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RESEARCH REPORT NO. 1034917

Clinical Study Report – Phase II, multicenter, randomized, parallel-group, partially blinded, placebo and Avonex® controlled dose finding study to evaluate the efficacy as measured by brain MRI lesions, and safety of 2 dose regimens of ocrelizumab in patients with RRMS. Report No. 1034917, November 2012

Date of Report:	November 2012
Study Sponsor(s)	F. Hoffmann-La Roche Ltd. / Genentech Inc.
Study Dates:	13 January 2008 – 9 March 2012 (cut-off for this report)
Trial Phase:	II
Indication:	Relapsing Remitting Multiple Sclerosis (RRMS)

Name of Principal Investigator:	**Affiliation:**
[redacted]	[redacted] Switzerland

Sponsor's Signatory: [redacted]

Personnel Responsible for Clinical and Statistical Analyses:

[redacted]	Clinical Development Neuroscience
[redacted]	Project Statistician

GCP Compliance: **This study was conducted in accordance with the principles of GCP**

SYNOPSIS OF RESEARCH REPORT {1034917} (PROTOCOL {WA21493/ACT4422G})

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

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Phase II, multicenter, randomized, parallel-group, partially blinded, placebo and Avonex® controlled dose finding study to evaluate the efficacy as measured by brain MRI lesions, and safety of 2 dose regimens of ocrelizumab in patients with RRMS. Report No. 1034917, November 2012		
INVESTIGATORS / CENTERS AND COUNTRIES	79 centers from Europe and North America		
PUBLICATION (REFERENCE)	Kappos L., Li D., Calabresi PA. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomized, placebo-controlled, multicenter trial. Published online 1 November 2011 DOI:10.1016/S0140-6736(11)61649-8		
PERIOD OF TRIAL	13 January 2008 – 9 March 2012 (cut-off for this report)	CLINICAL PHASE	II
OBJECTIVES	Primary • To investigate the effect of ocrelizumab given as two dose regimens of 600 or 1000 mg intravenously on the total number of gadolinium-enhancing T1 lesions observed on magnetic resonance imaging (MRI) scans of the brain at weeks 12, 16, 20 and 24 as compared to placebo. Secondary • annualized protocol-defined relapse rate (ARR) by week 24 • proportion of patients who remained relapse free by week 24 (protocol-defined relapses) • total number of gadolinium-enhancing T1 lesions observed on MRI scans of the brain at weeks 4, 8, 12, 16, 20, and 24 • total number of new gadolinium-enhancing T1 lesions on MRI scans of the brain at weeks 4, 8, 12, 16, 20, and 24 • change in total volume of T2 lesions on MRI scans of the brain from baseline to week 24 • evaluation of the safety and tolerability of two dose regimens of OCR in patients with RRMS as compared with placebo and Avonex® at week 24 and the overall safety of OCR administered for up to 96 weeks • investigation of the pharmacokinetics and other pharmacodynamic study endpoints of OCR		
STUDY DESIGN	Multicenter, randomized, parallel-group, partially blinded, placebo and Avonex® controlled dose-finding study.		

NUMBER OF SUBJECTS	Of the 220 patients randomized, 218 received study treatment and 205 (93%) completed the 24-week placebo-controlled study period
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Men and women ranging from 18-55 years of age inclusive, with relapsing remitting MS in accordance with the McDonald criteria (2005). Patients must have experienced at least two documented relapses within the last 3 years prior to screening, at least one of which occurred within the last year prior to screening.
TRIAL DRUG BATCH NUMBERS	blinded OCR and placebo: [redacted] Avonex®: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Group A (OCR 1000 mg group): Two IV infusions of OCR 1000 mg separated by 14 days in Cycle 1, followed by an infusion of OCR 1000 mg on Day 1 and an infusion of placebo on Day 15 of Cycle 2. A single infusion of OCR 1000 mg or 600 mg was administered on Day 1 of Cycles 3 and 4, respectively. Group B (OCR 600 mg group): Two IV infusions of OCR 300 mg separated by 14 days in Cycle 1, followed by an infusion of OCR 600 mg on Day 1 and an infusion of placebo on Day 15 of Cycle 2. A single infusion of OCR 600 mg was administered on Day 1 of Cycles 3 and 4. Group C (placebo group): Two IV infusions of placebo separated by 14 days in Cycle 1, followed by two infusion of OCR 300 mg separated by 14 days in Cycle 2. A single infusion of OCR 600 mg was administered on Day 1 of Cycles 3 and 4 (following selection of the preferred dose). Group D (Avonex® group): Weekly IM injections of Avonex® 30 µg in Cycle 1, followed by two infusion of OCR 300 mg separated by 14 days in Cycle 2. A single infusion of OCR 600 mg was administered on Day 1 of Cycles 3 and 4 (following selection of the preferred dose).
CRITERIA FOR EVALUATION	
EFFICACY:	Primary Efficacy Parameters: The primary efficacy endpoint was the total number of gadolinium-enhancing T1 lesions observed on MRI scans of the brain at weeks 12, 16, 20, and 24. Secondary Efficacy Parameters: • ARR by week 24 • proportion of patients who remained relapse-free by week 24 (protocol-defined relapses) • total number of gadolinium-enhancing T1 lesions observed on MRI scans of the brain at weeks 4, 8, 12, 16, 20, and 24

	• total number of new gadolinium-enhancing T1 lesions observed on MRI scans of the brain at weeks 4, 8, 12, 16, 20, and 24 • change in total volume of T2 lesions on MRI scans of the brain from baseline to week 24.
PHARMACODYNAMICS:	Pharmacodynamic assessments included CD19+ peripheral B cell counts, as well as CD4 T cells, CD8 T cells, total CD3 T cells, NK cells (CD3- CD56+/CD16+), memory B cells (CD19+ CD38lo CD27+), plasma cells (CD19lo CD38hiIgD-CD27+), mature naive B cells (CD19+ CD21+ IgM+, IgD+), regulatory T cells (CD3+ CD4+ CD127lo CD25hi), and memory cytotoxic T cells (CD3+ CD8+ CD45RO+). Serum immunoglobulin (Ig, IgG, IgA and IgM) levels were also measured.
PHARMACOKINETICS:	OCR serum concentration-time data were modeled using a population pharmacokinetic approach. The primary population pharmacokinetic parameters (clearance and volume) for OCR were estimated by means of nonlinear mixed-effects modeling of the sparse pharmacokinetic data. Individual exposure parameters (AUC and C_{max}) for OCR were estimated.
SAFETY:	Safety was assessed through the occurrence of adverse events (AEs), regular neurologic and physical examinations, vital signs, and electrocardiogram (ECG). In addition, the following were examined: • complete routine hematology, chemistry, and urinalysis laboratory assessments • thyroid function tests • HAHA assessment • antibody titers for mumps, rubella, varicella, S. pneumoniae, and Epstein-Barr virus • serial pregnancy tests (serum/urine β-hCG) for women of childbearing potential.
STATISTICAL METHODS	For the primary efficacy endpoint, the van Elteren test stratified by geographic region and presence of baseline gadolinium-enhancing lesions (absent or present) was applied to compare the differences between each OCR group and the placebo group in the total number of gadolinium-enhancing T1 lesions observed on MRI scans of the brain at weeks 12, 16, 20, and 24. ARR for each OCR group and the placebo group at week 24 was calculated using Poisson regression, offsetting for exposure time in years. The primary population pharmacokinetic parameters (clearance and volume) for OCR were estimated by means of nonlinear mixed effects modeling of the sparse pharmacokinetic data. Individual exposure parameters (AUC_{τ} and C_{max}) for OCR were estimated.

METHODOLOGY

Study WA21493 was a Phase II, multicenter, randomized, parallel-group, partially blinded, placebo- and Avonex®-controlled, dose-finding trial designed to evaluate the efficacy, as measured by brain MRI lesions, and safety of two dose regimens of OCR in patients with RRMS.

Patient eligibility was determined during a 4-week screening period. Eligible patients were randomized (1:1:1:1) to one of four treatment groups, A, B, C, or D. The treatment allocation was pre-assigned using an interactive voice response system (IVRS). The two doses of OCR and placebo (Groups A, B, and C) were allocated in a double-blind manner, until the preferred dose was chosen, whereas treatment in the Avonex® active comparator group (Group D) was open label.

The first administration of study treatment defined the start of the treatment period (Day 1). All patients were scheduled to undergo 96 weeks of study treatment, representing four 24-week treatment cycles. In the case of Avonex® and placebo patients, this included time on the originally randomized treatment and time on OCR.

In Cycle 1, patients in Groups A and B received two IV infusions of OCR (1000 or 300 mg) separated by 14 days. To maintain the blind in Cycle 2, patients in Groups A and B received two infusions separated by 14 days; the first was OCR at the assigned dose (1000 or 600 mg) and the second infusion was placebo.

Patients in Group C received two IV infusions of placebo separated by 14 days in Cycle 1. Thereafter, Group C patients were placed on the 600 mg OCR dose regimen, starting with two double-blind infusions of OCR 300 mg separated by 14 days in Cycle 2.

Patients in Group D received Avonex® 30 µg by intramuscular (IM) injection weekly in Cycle 1. Thereafter, patients were offered, on a voluntary and open-label basis, the 600 mg OCR dose regimen, starting with two infusions of OCR 300 mg separated by 14 days in Cycle 2.

Patients received a single infusion of OCR 600 mg in Cycles 3 and 4, except for patients randomized to OCR 1000 mg who received a single infusion of OCR 1000 mg in Cycle 3 and 600 mg in Cycle 4.

EFFICACY RESULTS

This study met its primary endpoint and key secondary endpoints. A statistically significant treatment effect on total gadolinium-enhancing T1 lesions at weeks 12, 16, 20, and 24, on total new gadolinium-enhancing T1 lesions at weeks 4, 8, 12, 16, 20, and 24, and on ARR at week 24 was demonstrated for both OCR doses (Table 1). The mean (standard deviation [SD]) number of gadolinium enhancing lesions at weeks 12, 16, 20, and 24 was reduced by 89%, to 0.6 (1.52), in the OCR 600 mg group and by 96%, to 0.2 (0.65), in the OCR 1000 mg group, compared with 5.6 (12.53) in the placebo group. No clear separation in the primary endpoint was observed between the OCR 600 mg group and the OCR 1000 mg groups ($p = 0.15$).

Table 1 Overview of Efficacy (Primary Analysis at 24 Weeks) (ITT Population)

Endpoint p-value vs Placebo	Placebo	OCR 600 mg Arm	OCR 1000 mg Arm	Avonex
Total No. of Gd T1 lesions (Week 12 to 24) Mean (SD)	5.6 (12.53)	0.6 (1.52) <0.0001	0.2 (0.65) <0.0001	6.9 (16.01) 0.3457
Adjusted ARR [a] (95% CI)	0.557 (0.370,0.839)	0.127 (0.054,0.299) 0.0019	0.213 (0.110,0.414) 0.0136	0.364 (0.220,0.602) 0.1814
Proportion of relapse-free patients (95% CI)	75.9% (64.5%,87.3%)	85.5% (76.1%,94.8%) 0.1978	87.3% (78.5%,96.1%) 0.1310	77.8% (66.7%,88.9%) 0.8206
Total No. of Gd T1 lesions (Week 4 to 24) Mean (SD)	8.7 (17.54)	2.5 (5.10) <0.0001	1.8 (5.26) <0.0001	10.3 (22.15) 0.2725
Total No. of new Gd T1 lesions (Week 4 to 24) Mean (SD)	5.1 (11.99)	0.8 (1.95) <0.001	0.8 (2.16) <0.001	6.2 (13.79) 0.4985
Total T2 volume (change from BL to Week 24) Median (95% CI)	23.7 (-121.2,192.3)	-76.3 (-297.6,-34.2) 0.1391	-163.4 (-679.5,60.5) 0.1596	2.6 (-121.2,555.8) 0.4740

Gd = gadolinium, BL = baseline

[a] adjusted for geographic region

The change in the volume of T2 lesions at week 24 was not statistically reduced in OCR patients compared with placebo and Avonex patients. The treatment benefit of OCR on the total number of gadolinium-enhancing T1 lesions at weeks 12, 16, 20, and 24, and the unadjusted ARR at week 24 were consistently positive across all OCR subgroups based on a wide range of patient characteristics. The robustness of the primary and key secondary analyses was demonstrated by the consistent results of sensitivity analyses. Exploratory endpoints presented in this report consistently favored both OCR doses over Avonex and placebo.

The treatment benefit of OCR was maintained throughout the study up to Week 144.

PHARMACODYNAMIC RESULTS

Both doses of OCR led to a rapid and complete depletion of peripheral $CD19^+$ B cells, which was sustained through the 24 weeks of the placebo-controlled period. OCR patients also demonstrated a reduction in serum IgM levels, but not IgG or IgA levels, which is consistent with the known pharmacodynamic effects of OCR in other autoimmune disorders.

PHARMACOKINETIC RESULTS

At the dose range tested in this study, OCR $AUC\tau$ and C_{max} were approximately dose proportional. A two compartment model with first-order elimination adequately characterized the

pharmacokinetic data. Clearance, central volume of distribution, inter compartmental clearance, and peripheral volume of distribution were 217 mL/day, 3240 mL, 196 mL/day, and 2420 mL, respectively. The terminal elimination half-life for OCR was 22.7 days.

SAFETY RESULTS

The overall proportion of patients with AEs was similar between treatment groups (Table 2). During the placebo-controlled 24-week period, the number of AEs was similar between the placebo (117) and the OCR 600 mg group (116) and higher in the OCR 1000 mg group (142). The percentage of patients with at least one AE was similar across all 4 treatment groups. The higher number of AEs in the OCR 1000 group was driven mainly by higher number of IRRs reported during the first and the second infusion. The AE profile of OCR during the open label treatment period up to Week 96 and during follow-up and monitoring/observation periods up to Week 144 was consistent with observations during the first 24 weeks.

Table 2 Overview of Adverse Events

	Placebo	Ocrelizumab 600 mg Arm	Ocrelizumab 1000 mg Arm	Avonex
Cycle 1 (n)	54	55	55	54
Number of patients with AEs	38 (70.4%)	35 (63.6%)	36 (65.5%)	32 (59.3%)
Number of AEs	117	116	142	91
Number of patients with SAEs	2 (3.7%)	1 (1.8%)	2 (3.6%)	2 (3.7%)
	Ocrelizumab 600 mg	Ocrelizumab 600 mg	Ocrelizumab 1000 mg	Ocrelizumab 600 mg
Cycle 2 (n)	53	50	47	50
Number of patients with AEs	38 (71.7%)	27 (54.0%)	24 (51.1%)	30 (60.0%)
Number of AEs	88	74	61	66
Number of patients with SAEs	1 (1.9%)	1 (2.0%)	2 (4.3%)	3 (6.0%)
	Ocrelizumab 600 mg	Ocrelizumab 600 mg	Ocrelizumab 1000 mg	Ocrelizumab 600 mg
Cycle 3 (n)	50	49	46	49
Number of patients with AEs	25 (50.0%)	24 (49.0%)	27 (58.7%)	19 (38.8%)
Number of AEs	43	53	40	46
Number of patients with SAEs	1 (2.0%)	3 (6.1)	2 (4.3%)	4 (8.2%)
	Ocrelizumab 600 mg	Ocrelizumab 600 mg	Ocrelizumab 600 mg	Ocrelizumab 600 mg
Cycle 4 (n)	49	46	44	46
Number of patients with AEs	24 (49.0%)	21 (45.7%)	21 (47.7)	16 (34.8)
Number of AEs	42	34	42	28
Number of patients with SAEs	-	-	1 (2.3%)	2 (4.3%)
	Ocrelizumab 600 mg	Ocrelizumab 600 mg	Ocrelizumab 600 mg	Ocrelizumab 600 mg
Safety follow-up (n) Week 120	49	48	50	49
Number of patients with AEs	16 (32.7%)	15 (31.3%)	26 (52%)	12 (24.5%)
Number of AEs	30	29	58	18
Number of patients with SAEs	-	1 (2.1%)	3 (6.0%)	-
	Ocrelizumab 600 mg	Ocrelizumab 600 mg	Ocrelizumab 600 mg	Ocrelizumab 600 mg
Monitoring/observation (n) Week 144	46	46	45	48
Number of patients with AEs	12 (26.1%)	7 (15.2)	18 (40.0)	10 (20.8%)
Number of AEs	18	9	30	15
Number of patients with SAEs	1 (2.1)	-	1 (2.2)	1 (2.1%)

Cycle 1: baseline to Week 24; Cycle 2, 3 and 4: Week 24 to Week 96, safety follow-up: Week 96 to Week 120 and monitoring/observation: Week 120 to Week 144.

The most frequently reported AEs were general disorders and administration site conditions, followed by infections and infestations. With the exception of MS relapse, IRRs and influenza-like illness, which was only reported in the Avonex arm during the placebo-controlled 24-week period, most common AEs were reported at similar frequency across treatment arms.

The single most common AE was IRRs, reported more often in OCR-treated patients after the first infusion on Day 1 (9.3% in placebo arm, 34.5% in the 600 mg arm and 43.6% in the 1000 mg arm in Cycle 1). The percentage of patients experiencing IRRs was similar in the OCR arms compared with placebo after the second infusion on Day 15 (11.1 % in placebo arm, 3.8% in the 600mg mg arm and 9.4% in the 1000 mg arm in Cycle 1). Most IRRs in both the OCR and placebo groups were mild or moderate in intensity. One Grade 3 IRR occurred during the placebo-controlled period in the OCR 1000 mg group. A total of six Grade 3 IRRs occurred during the study in five patients. One patient experienced an IRR of Grade 4 (life-threatening) on Day 1 in Cycle 2 (Avonex arm). No fatal IRR occurred during the study. Overall, 3 patients on OCR withdrew due to IRRs: 2 reported as IRRs (Grade 2 and 4) and the other one as serious hypersensitivity.

There was no increase in the incidence of infections in the OCR groups compared with the placebo group. The proportion of patients experiencing an infection during the placebo-controlled 24-week period was 37.0% in the placebo group, 43.6% in the OCR 600 mg group, and 30.9% in the OCR 1000 mg group. Infection rates remained consistent during subsequent study periods (open-label period, safety follow-up and monitoring/observation period). Most of the infections were mild or moderate in intensity. No AEs reported as infection led to withdrawal of treatment and no opportunistic or fatal infections were reported in this study.

One patient in the OCR 1000 mg arm died during the placebo-controlled 24-week period (Day 92). This patient was hospitalized with acute onset of encephalopathy and status epilepticus due to SIRS with disseminated intravascular coagulation of unknown cause, following infusion of gadolinium. The patient's course rapidly progressed to multi-organ failure. While hospitalized, the patient developed a nosocomial pneumonia in the setting of severe renal and hepatic insufficiency. After 2 weeks of intensive care the patient died of transforaminal herniation of the brain, due to massive cerebral edema. Despite a thorough clinical-pathological review, the exact cause of death could not be determined.

A patient randomized to placebo and who received OCR 600 mg in subsequent cycles died on Day 968 due to an injury. A patient randomized to OCR 600 mg arm died on Day 1,074 due to an unknown cause. Both events were considered unrelated to study drug by the investigator. Last doses for those patients (Cycle 4, Day 1) were on Day 512 and 505, respectively. Both events occurred during B-cell follow-up and patients had repleted B-cells at the time of event.

There was no safety signals associated with OCR treatment with regards to vital signs, ECGs or safety laboratory parameters.

CONCLUSIONS

Both 600 mg and 1000 mg doses of OCR were superior to placebo in reducing the total number of gadolinium-enhancing lesions and the formation of new gadolinium-enhancing lesions, as well as ARR. Exploratory analyses of these endpoints indicated that OCR was also superior to Avonex®.

No clear separation in efficacy was seen between the OCR doses.

At the doses studied, OCR exhibited dose-proportional pharmacokinetics, and both doses were associated with a rapid and complete pharmacodynamic depletion of peripheral $CD19^+$ B cells.

Both doses of OCR were well tolerated through the 24 weeks of the placebo-controlled period with a safety profile similar to placebo. The safety profile of OCR remained consistent throughout the 96-week treatment period. Both OCR doses were associated with a higher rate of IRRs compared with placebo after the first infusion; however, the rates of IRRs were similar to placebo after the second infusion. There was no increase in the incidence of infections or serious infections in the OCR groups compared with the placebo group. No opportunistic or fatal infections were reported.