-reactive protein (CRP) ≥ 0.6 mg/dL, measured using a high-sensitivity assay, or erythrocyte sedimentation rate (ESR) ≥ 28 mm/hour, or both. Patients could also receive stable doses of oral corticosteroids (or prednisone equivalent) up to 10 mg daily and stable doses of nonsteroidal anti-inflammatory drugs (NSAIDs).
TRIAL DRUG / STROKE (BATCH) No.	OCR: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Ocrelizumab was administered as a slow intravenous (iv) infusion during each course as either 200 mg on Day 1 and Day 15 (OCR 200×2) or as 400 mg given on Day 1 (OCR 400×1). Ocrelizumab was administered in combination with MTX. Patients and investigators were blinded to treatment assignment and dose. Patients also received 100 mg iv methylprednisolone (or equivalent) at least 30 minutes prior to each infusion of study treatment. Prophylactic treatment with acetaminophen (1g) and antihistamine (diphenhydramine HCl 50 mg or equivalent) 30-60 minutes prior to start of the infusion of study treatment was also recommended.
REFERENCE DRUG / STROKE (BATCH) No.	Placebo: [redacted]

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DOSE / ROUTE / REGIMEN / DURATION	Placebo was administered as a slow iv infusion on Day 15 to patients who were administered OCR 400 mg on Day 1 of a course in combination with MTX or Placebo administered as a slow iv infusion on both Days 1 and Day 15 of Course 1 to patients who were randomized to the placebo + MTX group Patients also received 100 mg iv methylprednisolone (or equivalent) at least 30 minutes prior to each infusion of study treatment. Prophylactic treatment with acetaminophen (1g) and antihistamine (diphenhydramine HCl 50 mg or equivalent) 30-60 minutes prior to start of the infusion of study treatment was also recommended.
CRITERIA FOR EVALUATION	
EFFICACY:	**The primary efficacy endpoint** was the proportion of patients with an ACR20 response at Week 24. **Secondary Endpoints:** **Week 24 Signs and Symptoms Endpoints** • Proportion of patients achieving Disease Activity Score 28 (DAS28) remission (DAS28 < 2.6) • Change in DAS28 from baseline • European League Against Rheumatism (EULAR) response rates (Categorical DAS responders) • Proportion of patients achieving an ACR50 response • Proportion of patients achieving an ACR70 response • Change from baseline in the individual parameters of the ACR core set **Week 24 Patient-Reported Endpoints** • Proportion of patients with a reduction of greater than or equal to 0.25 units in the HAQ-DI score • Change in SF-36 subscale and summary scores from baseline • Change in FACIT-F fatigue assessment from baseline **Week 48 Endpoints** • Proportion of patients achieving an ACR20 response • Proportion of patients achieving an ACR50 response • Proportion of patients achieving an ACR70 response • Proportion of patients achieving DAS28 remission (DAS28 < 2.6)

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Exploratory Endpoints (Both Week 24 and Week 48):

- The proportion of patients achieving DAS28 low disease activity (DAS28 ≤ 3.2)
- ACRn score
- Area under the curve (AUC) of the ACRn
- Plots of cumulative density function of ACRn over time
- The proportion of patients who received add-on therapy and/or increased the dose of background medication (corticosteroid and/or MTX) above baseline during the study
- Duration of DAS28 low disease activity and remission
- Proportion of patients achieving an ACR remission and the duration of remission if achieved
- Disease status over time

Exploratory Endpoints (Week 48 Only)

- EULAR response rates (categorical DAS responders)
- Change from baseline in the individual parameters of the ACR core set
- Proportion of patients with a reduction of ≥ 0.25 units in the HAQ-DI score
- Change from baseline in SF-36 subscale and summary scores
- Change from baseline in the FACIT-Fatigue assessment

PHARMACOKINETICS /PHARMACODYNAMICS:

The following PK parameters were estimated from ocrelizumab serum concentrations:

- $C_{first:}$ maximum observed serum concentration following first infusion
- $C_{second:}$ maximum observed serum concentration following second infusion ("nominally" on Day 15 per study protocol, and for dual infusion regimen ONLY)
- $t_{½:}$ terminal elimination half-life

The PD of ocrelizumab were defined by, but were not limited to, the extent and duration of peripheral B-cell depletion. The PD evaluations consisted of the lymphocyte subsets CD19+, CD19+CD27+, CD19+CD27-, CD3, CD4, CD8, and CD16+CD56+. Other PD parameters included immunoglobulins (IgA, IgG, and IgM), RF (total RF, IgA RF, IgG RF, and IgM RF), anti-CCP antibody, HAHA titers, and ANA.

Exploratory analyses assessed the possible relationship between

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	PD markers, PK, and clinical response.
QUALITY OF LIFE:	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) • Incidence of clinical laboratory abnormalities • Incidence of human anti-ocrelizumab antibodies (HAHA). Note: The HAHA results will be documented in a separate report.
STATISTICAL METHODS	**The primary variable** was the proportion of patients in the ITT Population (original randomization) with ACR20 responses at Week 24. The primary pairwise comparison was OCR 400×1 vs placebo. The difference in ACR20 response rates between the placebo and OCR 400×1 groups at Week 24 was tested using the CMH test statistic, stratified by region (US, ROW). At Week 24, the OCR 400×1 group was deemed superior compared with placebo if there was sufficient statistical evidence to reject the following null hypothesis (the proportion of patients with an ACR20 response was represented by p1 for the placebo group and by p2 for the OCR 400×1 group). H0: p2 = p1 ie, there was no evidence that the proportion of patients achieving ACR20 in the OCR 400×1 group was different to the placebo group, after adjustment for the stratification factor; and accept the alternative hypothesis: H1: p2 ≠ p1 ie, the proportion of patients achieving ACR20 in the OCR 400×1 group was different from the placebo group, after adjustment for the stratification factor. OCR 400×1 was considered superior to placebo if the OCR 400×1 group demonstrated a higher proportion of ACR20 responders (p2 > p1) and if the test result was statistically significant at $\alpha < 0.05$ level (two-sided test). The control of the type I error rate played a role in the analysis of two endpoints only: the primary endpoint, the proportion of patients with ACR20 response at Week 24 and a key secondary endpoint, the proportion of patients with a reduction of ≥ 0.25 units in the HAQ-DI at Week 24. **Secondary efficacy analysis:** Hypotheses for secondary efficacy analysis variables were only to be tested if the primary efficacy analysis was significant. The key

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secondary endpoint was the HAQ-DI at Week 24. Change in SF-36 summary scores from baseline at Week 24 was the important supportive secondary endpoint.

The Week 24 analyses for the secondary variables were carried out for the ITT population according to the three treatment groups. The three pairwise comparisons were performed, namely OCR 400×1 vs placebo, OCR 200×2 vs placebo, and OCR 200×2 vs OCR 400×1. P-values of corresponding analyses are presented for the first pair-wise comparison only. The sensitivity and robustness checks were performed at Week 24.

The Week 48 analyses for the secondary variables were carried out for the Re-randomized ITT Population based on the five treatment groups. The pairwise comparisons of interest were OCR 200/OCR 200 vs OCR 200/OCR 400 and OCR 200/OCR 200 vs OCR 400/OCR 400. These are presented for descriptive purposes only. The sensitivity and robustness checks were also performed at Week 48, with the exception that only the CMH procedure was conducted for proportion data on certain variables.

For patients that received rescue therapy (sponsor definition of rescue for signs and symptoms) or that withdrew prematurely from the study, continuous endpoints were set to missing from the day after the date at which they first received rescue therapy or withdrew and data were not to be carried forward beyond this point. For categorical endpoints, patients who withdrew, received rescue therapy, or had insufficient data were considered as non-responders.

Safety data included AE data, laboratory data, previous and concomitant treatment data, infusion information, IRR data, withdrawal data, death data, vital signs, and dosing information. The safety analyses up to Week 48 included all safety data available up to the date of data cut and included any post withdrawal safety follow-up data. The Safety Population only included data up to Week 24. The Re-randomized Safety Population only included safety data up to Week 48 for this interim report. All patients (including those not re-randomized at Week 24) who received any part of the second course and provided at least one assessment of safety prior to Week 48 were included in the Re-randomized Safety Population.

All data relating to safety are listed. Summaries were generated separately for the original and Re-randomized Populations.

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METHODOLOGY:

This was a Phase III, randomized, double-blind, multicenter, placebo-controlled, parallel-group study to investigate the efficacy and safety of a single infusion of OCR in combination with MTX at Week 24 (placebo-controlled) and Week 48 (re-randomized, double-blind; not placebo-controlled). The target population for enrollment was patients with active RA who had an inadequate clinical response to at least 12 weeks of prior MTX therapy. The patients were required to have received MTX in the range of 7.5 to 25 mg/week for at least 12 weeks prior to study entry and to be on a stable dose for at least four weeks before receiving their initial dose of study drug (OCR or placebo).

Patients were randomized in a double-blind manner to OCR 400×1, OCR 200×2, or placebo at baseline.

At Week 24, all patients were re-randomized into the 24-week double-blind, randomized (not placebo-controlled) treatment period in the following manner:

- Patients who received two 200 mg infusions of OCR + MTX during Course 1 were re-randomized (1:1 randomization ratio) to receive either a single infusion of 400 mg OCR + MTX (hereafter referred to as "OCR 200/OCR 400") or two infusions of 200 mg OCR + MTX (hereafter referred to as "OCR 200/OCR 200") during Course 2
- Patients who received a single 400 mg infusion of OCR + MTX during Course 1 received a second single-infusion of 400 mg OCR + MTX (hereafter referred to as "OCR 400/OCR 400") during Course 2
- Patients who received placebo during Course 1 were re-randomized (1:1 randomization ratio) to receive either a single infusion of 400 mg OCR + MTX (hereafter referred to as "placebo/OCR 400") or two infusions of 200 mg OCR + MTX (hereafter referred to as "placebo/OCR 200") during Course 2

The study consisted of a 24-week double-blind, randomized, placebo-controlled treatment period, followed by a 24-week double-blind, randomized (not placebo-controlled) treatment period, an open-label study-extension period, and a safety follow-up period. During this continued period of follow-up, eligible patients could have received open-label OCR, if it was considered appropriate by the investigator.

However, once open-label treatment with OCR was suspended, patients were to remain within the study extension period and to continue their scheduled visits without OCR dosing. Patients were allowed additional therapies for control of their disease activity. The open-label study-extension period was changed to the study-extension period. The database lock for this clinical study report occurred when the last patient completed his or her Week 48 assessment. Only data up to Week 48 are presented in this report.

EFFICACY RESULTS:

The primary efficacy endpoint was the proportion of patients in the ITT Population (original randomization) with an ACR20 response at Week 24. Since the primary endpoint was not met, the type I error control plan dictated that any further efficacy analysis was for descriptive purposes only. No statistically significant difference was observed in the proportion of patients with an ACR20 response at Week 24 OCR 400×1 group and the placebo group ($p = 0.2253$).

At Week 24, the results for ACR50 and ACR70 responses were consistent with those for ACR20. At Week 48, OCR 200 and OCR 400 maintained response similarly. The 95% CIs for the percentages of patients with a response at Week 48 who had a response at Week 24 for the OCR 200/OCR 200 group and

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the OCR 200/OCR 400 group overlapped for ACR20 response, ACR50 response, and ACR70 response. The relationships seen between the percentages of ACR20, ACR50, and ACR70 responders in each of the treatment groups at Week 24 and at Week 48 were consistent over time.

Key Efficacy Results at Week 24 and Week 48

ITT Population Results at Week 24	**Placebo N = 64**	**OCR 400x1 N = 117**	**OCR 200x2 N = 131**
Primary endpoint			
ACR20 (%)	28.1	37.6	52.7
Weighted difference vs placebo		8.6	24.5
p-value[a]		0.2253	
Secondary endpoints			
ACR50 (%)	7.8	18.8	30.5
ACR70 (%)	1.6	6.8	7.6
Change in ACR core set parameters (adjusted mean)			
SJC	-4.6	-7.5	-8.7
TJC	-8.2	-10.2	-12.0
Patient's global assessment	-7.6	-21.2	-24.3
Physician's global assessment	-16.0	-24.3	-26.0
Patient's pain assessment	-8.0	-17.2	-21.0
CRP	-0.2	-1.0	-0.8
HAQ-DI	-0.2	-0.4	-0.5
ESR	-3.0	-14.2	-11.1
DAS28 Low Disease Activity (%)	4.7	15.4	14.5
DAS28 remission (%)	3.1	4.3	5.3

[a] p-value calculated using Cochran-Mantel-Haenszel analysis stratified by region (US, RoW).

Re-randomized Population Results at Week 48	**OCR 200 /OCR 200 N = 61**	**OCR 200 /OCR 400 N = 61**	**OCR 400 /OCR 400 N = 109**	**Placebo /OCR 200 N = 29**	**Placebo /OCR 400 N = 28**
Secondary endpoints					
ACR20 (%)	59.0	54.1	56.9	44.8	42.9
ACR50 (%)	36.1	27.9	34.9	20.7	14.3
ACR70 (%)	19.7	16.4	19.3	6.9	7.1
ACR20 by ACR20 at Week 24 (%)	77.8	78.1	88.4	60.0	62.5
ACR50 by ACR50 at Week 24 (%)	66.7	54.5	81.0	100.0	33.3
ACR70 by ACR70 at Week 24 (%)	50.0	16.7	75.0	0.0	100.0
Change in ACR core set parameters (adjusted mean)					
SJC	-10.8	-10.9	-8.9	-	-
TJC	-14.9	-15.9	-13.9	-	-
Patient's global assessment	-31.0	-23.8	-25.8	-	-

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Physician's global assessment	-34.1	-31.5	-34.1	-	-
Patient's pain assessment	-25.4	-19.7	-21.7	-	-
CRP	-1.1	-1.3	-1.1	-	-
HAQ-DI	-0.6	-0.5	-0.5	-	-
ESR	-16.6	-9.4	-20.7	-	-
DAS28 Low Disease Activity (%)	21.3	16.4	24.8	10.3	10.7
DAS28 remission (%)	13.1	3.3	11.0	6.9	3.6

PHARMACODYNAMIC RESULTS:

Results to Week 24

Following the initiation of treatment, rapid depletion of CD19+ B-cells was observed in the OCR groups as early as the first evaluation time point at Week 2, in contrast to the placebo group.

- Mean CD19 B-cell counts stayed generally low between Week 2 and Week 24 in the OCR groups.
- At Week 24, the proportions of patients who remained B-cell depleted were 91.6% in the OCR 400×1 group, 96.4% in the OCR 200×2 group, and 13.2% in the placebo group, suggesting a trend for slightly faster peripheral B-cell recovery in the single-infusion arm.
- At most of the time points following the first infusion of study medication through Week 24, the CD3, CD4, and CD8 T-cell counts were reduced in the OCR groups compared with the placebo group. CD16+CD56+ lymphocyte counts were reduced in the OCR groups at Week 2 following the first dose of OCR but an improvement in mean cell count was observed by Week 4 in the OCR 200×2 group and by Week 24 in the OCR 400×1 group.
- There was minimal change in mean IgA and IgG levels in all three treatment groups from baseline through Week 24. Treatment with OCR resulted in a reduction in IgM levels compared with placebo over 24 weeks. However, values for all Ig tested remained within the normal range throughout.
- There was a marked decrease from baseline in mean total RF in the OCR groups as compared to the placebo group.

Results from Week 24 to Week 48

In the Re-randomized Safety Population, receipt of an infusion of OCR at Week 24 maintained the decreases in CD19+ B-cells in the three OCR/OCR groups and resulted in similar decreases in the two placebo/OCR groups by Week 26.

- At Week 48, the proportions of patients who remained B-cell depleted ranged between 91.7% for the placebo/OCR 200 group and 96.0% for the placebo/OCR 400 group. The proportion of B-cell depleted patients for the OCR/OCR treated groups was similarly low and ranged from 92.7% to 94.2%.
- After the first infusion of study medication (ie, Week 2), all three OCR/OCR groups and the placebo/OCR 200 group demonstrated mean decreases from baseline in CD3 (range: -57.564 to -158.041 cells/µL), CD4 (range: -10.055 to -119.280 cells/µL), and CD8 T-cell counts (range: -26.760 to -61.732 cells/µL). However, these changes were not clinically meaningful as the mean value for various T-cell subtypes remained within the normal range at all time points tested including Week 48.

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- Following the first infusion of study medication (ie, Week 2), CD16+CD56+ lymphocyte counts were reduced in the three OCR/OCR groups (range: -18.000 to -26.619 cells/µL mean change from baseline) and increased in the two placebo/OCR groups (6.640 and 11.130 cells/µL mean change from baseline.
- All five treatment groups demonstrated mean decreases from baseline in IgA, IgG, and IgM levels at most of the post-baseline time points.
- All five treatment groups demonstrated decreases from baseline in mean total RF (range: -140.42 to -246.38 IU/mL) and mean percentage change (range: -31.14% to -60.24%), with no patterns noted among the treatment groups.

PHARMACOKINETIC RESULTS:

- During Course 1, mean (± SD) maximum serum concentrations following the first and second infusions (C_{first} and C_{second}) were 73.1 (± 63.8) and 71.7 (± 18.0) µg/mL, respectively, in those patients who received dual infusions of 200 mg (OCR 200×2). Mean (± SD) C_{first} was 133 (± 38.5) µg/mL in those patients who received a single infusion of 400 mg (OCR 400×1).
- For Course 2, mean (± SD) maximum serum concentrations following the first and second infusions (C_{first} and C_{second}) were 67.7 (± 27.0) and 77.6 (± 27.4) µg/mL, respectively, for the OCR 200×2 (dual infusion) group. Mean (± SD) C_{first} was 137 (± 45.4) µg/mL for the OCR 400×1 (single infusion) group.
- As expected, maximum serum concentration following single infusion of 400 mg OCR was approximately twice that seen following the first infusion of 200 mg, indicating that OCR PK was approximately dose proportional over the limited dose range studied.
- Mean (± SD) $t_{1/2}$ ranged from 16.5 ± 4.8 to 17.4 ± 5.9 days following Course 1 and from 17.5 ± 4.9 to 18.0 ± 4.7 days following Course 2.
- Half-life was comparable between dose regimens and did not appear to change upon re-treatment. Following the dual infusion dose regimen, maximum concentrations following the second infusion of each course were approximately 0 to 15% higher on average than that seen after the first infusion.
- OCR PK for the first course and re-treatment were comparable.

SAFETY RESULTS:

After 24 weeks of treatment, the proportion of patients who experienced an AE was balanced across the three treatment groups (64.1% OCR 400×1, 66.4% OCR 200×2, and 62.5% placebo). The most common AEs (experienced by at least 10% of the patients in a treatment group) were IRRs (10.9% to 21.4%) and upper respiratory tract infections (7.8% to 12.2%). No deaths, Grade 4 (life-threatening) AEs, or serious IRRs before Week 24 were reported. Most patients who reported an IRR experienced a Grade 1 or Grade 2 event. The most commonly reported symptoms (by at least 10% of the patients who experienced an IRR in any treatment group) were flushing, rash, laryngeal/throat irritation, headache, fever/pyrexia, nausea, pruritus, hypertension, and chills/rigors. Percentages of patients with an SAE by Week 24 were 2.6% in the OCR 400×1 group, 1.5% in the OCR 200×2 group and 7.8% in the placebo group. The proportion of patients who experienced an infection (including those reported under body systems other than 'infections and infestations' class) by Week 24 was similar between the OCR 200×2 (39.7%) and placebo (37.5%)

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groups but was less in the OCR 400×1 group (32.5%). The most common types of infections (all treatment groups combined) were upper respiratory tract infections (7.8% to 12.2% of patients) and urinary tract infections (2.6% to 7.8% of patients), and were either bacterial or viral in nature. One patient each in the OCR 400×1 and placebo groups experienced an infection that led to withdrawal from treatment by Week 24. The patient in the OCR 400×1 group had an upper respiratory tract infection, while the patient in the placebo group had an infection with mycobacterium abscessus of the skin. This case was classified as an opportunistic infection (OI) and was the only OI during the study. One patient in the OCR 400×1 group reported a malignancy (basal cell carcinoma) by Week 24, which was unrelated and present prior to [redacted] participation in this study.

Adverse Events Occurring up to Week 24 in Safety Population:

Number (%) of patients with:	Placebo N = 64	OCR 400x1 N = 117	OCR 200x2 N = 131
Any AE	40 (62.5%)	75 (64.1%)	87 (66.4%)
Grade 3	4 (6.3%)	4 (3.4%)	45 (3.1%)
Grade 4	0	0	0
Related	17 (26.6%)	46 (39.3%)	53 (40.5%)
Serious	5 (7.8%)	3 (2.6%)	2 (1.5%)
Serious Related	3 (4.7%)	1 (<1%)	2 (1.5%)
AE leading to withdrawal from Treatment	2 (3.1%)	2 (1.7%)	1 (<1%)
Any Deaths	0	0	0)
Any Infusion Related Reaction	7 (10.9%)	25 (21.4%)	28 (21.4%)
Serious	0	0	0
Any infection	24 (37.5%)	38 (32.5%)	52 (39.7%)
Serious	2 (3.1%)	3 (2.6%)	2 (1.5%)
Any Malignancies	0	1 (<1%)	0

In the Re-randomized Safety Population, by Week 48 the proportion of patients who experienced an AE was smallest in the placebo/OCR 200 group (69.0%) followed by the OCR 200/OCR 200 group (74.2%) and balanced across the remaining three treatment groups (78.6% to 80.3%). The most common AEs (experienced by at least 10% of the patients in a treatment group) were IRRs, which were experienced by 17.2% to 30.6% of patients. Most patients who reported an IRR experienced a Grade 1 or Grade 2 event. No serious IRRs were reported and few patients across all five treatment groups experienced a Grade 4 (life-threatening) AE, an AE that led to treatment withdrawal, and/or a malignancy. None of the patients in the placebo/OCR 400 group, 10.3% of the patients in the placebo/OCR 200 group, and approximately 8% of the patients in each of the three OCR/OCR groups experienced an SAE by Week 48. The percentages of patients who experienced an infection by Week 48 was higher in the OCR 200/OCR 400 (55.7%) and placebo/OCR 400 (53.6%) groups than in the other three treatment groups (43.5% to 45.0%). The most common types of infections were urinary tract infection in the OCR 200/OCR 200 (9.7% of patients) and placebo/OCR 200 (10.3% of patients) groups and upper respiratory tract infection in the remaining three treatment groups. There was one death by the Week 48 endpoint in the OCR 400/OCR 400 group

SYNOPSIS OF RESEARCH REPORT NO. [redacted] (PROTOCOL WA20496)

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(anastomotic ulcer hemorrhage). A further 2 deaths occurred after the Week 48 snapshot (one in the placebo/OCR 200 mg group [pneumonia], and another in the placebo/OCR 400 mg group [lung adenocarcinoma]). None of the deaths were related to study treatment. Two patients each in the OCR 400/OCR 400 and OCR 200/OCR 200 groups reported a malignancy by Week 48. Malignancies reported in the OCR 400/OCR 400 group consisted of a basal cell carcinoma in one patient and three malignancies reported in a second patient: malignant melanoma on the left lower side of his back and dysplastic nevus syndrome, both of which were considered by the investigator to be remotely related to study treatment, as well as a malignant melanoma in situ on his left scapula that was considered by the investigator to be possibly related to study treatment. The malignancies reported in the OCR 200/OCR 200 group consisted of a basal cell carcinoma in one patient and prostate cancer in a second patient, both of which were considered by the investigators to be unrelated to study treatment. No clinically meaningful mean or median changes from baseline in any laboratory parameter were seen during the 48-week period. However, a trend towards a decrease in the mean and median uric acid levels was observed particularly in the OCR-treated groups. Two pregnancies occurred during the study. In one of these cases, the pregnancy was carried to term resulting in a normal birth. In the second, the patient was lost to follow up and no further information on the outcome of the pregnancy could be obtained.

Adverse Events Occurring up to Week 48 in Re-randomized Population

Number (%) of patients with:	OCR 200 /OCR 200 N = 62	OCR 200 /OCR 400 N = 61	OCR 400 /OCR 400 N = 109	Placebo /OCR 200 N = 29	Placebo /OCR 400 N = 28
Any AE	46 (74.2%)	49 (80.3%)	86 (78.9%)	20 (69.0%)	22 (78.6%)
Grade 3	8 (12.9%)	1 (1.6%)	6 (5.5%)	0	2 (7.1%)
Grade 4	0	0	2 (1.8%)	0	0
Related	26 (41.9%)	34 (55.7%)	53 (48.6%)	12 (41.4%)	13 (46.4%)
Serious	5 (8.1%)	5 (8.2%)	9 (8.3%)	3 (10.3%)	0
Serious Related	2 (3.2%)	3 (4.9%)	4 (3.7%)	2 (6.9%)	0
AE leading to w/d from trt	1 (1.6%)	0	1 (<1%)	1 (3.4%)	0
Any Deaths	0	0	1 (<1%)	0	0
Any IRR	19 (30.6%)	17 (27.9%)	28 (25.7%)	5 (17.2%)	6 (21.4%)
Serious	0	0	0	0	0
Any infection	27 (43.5%)	34 (55.7%)	49 (45.0%)	13 (44.8%)	15 (53.6%)
Serious	1 (1.6%)	4 (6.6%)	5 (4.6%)	1 (3.4%)	0
Any Malignancies	2 (3.2%)	0	2 (1.8%)	0	0

CONCLUSIONS:

- The primary study endpoint was not met; the proportion of patients who achieved an ACR20 response at Week 24 was not statistically significantly different between the OCR 400×1 group and the placebo group (*p*-value = 0.2253);
- Over the 24 week placebo-controlled treatment period the effect of dual infusion with OCR 200x2 on signs and symptoms of RA appeared to be more pronounced than that of the OCR 400 mg single infusion;

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- PK characteristics suggested that administration of OCR 200×2 maintains above-threshold drug levels over a longer period of time than administration of OCR 400×1;
- Initial effects on peripheral CD19+ B-cell counts were depletion (immediately after dosing) and were generally similar between the two OCR regimens, but B-cell recovery at Week 24 appeared to occur slightly faster after administration in the OCR 400×1 group than the OCR 200×2 group. It is possible that this difference in PD effect could account for differences in efficacy between the two dosing regimens;
- Both the single and dual infusions of OCR were generally well tolerated;
- Most common adverse events were IRRs, which were manageable with symptomatic treatment. No serious IRRs were reported in the study;
- No unexpected safety signals were noted in this study.